Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

DABRTRAM Regimen

Dabrafenib-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

daBRAFenib
Exceptional Access Program (daBRAfenib - In combination with trametinib for the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, according to specific clinical criteria) (EAP Website)

trametinib
Exceptional Access Program (trametinib - In combination with dabrafenib for

the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, according to specific clinical criteria)

back to top

B - Drug Regimen

daBRAFenib	150 mg	PO	BID
trametinib	2 mg	PO	Daily

back to top

C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions with dabrafenib.
- 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) applied at least twice daily
  - a thick, alcohol-free emollient cream applied to dry areas of the body at least twice daily
- Also consider:
  - a mild strength topical steroid (e.g. 1% hydrocortisone) applied twice daily x 6 weeks
  - doxycycline 100mg bid or minocycline 100mg bid or topical antibiotic x 6 weeks

Also refer to CCO Antiemetic Recommendations.

back to top

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	Dabrafenib Dose	Trametinib Dose
0	150 mg BID	2 mg DAILY
-1	100 mg BID	1.5 mg DAILY
-2	75 mg BID	1 mg DAILY
-3	Discontinue	

Toxicity	Dabrafenib Dose	Trametinib Dose
Fever of 38.5 to 40°C	Hold until resolution (no symptoms for ≥ 24 hours*); monitor creatinine and for infection. Restart at same dose or ↓ 1 dose level if associated with dehydration or hypotension. Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions.	Consider hold until resolution (no symptoms for ≥ 24 hours) and restart at same dose*.
Fever > 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure	Monitor creatinine and for infection. Discontinue. OR Hold until ≤ Grade 1 and ↓ 1 dose level. Prophylaxis with antipyretics +/- oral corticosteroids may be	Hold until recovery and restart at same dose OR ↓ 1 dose level.

	required if prior severe febrile reactions.	
Uveitis that responds to local ocular therapies	Continue treatment without dose modifications and monitor.	Continue trametinib at the same dose.
Uveitis that does not improve despite local ocular therapy	Hold until resolved and ↓ 1 dose level.	Hold until resolved and resume trametinib at the same dose or ↓ 1 dose level.
Pancreatitis	Discontinue OR Hold until resolved and then restart ↓ 1 dose level; monitor carefully.	Continue at same dose.
Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, DRESS)	Discontinue.	
Cutaneous squamous cell carcinoma or new primary melanoma	No dose modification or interruptions recommended.	
RAS associated malignancy	Consider risk benefit before making decision to continue treatment.	
Grade 1 rash	No dose modification or interruptions recommended.	Treat symptomatically and continue with same dose.
Grade 2 rash (tolerable)	No dose modification or interruptions recommended if tolerable.	Treat symptomatically and ↓ 1 dose level. If no recovery, hold for up to 3 weeks; if recovers restart with a further reduction. If no recovery within 3 weeks, discontinue.
Intolerable Grade 2 or ≥ Grade 3 rash	Consider discontinuing if Grade 4. Hold until ≤ Grade 1, restart at ↓ 1 dose level. If no recovery within 3 weeks, discontinue.	Treat symptomatically. Hold until ≤ Grade 2, restart at ↓ 1 dose level. If no recovery within 3 weeks, discontinue.
Grade 1 or Grade 2 diarrhea (uncomplicated)	No dose modification or interruptions recommended if tolerable.	Treat symptomatically; may continue at same dose or hold for up to 3 weeks until improved and then restart at same dose.

