BC Cancer Protocol Summary for the Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma using vemURAFenib and Cobimetinib

Protocol Code	*SMAVVC*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Vanessa Bernstein*

ELIGIBILITY:

- Previously untreated BRAF V600 mutation-positive unresectable or metastatic melanoma stage III or IV
- Good performance status
- Life expectancy of at least 3 months
- 18 years and older (for patients younger than 18 years old, CAP will review the eligibility on a case-by-case basis)
- Adequate hematological, hepatic and renal function
- If brain metastases are present, they must have been previously treated and be stable
- **Note:** only one BRAF/MEK targeted treatment will be funded (daBRAFenib, trametinib, or combination)
- May have subsequent BRAF/MEK inhibitors if relapse > 6 months after end of USMAJDT

EXCLUSIONS:

- Active central nervous metastases
- Concomitant treatment with any anticancer therapy
- Long QT syndrome
- Corrected QT-interval (QTc) longer than 500 milliseconds
- Uncontrolled electrolyte abnormalities(e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Symptomatic congestive heart failure of NYHA class 2 or higher
- Decreased LVEF at baseline (below institutional LLN or 50%)
- History of retinal vein occlusion
- Previous progressive disease on any BRAF targeted treatment
- Cobimetinib monotherapy

TESTS:

- **Baseline:** CBC and diff, platelets, creatinine, creatine kinase (CK), sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, GGT, albumin, LDH, ECG, MUGA scan or echocardiogram (if not performed within a year), blood pressure, dermatologic evaluation for other skin cancer, Chest-CT (included with metastatic melanoma staging), Pap smear in women younger than 65 years old (if not done within 3 years and no hysterectomy; 65 years and older do not need pap smear unless clinically indicated)

- **During treatment:**
  - **Prior to each cycle:** CBC and diff, platelets, creatinine, creatine kinase (CK), sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, GGT, albumin, LDH, blood pressure
  - **ECG:** every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification
  - **MUGA scan or echocardiogram:** at week 4, then every 12 weeks
  - **Dermatologic evaluation:** at week 8 (assess for other skin cancers and new primary melanoma); monitoring beyond 8 weeks can be performed by the oncologist or dermatologist every 12 weeks
  - **Chest-CT:** every 6 months and with monitoring of metastases
    - Skin cancers (SCC and KAs) have been reported at an increased frequency and there have been 2 reports (as of August 2012) of oral SCC cancers. There are theoretical concerns of lung cancer.

PREMEDICATIONS:

- Antiemetic protocol for low emetogenicity (see SCNAUSEA). Antiemetics are not usually required.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
vemURAFenib	960 mg BID (approximately 12 hours apart) continuously	PO
cobimetinib	60 mg daily on days 1-21	PO

- Repeat every 4 weeks (1 cycle = 4 weeks) until disease progression or unacceptable toxicity develops.

DOSE MODIFICATIONS:

1. QT Prolongation (QTc Interval)

- QTc-interval longer than 500 milliseconds (grades 3-4) during treatment
  1) Temporarily interrupt treatment
  2) Correct electrolytes and control cardiac risk factors
  3) When QTc-interval decreases to shorter than or equal to 500 milliseconds (grades 0-2), resume treatment at lower dose.
     - 1st appearance: vemURAFenib 720 mg twice daily (or 480 mg twice daily if dose already lowered to 720 mg twice daily)
     - 2nd appearance: vemURAFenib 480 mg twice daily (or discontinue permanently if dose already lowered to 480 mg twice daily)
     - 3rd appearance: Permanently discontinue treatment
- QTc-interval persisting longer than 500 milliseconds and longer than 60 milliseconds above baseline (grade 4): Permanently discontinue treatment

2. **For other toxicities:** Follow below general guideline.

