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

Protocol Code *SMAVTRA*

Tumour Group *Skin and Melanoma*

Contact Physician *Dr. Vanessa Bernstein*

ELIGIBILITY:

- BRAF V600 mutation-positive unresectable or metastatic melanoma
- Previously untreated or as second line treatment for patients previously treated with first line pembrolizumab or ipilimumab or nivolumab
- 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
- ECOG 0 to 1
- Adequate hematological, hepatic and renal function
- If brain metastases are present, patients should be asymptomatic or stable

EXCLUSIONS:

- Active central nervous metastases
- Clinically significant cardiovascular disease
- History of retinal vein occlusion
- Decreased LVEF at baseline
- Uncontrolled hypertension
- Previous progressive disease on any BRAF targeted treatment

TESTS:

- **Baseline:** CBC and diff, platelets, creatinine, sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, albumin, ECG, echocardiogram, blood pressure
- **During treatment:**
  - **Prior to each cycle:** alkaline phosphatase, ALT, albumin, blood pressure
  - **Echocardiogram:** at week 8, 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
  - **Skin toxicity:** at week 2 after initiating treatment

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
trametinib	2 mg daily	PO

- Repeat every 30 days until disease progression or unacceptable toxicity develops.

DOSE MODIFICATIONS:

Dose level	trametinib dose
First reduction	1.5 mg once daily
Second reduction	1 mg once daily
If unable to tolerate 1 mg once daily	Discontinue

1.Toxicity

Adverse reaction	trametinib
Cutaneous	
Grade 2 rash (tolerable) (Covering 10-30% BSA with or without symptoms; limiting instrumental ADL)	Reduce dose by 0.5 mg or discontinue if taking 1 mg daily
Intolerable grade 2 rash or ≥ grade 3 rash. (Covering >30% BSA with or without symptoms; limiting self-care ADL)	Withhold for up to 3 weeks. If improved within 3 weeks, resume at a lower dose (reduced by 0.5 mg) or discontinue in patients taking 1 mg daily
Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks despite interruption of dosing	Permanently discontinue
Cardiac	
Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pre-treatment value	Withhold for up to 4 weeks
Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below LLN that improves to normal LVEF value within 4 weeks following interruption	Resume at a lower dose (reduced by 0.5 mg) or discontinue in patients taking1 mg daily

Adverse reaction	trametinib
Absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption	Permanently discontinue
Absolute decrease in LVEF of greater than 20% from baseline that is below LLN or symptomatic congestive heart failure	Permanently discontinue, consult cardiologist
Febrile Drug Reaction	
38.5 to 40°C without complications	Continue at same dose
Greater than 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure	Hold until toxicity is grade 0-1, then resume at same or one lower dose level
Ocular	
Grade 2-3 retinal pigment epithelial detachments (RPED)	Withhold for up to 3 weeks and consult ophthalmologist
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume at a lower dose (reduced by 0.5 mg) or discontinue in patients taking 1 mg daily
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks OR recurrence of RPED (any Grade) after dose interruption or reduction OR retinal vein occlusion	Permanently discontinue and consult ophthalmologist
Uveitis that responds to local ocular therapy	Continue at same dose
Uveitis that does not improve despite ocular therapy	Withhold until resolves and resume at the same or a reduced dose
Pulmonary	
Interstitial lung disease / pneumonitis	Permanently discontinue

2. Renal failure
No adjustment recommended for mild or moderate impairment; no information found for severe renal impairment.
3. Hepatic failure
No adjustment recommended for mild impairment; no information found for moderate or severe hepatic impairment.

PRECAUTIONS:

1. **Left ventricular dysfunction:** decreases in left ventricular ejection fraction (LVEF) have been reported. Use with caution in patients with conditions that could impair LVEF.
2. **Retinal pigment epithelial detachment and retinal vein occlusion:** perform ophthalmological evaluation anytime a patient reports any new visual disturbances. Patients

with hypertension, diabetes, hypercholesterolemia, or glaucoma are at higher risk of retinal vein occlusion.

3. **Interstitial lung disease or pneumonitis:** reported in 2.8% of patients. All cases were serious and lead to permanent treatment discontinuation.
4. **Skin toxicity:** severe skin toxicities have been reported in 12% of patients presenting as rash, dermatitis acneiform and palmar-plantar erythrodysesthesia syndrome. Serious skin infections including dermatitis, folliculitis, paronychia, cellulitis and infective skin ulcer were also reported. Patients should be monitored 2 weeks after initiating treatment, then as indicated.
5. **Venous thromboembolism:** deep vein thrombosis and pulmonary embolism can occur.
6. **Major hemorrhagic events:** the risk of hemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy or in patients who develop brain metastases while on treatment.
7. **PR interval prolongation:** has been associated with trametinib. Use with caution when used concomitantly with other drugs that prolong the PR interval, including, but not limited to, antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, sphingosine-1 phosphate receptor modulators and some HIV protease inhibitors.
8. **Hypertension:** elevations in blood pressure have been reported in patients with or without pre-existing hypertension. Treat hypertension by standard therapy. See caution above.
9. **Rhabdomyolysis:** many reported cases were severe and required hospitalization. Interruption of trametinib until resolution. Carefully consider risk versus benefit for re-initiation of trametinib at a reduced dose.

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. Flaherty KT, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367(2):107-14
2. Product monograph, Mekinist, Novartis Pharmaceuticals Canada Inc., May 12, 2016.
3. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation of trametinib (Mekinist) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. 22 October 2013.