≥ Grade 3 diarrhea or intolerable or complicated Grade 2 diarrhea	Consider discontinuing if Grade 4. Hold until ≤ Grade 1, restart at ↓ 1 dose level.	Treat symptomatically. Hold until resolves to ≤ Grade 1, restart at ↓ 1 dose level.
Grade 2 or Grade 3 retinal pigment epithelial detachment (RPED)	No dose modification or interruptions recommended.	Hold and consult ophthalmologist. If resolves to ≤ Grade 1, restart at ↓ 1 dose level. If does not resolve or recurs, discontinue.
Grade 4 RPED, any grade retinal vein occlusion	No dose modification or interruptions recommended.	Discontinue and consult ophthalmologist.
Pneumonitis	Continue at same dose.	Hold; investigate and treat as appropriate; discontinue if confirmed.
Rhabdomyolysis	Hold until stable.	Hold and treat; carefully consider risk-benefit when deciding whether to restart at a reduced dose after recovery.
Other Grade 1 or Grade 2	No dose modification or interruptions recommended if tolerable.	No dose modification or interruptions recommended if tolerable.
Other Grade 3 or intolerable Grade 2	Hold until ≤ Grade 1 for up to 3 weeks, then restart at ↓ 1 dose level when recovered. If does not recover, discontinue.	Hold until ≤ Grade 1 for up to 3 weeks, then restart at ↓ 1 dose level when recovered. If does not recover, discontinue.
Other Grade 4	Discontinue or hold until ≤ Grade 1, restart at ↓ 1 dose level.	Discontinue.

*CCO melanoma disease site group recommendation; refer to Atkinson et al. 2016 for more information.

Cardiotoxicity:

Left Ventricular Ejection Fraction	Treatment		
	Action	**LVEF at Re-assessment**	**Dose**
Asymptomatic plus LVEF below LLN AND 10-20% ↓ from baseline	Hold and repeat MUGA or ECHO in 4 weeks.	Improves to normal institutional LVEF limits	Restart trametinib at ↓ 1 dose level. Restart dabrafenib at previous dose.
		Does not improve to normal institutional LVEF limits within 4 weeks OR Symptomatic	Discontinue trametinib. Consider restarting dabrafenib monotherapy.
Symptomatic OR LVEF below LLN and > 20% ↓ from baseline	Discontinue treatment and consult cardiologist.	If recovers	Discontinue trametinib. Consider restarting dabrafenib monotherapy.

*LLN = Lower limit of normal

Hepatic Impairment

Hepatic Impairment	Dabrafenib and Trametinib Dose
Mild	No dose adjustment required.
Moderate	No data.
Severe	No data.

Renal Impairment

Creatinine Clearance (mL/min)	Dabrafenib and Trametinib Dose
30-89	No dose adjustment required.
< 30	No data; use with caution.

Dosage in the Elderly

No dose adjustment required. More adverse events were observed in elderly patients (≥ 65 years). Peripheral edema and decreased appetite were reported more frequently in elderly patients.

back to top

F - Adverse Effects

Refer to dabrafenib, 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
• Fever (non-infection related; may be severe) • Fatigue	• Nausea, vomiting • Headache • Rash (may be severe) • Diarrhea (may rarely be severe) • Musculoskeletal pain • Abnormal electrolyte(s)	• Cough, dyspnea • ↑ LFTs • Abdominal pain • Edema • Bleeding • Constipation • Nasopharyngitis • Hypertension • Anorexia • Dizziness • Myelosuppression	• Cardiotoxicity (ejection fraction decreased) • Venous thromboembolism • Arrhythmia • Prolonged QT/PR interval • Worsening of heart valve disease • Secondary malignancy • Hemorrhage • GI perforation • Pancreatitis • Renal failure • Nephritis • Rhabdomyolysis • Hyperglycemia • Hypersensitivity • Uveitis • Retinopathy • Hand-foot syndrome • Photosensitivity • Severe cutaneous adverse reactions

			(SCARs) • Sarcoidosis • Pneumonitis

back to top

G - Interactions

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

- Avoid strong CYP3A4 & CYP2C8 inducers due to ↓ dabrafenib concentration and/or efficacy.
- Avoid strong CYP3A4 & CYP2C8 inhibitors due to ↑ dabrafenib and metabolite exposure and/or toxicity.
- Avoid hormonal contraceptives as dabrafenib can decrease their efficacy.
- Increased risk of QT or PR interval prolongation; avoid other drugs that prolong QTc and monitor when given with drugs that prolong PR interval.
- Dabrafenib can ↓ substrate concentration of CYP2B6, 2C8, 2C9, 2C19, UGTs and Pgp; use alternate medications if possible or monitor for efficacy.

back to top

H - Drug Administration and Special Precautions

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

Administration: Dabrafenib

- Dabrafenib doses should be given approximately 12 hours apart on an empty stomach, at least 1 hour before or 2 hours after a meal.
- Capsules should be swallowed whole with a full glass of water.
- If a dose is missed and it is less than 6 hours until the next dose, skip it and give the next dose as scheduled. Do not give extra doses to make up for a missed dose.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during treatment.
- Store at room temperature (15-30°C).