General Guideline

Grade (CTC-AE)*	Recommended Dose Modification for vemURAFenib	
Grades 1-2 (tolerable)	No dose reduction	
Grade 2 (intolerable) or Grade 3	1st Appearance	Interrupt treatment until grades 0 – 1 Resume dosing at 720 mg twice daily (or 480 mg twice daily if dose already lowered to 720 mg twice daily)
	2nd Appearance	Interrupt treatment until grades 0 – 1 Resume dosing at 480 mg twice daily (or discontinue permanently if dose already lowered to 480 mg twice daily)
	3rd Appearance	Discontinue treatment permanently
Grade 4	1st Appearance	Discontinue treatment permanently or interrupt treatment until grades 0–1 Resume dosing at 480 mg twice daily (or discontinue permanently if dose already lowered to 480 mg twice daily)
	2nd Appearance	Discontinue treatment permanently

Grade (CTC-AE)*	Recommended Dose Modification for cobimetinib	
Grades 1-2 (tolerable)	No dose reduction	
Grade 2 (intolerable) or Grade 3/4	1st Appearance	Interrupt treatment until grades 0 – 1 Resume dosing at 40 mg daily on days 1-21
	2nd Appearance	Interrupt treatment until grades 0 – 1 Resume dosing at 20 mg daily on days 1-21
	3rd Appearance	Discontinue permanently

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

- Dose modification of cobimetinib is independent of vemURAFenib dose modification.
- Dose reduction below vemURAFenib 480 mg twice daily or cobimetinib monotherapy is not recommended.
- Dose escalation after dose reduction is generally not recommended unless under special circumstances (i.e. increased likelihood of clinical benefit for the dose increase and no safety concerns).

3. Recommended cobimetinib dose modifications based on specified adverse drug reactions

Adverse drug reaction	Dose Modification for cobimetinib	
Rhabdomyolysis and CK (CPK) elevations	Grade 4 CK elevations or Any CK elevation and myalgia	Hold for up to 4 weeks ▪ If improved to grade ≤3, resume at next lower dose level ▪ If not resolved within 4 weeks, permanently discontinue
Laboratory liver abnormalities and hepatotoxicity	1st Appearance Grade 4	Hold for up to 4 weeks ▪ If improved to grade ≤ 1, resume at next lower dose level ▪ If not improved to grade ≤ 1 within 4 weeks, permanently discontinue
	Recurrent Grade 4	Discontinue permanently
Retinal vein occlusion	Discontinue permanently	
Serous Retinopathy	Hold for up to 4 weeks ▪ If improved to grade ≤ 1, resume at next lower dose level ▪ If not resolved within 4 weeks, permanently discontinue	
Rash	Grade ≤ 2 (tolerable)	Supportive care
	Grade 2 (intolerable) or Grade ≥ 3	*Acneiform*: follow general guidelines *Non-acneiform or maculopapular*: continue at current dose if indicated
Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% and less than lower limit of normal (LLN)	Hold for 2 weeks; repeat LVEF Resume at next lower dose if all of the following are present: ▪ LVEF ≥ LLN and ▪ Absolute decrease from baseline LVEF is ≤ 10% Permanently discontinue if any of the following are present ▪ LVEF ≤ LLN or ▪ Absolute decrease from baseline LVEF > 10%	
Symptomatic LVEF decrease from baseline	Hold for up to 4 weeks; repeat LVEF Resume at next lower dose if all of the following are present: ▪ Symptoms resolve and ▪ LVEF is ≥ LLN and ▪ Absolute decrease from baseline LVEF is ≤10% or less Permanently discontinue if any of the following are present: ▪ Symptoms persist, or ▪ LVEF < LLN, or ▪ Absolute decrease from baseline LVEF > 10%	
Hemorrhage	Grade 3	Hold for up to 4 weeks. Resume at the next lower dose level if improved to grade ≤ 1 and if clinically appropriate and improved. If not improved within 4 weeks or if clinically indicated, permanently discontinue.
	Grade 4	Discontinue permanently

PRECAUTIONS:

