**Regimen Monograph**



## A - Regimen Name

# DABR Regimen

**Dabrafenib**

| | |
|---|---|
| **Disease Site** | Skin - Melanoma |
| **Intent** | Palliative |
| **Regimen Category** | **Evidence-Informed :**<br><br>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.<br><br>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**<br>Exceptional Access Program (daBRAfenib - As monotherapy for the treatment of patients with BRAF V600 mutation-positive unresectable melanoma or metastatic disease, according to specific criteria) (EAP Website) |

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## B - Drug Regimen

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| **daBRAFenib** | 150 mg | PO | BID |

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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.

**Other Supportive Care:**

Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions with dabrafenib.

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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 | Dabrafenib Dose (mg BID) |
|---|---|
| 0 | 150 |
| -1 | 100 |

| | |
|---|---|
| -2 | 75 |
| -3 | 50 |
| -4 | Discontinue |

Recommended dose modifications for monotherapy and combination therapy with trametinib:

| Toxicity | Dabrafenib Dose |
|---|---|
| ↓ LVEF below LLN and > 20% decrease from baseline | Hold until resolution, then restart at the same or reduced dose level. |
| Symptomatic cardiac failure | Hold until resolution, then restart at the same or reduced dose level. |
| Fever of 38.5-40°C without complications | Hold until resolution; monitor creatinine and for signs and symptoms of infection. Restart at same dose or by ↓ 1 dose level.<br><br>Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions. |
| Fever > 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure | Monitor creatinine and for signs and symptoms of infection.<br><br>Discontinue.<br><br>OR<br><br>Hold until ≤ Grade 1, then restart by ↓ 1 dose level.<br><br>Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions. |
| Intolerable Grade 2 or ≥ Grade 3 rash | Hold until ≤ Grade 1, then restart by ↓ 1 dose level. |
| Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks of holding treatment | Discontinue. |
| Uveitis that responds to local ocular therapies | Continue treatment without dose modifications and monitor. |
| Uveitis that does not improve despite local ocular therapy | Hold until resolved, then restart by ↓ 1 dose level. |

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| Pancreatitis | Discontinue.<br><br>OR<br><br>Hold until resolved, then restart by ↓ 1 dose level; monitor carefully. |
| 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. |
| Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, DRESS) | Discontinue. |
| Other Grade 1 or tolerable Grade 2 | No change; monitor. |
| Other Grade 2 (intolerable) or Grade 3 | Hold until ≤ Grade 1, then restart by ↓ 1 dose level. |
| Other Grade 4 or Grade 3 that does not improve to ≤ Grade 1 | Discontinue<br><br>OR<br><br>Hold until ≤ Grade 1, then restart by ↓ 1 dose level. |

**Hepatic Impairment**

Hepatic metabolism and biliary secretion are the main routes of dabrafenib elimination; hepatic impairment may lead to increased exposure and toxicities. Population pharmacokinetics in mild hepatic impairment suggest no dose adjustment is required, but no data are available for moderate to severe hepatic impairment.

| Hepatic Impairment | Dabrafenib Dose |
|---|---|
| Mild | No dose adjustment required. |
| Moderate | No data. |
| Severe | No data. |

**Renal Impairment**

There are no clinical data in patients with severe renal impairment. With mild to moderate impairment, population pharmacokinetics suggest that no adjustments are required.

| Creatinine Clearance (mL/min) | Dabrafenib Dose |
|---|---|
| 30-89 | No dose adjustment needed. |
| < 30 | No data found. Use with caution. |

**Dosage in the Elderly**

No dose adjustment required. In unresectable or metastatic melanoma, more serious adverse events were observed in elderly patients (≥ 65 years); peripheral edema and decreased appetite were reported more frequently.

**Dosage based on ethnicity:**

Dabrafenib clearance is similar in Asian and Caucasian cancer patients with similar liver function.

**Children:**

Not recommended for use inf children and adolescents < 18 years of age; safety and efficacy have not been established in this population. Adverse growth effects and renal toxicity have been observed in developing animals.

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## F - Adverse Effects

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

| Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|
| • Hyperkeratosis<br>• Headache, musculoskeletal pain | • Fatigue<br>• Hand-foot syndrome<br>• Rash | • Photosensitivity<br>• Arrhythmia<br>• Venous |

| | | |
|---|---|---|
| • Febrile reactions (may be severe)<br>• Alopecia<br>• Nausea/vomiting | • Nasopharyngitis<br>• Bleeding<br>• Diarrhea<br>• Cough<br>• Constipation<br>• ↑LFTs<br>• Anorexia<br>• New primary or secondary malignancies (cutaneous or non-cutaneous) | thromboembolism<br>• QT prolongation<br>• Worsening of heart valve disease<br>• Hemorrhage<br>• Hypersensitivity<br>• Pancreatitis<br>• Renal failure<br>• Nephritis<br>• Hyperglycemia<br>• Uveitis<br>• Retinopathy |

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## G - Interactions

Refer to daBRAFenib 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.
- Avoid other drugs that prolong QTc due to increased risk of QT prolongation.
- Dabrafenib can ↓ substrate concentration of CYP2B6, 2C8, 2C9, 2C19, UGTs and Pgp; use alternate medications if possible or monitor for efficacy.

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## H - Drug Administration and Special Precautions

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

### Administration

- 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).

### Contraindications

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

### Warnings/Precautions

- Dabrafenib should not be used in patients with BRAF wild-type or unknown disease. BRAF mutation must be confirmed using a validated test before starting dabrafenib treatment. Phase II studies reported fewer responses in BRAF V600K patients compared to BRAF V600E patients.
- Dabrafenib monotherapy has not been studied in patients who have had previous treatment with BRAF inhibitors.
- Exercise caution in patients with risk factors for QT prolongation or Torsades de pointes (low potassium/magnesium, congenital QT prolongation, or history of arrhythmia, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy.
- Patients were excluded from 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.

### Pregnancy/Lactation

- Dabrafenib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 weeks** after the last dose when given as monotherapy.
- Efficacy of hormonal contraceptives is likely to be decreased; use effective alternative methods of contraception.
- Breastfeeding is not recommended.
- Fertility effects: Likely

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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.

Recommended Clinical Monitoring

- Liver function tests; Baseline and every 1 to 2 months
- Renal function tests and electrolytes, including phosphate; Baseline, every 1 to 2 months, during and after febrile events
- Skin examination for cutaneous squamous cell carcinoma and new primary melanoma; Baseline, every 2 months during treatment, continue every 2-3 months 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
- Blood glucose; Baseline, every 1 to 2 months, more regularly (at each visit) in patients with diabetes or hyperglycemia
- Blood pressure; Baseline and as clinically indicated
- Clinical toxicity assessment for febrile events, pancreatitis, musculoskeletal pain, ocular, dermatologic and cardiac effects, hypersensitivity; 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 as clinically indicated

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## J - Administrative Information

Outpatient prescription for home administration

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## K - References

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

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a

multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012 Jul 28;380(9839):358-65.

Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13(11):1087-95.

**June 2021** Updated rationale and uses, drug administration and special precautions, dose modifications and monitoring sections

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## M - Disclaimer

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***Regimen Monographs***

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