BRAF/MEK Inhibitor Therapy

Consensus statement from the faculty of the Melanoma Nursing Initiative on managing adverse events and potential drug interactions

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BACKGROUND: BRAF/MEK inhibitor therapy improves outcomes in *BRAF* V600E- and V600K-mutated unresectable or metastatic melanoma. However, these regimens are associated with adverse events (AEs) that may lead to unnecessary drug modifications and discontinuations or potentially serious sequelae. In addition, drug–drug interactions (DDIs) may result in AEs or altered therapeutic efficacy.

OBJECTIVES: This article presents consensus statements to guide nurses in the prevention, recognition, and management of AEs and potential DDIs associated with BRAF/MEK inhibitor therapy.

METHODS: Members of the Melanoma Nurse Initiative reviewed the current literature and clinical experience related to AEs and DDIs associated with BRAF/MEK inhibitor therapy.

FINDINGS: The care step pathways provided for select AEs represent a proactive, comprehensive nursing care plan to support optimal patient outcomes. Recommendations are also offered for preventing and managing DDIs.

KEYWORDS
melanoma; targeted therapy; BRAF; MEK; adverse events; drug–drug interactions

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IN THE PAST SEVERAL YEARS, novel therapeutic options have been developed for patients with v-Raf murine sarcoma viral oncogene homolog B (BRAF)–mutant unresectable, high-risk, or metastatic melanoma (Eroglu & Ribas, 2016). About 50% of all advanced melanomas have an activating mutation in the *BRAF* proto-oncogene, which encodes a kinase in the mitogen-activated protein kinase (MAPK) pathway that helps regulate cell growth. Mutations in the *BRAF* gene can cause uncontrolled activation of the BRAF protein, thereby initiating a series of intracellular phosphorylation events that promote oncogenesis. Two of the most common BRAF-activating mutations are found in codon 600 of this protein and are designated V600E and V600K (Medina & Lewis, 2016). Vemurafenib (Zelboraf®) and dabrafenib (Tafinlar®) are inhibitors of BRAF that are approved by the U.S. Food and Drug Administration (FDA) as single agents for patients with metastatic melanoma with the *BRAF* V600E mutation (Genentech, 2017; Novartis, 2016).

Single-agent BRAF inhibitor therapy is associated with high rates of resistance and the development of secondary cutaneous malignancies, owing to paradoxical MAPK pathway activation in skin cells that do not have a *BRAF* mutation (wild-type cells) (Medina & Lewis, 2016). Mitogen-activated protein kinase kinase (MEK), a downstream kinase in the MAPK pathway, provides another therapeutic target for regulating cellular proliferation (Eroglu & Ribas, 2016). Drugs that inhibit MEK include trametinib (Mekinist®) and cobimetinib (Cotellic®) (Genentech, 2016; Novartis, 2017a). These agents inhibit hyperactive signaling in the MAPK pathway but have relatively low response rates as single agents compared with BRAF inhibitors (Medina & Lewis, 2016). Combination BRAF/MEK inhibitor therapy is associated with superior overall and progression-free survival, overall response rate, and duration of response versus single-agent BRAF inhibitor therapy (Larkin et al., 2014; Long et al., 2014; Robert et al., 2015). In addition, in these studies, the incidence of new primary melanomas, cutaneous squamous cell carcinoma, basal cell carcinoma, and keratoacanthoma decreased with the combination therapy versus single-agent BRAF inhibitor therapy. Two FDA-approved BRAF/MEK inhibitor combination regimens are available: (a) dabrafenib and trametinib and (b) vemurafenib and cobimetinib

(Genentech, 2016, 2017; Novartis, 2016, 2017a). A third BRAF/MEK inhibitor combination therapy, encorafenib and binimetinib, has demonstrated similarly favorable results (in efficacy and safety profiles) in a phase 3 clinical trial (Dummer et al., 2016) and is undergoing FDA review. To date, no controlled clinical trials have directly compared BRAF/MEK inhibitor combination therapy regimens. These drugs are referred to as targeted therapies because they act on specific protein targets in the MAPK pathway.

BRAF/MEK inhibitor drugs are orally administered and have enhanced convenience compared with injectable therapies, but some barriers hamper appropriate use. Adverse events (AEs) associated with BRAF/MEK inhibitors differ from those seen with chemotherapy or immunotherapy and can be challenging to recognize and manage (Dy & Adjei, 2013). Faculty of the Melanoma Nursing Initiative (MNI) convened to define supportive care challenges associated with the use of BRAF/MEK inhibitor therapy. The MNI evaluated the literature and clinical experience to recommend nursing interventions to improve patient and therapeutic outcomes. The authors made recommendations in the following areas:

- Patient counseling and education about BRAF testing
- Administration and dosing, with a focus on dosage adjustments related to AEs
- AE management, including strategies to educate and assess patients' understanding, as well as specific care step pathways (CSPs) to guide nursing interventions regarding prompt recognition and management of AEs of particular concern
- Drug–drug interactions (DDIs), with a focus on identifying concomitant medications for which potential exists for an interaction that would decrease drug effectiveness or exacerbate toxicities

Testing

Both FDA-approved BRAF/MEK inhibitor combination therapies require positive identification of the *BRAF* V600E or V600K mutation as detected by an FDA-approved test. Patients with wild-type *BRAF* melanoma are not suitable candidates for these treatments (Genentech, 2017; Novartis, 2017b) because BRAF inhibitors may promote tumor growth in cells with wild-type *BRAF* (Medina & Lewis, 2016). Two tests are approved by the FDA for the detection of *BRAF* V600 mutations: the THxID™ BRAF kit (for dabrafenib and trametinib) and the cobas 4800 BRAF V600 Mutation Test (for vemurafenib and cobimetinib) (FDA, 2017). Both use polymerase chain reaction technology to evaluate melanoma tissue for V600 mutations. The THxID test detects either V600E or V600K mutations, whereas the cobas test detects only V600E. Other assays based on sequencing methods are being evaluated by the FDA and are used at some centers because of their improved sensitivity and ability to analyze multiple genes (Ma et al., 2016); however, insurance coverage may vary.

"Adverse events associated with BRAF/MEK inhibitors differ from those seen with chemotherapy or immunotherapy and can be challenging to recognize and manage."

A link to the FDA website that lists approved companion diagnostic tests, along with links to other nursing and patient resources, can be found in Figure 1. Oncology nurses are in a key position to field questions related to testing. Patients should be informed about the need for specific *BRAF* testing that is tailored to the treatment planned and that is likely to be reimbursed. If testing has previously been performed, but not via an approved method, clearly explaining the rationale for repeat testing is necessary, given the potential reimbursement issues. Anticipating the need for possible repeat analysis and expediting necessary arrangements will not only minimize delays in commencing therapy but will improve patient satisfaction.

Drug Administration and Dosages

BRAF and MEK inhibitors are self-administered oral agents. Approved doses and recommended dose modifications are shown in Table 1. To reiterate, dabrafenib dosed at 150 mg twice a day is combined with trametinib at 2 mg daily. Vemurafenib dosed at 960 mg twice a day is combined with cobimetinib at 60 mg daily. Dabrafenib (at the 150 mg dose, twice a day) and vemurafenib (at the 960 mg dose, twice a day) are also approved as monotherapy. Some global comments can be made about dosing. Of note, dabrafenib and trametinib should be taken on an empty stomach. All the agents are stored at room temperature, except for trametinib, which requires refrigeration. Dabrafenib, trametinib, and vemurafenib are given on a continuous daily basis (Genentech, 2017; Novartis, 2016, 2017a), although some clinics use drug holidays (brief treatment breaks) during the treatment course when patients are having AEs that affect their activities of daily living. Cobimetinib is given for the first 21 days of a 28-day

cycle, followed by seven days off of the drug (Genentech, 2016). A generalized dose-reduction scheme for toxicity is shown, and dose-reduction schemes for specific AEs are outlined in more detail in the CSPs.

