BC Cancer Protocol Summary for the Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma using Encorafenib and Binimetinib

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

ELIGIBILITY:

Patients must have:
- BRAF V600 mutation-positive unresectable or metastatic melanoma, and
- 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 500 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
- Uveal or mucosal melanoma
- History of leptomeningeal metastases

CAUTIONS:

- Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Decreased LVEF at baseline (below institutional LLN or 50%)

TESTS:

- **Baseline:** CBC & Diff, platelets, creatinine, creatine kinase, sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, GGT, albumin, LDH, random glucose, ECG, MUGA scan or echocardiogram (if not performed within a year), blood pressure, pregnancy test prior to treatment in females of child-bearing potential. If clinically indicated: ophthalmologic consult
- **Every 4 weeks (prior to each cycle) for the first 12 weeks, then prior to each physician visit :** CBC & Diff, platelets, creatinine, creatine kinase, sodium, potassium, calcium, magnesium, alkaline phosphatase, ALT, GGT, albumin, LDH, blood pressure, pregnancy test prior to treatment in females of child-bearing potential.
- **If clinically indicated:** random glucose, hemoglobin A1C (HbA1c), pap smear in women, ophthalmologic consult
- **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 moderate emetogenicity (see SCNAUSEA).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
encorafenib	450 mg daily	PO
binimetinib	45 mg BID	PO

Repeat every 30 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Dose level	Encorafenib dose	Binimetinib dose
First reduction	300 mg PO daily	30 mg PO BID Discontinue if unable to tolerate
Second reduction	225 mg PO daily Discontinue if unable to tolerate	n/a

If binimetinib is withheld, reduce encorafenib to a maximum dose of 300 mg once daily until binimetinib therapy is resumed. If encorafenib is temporarily interrupted, binimetinib should be interrupted. If either medication is permanently discontinued, the other medication should also be discontinued.

Uveitis:

Severity	Encorafenib and Binimetinib
Grade 1	Hold encorafenib and binimetinib until Grade 0. Resume at same doses.
Grade 2 or 3	Hold encorafenib and binimetinib until Grade 0 or 1. Once recovered, restart at next lower doses.
Grade 4	Permanently discontinue encorafenib and binimetinib

QT prolongation:

QTc prolongation. In milliseconds (ms)	Encorafenib
First occurrence QTc greater than 500 ms And Less than or equal to 60 ms increase from baseline	Delay encorafenib. When QTc less than or equal to 500 ms, resume at reduced dose.
Second occurrence QTc greater than 500 ms And Less than or equal to 60 ms increase from baseline	Discontinue encorafenib
Any occurrence QTc greater than 500 ms And Greater than 60 ms increase from baseline	Discontinue encorafenib

Cardiomyopathy:

Left Ventricular Ejection Fraction	Binimetinib
Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is also below lower limit of normal (LLN)	Delay binimetinib. Evaluate LVEF every 2 weeks. Resume binimetinib at reduced dose if: ▪ LVEF recovers to above the lower limit of normal, ▪ the absolute decrease from baseline is 10% or less, and ▪ patient is asymptomatic If the LVEF does not recover within 4 weeks, discontinue binimetinib
Symptomatic congestive heart failure Or Absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Discontinue binimetinib.

Hepatotoxicity during treatment:

AST or ALT elevation	Encorafenib and Binimetinib	Doses Once Recovered
Grade 2	Continue treatment. If no improvement within 2 weeks: ▪ delay encorafenib and binimetinib until improved to less than or equal to Grade 1 or to baseline level	Resume encorafenib and binimetinib at previous doses
Grade 3	Delay encorafenib and binimetinib until improvement to less than or equal to Grade 1 or to baseline level	First occurrence: Restart encorafenib and binimetinib at reduced doses
		Recurrent Grade 3: Consider discontinuing encorafenib and binimetinib
Grade 4	Discontinue encorafenib and binimetinib Or Delay encorafenib and binimetinib If improvement to less than or equal to Grade 1 or to baseline levels	First occurrence: Restart encorafenib and binimetinib at reduced doses
		Recurrent Grade 4: Discontinue encorafenib and binimetinib

Dermatologic:

Severity	Encorafenib and Binimetinib	Doses Once Recovered
Grade 2	Continue treatment. If no improvement within 2 weeks: ▪ delay encorafenib and binimetinib until improved to less than or equal to Grade 1	First occurrence: Resume encorafenib and binimetinib at previous doses
		Recurrent Grade 2: Restart encorafenib and binimetinib at reduced doses
Grade 3	Delay encorafenib and binimetinib until less than or equal to Grade 1.	First occurrence: Resume encorafenib and binimetinib at previous doses
		Recurrent Grade 3: Restart encorafenib and binimetinib at reduced doses
Grade 4	Discontinue encorafenib and binimetinib	Discontinue encorafenib and binimetinib

PRECAUTIONS:

