Regimen Monograph

A - Regimen Name

VEMU Regimen

Vemurafenib

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

For the treatment of BRAF V600 mutation-positive unresectable Stage 3 or 4 melanoma. Brain metastases, if present, should be asymptomatic or stable

Data supporting use with BRAF mutations other than V600E are limited.

Supplementary Public Funding

vemURAFenib
Exceptional Access Program (vemURAFenib - Monotherapy in patients with BRAF V600 mutation-positive unresectable stage III or stage IV melanoma, with specific criteria) (EAP Website)

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B - Drug Regimen

vemURAFenib	960 mg	PO	BID

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression, no evidence of further response, or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – 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.

Other Supportive Care:

- Patients should be advised to avoid sun exposure and use sunscreen.

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E - Dose Modifications

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

Only patients with BRAF V600 mutations identified by a validated test should be treated. Data supporting effectiveness in patients with BRAF mutations other than V600E are limited.

Patients with QTc > 500 ms at baseline should not be treated.

Dosage with toxicity

Dose levels:

Dose Level	Vemurafenib Dose
0	960 mg BID
-1	720 mg BID
-2	480 mg BID
-3	Discontinue

Dose modifications are not recommended for cutaneous squamous cell carcinoma.

Table A

Toxicity / Grade*	Occurrence	Recommendation
Grade 1 or Grade 2 (tolerable)	Any	No change
Grade 2 (Intolerable) or Grade 3, including photosensitivity	1st	Hold until ≤ grade 1, then restart with 1 dose level ↓
	2nd	Hold until ≤ grade 1, then restart with 1 additional dose level ↓
	3rd	Discontinue
Grade 4	1st	Discontinue permanently for skin reactions or hypersensitivity or other life-threatening organ toxicity. If other toxicity, discontinue OR hold until ≤ grade 1, then restart with 2 dose level ↓
	2nd	Discontinue

Hepatotoxicity**	Any	Consider temporary hold, dose reduction or discontinuation
Pancreatitis	Any	Hold, then consider restart with 1 dose level ↓
DRESS syndrome, Stevens-Johnson syndrome, Toxic epidermal necrolysis	Any	Discontinue permanently

* Graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)
** Defined as ALT ≥ 3 x ULN plus bilirubin ≥ 2 x ULN, or ALT ≥ 5 x ULN, or ALP ≥ 2 x ULN (without bone pathology)

Table B:

QT Prolongation:

Criteria	Occurrence	Action
QTc > 500 ms and > 60 ms increase from baseline	Any	Discontinue permanently
QTc > 500 ms during treatment and ≤ 60 ms increase from baseline	1st	Hold until QTc < 500 ms. Resume with 1 dose level ↓
	2nd	Hold until QTc < 500 ms. Resume with 1 additional dose level ↓
	3rd	Discontinue permanently

Hepatic Impairment

Hepatic impairment may result in higher vemurafenib exposure and related adverse effects. Refer to Table A for management of hepatic impairment during treatment.

Hepatic Impairment	Bilirubin	Starting Dose
Mild	> 1 to 1.5 x ULN	100%, caution
Moderate	> 1.5 to 3 x ULN	100%, caution
Severe	> 3 x ULN	No data

Renal Impairment

The appropriate dose has not been established in severe renal impairment. Refer to Table A for dose modifications with renal toxicity.

Dosage in the Elderly

Elderly patients (≥ 65 years) are at greater risk of experiencing side effects such as cuSCC, decreased appetite and cardiac effects. No adjustment to starting dose is indicated.

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F - Adverse Effects

Refer to vemurafenib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Musculoskeletal pain	• Alopecia • Fatigue • Photosensitivity (may be severe) • Rash (may be severe) • Nausea, vomiting • Diarrhea • Headache • Secondary malignancy (cutaneous squamous cell carcinoma, basal cell carcinoma, new primary melanoma) • Increased Creatinine (may be severe, including nephritis)	• ↑ LFTs (may be severe) • Anorexia, weight loss • Constipation • Abdominal pain • Cough, dyspnea • Insomnia • Edema • Fever • Dysgeusia • Dizziness	• Arrhythmia • Cardiotoxicity • Prolonged QT interval • Venous thromboembolism • Radiation sensitization and recall reaction • Hypersensitivity • Vasculitis • DRESS • Stevens-Johnsons syndrome • Toxic epidermal necrolysis • Pancreatitis • Tumour lysis syndrome • Ocular effects, including retinal vein occlusion, uveitis • Dupuytren's contracture

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G - Interactions

Refer to vemurafenib drug monograph(s) for additional details.