Adverse Events and Care Step Pathways

Table 2 lists some common AEs associated with BRAF/MEK inhibitors. Although some similarities can be found in the AE profiles across the targeted therapy combinations, some individual differences exist. In particular, photosensitivity is more frequently associated with vemurafenib-containing regimens, whereas pyrexia is more frequently associated with dabrafenib-containing regimens. MEK inhibitor drugs are associated with cardiomyopathy, while BRAF inhibitor drugs are associated with QT interval prolongation.

The available AE data were obtained from trials of BRAF/MEK inhibitor combination therapies in patients with previously untreated melanoma. As the therapeutic options available for patients with BRAF-mutated melanoma expand, whether the toxicity profile will differ is unknown. Members of the MNI agreed that patients receiving targeted therapies who were previously treated with immunotherapy should be monitored carefully for overlapping toxicities, such as rash, fatigue, joint pain, diarrhea, and altered liver function, because these AEs are also observed with immune checkpoint inhibitors and may result in cumulative toxicities (Welsh & Corrie, 2015).

Each of the four CSPs presented in this article represents a notable AE associated with targeted therapy and incorporates essential components of the nursing assessment specific to that AE. Look, listen, and recognize categories within the nursing assessment section direct the nurse to a specific set of symptom-related queries to ask the patient and/or caregiver and highlights additional information important to optimal management. Wherever possible, the grading in the CSPs is based on the

FIGURE 1.
NURSE AND PATIENT RESOURCES RELATED TO USE OF TARGETED THERAPIES IN MELANOMA

FOR NURSES

ARRAY PHARMACEUTICALS: BINIMETINIB (MEK162)
- www.arraybiopharma.com/product-pipeline/binimetinib

ARRAY PHARMACEUTICALS: ENCORAFENIB (LGX818)
- www.arraybiopharma.com/product-pipeline/encorafenib-lgx818

COTELLIC® PACKAGE INSERT
- www.gene.com/download/pdf/cotellic_prescribing.pdf

CYTOCHROME P450 DRUG INTERACTION TABLE
- http://medicine.iupui.edu/CLINPHARM/ddis/main-table

GENENTECH BIO ONCOLOGY ACCESS SOLUTIONS
- www.genentech-access.com/hcp/brands/cotellic.html

INTERNATIONAL SOCIETY OF NURSES IN CANCER CARE
- www.isncc.org

MEKINIST® (TRAMETINIB) PACKAGE INSERT
- http://bit.ly/2tNik2G

NOVARTIS ACCESS
- www.hcp.novartis.com/access
- 1-800-282-7630

STRATEGIES FOR MANAGING PYREXIA IN YOUR PATIENTS TAKING TAFINLAR + MEKINIST
- http://bit.ly/2rQJ3yX

TAFINLAR® (DABRAFENIB) PACKAGE INSERT
- http://bit.ly/2rUKCqE

U.S. FOOD AND DRUG ADMINISTRATION LIST OF CLEARED OR APPROVED COMPANION DIAGNOSTIC DEVICES
- http://bit.ly/1whiCOt

ZELBORAF® (VEMURAFENIB) PACKAGE INSERT
- www.gene.com/download/pdf/zelboraf_prescribing.pdf

FOR PATIENTS

AIM AT MELANOMA FOUNDATION

Nurse on Call
- www.aimatmelanoma.org/living-with-melanoma/nurse-on-call
- 1-877-246-2635

Patient and caregiver resources
- www.aimatmelanoma.org/living-with-melanoma/patient-caregiver-resources

Patient and caregiver symposiums
- www.aimatmelanoma.org/living-with-melanoma/patient-caregiver-symposiums

AMERICAN CANCER SOCIETY: TARGETED THERAPY FOR MELANOMA SKIN CANCER
- http://bit.ly/2sTeYyI

COTELLIC® (COBIMETINIB) + ZELBORAF® (VEMURAFENIB) PATIENT PAGE
- www.cotellic.com

COTELLIC®/ZELBORAF® ACCESS SOLUTIONS (PATIENT VERSION)
- www.genentech-access.com/patient.html
- 1-866-422-2377

GENENTECH ACCESS TO CARE FOUNDATION
- http://bit.ly/2rC193C

NOVARTIS PATIENT ASSISTANCE NOW ONCOLOGY
- www.oncologyaccessnow.com/index.jsp
- 1-800-282-7630

TAFINLAR® (DABRAFENIB) AND MEKINIST® (TRAMETINIB) PATIENT SITE
- www.us.tafinlarmekinist.com/advanced-melanoma

TABLE 1.
DOSING INFORMATION AND MODIFICATIONS FOR BRAF/MEK INHIBITOR COMBINATIONS

REGIMEN	DOSAGE	FOOD EFFECT	MISSED DOSES	DOSE MODIFICATION FOR TOXICITY		
				FIRST OCCURRENCE	SECOND OCCURRENCE	THIRD OCCURRENCE
Dabrafenib and trametinib						
Dabrafenib (stored at room temperature)	150 mg BID	On an empty stomach (at least one hour before or two hours after a meal)	Do not take a missed dose within six hours of the next dose.	100 mg BID	75 mg BID	50 mg BID; discontinue if unable to tolerate 50 mg BID.
Trametinib (refrigerated[a])	2 mg QD		Do not take a missed dose within 12 hours of the next dose.	1.5 mg QD	1 mg QD	Discontinue.
Vemurafenib and cobimetinib						
Vemurafenib (stored at room temperature)	960 mg BID	With or without food	Take as many as four hours prior to the next dose.	720 mg BID	480 mg BID	Discontinue (doses of less than 480 mg are not recommended).
Cobimetinib (stored at room temperature)	60 mg QD for the first 21 days of each 28-day cycle		Take if four hours or less after scheduled time; otherwise, resume dosing with the next scheduled dose.	40 mg QD	20 mg QD	Permanently discontinue.

[a] Temperature exclusion data indicate that trametinib (in an opened bottle) is not damaged by storage outside of the refrigerator for as many as 30 days, if it is maintained at a temperature below 86°F (30°C). Nurses may advise patients who have left trametinib out of the refrigerator to simply keep the medication cool and return it to the refrigerator as soon as possible.
BRAF—v-Raf murine sarcoma viral oncogene homolog B; MEK—mitogen-activated protein kinase kinase; QD—once daily
Note. Based on information from Genentech, 2016, 2017; Novartis, 2016, 2017a, 2017b.

National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events (CTCAE), which is, in some cases, supplemented with information from the package inserts of the drugs (Genentech, 2016, 2017; Novartis, 2016, 2017a). Each CSP describes overall management strategies and nursing-specific interventions. Where applicable, prevention strategies, as well as strategies specific to each AE grade, are listed, including dose reductions or modifications. Patient counseling, recommendations for additional care, and referral to specialty or ancillary care providers are included in the management section, as appropriate.