1. **Risk Factors for Torsade de Points:** Treat with caution in patients with risk factors for torsade de points (i.e. 65 years and older, family history of sudden cardiac death at younger than 50 years old, cardiac disease, history of arrhythmia, bradycardia, acute neurological events, diabetes and autonomic neuropathy)
2. **Cutaneous Squamous Cell Carcinoma (cuSCC):** Dose modification or interruption is not recommended. Cases of cuSCC are typically managed with simple excision, and patients are able to continue treatment without dose adjustment.
3. **Other Cancers:** new cases of squamous cell carcinoma of the head and neck and progression of RAS-mutant leukemia have been reported.
4. **Photosensitivity:** Mild to severe photosensitivity have been reported with. All patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF 30 or higher) when outdoors to help protect against sunburn. For photosensitivity, grade 2 (intolerable) or greater adverse events, **dose modifications are recommended for vemURAFenib** (see general guideline).
5. **Other skin toxicities:** rash, skin irritation or dermatitis may be managed with hydrocortisone 1% cream. Itching may be treated with over-the-counter antihistamines. If still problematic, assess by health professional and refer to dermatologist if necessary.
6. **Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome):** These are characterized by rash, eosinophilia, and systemic involvement (e.g. fever, lymphadenopathy, elevated transaminases, renal insufficiency) with typical onset of 7-25 days. Vemurafenib should be permanently discontinued.
7. **Hepatic Impairment:** Vemurafenib and cobimetinib are primarily eliminated by the liver. Patients with severe hepatic impairment may have more frequent exposure-related adverse events including QT prolongation. The safety and efficacy of vemurafenib and cobimetinib have not been studied in patients with moderate to severe hepatic impairment. Vemurafenib and cobimetinib should be used with caution in patients with moderate to severe hepatic impairment.
8. **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis have been reported. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalized rash, erythema or hypotension. Treatment with should be permanently discontinued.
9. **Ophthalmologic:** Vemurafenib and cobimetinib treatment-related serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions and refer to an Ophthalmologist if clinically indicated.
10. **Drug Interaction:**
    - **QT-prolonging Medications:** Vemurafenib causes QT prolongation. Concomitant use of QT-prolonging medications (e.g. amiodarone, sotalol, haloperidol, amitriptyline, methadone, fluconazole, erythromycin, ciprofloxacin, ondansetron, formoterol, quinidine, TACrolimus) should be avoided if possible.
    - Vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer. Caution should be exercised when used with medications predominantly metabolized by CYP1A2, CYP2D6 and CYP3A4.
        - Vemurafenib is a substrate of CYP3A4. Caution should be exercised when used with strong CYP3A4 inhibitors or inducers (including St. John's Wort).
        - Coadministration of vemurafenib resulted in a 20% increase in AUC of warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

- Cobimetinib is a CYP 3A substrate. Strong or moderate inhibitors and/or inducers of this enzyme may alter cobimetinib pharmacokinetics; avoid concurrent use.
  If concurrent short term (14 days or less) use of moderate CYP3A4 inhibitors (e.g., erythromycin, ciprofloxacin) cannot be avoided, reduce cobimetinib to 20 mg daily. Resume cobimetinib 60 mg daily once the moderate CYP3A4 inhibitor is discontinued. In patients who are already receiving reduced cobimetinib doses due to adverse reactions, strict avoidance of moderate CYP3A4 inhibitors is recommended
- **Current drug interaction databases or BC Cancer's Cancer Drug Manual should be consulted for more information.**

11. **Radiation Sensitization and Recall:** Radiation sensitization and recall reactions have been reported in targeted tissues in association with both concurrent and nonconcurrent vemurafenib. Sensitization is characterized by the potentiation of the radiation reaction, such that the severity of reaction experienced is greater than that expected for local radiation injury. The majority of sensitization reactions are reported during concurrent administration or when vemurafenib is administered within 3 days after completion of radiation. Recall reactions are evidenced by acute inflammation confined to a previously irradiated area and may be triggered by vemurafenib administration 7 days or more after completion of radiation. Most reported cases of radiation sensitization or recall are cutaneous in nature, however visceral organ involvement has also been reported, sometimes with fatal outcomes.

Call Dr. Vanessa Bernstein or tumour group delegate at 250-519-5570 or 1-800-670-3322 with any problems or questions regarding this treatment program.

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