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

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

ELIGIBILITY:

Patients must have:
- BRAF V600 mutation-positive unresectable or metastatic melanoma
- No prior treatment with BRAF and/or MEK inhibitor in the advanced setting

Note:
- Only one BRAF/MEK targeted treatment will be funded
- May have subsequent BRAF/MEK inhibitors if relapse > 6 months after SMAJDT

Patients should have:
- Adequate hematological, hepatic and renal function

EXCLUSIONS:

Patients must not have:
- Active central nervous system metastases (unless asymptomatic and/or stable)
- Long QT syndrome
- Corrected QT-interval (QTc) longer than 480 milliseconds
- Acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks
- Abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography, or known cardiac metastases. Clinically significant cardiovascular disease
- History of retinal vein occlusion
- Previous progressive disease on any BRAF targeted treatment

CAUTIONS:
- Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Decreased LVEF at baseline

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:**
  - **Every 4 weeks (prior to each cycle) for the first 12 weeks, then prior to each physician visit :** 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:** intermittent dermatologic evaluation for other skin cancers and new primary melanoma

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 until disease progression or unacceptable toxicity develops.

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

Cardiac adverse reaction	daBRAFenib	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	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**
38.0°C or higher, and/or chills, rigors, night sweats with or without flu-like symptoms (e.g., myalgia, fatigue). See Precautions	Hold. Resume at same or reduced dose once patient afebrile for 24 hours without antipyretic medication. (see Precautions)	Hold. Resume at same or reduced dose once patient afebrile for 24 hours without antipyretic medication. (see Precautions)
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

Ocular adverse reaction	daBRAFenib	Trametinib
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 when used as monotherapy or in combination with trametinib, with or without severe rigors or chills, dehydration, hypotension or renal failure. See the Canadian Consensus Statements for more details in management (https://www.mdpi.com/1718-7729/28/5/304).
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. Monitor serum creatinine and other evidence of renal function during treatment and in events of severe pyrexia.

Trametinib

1. **Non-infectious fever:** can occur with or without severe rigors or chills, dehydration, hypotension or renal failure, when used in combination with daBRAFenib. See the Canadian Consensus Statements for more details in management (https://www.mdpi.com/1718-7729/28/5/304).
2. **Left ventricular dysfunction:** decreases in left ventricular ejection fraction (LVEF) have been reported. Use with caution in patients with conditions that could impair LVEF.
3. **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.
4. **Interstitial lung disease or pneumonitis:** reported in 2.8% of patients. All cases were serious and lead to permanent treatment discontinuation.
5. **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.
6. **Venous thromboembolism:** deep vein thrombosis and pulmonary embolism can occur.
7. **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.
8. **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.
9. **Hypertension:** elevations in blood pressure have been reported in patients with or without pre-existing hypertension. Treat hypertension by standard therapy. See caution above.

10. **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 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Long et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877-88.
2. Robert et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
3. Larkin et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867-76.
4. Novartis Pharmaceuticals Canada Inc. TAFINLAR® product monograph. Dorval, Quebec; 15 May 2017.
5. Novartis Pharmaceuticals Canada Inc. MEKINIST® product monograph. Dorval, Quebec; 15 May 2017.
6.Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation of daBRAFenib (Tafinlar) in combination with trametinib (Mekinist) for treatment of patients with unresectible or metastatic melanoma with a BRAF V600 mutation. 21 July 2015.
5. Thawer A, Miller WH Jr, et al. Management of pyrexia associated with the combination of dabrafenib and trametinib: Canadian Consensus Statements. Curr Oncol 2021;28(5):3537-53.