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

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

ELIGIBILITY:

- Patients with **chronic phase CML**, who are resistant or intolerant to iMAtinib:
  - No complete hematologic response (CHR) after 3 months of iMAtinib
  - Lack of any cytogenetic response after 3 months of iMAtinib
  - Lack of major cytogenetic response (MCR/1 log reduction bcr-abl) after 6 months of iMAtinib
  - Lack of complete cytogenetic response (CCR/2 log reduction bcr-abl) after 12 months of iMAtinib
  - Cytogenetic relapse on iMAtinib (loss of CCR/less than 2 log or MCR/less than 1 log or any Ph+ increase greater than or equal to 30%)
  - Loss of CHR
  - Progression to accelerated phase CML

- Patients with **accelerated phase CML**, who are resistant to iMAtinib. No hematologic response (HR) after a minimum of 4 weeks of iMAtinib
  - Lack of any cytogenetic response after 6 months of iMAtinib
  - Progression with greater than 50% increase in WBC, blast count, platelets or basophils during iMAtinib therapy
  - Progression from chronic phase to accelerated phase during iMAtinib therapy

- Patients with **accelerated phase CML,** who are **intolerant** to iMAtinib, including patients with:
  - greater than or equal to Grade 3 non-hematologic toxicity, not responding to symptomatic treatment or temporary dose reduction
  - Grade 4 hematologic toxicity lasting greater than 7 days
  - Sustained, highly symptomatic Grade 2 non-hematologic toxicity
- Patients with intolerance to daSATinib (grade 3 or 4 non-hematologic toxicity). Note: sequential use between daSATinib and nilotinib for disease progression is not allowed unless a specific kinase domain mutation is demonstrated mediating resistance to one second generation TKI but maintains sensitivity to the other second generation TKI.
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to https://cap.phsa.ca/).
- May be used in combination with busulfan, dexamethasone, hydroxyUREA, interferon, melphalan or predniSONE

EXCLUSIONS:

- Patients with **blast phase CML, including Ph+ acute lymphoblastic leukemia (ALL)** patients:
- Patients with uncorrected hypokalemia, and/or hypomagnesemia
- 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, such as amiodarone, arsenic, chloroquine, chlorpromazine, clarithromycin, disopyramide, domperidone, droperidol, erythromycin, haloperidol, ibutilide, methadone, MOXIfloxacin, pentamidine, pimozide, procainamide, quinine, quinidine, sotalol, and so on.

TESTS:

- Baseline: CBC and diff., platelets, ALT, alkaline phosphatase, bilirubin, GGT, serum creatinine, BUN, Lipase, body weight, bone marrow examination for cytogenetic analysis, FISH, RT-PCR, 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, HBcoreAb
- *Monitoring for disease progression* (www.healthcareprofessionals.leukemiabmtprogram.com/CMG/CML/Treatment.aspx)
  - CBC & diff, platelets: weekly until **CHR** then monthly; after 6 months and if patient is clinically stable, may increase interval to every 3 months at the physician's discretion
  - Serum creatinine, uric acid, ALT, bilirubin: weekly until stable then monthly; after 6 months and if patient is clinically stable, may increase interval to every 3 months at the physician's discretion
  - Peripheral blood QPCR: every 3 months until **MMR** achieved and maintained for at least 12 months, then QPCR is measured every 6 months
  - Bone marrow aspirate and biopsy: at diagnosis, then as clinically indicated
- *Monitoring for dose modifications*: CBC & diff, Platelets, ALT, Bilirubin, lipase, random glucose
  - first month: every 1-2 weeks (physician will be responsible to check and advise patient on dose adjustment)
  - months 2-6: every month
  - after 6 months: every 3 months
- ECG should be repeated seven days after start of treatment and as clinically indicated, including seven days after dose changes.

