Cobimetinib and Vemurafenib Combination Therapy for Melanoma

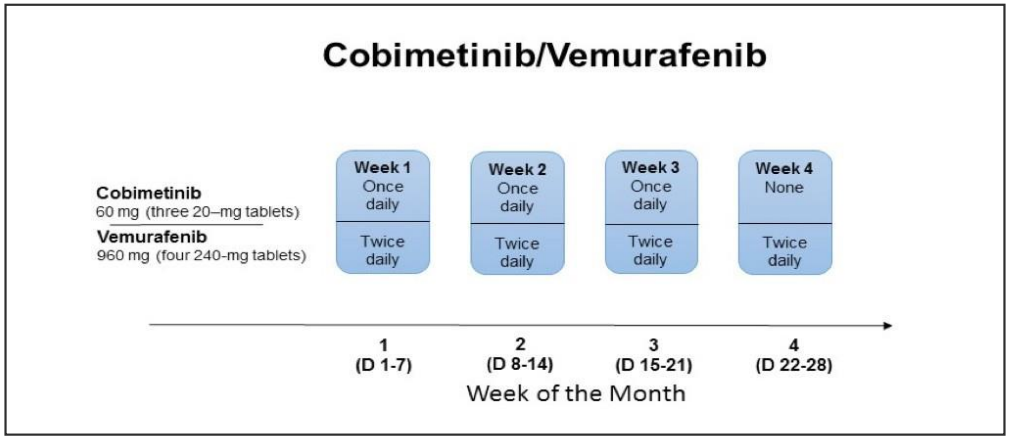
Cobimetinib (Cotellic®)/vemurafenib (Zelboraf®) combination therapy is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Cobimetinib is a MEK1 and MEK2 inhibitor, and vemurafenib is an inhibitor of some mutated forms of BRAF kinase, including 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 health care provider toolkit intended to assist 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 continuously, 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
- For general information that may be relevant for prescribers or pharmacists, 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.
- For general information that may be relevant for prescribers or pharmacists, 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
Most common	Fever/pyrexia Chills Edema Headache Gastrointestinal Diarrhea Nausea & vomiting Constipation/abdominal pain Skin toxicities (rash/photosensitivity) Joint/muscle pain (arthralgias/myalgias) Fatigue/tiredness
Less common but serious	New primary cancers. - Cutaneous (eg, basal cell or squamous cell carcinoma, keratocanthoma, new melanoma) - Non-cutaneous Ocular toxicity Cardiovascular - Cardiomyopathy (↓ LVEF) - Hemorrhage - Venous thromboembolism (pulmonary embolism, deep vein thrombosis) - Hemolytic anemia - Colitis and gastrointestinal perforation - Interstitial lung disease/pneumonitis - Renal toxicity.

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

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.

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, including diarrhea, rash, and elevated liver enzymes.
- 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.
- A skin exam is recommended prior to starting and every couple of months. If new lesions appear, then the patient 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.

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 may order a LDH level, which is a lab test that can act as a marker for melanoma and can help assess the patient's response to treatment.

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

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

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

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

AIM at Melanoma Foundation (Ask an Expert program, patient symposia, drug resources, etc)
https://www.aimatmelanoma.org/

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

FINANCIAL ASSISTANCE

Genentech: A Member of the Roche Group
Patient Resource Center
1 (877) GENENTECH (436-3683)
http://www.genentech-access.com/cotellic/patients

Cancer Financial Aid Coalition
Facilitates communication, educates and advocates for patients.
www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)
Apply to determine if you are eligible for government assistance.
www.cms.gov or www.medicare.gov
800-633-4227

Lazarex Foundation
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.
www.lazarex.org

Needymeds
Database to search for free or low-cost medications, help with medical transportation and other resources.
www.needymeds.org

Patient Advocate Foundation
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.
www.patientadvocate.org
800-532-5274

The Sam Fund for Young Adult Survivors of Cancer
Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.
www.thesamfund.org
info@thesamfund.org

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation
Helps with the cost of medication. Availability of funds for patients with Stage IV melanoma subject to availability.
www.cancercarecopay.org
1-866-552-6729

Medicine Assistance Tool
Database to search for patient assistance resources offered by pharmaceutical companies.
www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief
Provides direct financial support to patients who medically qualify. Availability of funds for patients with Stage IV melanoma subject to availability.
www.copays.org
1-866-512-3861

Good Days
Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients with Stage IV melanoma subject to availability.
www.mygooddays.org

HealthWell Foundation
For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients with Stage IV melanoma subject to availability. Patient must also meet eligibility for financial assistance.
www.healthwellfoundation.org or grants@healthwellfoundation.org
1-800-675-8416

The Assistance Fund, Inc
Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients with Stage IV melanoma subject to availability.
www.theassistancefund.org
1-855-845-3663

PAN Foundation
Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients with Stage IV melanoma subject to availability.
www.panfoundation.org
1-866-316-PANF (7263)

Patient Assistance Program
Comprehensive database of patient assistance programs offering free medications.
www.rxassist.org
info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge
Provides free housing during treatment appointments. Requires a referral from your social worker.
www.cancer.org/
1-800-227-6333

TRANSPORTATION (AIR AND GROUND)

Medicaid
Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.
1-877-633-8747

Mercy Medical Angels
Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.
www.mercymedical.org/

Pilots for Patients
Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.
www.pilotsforpatients.org
318-322-5112

ADDITIONAL RESOURCES

- Cotellic® (cobimetinib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2023. Available at the Genentech website or: https://www.gene.com/download/pdf/cotellic_prescribing.pdf.
- Czupryn M, Cisneros J. BRAF/MEK inhibitor therapy: consensus statements from the faculty of the Melanoma Nursing Initiative on managing adverse events and potential drug interactions. *Clin J Oncol Nurs*. 2017;21(suppl):11-29.
- Davis ME. Ocular toxicity of tyrosine kinase inhibitors. *Oncol Nurs Forum*. 2016;43: 235-243. doi:10.1188/16.ONF.235-243
- de Golian E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous complications of targeted melanoma therapy. *Curr Treat Options Oncol*. 2016;17:57. doi:10.1007/s11864-016-0434-0
- Mavropoulos JC, Wang TS. Managing the skin toxicities from new melanoma drugs. *Curr Treat Options Oncol*. 2014;15:218-301.
- 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® (vemurafenib) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2020. Available at the Genentech website: https://www.gene.com/download/pdf/zelboraf_prescribing.pdf.