Regimen Monograph

A - Regimen Name

BINIENCO Regimen

Binimetinib-Encorafenib

Disease Site

Skin
Melanoma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

Treatment of patients with locally advanced unresectable or metastatic BRAF V600-mutant cutaneous melanoma or unknown primary melanoma, who have good performance status, adequate organ, bone marrow and cardiac function, and are treatment naive OR progressed on a prior line immunotherapy for locally advanced or metastatic disease.*

*may be considered in patients who have previously received a BRAF inhibitor/MEK inhibitor in the adjuvant setting if disease relapse occurs more than 6 months after completion of adjuvant BRAFi/MEKi treatment.

(Refer to EAP for full funding criteria)

Supplementary Public Funding

binimetinib
Exceptional Access Program (binimetinib - For the treatment of patients with locally advanced unresectable or metastatic melanoma with a BRAF V600 mutation, according to clinical criteria.) (EAP Website)

encorafenib
Exceptional Access Program (encorafenib - For the treatment of patients with locally advanced unresectable or metastatic melanoma with a BRAF V600 mutation, according to clinical criteria.) (EAP Website)

back to top

B - Drug Regimen

binimetinib	45 mg	PO	BID
encorafenib	450* mg	PO	Daily

*If binimetinib is held, reduce encorafenib (up to a dose of 300 mg once daily) until binimetinib is resumed.

back to top

C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

BRAF V600 mutation should be confirmed by a validated test prior to starting treatment.

Correct electrolyte imbalances prior to and during treatment.

A dermatologic evaluation should be performed prior to initiating treatment.

Refer to Interactions Section for dosing recommendations when co-administered with CYP3A4 inhibitors.

Dosage with toxicity

Dose Level	Binimetinib Dose (mg, BID)	Encorafenib Dose (mg, daily)
0	45	450
-1	30	300
-2	Discontinue	225
-3		Discontinue

Toxicity/Severity	Binimetinib Dose#	Encorafenib Dose#
Non-cutaneous malignancy*	Discontinue if encorafenib is discontinued.	Discontinue if RAS mutation-positive.
Asymptomatic cardiomyopathy Absolute ↓ LVEF >10% from baseline with LVEF < lower limit of normal (LLN)	Hold for up to 4 weeks. Evaluate LVEF every 2 weeks Resume at 1 dose level ↓ if: • LVEF ≥ LLN and • Absolute ↓ LVEF ≤10% from baseline and • Asymptomatic	Reduce encorafenib (up to a dose of 300 mg once daily) while binimetinib is on hold.
Symptomatic CHF	Discontinue.	

	Absolute ↓ LVEF >20% from baseline with LVEF < LLN		Discontinue.	
	QT Prolongation	QTcF > 500 ms AND ≤ 60 ms increase from baseline	Hold (while encorafenib is on hold), then resume binimetinib at same dose. Discontinue if encorafenib is discontinued.	Hold until QTcF ≤ 500 ms, then resume at 1 dose level ↓. If > 1 recurrence, discontinue.
		QTcF > 500 ms AND > 60 ms increase from baseline	Discontinue.	
	Uncomplicated DVT or PE		Hold for up to 4 weeks. If resolves to ≤ Grade 1 resume at 1 dose level ↓.	Reduce encorafenib (up to a dose of 300 mg once daily) while binimetinib is on hold.
	Life-threatening PE		Discontinue.	
	Any new or worsening visual disturbance		Refer to ophthalmologist within 24 hours.	
	Symptomatic serous retinopathy / RPEDs		Hold for up to 10 days. If asymptomatic, resume at same dose. If no improvement, resume at 1 dose level ↓ or discontinue.	Reduce encorafenib (up to a dose of 300 mg once daily) while binimetinib is on hold.
	Retinal Vein Occlusion		Discontinue.	
	Uveitis	Grade 1 not responding to ocular therapy	Hold for up to 6 weeks. If improves to < Grade 1, resume at same dose.	
		Grade 2 not responding to ocular therapy	Hold for up to 6 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.	
		Grade 3		
		Grade 4	Discontinue.	
	Pneumonitis	Grade 2	Hold for up to 4 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.	Reduce encorafenib (up to a dose of 300 mg once daily) while binimetinib is on hold.
		Grade 3 or 4	Discontinue.	
	Increase in AST OR ALT	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1 or baseline. Resume at same dose.	
		Grade 3 or 4	See Other Adverse Reactions below.	