General Education

Patient education regarding a recommended treatment regimen is a key component of the oncology nursing role. The general components of pretreatment education include reviewing treatment expectations (of provider, patient, and family members), addressing logistic and financial considerations, and discussing potential toxicities. Education should be comprehensive and individualized for patients and their plan of care. If possible, that education should be given in the presence of a patient caregiver or support person, with validation of patient comprehension and compliance. Foundational to any AE discussion is educating each patient to promptly recognize and report any new or worsening symptoms, whether or not the patient thinks they are related (Welsh & Corrie, 2015). Providing clear instruction on when, why, and how to contact the patient's oncology provider is critical and should be reiterated at every visit. New or worsening symptoms, and any symptoms indicative of a serious AE, such as vision change, bleeding, or cardiotoxicity, are critical to report (Welsh & Corrie, 2015).

General education also includes counseling concerning the use of nonhormonal methods of contraception to avoid embryofetal toxicity associated with these agents. Barrier (nonhormonal) methods are preferred because BRAF inhibitors may render hormonal contraceptives ineffective (attributable to DDIs). Given the importance of avoiding fetal toxicity and the potential impact on fertility, the oncology team should have open, candid discussions about family planning with patients of childbearing age and note any potential barriers or contraindications to future goals. A possible recommendation may be a referral to a fertility

specialist to discuss potential sperm or egg banking as an option. Nurses continue to support the process by reinforcing conversations and addressing patient concerns. Patients may also benefit from other educational materials and online resources to support them on their treatment journey, including resources from the manufacturers, as well as advocacy organizations.

Common Adverse Events

PYREXIA

One of the most common AEs associated with BRAF/MEK inhibitor combination therapy, particularly dabrafenib and trametinib, is pyrexia, which is elevated body temperature in the absence of clinical or microbiologic evidence of infection (Lee et al., 2014). In clinical trials of dabrafenib and trametinib, pyrexia usually appeared within one to two months and plateaued about six months after initiation of treatment (Long et al., 2014; Menzies et al., 2015). The etiology of pyrexia is not well understood but is hypothesized to be an off-target effect (i.e., related to interactions between the drug and proteins other than BRAF/MEK) (Atkinson et al., 2016; Lee et al., 2014; Menzies et al., 2015).

Figure 2 shows the MNI CSP for management of pyrexia. Current CTCAE grading criteria do not include grading categories

TABLE 2.
COMMON ADVERSE EVENTS FOR BRAF/MEK INHIBITOR THERAPIES

ADVERSE EVENT	DABRAFENIB AND TRAMETINIB	DABRAFENIB	VEMURAFENIB	TRAMETINIB	VEMURAFENIB AND COBIMETINIB
Blood and blood system					
Hemorrhage	✓				✓
Cardiovascular					
Hypertension	✓			✓	✓
Left ventricular dysfunction (decreased ejection fraction)	✓			✓	✓
Cutaneous disorders					
Benign/secondary skin neoplasms		✓	✓		✓
Photosensitivity			✓		✓
Rash	✓	✓	✓	✓	✓
Eye disorders (uveitis, retinal disorders)					
Vision impaired	✓	✓	✓	✓	✓
Gastrointestinal disorders					
Diarrhea, nausea, vomiting, or abdominal pain	✓		✓		✓
Hepatotoxicity (elevated liver function tests)			✓		✓
General disorders					
Pyrexia (fever) and chills	✓	✓		✓	
Musculoskeletal					
Arthralgia	✓	✓	✓	✓	✓
Renal toxicity	✓		✓		✓

BRAF—v-Raf murine sarcoma viral oncogene homolog B; MEK—mitogen-activated protein kinase kinase
Note. The adverse events listed are more likely to occur with the drugs in the associated columns, but may occur with any of the drugs. Drugs may not have all adverse events listed.
Note. Cobimetinib is not approved for use as a single agent and is not included.
Note. Based on information from Genentech, 2016; Larkin et al., 2014; Novartis, 2016, 2017a.

FIGURE 2.
CARE STEP PATHWAY FOR MANAGEMENT OF PYREXIA: ELEVATED BODY TEMPERATURE IN THE ABSENCE OF CLINICAL OR MICROBIOLOGIC EVIDENCE OF INFECTION

NURSING ASSESSMENT

Look

- Does the patient appear unwell?
  - ☐ Diaphoretic?
  - ☐ Pallor?
- 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, gastrointestinal or respiratory symptoms)
- Method of temperature assessment (oral, axillary, temporal)
- Self-management of fevers (over-the-counter agents, medications, tepid baths)
- Adequacy of fluid intake in the last 24 hours (how much, types)
- How the patient has been taking BRAF/MEK inhibitor drugs
- Potential infectious causes
  - ☐ Symptoms suggestive of infectious etiology (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, and hypotension (complex pyrexia syndrome)
- Potential infectious causes (via urinalysis, urine culture, throat cultures, and blood cultures)
- Impact of symptoms on quality of life and performance status

GRADING TOXICITY

Grade 1 (mild)

- Asymptomatic; mild, low-grade fevers (99°F–101.2°F [37.2°C–38.4°C])

Grade 2 (moderate)

- Fevers (101.3°F–104°F [38.5°C–40°C]); mildly symptomatic (e.g., chills); affecting ADLs

Grade 3 (severe)

- Any fever of greater than 104°F (40°C) or fever of 101.3°F–104°F (38.5°C–40°C) that is moderately symptomatic (rigors, chills, decreased urinary output, hypotension); limiting self-care ADLs

Grade 4 (potentially life-threatening)

- Any fever of greater than 101.3°F (38.5°C) that is highly symptomatic (e.g., acute renal insufficiency, hypotension requiring hospitalization and prompt supportive care)

Grade 5 (death)

ADLs—activities of daily living; BRAF—v-Raf murine sarcoma viral oncogene homolog B; MEK—mitogen-activated protein kinase kinase
Note. Based on information from Atkinson et al., 2016; Genentech 2016, 2017; Lee et al., 2014; Menzies et al., 2015; National Cancer Institute, 2010; Novartis,2016, 2017a.

for this novel effect; the fever criteria in the CTCAE were designed for the management of febrile neutropenia, which has a different etiology, and the temperature cut points in the CTCAE are different from those used for drug holds with targeted therapy. In addition to temperature elevation, management of pyrexia is also driven by symptoms (e.g., rigors, hypotension, dehydration, renal failure) or recurrent episodes. In general, management of pyrexia involves maintaining hydration, providing supportive care for symptoms, and ensuring that patients are adhering to treatment recommendations, particularly those concerning treatment holds or dose adjustments. Based on MNI members' experience, premedication with acetaminophen or nonsteroidal anti-inflammatory drugs is not useful in preventing pyrexia. This practice has been adopted by some clinicians in the community but is not evidence based.

