

BC Cancer Protocol Summary for Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using PONatinib

Protocol Code	<i>ULKCMLP</i>
Tumour Group	<i>Leukemia</i>
Contact Physician	<i>Dr. Donna Forrest</i>

ELIGIBILITY:

Patients must have:

- Chronic, accelerated or blast phase chronic myelogenous leukemia (CML), or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) resistant to at least two prior lines of TKI,
- Chronic or accelerated CML intolerant to iMAtinib, niLOtinib, daSATinib and bosutinib,
- Blast phase CML or Philadelphia positive ALL intolerant of iMAtinib and daSATinib,
- CML or Ph+ ALL that is T315I mutation positive, independent of previous TKI therapy, or
- Chronic phase CML in patients previously intolerant to asciminib, and
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to <https://cap.phsa.ca/>).

Patients should have:

- Good performance status

Note: May be used in combination with hydroxyurea, and/or predniSONE.

EXCLUSIONS:

Patients must not have:

- Hypersensitivity to this drug or to any of its components (contains lactose monohydrate),
- Unmanaged cardiovascular risk factors, including uncontrolled hypertension, history of myocardial infarction, prior revascularization or stroke, or peripheral vascular disease unless the potential benefit outweighs the risk, or
- Inadequate hydration and with uncorrected high uric acid levels

TESTS:

- **Baseline:** CBC & Diff., platelets, ALT, **total** bilirubin, serum creatinine, BUN, **sodium, potassium**, magnesium, calcium, phosphorous, serum lipase*, uric acid, body weight, bone marrow examination for cytogenetic analysis, FISH, RT-PCR (for BCR/ABL transcripts) and BCR-ABL mutational 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, HBcoreAb
- **Baseline and at each visit:** Clinical toxicity assessment for bleeding, infection, thromboembolism, fluid retention (including regular weight monitoring), hypertension, cardiac and GI effects, tumor lysis syndrome, ocular and neurologic effects.
- **Baseline, at 3 months and as clinically indicated:** Echocardiography
- **Baseline and as clinically indicated:** ECG
- **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:**

Months 1-3:

 - CBC & Diff, **platelets**, serum lipase* every 2 weeks for the first 3 months
 - ALT and **total bilirubin** monthly and as clinically indicated
 - Blood pressure: baseline and regular

After 3 months:

 - CBC & Diff, **platelets** monthly
 - ALT and **total bilirubin** monthly and as clinically indicated (in patients with transaminase elevations, perform hepatic enzyme tests more frequently)
 - **Sodium, potassium**, magnesium, calcium, phosphorous, serum creatinine, uric acid, **sodium, potassium**, magnesium, calcium, phosphorous, serum lipase periodically or as clinically indicated (see pancreatitis under Precautions)

PREMEDICATIONS:

- Antiemetic protocol for *emetogenic potential*: low chemotherapy protocols. (see SCNAUSEA).

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

TREATMENT:

Prescribing physician must complete certification with the **ICLUSIG Controlled Distribution Program** (tel 1-855-552-7423, www.icluigcdpca). Before starting treatment, the cardiovascular status should be assessed and cardiovascular risk factors should be actively managed.

Drug	Dose	BCCA Administration Guideline
PONAtinib	45 mg once daily	PO

- Continue until disease progression or until no longer tolerated
- Consider discontinuation if a hematologic response has not been achieved by 3 months.
- Consider reducing the dose from 45 mg to 15 mg once daily for chronic phase CML patients who have achieved a MCR (major cytogenetic response).

DOSE MODIFICATIONS for toxicity:

Dose levels for toxicity

	0 (Starting Dose)	-1	-2
PONAtinib	45 mg once daily	30 mg once daily	15 mg once daily

- Doses reduced for toxicity may be re-escalated after toxicity has resolved, if clinically appropriate.

