Regimen Monograph

A - Regimen Name

TRAM Regimen

Trametinib

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 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Not funded by EAP in patients who have progressed on prior BRAF inhibitor treatment. Treatment beyond third line will not be considered for funding. Brain metastases (if present) should be asymptomatic or stable. Refer to EAP funding criteria details.

Supplementary Public Funding

trametinib
Exceptional Access Program (trametinib - As monotherapy in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, according to specific criteria) (EAP Website)

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B - Drug Regimen

trametinib	2 mg	PO	daily

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression 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 have a supply of loperamide ready in order to start at the first signs of diarrhea.
- Consider a prophylactic skin regimen; one example is:
  - avoidance of unnecessary exposure to sunlight
  - an SPF ≥30 broad-spectrum sunscreen (containing titanium dioxide or zinc oxide)
  - a thick, alcohol-free emollient cream applied on dry areas of the body daily
- Also consider:
  - a mild strength topical steroid (e.g. 1% hydrocortisone) applied daily
  - doxycycline 100mg bid or minocycline 100mg bid or topical antibiotic for the first 2-3 weeks of treatment

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E - Dose Modifications

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

A validated test is required to identify BRAF V600 mutation status.

Dosage with toxicity

Dose Level	Trametinib Dose (mg/day)
0	2
-1	1.5
-2	1
-3	Discontinue

Toxicity	Trametinib Dose
Grade 2 rash (tolerable)	Continue treatment with 1 dose level reduction. If does not improve with reduced dose, hold for up to 3 weeks until improves and then restart with a further 1 dose level reduction. Discontinue if no improvement after 3 weeks.
Intolerable grade 2 or ≥ grade 3 rash	Hold up to 3 weeks until ≤ grade 1 then ↓ 1 dose level. Discontinue if no recovery within 3 weeks.
Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, DRESS)	Discontinue.
Fever of 38.5 to 40◦C (no complications)	Continue at same dose.
Fever >40◦C or any fever with complications (rigors, hypotension, dehydration, renal failure)	Hold until resolved, then resume at the same dose, or ↓ by one dose level.
Grade 1 or uncomplicated grade 2 diarrhea	May continue with same dose. OR Hold up to 3 weeks until improved then restart with the same dose.
Grade 3 or 4 diarrhea or complicated Grade 1 or 2 diarrhea	Hold up to 3 weeks until ≤ grade 1 and restart by ↓ 1 dose level.

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Grade 2 or 3 retinal pigment epithelial detachments (RPED)	Hold up to 3 weeks until ≤ grade 1, then restart by ↓ 1 dose level. Discontinue if no improvement or if it recurs.
Grade 4 RPED, Any grade retinal vein occlusion	Discontinue.
Uveitis	Use local ocular therapy; if responds, continue dose. If does not improve, hold until resolves then restart at same dose or consider a 1 dose level decrease.
Rhabdomyolysis	Hold and manage appropriately. When recovers consider risk – benefit before restarting at a reduced dose; otherwise, discontinue.
Pneumonitis	Hold and investigate; if confirmed, discontinue.
Other grade 1 and 2 (tolerable)	Continue at the same dose.
Other grade 3 or intolerable grade 2 related organ	Hold up to 3 weeks until ≤ grade 1 then ↓1 dose level. Discontinue if no improvement.
Other grade 4 related organ	Discontinue.

Cardiotoxicity:

Left Ventricular Ejection Fraction	**Trametinib**		
	Action	**LVEF at Re-assessment**	**Dose**
Asymptomatic plus LVEF below LLN AND 10-20% ↓ from baseline	Hold and repeat MUGA in 4 weeks	Improves to normal institutional LVEF limits	Restart with ↓ 1 dose level
		Does not improve to normal institutional LVEF limits within 4 weeks OR Symptomatic	Discontinue
Symptomatic OR LVEF below LLN and > 20% ↓ from baseline	Discontinue	Not applicable	Not applicable

*LLN = Lower limit of normal

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Hepatic Impairment

No formal studies have been conducted. Population pharmacokinetics in patients with mild hepatic impairment showed no significant effects.