Management strategies for recurrent pyrexia are also discussed in the CSP. Corticosteroids (e.g., prednisone 10 mg

MANAGEMENT BY GRADE

Grade 1 (mild)

- Acetaminophen or ibuprofen every four to six hours until fever resolves (less than 99°F [37.2°C]) for at least 24 hours off antipyretics
  - ☐ Monitor renal and hepatic function during antipyretic treatment.
  - ☐ Do not exceed 4,000 mg acetaminophen or 3,200 mg ibuprofen per day.
- Increase oral hydration to minimize insensible losses. Suggested fluids include water, juice, and sports drinks (e.g., Gatorade®, POWERADE®, Pedialyte®).
- Review medication profile with patient and family, including prescriptions, over-the-counter and herbal medications, supplements, and other complementary therapies.
  - ☐ Determine if concomitant medications contain antipyretics.
  - ☐ Assess for potential drug–drug interactions.
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grade 2 (moderate)

- For temperatures of greater than 101.3°F (38.5°C), dabrafenib should be held, and trametinib should be continued.
- Acetaminophen or ibuprofen every four to six hours until fever resolves (less than 99°F [37.2°C]) for at least 24 hours
  - ☐ Monitor renal and hepatic function during antipyretic treatment.
  - ☐ Do not exceed 4,000 mg acetaminophen or 3,200 mg ibuprofen per day.
- Institute rehydration strategies, particularly if the patient is hypotensive or another clinical concern exists. Set hydration goals.
  - ☐ Increase oral hydration (e.g., water, rehydration drinks [Pedialyte], juice, sports drinks [Gatorade, POWERADE], Popsicles®).
  - ☐ IV fluids, as needed
- For pyrexia refractory to antipyretics, corticosteroid with prednisone or equivalent will be used (25 mg per day with downward titration); consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fevers are persistent and refractory to antipyretics or prednisone treatment, causing moderate changes in the patient's ADLs).
- Assess patient and family understanding of recommendations and rationale.
- Identify barriers to adherence.
- On symptom and fever resolution (less than 99°F [37.2°C]) for 24 hours, possible treatment restart with appropriate dose reduction
- For recurrent pyrexia, corticosteroid with prednisone or equivalent will be used (10 mg per day for at least five 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 of greater than 104°F (40°C) or any fever accompanied by chills, hypotension, dehydration, or renal failure, dabrafenib and trametinib should be held.
- For intolerable temperatures of 102.3°F–104°F (39.1°C–40°C) and all temperatures of greater than 104°F (40°C), vemurafenib and cobimetinib should 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 every four to six hours until fever resolves (less than 99°F [37.2°C]) for at least 24 hours
  - ☐ Monitor renal and hepatic function during antipyretic treatment.
  - ☐ Do not exceed 4,000 mg acetaminophen or 3,200 mg ibuprofen per day.
- Aggressive hydration management to address hypotension
- For pyrexia refractory to antipyretics, corticosteroid with prednisone or equivalent will be used (25 mg per day with downward titration); consider change in targeted therapy, if clinically appropriate (e.g., dabrafenib to vemurafenib).
- Grade 3: On symptom and fever resolution (less than 99°F [37.2°C]) for 24 hours, possible treatment restart
  - ☐ Same agents with appropriate dose reductions
  - ☐ Oral corticosteroid premedication (10 mg per day) to be used for second or subsequent pyrexia with dabrafenib if prolonged (more than three 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 and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

FIGURE 3.
CARE STEP PATHWAY FOR MANAGEMENT OF SKIN TOXICITY

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 or new lesion(s): photosensitivity reactions, sunburn, or other cutaneous lesions suspicious for actinic keratoses, keratoacanthomas, basal cell carcinomas, cutaneous squamous cell carcinomas, or new melanomas?

Listen

- Rash and/or pruritus?
- Other cutaneous symptoms (e.g., photosensitivity)?
- Are symptoms interfering with ADLs? With sleep?
- Have symptoms worsened?
- What interventions has patient tried (if any)? Which were effective and ineffective?
- Question patient and family regarding history of skin problems (sun damage, dermatitis [with prior immunotherapy], 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 or preexisting skin issues (psoriasis, skin cancer, wounds)?
- Is there evidence of scratching, such as abrasions?
- Is skin integrity 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 quality of life?
- Relevant social history (occupational, environmental, leisure-type activities)

GRADING TOXICITY: RASH (MACULOPAPULAR RASH, ACNEIFORM RASH, OR DERMATITIS)

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

Grade 1 (mild)

- Macules and papules covering less than 10% BSA, with or without symptoms (e.g., pruritus, burning, tightness)

Grade 2 (moderate)

- Macules and papules covering 10%–30% BSA, with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs

Grade 3 (severe)

- Macules and papules covering more than 30% BSA, with or without associated symptoms; limiting self-care ADLs; skin sloughing covering less than 10% BSA

Grade 4 (potentially life-threatening)

- Papules and pustules covering any percentage of BSA, with or without symptoms; associated with superinfection requiring IV antibiotics; skin sloughing covering 10%–30% BSA

Grade 5 (death)

GRADING TOXICITY: PRURITUS

A disorder characterized by an intense itching sensation

Grade 1 (mild)

- Mild or localized; topical intervention indicated

Grade 2 (moderate)

- Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing or crusts); oral intervention indicated; limiting instrumental ADLs

Grade 3 (severe)

- Intense or widespread; constant; limiting self-care ADLs or sleep; oral corticosteroid or immunosuppressive therapy indicated

Grade 4 (potentially life-threatening)

Grade 5 (death)

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, including herbals, supplements, and alternative or complementary therapies.
- Encourage patients to report any skin changes promptly.

MANAGEMENT BY GRADE

Intervention (at-risk patients)

- Gentle skin care
  - ☐ Avoid soap. Use nonsoap cleansers (mild, fragrance- and dye-free soap on the axillae, genitalia, and feet).
  - ☐ Avoid hot baths.
  - ☐ Avoid tight clothing and shoes.
  - ☐ Keep fingernails short (to avoid scratching).
  - ☐ Apply nonsteroidal moisturizers or emollients containing humectants (urea, glycerin) daily.
  - ☐ 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, and 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 and sunscreen
- Possible use of topical antihistamines
- Patient counseling
  - ☐ Emollients twice daily
  - ☐ Antihistamines and analgesics, if applicable
  - ☐ Strict UV protection with SPF 30 sunscreen and eye protection
  - ☐ Gentle exfoliation for follicular rash
  - ☐ Treatment with 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 or oral) to be started
- Persistent grade 2: Therapy to be held until grade 0 or 1
  - ☐ Start oral steroid; taper no longer than seven 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 less than grade 1; resume at a lower dose.
- Oral steroid to be started; taper no longer than seven 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, or electrolyte replacement.
- Patient counseling
  - ☐ Anticipatory guidance regarding treatment discontinuation or possible hospitalization for steroids and/or hydration
  - ☐ Refer to dermatologist.

Continued on the next page

FIGURE 3. *(CONTINUED)*
CARE STEP PATHWAY FOR MANAGEMENT OF SKIN TOXICITY

RED FLAGS
- Extensive rash (more than 50% BSA) or rapidly progressive
- Skin sloughing
- Oral involvement
- Concern for suprainfection

ADLs—activities of daily living; BSA—body surface area
Note. Based on information from Atkinson et al., 2016; de Golian et al., 2016; Genentech 2016, 2017; National Cancer Institute, 2010; Novartis, 2016, 2017a.

daily) for at least five days are recommended for a second or subsequent pyrexia if temperature does not return to baseline within three days of onset, or if pyrexia is associated with complications, including dehydration, hypotension, renal failure, and severe chills or rigors, in the absence of evidence of active infection (Novartis, 2017a). For patients with steroid-refractory pyrexia, an increased dosage of prednisone with a tapering course (for instance, beginning at 25 mg per day and titrating downward) in addition to withholding therapy until symptoms return to baseline or grade 1 may help to control pyrexia (Atkinson et al., 2016). Targeted therapy can then be restarted at a lower dose and gradually titrated upward. MNI members recommend that steroids be taken with food, preferably in the morning, to minimize problems with insomnia. They should not be taken at the same time as the BRAF/MEK inhibitors. If high temperatures continue to recur, even with antipyretics, prednisone, dose reductions, or drug holidays, severely affecting a patient's quality of life, a change in targeted therapy to a different combination regimen could be considered.

