BC Cancer Protocol Summary for the Adjuvant Treatment of Stage III and IV, BRAF mutated, fully resected Melanoma Using daBRAFenib and Trametinib

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

ELIGIBILITY:

- Cutaneous melanoma stage IIIA to IV NED (AJCC 8th edition). Disease metastasized to the regional nodes (if stage IIIA and only one node involved then metastatic deposit ≥ 1 mm), in-transit metastases or distant metastases must be completely surgically resected.
- Brain metastases must be completely resected (or definitively treated with stereotactic radiation)
- BRAF mutation (all BRAF V600 mutations)
- Adequate baseline hematological, renal and liver functions
- BC Cancer Compassionate Access Program (CAP) must be obtained.
- * Patients can receive one year of either adjuvant nivolumab, pembrolizumab OR combination dabrafenib/trametinib. Patients with BRAF mutated melanoma who are unable to tolerate up to a 3-month trial of combination dabrafenib/trametinib due to toxicities can apply for adjuvant nivolumab and complete a total of one year of therapy. A switch to combination cobimetinib/vemurafenib is not funded.
- May have subsequent BRAF/MEK inhibitors if relapse > 6 months after end of USMAJDT

EXCLUSIONS:

- Mucosal or ocular melanoma
- Cardiovascular risk including:
  - Corrected QTc ≥ 480ms
  - Uncontrolled arrhythmia
  - Acute coronary syndrome, coronary angioplasty, placement of stents within the previous 24 weeks of starting therapy Abnormal cardiac morphology grade 2 or higher on ECHO cardiography.
  - History of current ≥ NYHA class II CHF
  - Treatment refractory HTN SBP (>140mmHg and/or DBP >90mmHg)
  - Decreased LVEF at baseline (LVEF ≤ LLN)
  - Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- History or current risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)

TESTS:

- **Baseline:** CBC and diff, platelets, creatinine, sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, albumin, LDH, ECG, MUGA scan or echocardiogram (if not performed within a year), blood pressure
- **During treatment:**
  - **Prior to each cycle:** CBC and diff, platelets, creatinine, sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, 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 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
daBRAFenib	150 mg BID	PO
trametinib	2 mg daily	PO

- Repeat every 30 days for 12 cycles (12 months total treatment), unless disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Dose level	daBRAFenib dose	trametinib dose
First reduction	100 mg twice daily	1.5 mg once daily
Second reduction	75 mg twice daily	1 mg once daily Discontinue if unable to tolerate
Third reduction	50 mg twice daily Discontinue if unable to tolerate	

1. Toxicity

Cutaneous adverse reaction	daBRAFenib	trametinib
Grade 2 rash (tolerable) (Covering 10-30% BSA with or without symptoms; limiting instrumental ADL)	Continue at same dose	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 until resolves or improves to Grade 1 and reduce by one dose level when resuming therapy	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	Permanently discontinue

Cardiac adverse reaction	daBRAFenib	trametinib
Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pre-treatment value	Continue at same dose	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	Continue at same dose	Resume at a lower dose (reduced by 0.5 mg) or discontinue in patients taking1 mg daily
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	Continue at same dose	Permanently discontinue
Absolute decrease in LVEF of greater than 20% from baseline that is below LLN or symptomatic congestive heart failure	Withhold until resolves then resume at same or reduced dose	Permanently discontinue, consult cardiologist

Febrile drug reaction	daBRAFenib	trametinib
38.5 to 40°C without complications	Hold until fever resolves, then resume at same or reduced dose level	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 one lower dose level	Hold until toxicity is grade 0-1, then resume at same or one lower dose level
Pulmonary adverse reaction	**daBRAFenib**	**trametinib**
Interstitial lung disease / pneumonitis	Continue at same dose	Permanently discontinue

Ocular adverse reaction	daBRAFenib	trametinib
Grade 2-3 retinal pigment epithelial detachments (RPED)	Continue at same dose	Withhold for up to 3 weeks and consult ophthalmologist
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Continue at same dose	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	Continue at same dose	Permanently discontinue and consult ophthalmologist
Uveitis that responds to local ocular therapy	Continue at same dose	Continue at same dose
Uveitis that does not improve despite ocular therapy	Withhold until resolves and reduce by one dose level when resuming therapy	Withhold until resolves and resume at the same or a reduced dose

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:

daBRAFenib

1. **Non-infectious fever:** can occur with or without severe rigors or chills, dehydration, hypotension or renal failure.
2. **Secondary malignancies:** include cutaneous squamous cell carcinoma (CuSCC), new primary melanoma and malignancies associated with RAS mutations (colorectal and pancreatic adenocarcinoma). CuSCC is managed with simple excision and dose modification or interruption is not recommended.
3. **QT prolongation:** has been associated with daBRAFenib and it should be used with caution in patients at increased risk of torsade de pointes.
4. **Hyperglycemia:** may occur and patients with diabetes or hyperglycemia should be monitored closely.
5. **Pancreatitits:** has been reported in <1% of patients. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase.
6. **Uveitis:** including iridoyclitis was observed in 2% of patients. Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy.
7. **Drug Interaction:**
   - Concomitant use of QT-prolonging medications should be avoided if possible.
   - Caution should be exercised when used with medications predominantly metabolized by CYP3A4 and CYP2C8.
8. **Renal failure**: is reported in patients on dabrafenib monotherapy and may be associated with pyrexia and/or dehydration. Incidence may be increased when dabrafenib is given in combination with trametinib. Monitor serum creatinine and other evidence of renal function during treatment and in events of severe pyrexia.

Trametinib

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.

Combination

1. **Neutropenia:** including grade 3 and 4 occurrences, has been reported in association with the combination of daBRAFenib and trametinib. Complete blood counts with differential should be monitored during treatment.
2. **Hepatotoxicity:** hepatic adverse events have been reported. Most patients continued dosing. Treatment discontinuation was rare.
3. **Renal failure:** is reported in patients on dabrafenib monotherapy and may be associated with pyrexia and/or dehydration. Incidence may be increased when dabrafenib is given in combination with trametinib. Monitor serum creatinine and other evidence of renal function during treatment and in events of severe pyrexia.

Call Dr. Vanessa Bernstein or tumour group delegate at 250-519-5570 or 1-800-519-5500 with any problems or questions regarding this treatment program.

REFERENCES:

1. Long et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 2017; 377:1813-1823
2. Novartis Pharmaceuticals Canada Inc. TAFINLAR® product monograph. Dorval, Quebec; 21 September 2018.
3. Novartis Pharmaceuticals Canada Inc. MEKINIST® product monograph. Dorval, Quebec; 5 April 2019.
4. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation of daBRAFenib (Tafinlar) in combination with trametinib (Mekinist) for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection. 3 May 2019.