1. **Secondary malignancies**, including cutaneous squamous cell carcinoma, new primary melanoma, basal cell carcinoma, and noncutaneous malignancies have been reported during treatment with encorafenib and binimetinib. Screen for suspicious lesions prior to initiating encorafenib and binimetinib and monitor throughout treatment. Regular dermatologic evaluation is recommended throughout treatment and for up to 6 months following treatment discontinuation. Advise patients to promptly report any new skin lesions. Suspicious skin lesions should be excised. Permanently discontinue encorafenib for development of RAS mutation-positive non-cutaneous malignancies.
2. **Hemorrhage:** Hemorrhage occurred in 19% of patients taking encorafenib and binimetinib in the COLUMBUS trial. Monitor for signs of bleeding. Delay treatment with encorafenib and binimetinib for any recurrent grade 2 or first occurrence of grade 3 or higher hemorrhage. Delay, reduce doses, or discontinue encorafenib and binimetinib based on the severity of event.
3. **Ocular Toxicities** including uveitis, iritis, iridocyclitis, and retinal pigment epithelial detachment have been reported with encorafenib. Retinal vein occlusion, serous retinopathy, retinal detachment, macular edema, and uveitis have been reported with binimetinib. Assess patient during treatment for new or worsening visual disturbances. Patients reporting new or worsening visual disturbances such as diminished central vision, blurred vision, or loss of vision should be promptly (i.e., within 24 hours) referred for ophthalmological evaluation (and should hold therapy while awaiting evaluation). Refer to uveitis table, above. Delay treatment with binimetinib for serous retinopathy. Dose reduction may be required.
4. **QT prolongation:** QTc prolongation has been observed with encorafenib; monitor ECG and electrolytes in patients with known risk factors and correct hypokalemia and/or hypomagnesemia prior to treatment, and as clinically indicated. Refer to table, above.
5. **Left ventricular dysfunction:** decreases in left ventricular ejection fraction (LVEF) have been reported with binimetinib use. Use with caution in patients with conditions that could impair LVEF. Refer to table, above.
6. **Interstitial Lung Disease** (ILD) including pneumonitis has been reported in patients taking binimetinib. Delay treatment with binimetinib if ILD is suspected (new or progressive unexplained pulmonary symptoms). Delay, reduce dose, or based on severity.
7. **Drug interactions**: Encorafenib is a substrate of CYP3A4. Avoid concurrent use with moderate of strong CYP3A4 inhibitors if possible. If coadministration with strong or moderate CYP3A4 inhibitors is necessary, reduce encorafenib dose. Refer to BC Cancer Drug Manual for more information.
8. **Hyperglycemia**: Can occur in some patients taking encorafenib and binimetinib. Monitor during treatment as clinically indicated.
9. **Hypertension**: Hypertension or worsening of pre-existing hypertension may occur during treatment with encorafenib and binimetinib. Monitor at baseline and throughout treatment. Delay treatment with encorafenib and binimetinib if hypertension is severe. Initiate standard antihypertensive treatment if appropriate.

10. **Creatine kinase elevation i**s reported in 58% of patients receiving binimetinib. Binimetinib can also cause muscle pain, cramps, and joint stiffness. Rhabdomyolysis is reported in less than 1% of patients. Delay binimetinib for asymptomatic grade 4 creatine kinase elevation, any grade symptomatic creatine kinase elevation, or any grade creatine kinase elevation that occurs with renal impairment. Dose reduction or treatment discontinuation may be required.
11. **Venous Thromboembolism** has occurred in patients taking encorafenib and binimetinib. Delay treatment with binimetinib for venous thromboembolism until improvement to grade 1 or less.
12. Pre-existing **Hepatic Impairment:**

    Encorafenib: For patients with mild hepatic impairment (Child-Pugh A): consider dose reduction of encorafenib to 300 mg PO once daily. No data exists for encorafenib in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

    Binimetinib: No dose adjustment required for patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 X ULN and any AST, or total bilirubin ≤ ULN and AST > ULN). Treatment with binimetinib in patients with total bilirubin >1.5 X ULN and any AST is not recommended. May consider dose reduction of binimetinib to 30 mg PO BID.
13. **Hepatotoxicity during treatment**: Hepatotoxicity with increase in liver function tests can occur during treatment with encorafenib and binimetinib. Monitor at baseline and throughout treatment. Refer to table, above.
14. **Gastrointestinal toxicity** including nausea, vomiting, diarrhea, constipation, and abdominal pain can occur during treatment with encorafenib and binimetinib. Offer preventative and treatment measures as appropriate.
15. **Rash** can occur in up to 26% of patients taking encorafenib and binimetinib. Perform a dermatologic evaluation prior to initiation of treatment and monitor patients routinely while on therapy. Delay, reduce doses, or permanently discontinue encorafenib and binimetinib based on severity. Refer to table, above.
16. **Fever.** Can occur in up to 18% of patients taking encorafenib and binimetinib, 4% grade 3 or 4. Patients should hold both medications if they develop a fever of 38C or higher. They should take anti-pyretic agents and stay hydrated. They should not restart the medications until afebrile for 24 hours without the need for anti-pyretic agents. If they have symptoms of hypotension, dehydration or are severely unwell they should be evaluated.

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. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):603-615.
2. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5); Suppl: 1-254.
3. Ascierto PA, Dummer R, Gogas HJ, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. Eur J Cancer. 2020 Feb;126:33-44.