- Avoid strong CYP3A4 inducers or inhibitors, if possible. If vemurafenib is co-administered with strong CYP3A4 inhibitors, vemurafenib dose reduction may be required.
- Avoid concurrent use with CYP1A2 substrates with a narrow therapeutic range, and consider dose modification if they must be used together.
- Drugs that have been associated with QTc interval prolongation and/or torsade de pointes should not be administered with vemurafenib, if possible.

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H - Drug Administration and Special Precautions

Refer to vemurafenib drug monograph(s) for additional details

Administration:

- The daily doses should be given in the morning and in the evening, around 12 hours apart.
- May be administered with or without food (but administration in relation to food should be consistent).
- Film-coated tablet should be swallowed whole with a glass of water; do not crush or split.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Avoid excessive caffeine as this may increase side effects (refer to interactions).
- If vomiting occurs after taking a dose, do not take an additional dose. Continue to take the next dose as scheduled.
- If a dose is missed, it may be given if there are more than 4 hours before the next dose. Otherwise, skip this dose and give the next one as scheduled. Never give both doses at the same time.
- Store between 15-30°C, in the original package; protect from moisture.

Contraindications:

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

Warnings/Precautions:

- Vemurafenib should not be used in patients with baseline QTc > 500 ms, with wild-type BRAF tumours or where the BRAF mutation status is unknown.
- Consider benefits vs risks of starting vemurafenib in these patients:
  - Patients with uncontrolled hypertension (excluded from clinical trials)
  - Concurrent use with radiation therapy (possible severe/fatal radiation sensitization and radiation recall reaction).
- Caution in patients with increased QT interval or who are at risk (low potassium/magnesium, congenital QT prolongation, or history of arrhythmia, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy.
- Caution in patients with prior or concurrent cancers, especially those associated with RAS mutation.
- The concurrent use of ipilimumab and vemurafenib is not recommended since hepatotoxicity was observed in a clinical trial.
- Secondary malignancies (cutaneous squamous cell carcinoma, non-cutaneous squamous cell carcinoma, primary melanoma) are common - patients must be closely monitored and treated appropriately.
- Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery due to vision problems.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate 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 this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

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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

- ECG and electrolytes (including potassium, magnesium and calcium, especially in patients with risk factors for QT prolongation); baseline and after dose modification, Day 15, monthly for first 3 months then every 3 months, or more often as clinically indicated
- Liver function tests; baseline and periodic, monitor closely if abnormal
- Renal function tests; baseline and periodic, monitor closely if abnormal
- Blood pressure; baseline and periodic during treatment
- INR in patients taking warfarin; during initiation of vemurafenib and after dose modification or discontinuation
- Dermatologic evaluation; baseline and regular, until 6 months after the last dose
- Chest CT scan (for NCuSCC); baseline and every 6 months, until 6 months after the last dose
- Head and neck examination (at least a visual inspection of oral mucosa and lymph node palpation, for NCuSCC); baseline and every 3 months, until 6 months after the last dose
- Pelvic (females) / anal examinations (for NCuSCC); baseline, end of treatment and when clinically indicated, until 6 months after the last dose
- Clinical toxicity assessment for musculoskeletal, skin, ocular, GI toxicity; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Chapman PB et al. Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600EBRAF-mutated melanoma. J Clin Oncol 2011; 29 (suppl; abstr LBA4).

Chapman PB et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. NEJM 2011;364(26):2507-16.

Vemurafenib drug monograph, Ontario Health (Cancer Care Ontario).

August 2023 Modified Dose Modifications, Dosage in hepatic impairment, Adverse effects, Interactions, Warnings/Precautions, and Monitoring sections

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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.

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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.

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