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

Protocol Code	*SMAVDAB*
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, unless switch made due to toxicity and no documented progression on prior targeted therapy regimen
- 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
- QT-interval 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

TESTS:

- **Baseline:** CBC & Diff, creatinine, sodium, potassium, calcium, magnesium, alkaline phosphatase, ECG
- **During treatment:**
  - **Every 4 weeks (prior to each cycle) for the first 12 weeks, then prior to each physician visit :** creatinine, sodium, potassium, calcium, magnesium, alkaline phosphatase
  - **ECG:** every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification
  - **Dermatologic evaluation:** intermittent dermatologic evaluation for other skin cancers and new primary melanoma

Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/terms-of-use.

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

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

DOSE MODIFICATIONS:

Dose level	Dosing
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily
If unable to tolerate 50 mg twice daily	Discontinue

1. Febrile drug reaction

Fever	Management
38.5 to 40°C	Hold until fever resolves, then resume at same or reduced dose level
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

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PRECAUTIONS:

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 iritis was observed in 1% 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.
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.

Call Dr. Vanessa Bernstein or tumour group delegate at 250-519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Hauschild, A, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.
2. Novartis Pharmaceuticals Canada Inc. TAFINLAR® product monograph. Dorval, Quebec; 15 May 2017.
3. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation of daBRAFenib (Tafinlar) as monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. 5 December 2013.

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