BC Cancer Protocol Summary for Treatment of Chronic Myeloid Leukemia using Asciminib

Protocol Code	*LKCMLA*
Tumour Group	*Leukemia*
Contact Physician	*Dr. Donna Forrest*

ELIGIBILITY:

Patients must have:
- Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in chronic phase, and
- Resistant or intolerant to at least two prior lines of tyrosine kinase inhibitor (TKI) therapies.

Patients should have:
- Good performance status

Notes:
- May be used in combination with dexamethasone, hydroxyUREA, interferon, or predniSONE

EXCLUSIONS:

Patients must not have:
- Accelerated or blast phase CML, or
- T315I or V299L mutation.

CAUTIONS:

- Patients with history of QT prolongation or cardiac disease, and
- Concurrent therapy with other QT prolonging medications (correct electrolyte disturbances prior to treatment).

TESTS:

- **Baseline:** CBC & Diff, ALT, total bilirubin, serum creatinine, BUN, sodium, potassium, magnesium, calcium, phosphorous, lipase, uric acid, body weight, ECG, and blood pressure measurement.
- **Baseline if clinically indicated:** FISH, RT-PCR (for BCR/ABL transcripts), BCR-ABL mutational analysis, bone marrow examination for cytogenetic analysis
- **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: ALT, HBV viral load (see protocol SCHBV)

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: as clinically indicated

Monitoring for dose modifications: CBC & Diff, creatinine, uric acid, sodium, potassium, magnesium, calcium, phosphorous, lipase, blood pressure

  - First month: every 2 weeks (physician will be responsible to check and advise patient on dose adjustment)
  - Months 2 and 6: every month
  - After 6 months: every month or every 3 months if clinically indicated
- Albumin, triglycerides, cholesterol, creatine kinase, ALT, total bilirubin, alkaline phosphatase every 3 months if clinically indicated
- ECG should be repeated seven days after start of treatment and as clinically indicated thereafter

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic 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
asciminib	40 mg twice daily* (Total daily dose = 80 mg)	PO

* May be given as 80 mg once daily

- Continuously until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Dose levels:

Asciminib Starting Dose	Dose Level -1
40 mg twice daily	20 mg twice daily
80 mg once daily	40 mg once daily

1. Hematological

ANC ($x10^9$/L)		Platelets (x 10^9/L)	Asciminib Dose Modification
Greater than or equal to 1.0	and	Greater than or equal to 50	No dose adjustment
Less than 1.0	and/or	Less than 50	Hold until ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 50 x 10^9/L ▪ If recovery within 2 weeks: Restart at starting dose. For recurrence, restart at Dose Level -1 ▪ If more than 2 weeks to recover: Restart Dose Level -1

2. Lipase and/or amylase elevation

Lipase or Amylase	Asciminib Dose Modification
Asymptomatic elevation greater than 2 x ULN	Hold until less than 1.5 x ULN, then restart at Dose Level -1. If recurrence at reduced dose, discontinue. If no resolution, discontinue asciminib.
Any elevation with abdominal symptoms	Hold

3. **Hypersensitivity:** reactions occur in approximately 32% of patients, with grade 3 or 4 reactions in 2% of patients. Symptoms include rash, edema, and bronchospasm. Monitor patient and initiate supportive treatment as indicated. Hold asciminib for symptoms grade 3 or higher, until recovered to grade 1 or less. Re-challenge at reduced dose may be appropriate in some cases per physician discretion. Discontinue if hypersensitivity event recurs or persists.

4. **Hypertension:** temporary suspension of asciminib is recommended for blood pressure greater than or equal to 160 mmHg systolic or 100 mmHg diastolic. Manage hypertension with standard antihypertensive therapy as necessary.

5. **Non-hematologic**

Other Adverse Reaction	Asciminib Dose Modification
Grade 3 or higher	Hold until resolved to Grade 1 or lower, then restart at reduced dose per table, above. If not resolved, permanently discontinue

PRECAUTIONS:

1. **Cardiovascular toxicity:** including hypertension, ischemic stroke, fatal arterial thromboembolism, heart failure, and arrhythmias including QTc prolongation have been reported with asciminib treatment.
   Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities.
2. **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. Lipase and amylase cannot be ordered together at the same time. Serum lipase has a slightly higher sensitivity for acute pancreatitis, and elevations occur earlier and last longer as compared with elevations in amylase.
3. **Bone marrow suppression**, including thrombocytopenia, neutropenia, and anemia have occurred during treatment with asciminib. Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Hypersensitivity** reactions are reported. Asciminib treatment may need to be held, dose may need to be reduced or discontinued based on severity. See dose modifications, above.

5. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
6. **Drug interactions**: CYP 3A4 inhibitors may increase asciminib exposure. Dose adjustment is not required for concurrent use of CYP 3A4 inhibitors with asciminib 80 mg daily, as the change in AUC is not considered clinically meaningful. Strong CYP3A4 inducers given concurrently with asciminib could reduce asciminib exposure, clinical significance is unknown. Asciminib is an inhibitor of P-glycoprotein (P-gp), CYP 2C9, and CYP 2C8. Concomitant administration with a P-gp substrate or a substrate of these enzymes may increase the plasma concentration of the substrate; monitor for toxicity of the substrate.
   Drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible.

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

References:

1. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021;138(21):2031-2041
2. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019;381(24):2315-2326.
3. Asciminib (Scemblix) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2022;2(8):1-18.