SKIN TOXICITIES

Also associated with BRAF/MEK inhibitor combination therapy are skin toxicities, which may have a tremendous impact on quality of life. Rashes may have a variety of presentations, including maculopapular, verrucous, hyperkeratotic, keratosis pilaris-like, and acneiform (Lacouture et al., 2013; Livingstone, Zimmer, Vaubel, & Schadendorf, 2014; Segaert, 2008; Segaert & Van Cutsem, 2005). Pruritus (itching) and xerosis (dry skin) can occur in the absence of rash or after the rash resolves (Bryce & Boers-Doets, 2014; Valentine et al., 2015). Photosensitivity is a unique toxicity that is characterized by a burning sensation with marked erythema or edema on sun-exposed skin; it is most frequently observed with vemurafenib-based regimens and is attributed to exposure to ultraviolet A radiation (Bryce & Boers-Doets, 2014; Mavropoulos & Wang, 2014). If persistent photosensitive reactions do not respond to dose reductions or drug holidays, a change from vemurafenib to another combination therapy (such as dabrafenib and trametinib) should be considered.

As highlighted in Figure 3, nurses are in a key position to educate patients to institute appropriate self-care and prevention strategies to minimize skin toxicities. Because of photosensitivity issues, direct and indirect sunlight should be avoided whenever possible. Patients should be counseled to practice sun avoidance by using sunscreen and lip balm with an SPF of at least 30 and wearing sun-protective clothing, including sunglasses, when outside. Patients who work outdoors should be counseled about the possibility of modifying their jobs while on this therapy because of high risk for photosensitivity. Gentle skin care should be encouraged, including avoidance of harsh soaps (alcohol-based or with fragrances) and regular use of emollient-based, non-irritant moisturizers at least daily. Some skin toxicities are typically observed within days of initiation of therapy, so educating patients and their families about these preventive measures while emphasizing when to contact the oncology team is essential.

Another novel cutaneous toxicity related to these regimens is the development of benign, premalignant, or malignant secondary skin neoplasms, including actinic keratosis, keratoacanthoma, basal cell carcinoma, and squamous cell carcinoma (Flaherty et al., 2012; Larkin et al., 2014; Long et al., 2014). This toxicity is thought to be caused by activation of the MAPK pathway signaling in cells that have not yet acquired a mutation in the BRAF protein. For these reasons, a full skin examination (including oral and genital areas) by a dermatologist with expertise in skin cancer should be performed before beginning treatment, every two months during treatment, and as many as seven months after treatment discontinuation (Genentech, 2016; Novartis, 2016, 2017a). Suspicious lesions should be examined by a dermatologist; given the associated risk of secondary skin malignancy, a biopsy is recommended. Secondary malignancies are typically managed surgically without dose interruption or modification (Rubin, in press).

Other cutaneous disorders may occur. Benign growths (e.g., squamous papillomas, warts) may be a cosmetic or quality-of-life

concern for some patients and can be treated with topical agents, such as fluorouracil, or by cryotherapy or curettage (Mandalà, Massi, & De Giorgi, 2013; Welsh & Corrie, 2015). Palmoplantar hyperkeratosis, which often presents as thickened yellow plaques over friction sites (e.g., on the soles of the feet) (Macdonald, Macdonald, Golitz, LoRusso, & Sekulic, 2015), can occur rapidly after the initiation of BRAF inhibitor therapy (Anforth et al., 2012; Livingstone et al., 2014). Preventive measures include avoidance of tight-fitting shoes and clothing. Hyperkeratotic lesions can be pared down mechanically by a podiatrist or treated with keratolytic medications or topical steroids (Livingstone et al., 2014; Macdonald et al., 2015). For severe cutaneous symptoms, dose reductions or treatment holidays may be necessary until symptoms resolve or are reduced to grade 1. Alopecia has also been noted with BRAF/MEK inhibitor therapy (Livingstone et al., 2014; Sinha et al., 2012), although the authors have not observed this frequently. Hair changes (such as in curliness or graying) have also been noted (Mavropoulos & Wang, 2014). No medical management is necessary for these changes; however, if patients are bothered by these effects, topical minoxidil may be used for alopecia, and cosmetic techniques, such as hair coloring, may be employed (Rubin, in press).

Rare But Serious Adverse Events

OCULAR TOXICITIES

Eye-related AEs are rare, but may be serious if not recognized and promptly treated. The potential for patients to become blind should not be overlooked. These AEs appear to be related to an inflammatory response or breakdown of the blood–retina barrier (Huang et al., 2009). Uveitis appears to be associated with BRAF inhibitor therapy, whereas retinal disorders are associated with MEK inhibitor therapy (Schoenberger & Kim, 2013). In many instances, ocular AEs are transient and will resolve, but persistent symptoms necessitate dose interruption with dose reduction on improvement or, in severe cases, require permanent drug discontinuation (see Figure 4). Patients should be advised to immediately report any visual disturbances, and an ophthalmic examination should be completed at baseline and whenever patients report eye symptoms.

CARDIAC TOXICITIES

Cardiotoxicity, including cardiomyopathy and QT prolongation, is a potentially serious consequence of treatment with BRAF/MEK inhibitor therapy. Figure 5 provides a CSP for the evaluation and management of cardiotoxicity. A thorough history can reveal preexisting cardiac conditions that may preclude targeted therapy. Vemurafenib treatment should not be initiated in patients with uncorrectable electrolyte abnormalities, QTc of greater than 500 milliseconds, or long QT syndrome, or in patients who are taking drugs known to prolong the QT interval (e.g., anti-arrhythmics, azole antifungals, fluoroquinolones) (Nachimuthu, Assar, & Schussler, 2012). Thorough cardiac testing should be completed, with left ventricular ejection fraction assessed before initiation of therapy and at regular intervals during therapy (one month after initiation and every two to three months thereafter) (Genentech, 2016, 2017; National Cancer Institute, 2010; Novartis, 2016, 2017a). Both BRAF/MEK inhibitor combinations are associated with hypertension, so careful monitoring is required, particularly for patients with preexisting hypertension.

IMPLICATIONS FOR PRACTICE

- Educate patients and caregivers to recognize the possible early signs and symptoms of adverse events (AEs) associated with v-Raf murine sarcoma viral oncogene homolog B (BRAF) and protein mitogen-activated protein kinase kinase (MEK) inhibitor therapy to facilitate prompt intervention.
- Provide comprehensive nursing assessment and care for patients who present with AEs associated with BRAF/MEK inhibitor therapy.
- Assess medication plans for potential drug interactions with BRAF/MEK inhibitor therapy that may affect treatment efficacy or exacerbate toxicity.

Other Adverse Events

Table 3 lists additional AEs and laboratory abnormalities associated with BRAF/MEK inhibitors, along with information on appropriate questions to determine the AE and recommendations for drug holds, dose reductions, and discontinuations specific to the AE.

