

BC Cancer Protocol Summary for Treatment of Chronic Myeloid Leukemia Using Bosutinib

Protocol Code

LKCMLB

Tumour Group

Leukemia

Contact Physician

Dr. Donna Forrest

ELIGIBILITY:

- Chronic or accelerated Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant to at least two prior lines of TKI
- Chronic or accelerated Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) intolerant to iMAtinib, niLOtinib and daSATinib
- Good performance status
- May be used in combination with hydroxyurea, and/or predniSONE.

EXCLUSIONS:

- Patients who have a hypersensitivity to this drug or to any of its components (includes PEG, povidone and polyoxamer 188).
- Do not use bosutinib in patients with a known history of long QT syndrome or with a persistent QT interval of greater than 480 ms
- Do not use bosutinib in cases of uncorrected hypokalemia or hypomagnesemia
- Do not use bosutinib in hepatically impaired patients at baseline. Metabolism of bosutinib is mainly hepatic and clinical trials excluded patients with ALT and/or AST greater than 2.5 (or greater than 5, if related to disease) x ULN range and/or bilirubin greater than 1.5 x ULN range. Higher risk of QT prolongation has been seen in patients with declining hepatic function.

TESTS:

- **Baseline:** CBC & Diff, ALT, total bilirubin, creatinine, urea, sodium, potassium, magnesium, calcium, phosphorous, serum lipase, body weight, bone marrow examination for cytogenetic analysis, FISH, RT-PCR (for BCR/ABL transcripts), BCR-ABL mutational analysis and ECG
- **Baseline:** (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- **If clinically indicated:** HBV viral load

Monitoring for disease progression:

- Peripheral blood QPCR (for BCR/ABL transcripts): every 3 months until MMR achieved and maintained for at least 12 months, then QPCR (for BCR/ABL transcripts) is measured every 6 months
- Bone marrow aspirate and biopsy: at diagnosis, then as clinically indicated

Monitoring for dose modifications:

CBC & Diff, Platelets weekly for the first month

Months 1-3:

- CBC & Diff, ALT, [total](#) bilirubin, serum creatinine, uric acid, sodium, potassium, magnesium, calcium, phosphorous, serum lipase monthly for the first 3 months

After 3 months:

- CBC & Diff, creatinine, uric acid monthly.
- ALT, [total](#) bilirubin every 3 months or as clinically indicated (in patients with transaminase elevations, perform hepatic enzyme tests more frequently)
- Sodium, potassium, magnesium, calcium, phosphorous, serum lipase every 3 months or as clinically indicated
- ECG should be repeated seven days after start of treatment and as clinically indicated, including seven days after dose changes.
- Bone density as clinically indicated [patients with endocrine abnormalities (e.g. hyperparathyroidism) and/or severe osteoporosis should be monitored closely for changes in bone and mineral abnormalities]

PREMEDICATIONS:

- Antiemetic protocol for low-moderate [emetogenic](#) chemotherapy protocols (see SCNAUSEA).

SUPPORTIVE MEDICATIONS:

- [Moderate risk of hepatitis B reactivation](#). If HBsAg or HBcoreAb positive, [follow hepatitis B prophylaxis as per SCHBV](#).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
bosutinib	500 mg once daily	PO Take with food

- Continue until disease progression or until no longer tolerated

	Dose Levels			
	+1	0 (Starting Dose)	-1	-2
bosutinib	600 mg once daily*	500 mg once daily	400 mg once daily	300 mg once daily

* may be considered in patients with less than or equal to grade 2 adverse effects, AND did not reach complete hematological response by 8 weeks or complete cytogenetic response by 12 weeks.

DOSE MODIFICATIONS for toxicity:

Blood counts (x 10 ⁹ /L) / Toxicity while on Treatment	Action	Dose at restart
ANC less than 1.0 and/or Platelets less than 50	If not related to leukemia, hold until ANC equal or greater than 1 and Platelets greater than or equal to 50	If recovery in less than 2 weeks, restart at same dose. If recovery greater than 2 weeks, upon recovery, restart with ↓ 1 dose level. If cytopenia recurs, ↓ 1 dose level upon recovery.
Increased serum lipase + abdominal symptoms	Hold and investigate. Discontinue if pancreatitis is confirmed.	N/A
Liver transaminases greater than 5 x ULN	Hold until recovery to less than or equal to 2.5 x ULN	↓ 1 dose level Consider discontinuing if recovery takes greater than 4 weeks.
Liver transaminases greater than or equal to 3 x ULN (ALP 2 x ULN) AND bilirubin greater than 2 x ULN	Discontinue	N/A

Blood counts (x 10 ⁹ /L) / Toxicity while on Treatment	Action	Dose at restart
Grade 3 or 4 Fluid retention	Hold until less than or equal to grade 1, or Consider discontinuation depending on severity	↓ 1 dose level or N/A
Grade 3 or 4 Diarrhea (≥ 7 bowel movements over baseline)	Hold until less than or equal to grade 1, manage with antidiarrheals and/or fluid replacement.	↓ 1 dose level
Other clinically significant	Hold until less than or equal to grade 1	↓ 1 dose level. May consider ↑
Falls in creatinine clearance, renal failure	See table under renal impairment	See table under renal impairment

Hepatic Dysfunction:

Bosutinib is contraindicated in patients with hepatic impairment at baseline, as higher risk of QT prolongation has been observed in these patients. Clinical studies excluded patients with LFTs greater than 2.5 x ULN (or greater than 5 x ULN, if disease-related) and/or bilirubin greater than 1.5 x ULN. Refer to dose modifications above for hepatic toxicity during treatment.