Rhabdomyolysis or ↑ CPK	Grade 4 ↑ CPK (asymptomatic)	Hold for up to 4 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.	Reduce encorafenib (up to a dose of 300 mg once daily) while binimetinib is on hold.
	Symptomatic or with renal impairment		
Hand-foot syndrome	Grade 2, without improvement for 2 weeks	Hold (while encorafenib is on hold), then resume binimetinib at same dose.	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at same dose or with 1 dose level ↓ if recurrent.
	Grade 3		Hold until ≤ Grade 1. Resume with 1 dose level ↓.
Other dermatologic reactions*	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at 1 dose level ↓ if recurrent.	
	Grade 3		
	Grade 4	Discontinue.	
Other adverse reactions (including hemorrhage)	Grade 2, recurrent	Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.	
	Grade 3, 1st occurrence		
	Grade 3, recurrent	Consider discontinuing.	
	Grade 4, 1st occurrence	Discontinue. OR Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.	
	Grade 4, recurrent	Discontinue.	

#If binimetinib is held, encorafenib dose should be reduced (up to a dose of 300 mg once daily) until binimetinib is resumed. If either binimetinib or encorafenib is discontinued, the other drug must also be discontinued.

*No dose modification required for new primary cutaneous malignancies but patients with suspicious skin lesions should be referred for evaluation immediately.

Hepatic Impairment

For increased AST/ALT during treatment, refer to dose modifications table above.

Hepatic Impairment	Binimetinib Starting Dose	Encorafenib Starting Dose
Mild	No dose adjustment	300 mg Daily
Moderate	Use not recommended	No data available
Severe		

Renal Impairment

Creatinine Clearance (mL/min)	Binimetinib Starting Dose	Encorafenib Starting Dose
≥ 30	No dose adjustment recommended.	
< 30	No dose adjustment recommended.	No data available.

Dosage in the Elderly

No dose adjustment required. No overall differences in the safety or efficacy observed in patients ≥ 65 years compared to younger patients.

Higher incidences of diarrhea, pruritus, GGT and blood phosphatase alkaline elevation were reported in patients ≥ 65 years.

back to top

F - Adverse Effects

Refer to binimetinib, encorafenib drug monograph(s) for additional details of adverse effects.

More common (≥ 50)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• ↑ CPK (may be severe)	• Fatigue • Nausea, vomiting • Diarrhea • Abdominal pain • Musculoskeletal pain	• Hyperkeratosis • Rash, pruritus • Constipation • Headache • Eye disorders (may be severe) • Abnormal electrolyte(s) • Hemorrhage (may be severe) • Dizziness • Alopecia • Edema - limbs • Hyperglycemia • Hypertension • Peripheral neuropathy	• Cardiomyopathy • QT interval prolonged • Venous thromboembolism • Hepatotoxicity • Pancreatitis • Hypersensitivity • Pneumonitis • Rhabdomyolysis • Secondary malignancy

back to top

G - Interactions

Refer to binimetinib, encorafenib drug monograph(s) for additional details.

- Avoid if possible concomitant use of strong or moderate CYP3A4 inhibitors with encorafenib. Reduce encorafenib dose if used in combination; see dosage table below.
- Avoid concomitant use of strong or moderate CYP3A4 inducers with encorafenib.
- Avoid concomitant use with sensitive CYP3A4 substrates (e.g., hormonal contraceptives) where a minimal decrease in concentration may lead to therapeutic failure. If coadministration of a sensitive substrate cannot be avoided, adjust substrate dose based on its product monograph recommendations.
- Avoid concomitant use of QT/QTc prolonging agent with encorafenib due to additive risk of toxicity.