Hepatic Impairment	Bilirubin		AST	Trametinib Dose
Mild	≤ ULN	and	> ULN	No dose adjustment required
	>1 - 1.5 x ULN	and	Any	
Moderate or Severe	>1.5 x ULN	and	Any	No data

Renal Impairment

No formal studies have been conducted. Due to the low renal excretion of trametinib, renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics.

Creatinine Clearance (mL/min)	Trametinib Dose
≥ 30	No dose adjustment required
< 30	No data

Dosage in the Elderly

Elderly patients (≥ 65 years) experienced higher rates of severe events, discontinuation and dose interruptions / reductions than younger patients. No prospective dose adjustment is required. Peripheral edema and decreased appetite were reported more frequently in elderly patients (for both monotherapy and combination treatment).

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F - Adverse Effects

Refer to trametinib 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
• Rash (may be severe)	• Diarrhea • Edema • Fatigue	• Nausea, vomiting • Bleeding • Alopecia • Hypertension (may be severe) • Constipation • Headache • Abdominal pain • Fever • Cough, dyspnea (may be severe) • Nail changes • Dry mouth • ↑ LFTs (may be severe) • Musculoskeletal pain	• Cardiotoxicity (ejection fraction decreased) • PR interval prolonged • Venous thromboembolism • Hemorrhage • Hypersensitivity • Pneumonitis • Retinopathy • Uveitis • Rhabdomyolysis • GI perforation • Pancreatitis • Secondary malignancy

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G - Interactions

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

- Trametinib prolongs PR interval and caution should be taken when it is administered with other PR interval-prolonging agents (antiarrhythmics, beta-blockers, non-dihydropyridine Ca channel blockers, digoxin, some HIV protease inhibitors, sphingosine-1 phosphate receptor modulators).

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H - Drug Administration and Special Precautions

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

Administration:

- Give on an empty stomach, at least one hour before or 2 hours after a meal.
- Tablets should be swallowed whole with a glass of water and not crushed or chewed.
- If a dose is missed and it is less than 12 hours until the next dose, skip it and take the next dose at its scheduled time. Do not give extra doses to make up for a missed dose.
- Keep refrigerated at 2-8°C. Do not freeze and protect from light.
- Once opened, the bottle may be stored for 30 days at no more than 30°C.

Contraindications:

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

Warnings/Precautions:

- BRAF mutation must be confirmed using a validated test before starting trametinib treatment.
- Trametinib should not be used in patients with BRAF V600 mutation who progressed on a prior BRAF inhibitor.
- Use of trametinib is not recommended in patients with decreased LVEF at baseline. Exercise caution in patients with conditions that can impair left ventricular function, with pre-existing conduction disorders, a history of syncope of unknown etiology and medications that can result in PR prolongation.
- Use of trametinib is not recommended in patients with a history of retinal vein occlusion. Exercise caution in patients with risk factors for retinal vein occlusion such as diabetes, hypertension, hypercholesterolemia and glaucoma.
- Use with caution in patients with a history of diverticulitis, metastases to the GI tract and concomitant use of other medications with a risk of GI perforation.

Pregnancy and 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: Probable

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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

- Blood pressure; Baseline and at each visit
- LVEF; Baseline, periodic within 8 weeks of starting treatment, then as clinically indicated
- Ophthalmological evaluation; Baseline and as clinically indicated
- Skin, nail toxicity and secondary infections; 2 weeks after initiating treatment and then as clinically indicated
- Clinical toxicity assessment for diarrhea and other GI effects, edema, arrhythmia, thromboembolism, hypersensitivity, pneumonitis, bleeding, rhabdomyolysis and neurologic events; 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

Flaherty KT, Robert C, Hersey P, et al; METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012 Jul 12;367(2):107-14.

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

June 2025 Updated Pregnancy/Lactation section

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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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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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