Renal Dysfunction:

Bosutinib exposure is increased in moderate to severe renal impairment; reduced starting doses are recommended. Patients with serum creatinine greater than 1.5 x ULN were excluded from clinical trials.

Creatinine Clearance (mL/min)	Starting Dose
greater than 50	No change
30 to 50	400mg daily
less than 30	300mg daily

PRECAUTIONS:

1. **Diarrhea:** is the most frequent adverse event and should be managed early with supportive care, including antidiarrheals and/or fluid replacement, or dose modification. Diet changes: Take bosutinib with food, avoid lactose-containing products, alcohol, laxatives/stool softeners, spicy or fatty foods and caffeine.

2. **Bone marrow suppression**, especially neutropenia, thrombocytopenia, and anemia. Fever or other evidence of infection must be assessed promptly and treated aggressively
3. Fluid retention, exhibiting as **pericardial effusion**, **pleural effusion**, and **pulmonary/peripheral edema** has been reported with bosutinib. Weigh patients regularly and monitor for signs and symptoms of fluid retention; management may include dose interruption, reduction, and/or discontinuation as well as standard-of-care treatment (e.g., diuretics).
4. **Hepatic impairment** and increases in ALT/AST have occurred with bosutinib. Transaminase elevations usually occur within the first 3 months of treatment. Dose interruption/reduction and/or discontinuation may be necessary.
5. **Elevated lipase** and acute **pancreatitis** have been reported; use caution in patients with a history of pancreatitis. If patients develop elevated lipase with abdominal symptoms, interrupt treatment until pancreatitis is ruled out. MSP will only pay for either lipase or amylase. Serum lipase has a slightly higher sensitivity for acute pancreatitis, and elevations occur earlier and last longer as compared with elevations in amylase.
6. **QT Prolongation**: Additional caution should be used in patients who are at risk for QTc interval prolongation, based on their baseline ECG, medical conditions such as thiamine deficiency, or use of medications that may predispose them to QTc interval prolongation.
7. Patients with **coagulation dysfunction/platelet disorders** may be at higher risk of bleeding events. Additional caution should be used in patients who are at an increased risk for bleeding, including those receiving anticoagulant medications such as low molecular weight heparin, unfractionated heparin, warfarin, or antiplatelet therapy such as abciximab, ASA, clopidogrel, dipyridamole, eptifibatide, ticlopidine, etc.
8. **Hepatitis B Reactivation**: See [SCHBV protocol](#) for more details.
9. Exercise caution in patients with recent or ongoing **clinically significant GI disorders**, preexisting diarrhea or conditions that predispose to diarrhea, fluid retention or with previous history of pancreatitis.
10. **Pregnancy/Lactation/Pediatrics**: There is positive evidence of human fetal risk. If bosutinib is used during pregnancy, the patient should be advised of the potential serious risks to a developing fetus.
11. **Drug interactions**: Potent and Moderate CYP 3A4 **inhibitors** may increase bosutinib exposure; avoid concomitant use. Use caution if mild CYP3A inhibitors are used concomitantly. Potent and Moderate CYP 3A4 **inducers** may decrease bosutinib exposure; avoid concomitant use. Use caution if mild CYP3A inhibitors are used concomitantly. **Protein pump inhibitors** ↓ bosutinib exposure (up to 74%) and/or efficacy - pH dependent solubility. **Caution**: consider using short-acting antacids and separate admin times (morning and evening). Drugs that **prolong**

QT/QTc interval or disrupt electrolyte levels should be avoided if possible. Periodic monitoring of ECG and electrolytes is suggested. Bosutinib is a substrate and inhibitor of P-glycoprotein (P-gp); clinical significance is unknown. Avoid grapefruit and grapefruit juice, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 for duration of treatment with bosutinib.

Call Dr. Donna Forrest or tumour group delegate at (604) 875-4863 with any problems or questions regarding this treatment program.

References:

1. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood* 2011;118(17):4567-76.
2. Pfizer drug monograph for Bosulif (bosutinib), July 14, 2014
3. Ault PS, et al, Bosutinib Therapy in patients with chronic myeloid leukemia: practical considerations for management of side effects, *J Adv Pract Oncol* 2016;7(2):160-175.
4. Cancer Care Ontario formulary, Bosutinib, June 2016
5. BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC (imatinib mesylate), TASIGNA (nilotinib), BOSULIF (bosutinib), SPRYCEL (dasatinib) ICLUSIG (ponatinib hydrochloride)] – Risk of Hepatitis B Reactivation. Health Canada, May 4, 2016.