Encorafenib Dose with CYP3A4 Inhibitors

Planned Dose (mg)	Encorafenib Dose* (mg daily)	
	with Strong CYP3A4 inhibitors	with Moderate CYP3A4 inhibitors
300	75	150
225	75	75
150	75^	75

*Resume previous dose after the inhibitor has been discontinued for 3 to 5 elimination half-lives.

^Monitor patients for adverse reactions and use clinical judgment; encorafenib exposure at 75mg daily (with a strong CYP3A4 inhibitor) is expected to be similar to the exposure at the 225mg daily dose (in the absence of a CYP3A4 inhibitor).

back to top

H - Drug Administration and Special Precautions

Refer to binimetinib, encorafenib drug monograph(s) for additional details.

Administration: Binimetinib

- Binimetinib tablets should be taken twice daily, approximately 12 hours apart.
- Tablets should be swallowed whole with water and may be taken with or without food.
- If a dose is missed, the dose may be taken if there are ≥ 6 hours until the next dose. If there are < 6 hours until the next dose, the dose should be skipped and the next dose should be taken at the scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.
- If a dose is vomited, an additional dose should not be taken. The next dose should be continued as scheduled .
- Store between 15-30°C.

Administration: Encorafenib

- Administer encorafenib with or without food.
- Capsules should be swallowed whole with water. Do not crush, dissolve, or open capsules.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during encorafenib treatment.
- If a dose is missed, patient may take within 12 hours of the missed dose. If more than 12 hours has elapsed from the missed dose, the dose should be skipped and taken at the next scheduled time. Extra capsules should not be taken to make up for a missed dose.

- Do not take an additional dose if vomiting occurs after taking encorafenib.
- Store at 15 - 30°C in the original bottle. Protect from moisture and do not remove the desiccant.

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions

- Patients must have a validated test to confirm BRAF V600/E mutation before treatment; paradoxical activation of MAP-kinase signaling may occur when BRAF wild-type cells are exposed to BRAF inhibitors such as encorafenib.
- Patients with a history of Gilbert's syndrome, abnormal LVEF, prolonged QTc (>480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion were excluded from clinical trials. Consider benefits vs risks of using binimetinib and encorafenib in these patients.
- Exercise caution in patients with diabetes or with risk factors for QT prolongation, including known long QT syndromes, bradyarrhythmias, heart failure, and taking other QT prolonging agents.
- Patients should exercise caution when driving or operating a vehicle or potentially dangerous machinery as vision problems have been reported.
- Binimetinib tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate non-hormonal contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects
  - Binimetinib: Unknown
  - Encorafenib: Probable

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline, monthly, and as clinically indicated
- Liver function tests; Baseline, monthly, and as clinically indicated
- Renal function tests and electrolytes, including potassium and magnesium; Baseline, monthly, and as clinically indicated
- CPK (for rhabdomyolysis); Baseline, monthly and as clinically indicated
- Cardiac function tests (Echo or MUGA scans); Baseline, after 1 month, then every 2 to 3 months
- ECG (especially in patients at risk for QT prolongation); Baseline and as clinically indicated
- Blood pressure; Baseline and as clinically indicated
- Skin examination for any cutaneous malignancies; Baseline, every 2 months during treatment, and up to 6 months after the last dose
- Clinical toxicity assessment for bleeding, thromboembolism, hypersensitivity, fatigue, hyperglycemia, new primary non-cutaneous malignancies, rhabdomyolysis, pneumonitis, pancreatitis, skin, ocular, and GI effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

K - References

Binimetinib drug monograph. Ontario Health (Cancer Care Ontario).

CADTH reimbursement recommendation: Encorafenib in combination with binimetinib (for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation), July 2021.

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):603-15.

Dummer R, Flaherty KT, Robert C, et al.. COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600-Mutant Melanoma. J Clin Oncol. 2022 Dec 20;40(36):4178-4188.

Encorafenib drug monograph. Ontario Health (Cancer Care Ontario).

Summary of Product Characteristics: Braftovi. Pierre Fabre Limited. September 14, 2022.

April 2024 Modified Interactions section

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top