Regimen Monograph

A - Regimen Name

BRIG Regimen

brigatinib

Disease Site

Lung
Non-Small Cell

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:

- anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor, in patients with good performance status
- ALK-positive metastatic NSCLC, in patients who have progressed on or who were intolerant to an ALK inhibitor (crizotinib)*

*Not funded by EAP

Supplementary Public Funding	**brigatinib** Exceptional Access Program (brigatinib - For the treatment of anaplastic lymphoma kinase-positive locally advanced or metastatic non-small cell lung cancer according to clinical criteria) (EAP Website)

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B - Drug Regimen

ALK-positive status must be based on a validated assay, prior to starting treatment with brigatinib.

brigatinib	90 mg	PO	Daily on Days 1-7
Then,			
brigatinib	180 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:

- Blood pressure should be controlled prior to initiating brigatinib therapy.

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E - Dose Modifications

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

If therapy is interrupted for ≥14 days due to reasons **other than toxicity,** resume treatment at 90mg once daily for 7 days before escalating dose to the previously tolerated dose.

If dose is reduced **for toxicity**, do not subsequently escalate the dose.

See Interactions section for dosing recommendations when administered with CYP3A4 inhibitors/inducers.

Dosage with toxicity

Dose Level	Initial Brigatinib Dose (first 7 days) (mg/day)	Maintenance Brigatinib Dose (mg/day)
0	90	180
-1	60	120
-2	Discontinue	90
-3	N/A	60
-4	N/A	Discontinue

Toxicity	Severity	Action
Interstitial Lung Disease (ILD) /Pneumonitis	Grade 1	Hold until recovery to baseline; resume at same dose level. (if WITHIN first 7 days: Do not escalate to 180 mg). If recurs, discontinue.
	Grade 2	Hold until recovery to baseline; resume at 1 dose level ↓. (if WITHIN first 7 days: Do not escalate to 180 mg). If recurs, discontinue.
	≥ Grade 3	Discontinue.
Hypertension	Grade 3	Hold until recovery to ≤ grade 1; resume at same dose level. If recurs, hold until recovery to ≤ grade1; resume at 1 dose level ↓ **or** discontinue.
	Grade 4	Hold until recovery to ≤ grade 1; resume at 1 dose level ↓ **or** discontinue. If recurs, discontinue.
Bradycardia (HR <60 bpm)	Symptomatic	Hold until recovery to asymptomatic or resting heart rate ≥60 bpm. If contributing medication identified and discontinued (or dose-adjusted), resume at same dose. If no contributing medication identified (or cannot be discontinued or dose-adjusted), resume at 1 dose level ↓.
	Life-threatening (urgent intervention indicated)	Hold until recovery to asymptomatic or resting heart rate ≥60 bpm. If contributing medication identified and discontinued (or dose-adjusted), resume at 1 dose level ↓ If no contributing medication identified, discontinue. If recurs, discontinue.

Visual Disturbance	Grade 2-3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
	Grade 4	Discontinue.
Creatine Phosphokinase (CPK) Elevation	≥Grade 3 with ≥grade 2 muscle pain or weakness	Hold until recovery to ≤ grade 1 or baseline; resume at same dose level. If recurs, hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
Lipase/Amylase Elevation	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at same dose.
	Recurrent Grade 3 or grade 4	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
Hyperglycemia	Blood glucose >13.9 mmol/L	Hold until adequate hyperglycemic control; resume at 1 dose level ↓ **or** discontinue.
Elevation of hepatic enzymes	≥Grade 3 AST/ALT with bilirubin ≤2 × ULN	Hold until recovery to ≤3 x ULN or baseline; resume at 1 dose level ↓.
	≥Grade 2 AST/ALT with bilirubin >2 × ULN in the absence of cholestasis or hemolysis	Discontinue.
Other Toxicities	Grade 3	Hold until recovery to baseline; resume at same dose level. If recurs, hold until recovery to baseline; resume at 1 dose level ↓ **or** discontinue.
	Grade 4	Hold until recovery to baseline; resume at 1 dose level ↓. If recurs, hold until recovery to baseline; resume at 1 dose level ↓ **or** discontinue.

Hepatic Impairment

Hepatic Impairment	Brigatinib Dose (mg/day)
Mild or moderate (Child-Pugh class A or B)	No dose adjustment required
Severe (Child-Pugh class C)	Reduce dose by 1 dose level

Renal Impairment

Renal Impairment	Brigatinib Dose (mg/day)
Mild or moderate (CrCl ≥30 mL/min)	No dose adjustment required
Severe (CrCl <30 mL/min)	For 180mg dose: Reduce by 2 dose levels For 90mg dose: Reduce by 1 dose level

Dosage in the Elderly

No dosage adjustment is required. Use brigatinib with caution in elderly patients, especially patients > 85 years of age as there is no available data on patients in this age group. Increased age (≥ 65 years of age) was associated with an increased risk of early pulmonary adverse reactions.