Administration: Trametinib

- Give on an empty stomach, at least one hour before or 2 hours after a meal.
- When given in combination, trametinib should be administered once daily with either the morning or evening dose of dabrafenib.
- Tablets should be swallowed whole with a glass of water. Do not crush or chew.
- 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:

- Dabrafenib and trametinib are contraindicated in patients who have a hypersensitivity to these drugs or any of their components.

Warnings/Precautions:

- Dabrafenib and trametinib should only be used in patients with BRAF V600 mutation. BRAF mutation must be confirmed using a validated test before starting treatment.
- Dabrafenib and trametinib should not be used in patients with BRAF V600 mutation who progressed on a prior BRAF inhibitor.
- The incidence and severity of dabrafenib-associated non-infectious febrile events are increased when used in combination.
- Exercise caution in patients with risk factors for QT prolongation or Torsades de pointes (low potassium/magnesium, congenital QT prolongation, history of arrhythmia, CHF, anti-arrhythmic, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy.
- Patients were excluded from dabrafenib clinical trials if they had abnormal heart valve morphology ≥ grade 2.
- Monitor for hemolytic anemia in patients with G6PD deficiency as dabrafenib contains a sulfonamide moiety.
- Use combination therapy with caution in patients at risk of bleeding as severe or fatal events have been reported. The risk may be increased with concomitant use of antiplatelet/anticoagulant therapy or in patients who develop brain metastases while on treatment.
- 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:

- Dabrafenib and trametinib are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **16 weeks** after the last dose of treatment.
- Efficacy of hormonal contraceptives is likely to be decreased; use effective alternative methods of contraception.
- Breastfeeding is not recommended.
- Fertility Effects: Likely

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.

Recommended Clinical Monitoring

- CBC; Baseline and at each visit
- Liver function tests; Baseline and every 4 weeks for 6 months, therafter every 1 to 2 months
- Renal function tests and electrolytes (including phosphate); Baseline, at each visit and during febrile events
- Blood glucose; Baseline and every 1 to 2 months, more regularly (at each visit) in patients with diabetes or hyperglycemia
- Blood pressure; Baseline and at each visit.
- LVEF; Baseline, as indicated within 8 weeks of starting treatment, then as clinically indicated
- Ophthalmological evaluation; Baseline and as clinically indicated
- Skin examination for cutaneous squamous cell carcinoma, new primary melanoma; Baseline, every 2 months during treatment, then continue for 6 months after the last dose
- Non-cutaneous malignancies; Baseline, periodic or as clinically indicated during treatment, up to 6 months after the last dose
- Skin, nail toxicity and secondary infections; 2 weeks after initiating treatment, then as clinically indicated

- Clinical toxicity assessment for fever, diarrhea and other GI effects, pancreatitis, edema, cardiac effects, ocular effects, thromboembolism, bleeding, inflammatory effects, neurologic events, hypersensitivity, rhabdomyolysis, pneumonitis; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR for patients receiving warfarin; Baseline and at each visit

back to top

J - Administrative Information

Outpatient prescriptions for home administration

back to top

K - References

Atkinson A, Long GV, Menzies AM et al. Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: Guidelines from Australia melanoma medical oncologists. Asia-Pacific Journal of Clinical Oncology. 2016; 12(Suppl.7):5-12.

Dabrafenib and trametinib drug monographs. Ontario Health (Cancer Care Ontario).

Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014 Nov 13;371(20):1877-88.

June 2021 Updated rationale and uses, adverse effects, interactions, drug administration and special precautions sections

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