DRUG–DRUG INTERACTIONS

Dabrafenib, vemurafenib, and cobimetinib are metabolized by the cytochrome P450 (CYP450) system (Genentech, 2016, 2017; Novartis, 2016), which includes more than 50 CYP enzymes. This hepatic system metabolizes many other drugs; therefore, targeted therapies have significant potential for DDIs. Trametinib is metabolized by deacetylation and glucuronidation biotransformation pathways (Novartis, 2017a) and is, therefore, less likely to be involved in DDIs.

Because DDIs can diminish efficacy and promote AEs, nurses should have a working knowledge of these potential interactions, ensuring that all members of the medical team, including primary care providers and other specialists, communicate to address any potential DDIs. Table 4 shows important DDIs that may affect the use of BRAF/MEK inhibitors. In particular, dabrafenib induces CYP3A4, which can result in decreased concentrations and loss of efficacy for hormonal contraceptive substrates and proton pump inhibitors (Flockhart, 2007; Novartis, 2016).

Targeted therapies can also prolong the QT interval. Therefore, identifying concomitant medications that may also have this effect is important (Welsh & Corrie, 2015). Medications known to increase the risk of QT prolongation include anti-arrhythmics, certain antidepressants, some antiemetics (e.g., ondansetron), atypical antipsychotics, azole antifungals, fluoroquinolones, and methadone (Nachimuthu

FIGURE 4.
CARE STEP PATHWAY FOR MANAGEMENT OF 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 skin lesions surrounding the eye(s)?

Listen

- Patient and family descriptions of ocular health and eye problems, currently 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 include headache, vomiting, and nausea?

Recognize

- Patients at risk
- The specific ocular complaint (if possible); determine grade.
- Other treatment-related symptoms
- How vision limitations affect quality of life
- 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, irritiation, photosensitivity); visual acuity falls to 20/40 or better in affected eye(s); limiting instrumental ADLs

Grade 3 (severe)

- Highly symptomatic (pain, irritation, photosensitivity); 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 the patient is to start combination therapy.
- Follow-up examination should occur 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, and 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 because 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 and assistance, as appropriate.
  - ☐ Keratitis (inflammation of cornea): artificial tears, lubricants, 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, CSs, 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 or dose reduction or discontinuation
  - ☐ Retinal vein occlusion (vascular event leading to vision changes, macular edema, glaucoma): anti–vascular endothelial growth factor 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 or dose reduction or discontinuation

MANAGEMENT BY GRADE

Grade 1 (mild)

- In general, anticipate referral to ophthalmology.
- Specific targeted therapy dose modifications
  - ☐ Uveitis: BRAF inhibitor may be continued with caution. MEK inhibitor can be continued. Obtain prompt visit with ophthalmologist.
  - ☐ Other ocular adverse events: Follow standard dose modifications or holds based on grade.
- Support adherence to eye drops and topical therapy.

Grade 2 (moderate)

- Urgent referral to ophthalmology (within 24 hours); specific targeted therapy dose modifications or holds or discontinuations
  - ☐ Uveitis (persistent grade 2 or more than six weeks duration): Hold BRAF inhibitor therapy.
  - ☐ Serous retinopathy: Withhold MEK inhibitor 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 three weeks. Assess adherence to eye drops and topical therapy.
- Anticipate drug holds or dose modifications of targeted therapy for other moderate ocular toxicities, per prescribing information.
- Obtain ophthalmology clearance prior to restarting therapy.

Grades 3–4 (severe or life-threatening)

- Urgent referral to ophthalmology (within 24 hours)
- Specific targeted therapy drug modifications, holds, or discontinuations
  - ☐ Uveitis (severe): Hold dabrafenib; permanently discontinue if no improvement within six weeks.
  - ☐ Serous retinopathy: Withhold MEK inhibitor 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 three weeks.
  - ☐ Anticipate permanent discontinuation of targeted therapy for other severe ocular toxicities, per prescribing information.
  - ☐ Assess adherence to eye drops and 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; BRAF—v-Raf murine sarcoma viral oncogene homolog B; CS—corticosteroid; MEK—mitogen-activated protein kinase kinase

Note. Based on information from Davis, 2016; Genentech, 2016, 2017; National Cancer Institute, 2010; Novartis, 2016, 2017a.

et al., 2012). For vemurafenib, the risk of QT prolongation is known to be concentration dependent (Genentech, 2017). Accordingly, concomitant medications that increase vemurafenib plasma concentrations should be avoided in patients at risk for QT prolongation. By promoting open communication concerning concomitant therapies, nurses can help alert various members of the oncology team to the possible need for DDI-related dose modifications or alternative therapies. In addition, patients should be encouraged, whenever possible, to have all of their medications filled by one pharmacy to ensure familiarity with the full medication list and to avoid polypharmacy issues.

Implications for Nursing and Conclusion

Targeted therapy with BRAF/MEK inhibitor combinations improves overall survival in patients with *BRAF* V600E- or V600K-mutated metastatic melanoma but is also associated with AEs that need concerted management if patients are to stay on therapy. By educating patients and ensuring prompt AE recognition and management, nurses can minimize the impact of AEs on patients' lives and increase the likelihood of therapy continuation with limited interruptions. Nursing awareness and a proactive stance to DDIs across the entire multidisciplinary team can also improve therapeutic outcomes. Finally, nurses can improve AE

FIGURE 5.
CARE STEP PATHWAY FOR MANAGEMENT OF CARDIOTOXICITY

NURSING ASSESSMENT

Look
- Does the patient look unwell?
- Fatigued?
- Diaphoretic?
- Short of breath or in respiratory distress?
- Is there leg edema?

Listen
- Change in energy level?
- Shortness of breath or dyspnea on exertion?
- Leg edema?
- Palpitations?
- Changes in blood pressure?
- Dizziness or syncope?
- What exacerbates or improves symptoms?
- Any new prescribed or over-the-counter medications? Illicit substances?
- Any underlying cardiac disease (coronary artery disease, myocardial infarction, 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, dyspnea on exertion, shortness of breath, palpitations, edema
- Impact of symptoms on quality-of-life performance status
- Changes in cardiac function: electrocardiogram changes, decreased ejection fraction, elevated cardiac enzymes (troponin, creatine kinase)
- Assess other changes in oxygen saturation, blood pressure, and 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)
- Asymptomatic with laboratory or cardiac imaging abnormalities

Grade 2 (moderate)
- Symptoms with mild to moderate activity or exertion

Grade 3 (severe)
- Severe with symptoms at rest or with minimal exertion (intervention needed)

Grade 4 (potentially life-threatening)
- Life-threatening consequences (urgent intervention required)

Grade 5 (death)

GRADING TOXICITY: QTc INTERVAL PROLONGATION

A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval

Grade 1 (mild)
- QTc of 450–480 ms

Grade 2 (moderate)
- QTc of 481–500 ms

Grade 3 (severe)
- QTc of 501 ms or greater on at least two separate electrocardiograms

Grade 4 (potentially life-threatening)
- QTc of 501 ms or greater or greater than 60 ms change from baseline and torsades de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia

Grade 5 (death)

management by establishing connections with referral clinicians to care for more challenging or serious AEs and to ensure optimal AE management and prevention of more serious sequelae.