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F - Adverse Effects

Refer to brigatinib 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
• ↑CPK (may be severe) • ↑ LFTs (may be severe) • ↑ Amylase / lipase (may be severe) • Hyperglycemia (may be severe) • Diarrhea	• Rash, pruritus, dry skin (generally mild) • ↑ Creatinine • Cough, dyspnea • Hypertension (may be severe) • Fatigue • Nausea, vomiting • Musculoskeletal pain	• Abdominal pain • Headache • Fever • Constipation • Edema • Mucositis • Bradycardia (may be severe) • Peripheral neuropathy	• QT interval prolonged • Venous thromboembolism • Photosensitivity • Visual disorders • Interstitial lung disease

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G - Interactions

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

- Avoid co-administration with strong or moderate CYP3A inhibitors as concurrent use may increase brigatinib concentration and/or toxicity.
    - If concomitant use of **strong** inhibitors cannot be avoided, reduce brigatinib dose from 180mg to 90mg, or from 90mg to 60mg.
    - If concomitant use of **moderate** inhibitors cannot be avoided, reduce brigatinib dose from 180mg to 120mg, from 120mg to 90mg, or from 90mg to 60mg.
    - After discontinuation of **strong or moderate** CYP3A inhibitor, resume brigatinib at dose that was tolerated prior to the initiation of the CYP3A inhibitor.
- Do not administer with strong CYP3A inducers as concurrent use may decrease brigatinib concentration and/or efficacy.
- Avoid co-administration with moderate CYP3A inducers as concurrent use may decrease brigatinib concentration and/or efficacy.
    - If concomitant use cannot be avoided, increase brigatinib dose as follows: after 7 days at current tolerated dose, increase brigatinib dose in 30mg increments, up to a maximum of 2x the brigatinib dose that was tolerated prior to start of inducer.
    - After discontinuation of the moderate CYP3A inducer, resume brigatinib at the dose that was tolerated prior to the initiation of the inducer.
- Monitor closely when co-administered with substrates of CYP3A, PXR, P-gp, BCRP, OCT1, MATE1, and MATE2K with narrow therapeutic indices. Concurrent use may affect substrate efficacy or toxicity.
- Avoid if possible co-administration with agents that decrease heart rate. If concomitant use cannot be avoided, monitor heart rate more frequently.
- Use non-hormonal methods of contraception, since the efficacy of hormonal contraceptives may be decreased due to ↑ metabolism.

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H - Drug Administration and Special Precautions

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

Administration

- Administer with or without food.
- Tablets should be swallowed whole; do not crush or chew.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be given; administer the next dose at the regularly scheduled time.
- Store at 15°C to 30°C.

Contraindications

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions

- Caution in patients with bradycardia (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, congestive heart failure or on medications leading to bradycardia.
- Patients with a history of ILD or drug-induced pneumonitis were excluded from clinical trial.
- Brigatinib contains lactose; carefully consider use in patients with lactose intolerance, hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- Patients should avoid prolonged sun exposure while taking brigatinib and for at least 5 days after treatment discontinuation. A broad-spectrum UVA/UVB sun screen and lip balm (SPF ≥30) should be used.
- Caution with driving or using machinery as visual disturbances, dizziness, and fatigue may occur with treatment.

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
  Documented in animal studies with male animals

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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

- Heart rate and blood pressure; Baseline, after 2 weeks and at least monthly during treatment; more frequently in patients receiving medications known to cause bradycardia.
- Liver Function Tests; Baseline, every 2 weeks for the first 3 months of treatment then as clinically indicated.
- Lipase, amylase, CPK, fasting serum glucose; Baseline, regularly and as clinically indicated.
- Clinical toxicity assessment for fatigue, visual disturbances, pulmonary, dermatological, GI and musculoskeletal effects; At one week (pulmonary) and 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; drug administered by patient or caregiver

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K - References

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

Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. J Thorac Oncol 2021 Dec;16(12):2091-108.

Camidge DR, Kim HR, Ahn MJ. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018 Nov 22;379(21):2027-39.

Kim D, Tiseo M, Ahn M, et al. Brigatinib in patients With crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol 2017; 35:2490-2498.

PEBC Advice Documents or Guidelines

- Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH(CCO) Joint Guideline Update

July 2024 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

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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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