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

Protocol Code *SMAVVEM*

Tumour Group *Skin and Melanoma*

Contact Physician *Dr. Vanessa Bernstein*

ELIGIBILITY:

- BRAF V600 mutation-positive unresectable or metastatic melanoma
- ECOG 0 - 2
- 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 anti-BRA/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

TESTS:

- **Baseline:** CBC and diff, platelets, sodium, potassium, calcium, magnesium, creatinine, alkaline phosphatase, ALT, bilirubin, LDH, ECG, 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:** sodium, potassium, calcium, magnesium, creatinine, alkaline phosphatase, ALT, bilirubin, LDH
  - **ECG:** every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification
  - **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

- 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	
Grades 1-2 (tolerable)	Maintain 960 mg twice daily.	
Grade 2 (Intolerable) or Grade 3	1st Appearance	Interrupt treatment until grades 0 – 1. Resume dosing at 720 mg twice daily.
	2nd Appearance	Interrupt treatment until grades 0 – 1. Resume dosing at 480 mg twice daily.
	3rd Appearance	Discontinue permanently
Grade 4	1st Appearance	Discontinue permanently or interrupt treatment until grades 0–1. Resume dosing at 480 mg twice daily.
	2nd Appearance	Discontinue permanently

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

- Dose reduction below 480 mg twice daily 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).

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. 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** (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 is 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 have not been studied in patients with severe hepatic impairment. Vemurafenib should be used with caution in patients with 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 vemurafenib should be permanently discontinued.
9. **Ophthalmologic:** Vemurafenib treatment-related serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions and refer to 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.
    - **Current drug interaction databases or BC Cancer's Cancer Drug Manual should be consulted for more information.**

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.

REFERENCES:

1. Final Clinical Guidance report for Vemurafenib (Zelboraf) for advanced melanoma. Pan-Canadian Oncology Drug Review, June 1, 2012
2. Final Recommendations for Vemurafenib (Zelboraf) for advanced melanoma. Pan-Canadian Oncology Drug Review, May 17, 2012
3. Product Monograph, Zelboraf, Hoffmann-La Roche Canada, February 14, 2012
4. US Prescribing Information for Zelboraf, Genentech USA, Inc., August 2011
5. J. A. Sosman et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib (BRIM-2). N Engl J Med 2012;366:707-14.
6. P.B. Chapman et al. Improved survival with vemurafenib in melanoma with BRAFV600E mutation (BRIM-3). N Engl J Med 2011;364:2507-16.
7. Hoffman La Roche Oncology Protocol MO25515 (Version 3), November 30, 2011