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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: electrocardiogram (for vemurafenib), echocardiogram/multigated acquisition scan (for any MEK-containing regimen), cardiac enzymes, complete blood count, complete metabolic panel, brain natriuretic peptide, C-reactive protein, and chest radiograph. Do not start MEK inhibitor therapy if QTc is greater than 500 ms.
- Repeat echocardiogram for MEK-containing regimen at one month and every two to three months while on treatment. If electrocardiogram performed (on vemurafenib), repeat at 14 days, monthly for three months, and then every two to three months while on treatment—but more frequently if on medications affecting QTc, or as needed if patient starts new agents that may prolong QT interval.
- Prevention (no known strategies); encourage healthy lifestyle.
- Introduce concept of dose reduction or dose holding when educating patients prior to initiation of therapy.
- Assess adherence with blood pressure medications if patients are hypertensive.

MANAGEMENT BY GRADE

Grade 1 (mild)

- Anticipate cardiology referral if condition worsens.
- MEK inhibitors (cobimetinib and trametinib) to be held for a LVEF value decreased more than 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% or more from baseline and below the institution's LLN
- Cobimetinib to be discontinued for a persistent LVEF value decreased more than 10% from baseline and below the institution's LLN or for persistent symptoms
- Dabrafenib to be held for a LVEF value decreased more than 20% from baseline and below the institution's LLN
- Anticipate prompt evaluation of current cardiac symptoms by oncologist or cardiologist if non-urgent cardiac symptoms exist.
- Seek immediate care in emergency department for chest pain and pressure to evaluate for myocardial infarction.

Grades 3–4 (severe or life-threatening)

- Anticipate urgent cardiology referral.
- For QTc of greater than 500 ms, vemurafenib to be held and permanently discontinued if QTc remains at greater than 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, electrocardiogram, echocardiogram/multigated acquisition scan, stress test, brain natriuretic peptide, and cardiac enzymes.
- Seek immediate care in emergency department for chest pain and pressure to evaluate for myocardial infarction.

LLN—lower limit of normal; LVEF—left ventricular ejection fraction; MEK—mitogen-activated protein kinase kinase
Note. Based on information from Genentech, 2016, 2017; National Cancer Institute, 2010; Novartis, 2016, 2017a.

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TABLE 3.
DT AND VC ADVERSE EVENTS AND LABORATORY ABNORMALITIES

VARIABLE	COMMON SYMPTOMS	ASSOCIATED REGIMEN	COMMON MANAGEMENT AND ANTICIPATORY GUIDANCE
Anorexia	Decreased appetite	DT, occurs at higher rates in older adults.	Monitor weight; query about appetite and eating habits; advise dietary modification if necessary. Anticipate treatment hold for intolerable grade 2 (oral intake altered) or grades 3–4 (significant weight loss or life-threatening consequences).
Arthralgias and myalgias	Joint pain, swelling, or stiffness; feeling tired	VC > DT	Query about joint symptoms; provide 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 the absence of fever	DT > VC	Query about symptoms, including those 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 or abdominal pain	Infrequent stools; difficulty stooling; abdominal pain	DT and VC	Increase fluid, fiber, and 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 grades 3–4 (obstipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences).
Cough	Dry cough; shortness of breath; dyspnea on exertion	DT	Advise patients to report any symptoms; rule out infectious causes and pneumonitis (interstitial lung disease); monitor oxygen saturation (pulse oximetry); consider chest x-ray; provide standard supportive care. Consider referral to pulmonary specialist or hospitalization for management of shortness of breath. Anticipate treatment hold for intolerable grade 2 (moderate symptoms limiting instrumental ADLs) or grade 3 (severe symptoms).
Deep vein thrombosis	Swelling; leg pain; shortness of breath	DT	Consider management with anticoagulant therapy and hematology referral as needed. Advise patients to seek medical care if they have acute onset arm or leg swelling. Anticipate treatment hold of trametinib for grade 2 (uncomplicated deep vein thrombosis) and permanent discontinuation if not improved after three weeks; no dose modification is needed with dabrafenib for uncomplicated venous thromboembolism.
Edema	Swelling of limbs or other body parts	DT > VC	For DT, edema occurs at higher rates in older adults. Advise patients to report swelling; provide standard supportive care; cardiac workup may be indicated. 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	–	DT and VC	Advise women with reproductive potential of risk to fetus and to use effective contraception (non-hormone–based for DT). Advise patients to tell healthcare provider immediately if they suspect they are pregnant while taking targeted therapy. Consider pregnancy testing at baseline and periodically throughout treatment for women with childbearing potential.
Fatigue	Feeling tired; having low energy	VC > DT	Query about energy level; evaluate possible contributory factors, including infection, disease progression, and hematologic and biochemical abnormalities; provide standard supportive care. Anticipate treatment hold for fatigue not relieved by rest and limiting ADLs (grades 2–3).
Headaches	Pain and/or change in vision	DT and VC	Headaches may be multifactorial and could involve bleeding in the brain, uncontrolled hypertension, dehydration, new central nervous system disease, or other causes; consider brain magnetic resonance imaging and evaluations for hypertension. Anticipate treatment hold for intolerable grade 2 (moderate pain) or grade 3 (severe pain limiting self-care ADLs).
Hemolytic anemia (in patient with G6PD deficiency)	Yellow skin; weakness or dizziness; shortness of breath	DT	Monitor patients with G6PD deficiency for signs of hemolytic anemia. Advise patients to report any symptoms.
Hemorrhage	Red or black/tarry stools; blood in urine; headaches; coughing or vomiting blood; abdominal pain; unusual vaginal bleeding; fatigue; dizziness or weakness	DT and VC	Provide standard supportive care and medical intervention as indicated. Anticipate treatment hold for intolerable grade 2 (moderate bleeding) or grades 3–4 (severe bleeding requiring transfusion or radiologic, endoscopic, or operative intervention or life-threatening consequences).