Toxicity while on Treatment	Severity - Blood counts (x 10 ⁹ /L)	Dose at restart
Myelosuppression	<p>ANC less than 1 and/or Platelets less than 50</p> <p>If not related to leukemia, Hold* until ANC greater than or equal to 1.5 and Platelets greater than or equal 75</p>	<p>1st occurrence: Restart at same dose</p> <p>2nd occurrence: Restart at ↓ 1 dose level from previous dose</p> <p>3rd occurrence: Restart at ↓ 1 dose level from previous dose</p>
Suspected Pancreatitis: Increased serum lipase +/- abdominal symptoms	Amylase/lipase greater than 2 X ULN and asymptomatic	Hold until recovery to less than or equal to grade 1 then restart at ↓ 1 dose level from previous dose
	Amylase/Lipase elevations and symptomatic	Hold and investigate for pancreatitis
	Grade 3 pancreatitis	Hold until recovery to less than grade 2 then restart at ↓ 1 dose level from previous dose
	Grade 4 pancreatitis	Discontinue
Liver transaminases	AST/ALT greater than 3 x ULN	Hold until recovery to less than or equal to grade 1 then restart at ↓ 1 dose level from previous dose
	AST/ALT greater than or equal 3 x ULN AND total bilirubin greater than 2 x ULN AND ALP less than 2 x ULN	Discontinue PONAtinib
Cardiac	Arterial or venous thromboembolic event	Discontinue unless benefit outweighs risk
	LVEF less than 50% and greater than 10% below baseline and asymptomatic	Hold until recovery. Discontinue if does not resolve within 4 weeks or is greater than or equal to grade 3.
	Symptomatic CHF	Discontinue
	Arrhythmias	Hold and investigate
	Hypertension	Treat to normalize blood pressure. Hold if not medically controlled.
	Blurred or decreased vision	Hold until recovery. Discontinue if does not resolve within 4 weeks or is greater than or equal to grade 3.

Toxicity while on Treatment	Severity - Blood counts (x 10 ⁹ /L)	Dose at restart
Fluid retention		Hold, reduce or discontinue PONAtinib as clinically indicated.

- Hepatic Dysfunction:** Caution is recommended when administering PONAtinib to patients with hepatic impairment. The recommended starting dose is 30mg once daily in patients with hepatic impairment (Child-Pugh A, B & C)
- Renal Dysfunction:** Renal excretion is not a major route of PONAtinib elimination. PONAtinib has not been studied in patients with renal impairment. Caution is recommended when administering PONAtinib to patients with estimated creatinine clearance of less than 50 mL/min, or end stage renal disease.
- Dosage in Elderly:** Patients aged 65 and older were more likely to experience reduced efficacy and increased adverse effects compared to younger patients. The dose should be selected with caution given the greater frequency of decreased hepatic, renal or cardiac function, other diseases and drug therapies in older patients.

PRECAUTIONS:

- Vascular Occlusion** (arterial and venous thrombosis and occlusions). In clinical trials, serious treatment-emergent arterial thrombosis (cardiovascular, cerebrovascular, and peripheral vascular) and occlusions were seen in 14% of the patients including fatal myocardial infarction, fatal cerebral infarction, stroke, disseminated intravascular coagulation, and arterial stenosis sometimes requiring urgent revascularization procedures. Some of these events occurred within 2 weeks of starting treatment. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or consider discontinuation in patients who develop arterial thrombotic events. Monitor blood pressure at baseline and regular; ensure hypertension is controlled to minimize risk of arterial thromboembolism.
- Heart failure** (in some cases, fatal), including left ventricular dysfunction and ejection fraction decreases, occurred in 8% of patients, 5% of which were serious.
- Hemorrhage events** (some fatal) including intracranial hemorrhage, hemorrhagic gastritis, (fatal), hemorrhagic cerebral infarction (fatal). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia.
- Hepatotoxicity** (including fatal acute hepatic failure) has been reported. Monitor hepatic function prior to and during treatment. Consider dose interruption followed by dose reduction or discontinuation in patients with hepatotoxicity.
- Myelosuppression** (thrombocytopenia, neutropenia, and anemia).
- Pancreatitis** (7%) and elevations in amylase (2% grade 3 or greater) or lipase (12% grade 3 or greater) have been reported. 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.

7. **HBV infection reactivation risk:** Risk of Hepatitis B Reactivation can occur in chronic HBV carriers after they receive BCR-ABL TKIs. All patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
8. **Pregnancy:** Women of childbearing should be advised of the potential risk to a fetus, and advised not to become pregnant. Men should be advised not to father a child during treatment.
9. **Drug interactions:** Ponatinib is primarily metabolized by CYP3A4. Caution should be exercised and a reduction of the starting dose to 30 mg should be considered with concurrent use of ponatinib and strong CYP3A4 inhibitors. Potent and moderate CYP 3A4 **inducers** may decrease ponatinib exposure. Avoid strong CYP3A4 inducers if possible. If not possible, monitor for reduced efficacy of ponatinib. Ponatinib is an inhibitor of P-glycoprotein (P-gp) and BCRP. Close clinical surveillance is recommended when ponatinib is administered with medicinal product substrates of p-gp or BCRP. Avoid grapefruit and grapefruit juice, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 for duration of treatment. **Protein pump inhibitors:** Ponatinib may be administered concurrently with proton pump inhibitors or other drugs that raise gastric pH without the need for adjustment of ponatinib dose or separation of administration.

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, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013;369(19):1783-96.
2. ARIAD Pharmaceuticals Inc. Iclusig product monograph. March 2015.
3. 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.
4. Ponatinib drug monograph, Cancer Care Ontario.