Continued on the next page

TABLE 3. *(CONTINUED)*

DT AND VC ADVERSE EVENTS AND LABORATORY ABNORMALITIES

VARIABLE	COMMON SYMPTOMS	ASSOCIATED REGIMEN	COMMON MANAGEMENT AND ANTICIPATORY GUIDANCE
Hepatotoxicity	Abdominal pain or swelling; yellowing of skin or eyes; dark urine; easy bruising; loss of appetite; feeling tired or weak	VC	Monitor liver function tests (including transaminases) at baseline and monthly during treatment or as clinically indicated. Anticipate treatment hold of cobimetinib at first occurrence of grade 4 (more than 20 times the ULN for transaminases and alkaline phosphatase; more than 10 times the ULN for bilirubin) and permanent discontinuation if not improved within four weeks. Anticipate treatment hold of vemurafenib for intolerable grade 2 (more than 3 times the ULN for transaminases; more than 2.5 times the ULN for alkaline phosphatase; more than 1.5 times the ULN for bilirubin) or grades 3–4 (more than 5 times the ULN for transaminases or alkaline phosphatase; more than 3 times the ULN for bilirubin) and permanent discontinuation if no recovery to grades 0–1 or recurrent grade 4 event.
Hyperglycemia	Fatigue; polyuria; polydipsia; headaches	DT	Monitor fasting glucose and hemaglobin A1c (particularly in patients with preexisting diabetes or hyperglycemia); advise patients to report increased thirst or increased urination, and provide anti-diabetic medication. Anticipate treatment hold for intolerable grade 2 (fasting glucose of greater than 160–250 mg/dl) or grades 3–4 (fasting glucose of greater than 250 mg/dl).
Hypersensitivity reaction (swelling or feeling faint)	Swelling; feeling faint; rash; erythema; anaphylaxis	VC (specifically vemurafenib)	Possible hospitalization is recommended. Anticipate immediate and permanent discontinuation of vemurafenib for patients with severe hypersensitivity reactions.
Nausea and vomiting	Vomiting; queasiness; left or right upper quadrant pain	DT and VC	Nausea and vomiting may indicate hepatotoxicity; check liver function tests, lipase, and amylase; provide standard supportive care. Anticipate treatment hold for intolerable grade 2 (oral intake decreased or 3–5 episodes of vomiting in 24 hours) or grades 3–4 (inadequate oral intake or 6 or more episodes of vomiting in 24 hours or life-threatening consequences).
Pulmonary embolism	Shortness of breath; chest pain	DT	Advise patients to seek medical care if they have shortness of breath or chest pain; an appropriate workup, including imaging and computed tomography angiogram, is recommended. Anticipate treatment hold of trametinib and permanent discontinuation if not improved after three weeks or for life-threatening pulmonary embolism. Anticipate treatment hold of dabrafenib and permanent discontinuation if no recovery to grades 0–1. Anticipate anticoagulant therapy for at least six months.
Pneumonitis (interstitial lung disease)	New cough; dyspnea; hypoxia; pleural effusion or infiltrates	DT (specifically trametinib)	Advise patients to report any new or worsening symptoms of lung or breathing problems (shortness of breath or cough). Anticipate permanent discontinuation of trametinib; do not modify the dose of dabrafenib.
Radiation sensitization or recall	Inflammatory skin reaction in areas treated with radiation	VC (specifically vemurafenib)	Use vemurafenib with caution in patients with prior or ongoing radiation therapy 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	VC > DT	Closely monitor patient's renal function to include serum creatinine clearance, blood urea nitrogen, and estimated glomular filtration rate prior to initiation of therapy and during treatment; this is particularly important during and following persistent fevers. Anticipate treatment hold for persistent grade 2 (estimated glomerular filtration rate or creatinine clearance rate of 59–30 ml/minute/1.73 m^2) or grades 3–4 (estimated glomerular filtration rate or creatinine clearance rate of less than 29 ml/minute/1.73 m^2).

ADLs—activities of daily living; DT—dabrafenib and trametinib; G6PD—glucose-6-phosphate dehydrogenase; ULN—upper limit of normal; VC—vemurafenib and cobimetinib
Note. Grading is based on the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events.
Note. Based on information from Genentech, 2016, 2017; Novartis, 2016, 2017a.

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TABLE 4.
POTENTIAL DRUG–DRUG INTERACTIONS WITH BRAF/MEK INHIBITOR COMBINATION THERAPIES

INTERACTION	MECHANISM/ENZYME AFFECTED	RECOMMENDATIONS	POTENTIAL EFFECTS	DRUGS TO AVOID OR USE WITH CAUTION
Dabrafenib and trametinib				
Interactions affecting dabrafenib	Dabrafenib is metabolized by CYP2C8 and 3A4.	Avoid strong inducers of CYP2C8 or CYP3A4; if unavoidable, monitor for loss of efficacy.	Lower dabrafenib levels; loss of efficacy	Carbamazepine; clarithromycin, gemfibrozil; HIV antivirals; ketoconazole; nefazodone; phenobarbital; phenytoin; pioglitazone; rifampin; St. John's wort
Interactions affecting other drugs	Dabrafenib induces CYP3A4, 2B6, 2C8, 2C9, and 2C19.	Coadministration of dabrafenib may result in decreased concentrations and loss of efficacy of other drugs. Substitute if possible; if unavoidable, monitor for loss of efficacy. Monitor international normalized ration levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib.	Lower concentrations of concomitant drugs; loss of efficacy	Carbamazepine; citalopram; dexamethasone; diazepam; erythromycin; HIV antivirals; hormonal contraceptives; midazolam; ondansetron; pioglitazone; proton pump inhibitors; sirolimus; tacrolimus; warfarin (R- or S-warfarin)
Other potential interactions	Changes in dabrafenib solubility	Drugs that alter the pH of the upper gastrointestinal tract may decrease systemic exposure of dabrafenib, but the effect on efficacy is unknown.	Lower dabrafenib solubility and bioavailability	Antacids; histamine-2 receptor antagonists; proton pump inhibitors
Vemurafenib and cobimetinib				
Interactions affecting vemurafenib or cobimetinib	Vemurafenib and cobimetinib are metabolized by CYP3A4.	Avoid strong or moderate inducers of CYP3A4, and replace with alternative drugs when possible. For vemurafenib, if concomitant CYP3A4 inducer use is unavoidable, increase the dose of vemurafenib by 240 mg (one tablet) as tolerated. After discontinuation of the strong CYP3A4 inducer for two weeks, resume the dose of vemurafenib that was taken prior to initiation of the strong CYP3A4 inducer.	Lower vemurafenib and cobimetinib levels; loss of efficacy	Carbamazepine; efavirenz; phenobarbital; phenytoin; pioglitazone; rifabutin; rifampin; rifapentine; St. John's wort
Interactions affecting vemurafenib or cobimetinib	Vemurafenib and cobimetinib are metabolized by CYP3A4.	Avoid strong or moderate inhibitors of CYP3A4 and replace with alternative drugs when possible. If short-term use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin) is unavoidable, reduce cobimetinib dose to 20 mg.	Higher vemurafenib and cobimetinib levels; adverse reactions	Atazanavir; ciprofloxacin; clarithromycin; erythromycin; indinavir; itraconazole; ketoconazole; nefazodone; nelfinavir; saquinavir; suboxone; telithromycin; ritonavir; voriconazole
Interactions affecting other drugs	Vemurafenib inhibits CYP1A2.	Coadministration of vemurafenib with CYP1A2 substrates may increase systemic exposure. Avoid concomitant use of vemurafenib with drugs that are predominantly metabolized by CYP1A2 and have a narrow therapeutic window. If unavoidable, monitor closely for toxicities and consider a dose reduction of CYP1A2 substrates.	Higher concentrations of concomitant drugs and adverse reactions	Apixaban; clozapine; haloperidol; olanzapine; theophylline; tizanidine; zolmitriptan
Interactions affecting other drugs	Vemurafenib inhibits CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.	Coadministration of vemurafenib with substrates for these enzymes may increase systemic exposure.	Higher concentrations of concomitant drugs and adverse reactions	Apixaban; duloxetine; fluoxetine; haloperidol; ondansetron; oxycodone; venlafaxine
Other potential interactions	Vemurafenib with concurrent ipilimumab may result in increased liver enzyme abnormalities.	The safety and effectiveness of vemurafenib in combination with ipilimumab has not been established.	Higher transaminases and bilirubin	Ipilimumab
Other potential interactions	Vemurafenib inhibits P-gp transport.	Avoid concurrent use of P-gp substrates with narrow therapeutic indices.	Higher concentrations of concomitant drugs	Apixaban; colchicine; digoxin

BRAF—v-Raf murine sarcoma viral oncogene homolog B; MEK—mitogen-activated protein kinase kinase; P-gp—p-glycoprotein
Note. The medications listed in this table are examples of those commonly used in the population of patients with melanoma. This list is not all inclusive.
Note. Based on information from Bristol-Myers Squibb, 2017; Flockhart, 2007; Genentech, 2017; Mutual Pharmaceutical Company, 2009; Novartis, 2016, 2017a.

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