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic 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:

Drug	Dose	BC Cancer Administration Guideline
niLOtinib	400 mg bid	PO On an empty stomach

DOSE MODIFICATIONS:

1. **Hematological:**[2]

ANC (x10^9/L)	Dose	Platelets (x10^9/L)	Dose
greater than or equal to 1.0	100%	greater than or equal to 50	100%
less than 1.0	Hold until ANC greater than or equal to 1: • if greater than or equal to 1 within 2 weeks: continue at 400 mg bid • if less than 1 for greater than 2 weeks: reduce to 400 mg once daily	less than 50	Hold until PLT greater than or equal to 50: • if greater than or equal to 50 within 2 weeks: continue at 400 mg bid • if less than 50 for greater than 2 weeks: reduce to 400 mg once daily

2. Non-Hematological:

Lipase	Dose (PO)
greater than or equal to 2 times ULN	Hold treatment, monitor serum lipase: ▪ when lipase returns to less than or equal to 1.5 times ULN, resume treatment at niLOtinib 400 mg once daily
QT Prolongation	
QT greater than 480 msec	Hold treatment, monitor and correct potassium and magnesium levels. • If QTcF returns to less than 450 msec and to within 20 msec of baseline within 2 weeks: continue at 400 mg twice daily • If QTcF returns to 450-480 msec: reduce dose to 400 mg once daily • If QTcF is greater than 480 msec after dosage reduction to 400 mg once daily, discontinue therapy
Clinically-significant moderate or severe non-hematological toxicity	Hold treatment, upon resolution of toxicity: • resume at 400 mg once daily; may escalate back to 400 mg twice daily if clinically appropriate

3. **Hepatic Dysfunction:** Despite the lack of clinical trial data with niLOtinib in patients with hepatic impairment, niLOtinib should be used with caution in patients with moderate to severe hepatic dysfunction. Nilotinib is mainly metabolized through the liver, and therefore exposure to niLOtinib is expected to increase in patients with hepatic impairment.

Hepatotoxicity during treatment	
Bilirubin greater than 3 times ULN	Hold treatment, monitor bilirubin, resume treatment at 400 mg once daily when bilirubin returns to less than or equal to 1.5 times ULN
ALT or AST greater than 5 times ULN	Hold treatment, monitor transaminases, resume treatment at 400 mg once daily when ALT or AST returns to less than or equal to 2.5 times ULN

4. **Renal Dysfunction:** Not studied in patients with serum creatinine greater than 1.5 times ULN, however, niLOtinib and its metabolites have minimal renal excretion; dosage adjustments for renal dysfunction may not be needed. The effect of dialysis on the pharmacokinetics of niLOtinib has not been studied.

PRECAUTIONS:

1) **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. **Bone marrow suppression**, especially neutropenia, thrombocytopenia, and anemia is more common in patients with advanced CML or Ph+ ALL, than in patients with chronic phase CML. Management includes dose reduction, interruption or (rarely) discontinuation of niLOtinib.
2) **Pancreatitis:** Use with caution in patients with a history of pancreatitis, may cause dose-limiting elevations of serum lipase and amylase; lipase increased (grades 3-4: 15-17%), monitor. 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.
3) **Electrolyte Abnormalities:** The use of niLOtinib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Electrolyte abnormalities must be corrected prior to initiating niLOtinib and these electrolytes should be monitored periodically during therapy.
4) **Diarrhea:** May occur in about 19-22% of patients. Sources of infection should be ruled out and standard supportive care and antidiarrheal treatment provided, when indicated for the management of diarrhea. Treatment with niLOtinib should be withheld for patients with severe diarrhea, until the condition improves or resolves.
5) **Other common adverse events (greater than 10%):** These include headaches (21-31%), nausea (18-31%), fatigue (16-28%), rash (28-33%),pruritus (20-30%), fever (14-24%), constipation (18-21%), cough (13-17%), arthralgia (16-18%), limb pain (13-16%), myalgia (14%). Treatment with niLOtinib should be withheld for patients with severe events, until their condition improves or resolves.
6) **Cardiotoxicity:** QT interval prolongation may occur in 1-10% of patients treated with niLOtinib. Therefore, niLOtinib should be used with caution in patients with pre-existing or those predisposed to QTc prolongation. Additional care should also be taken in patients experiencing or at risk for hypokalemia, hypomagnesemia, congenital long QT syndrome, those taking anti-arrhythmic medications, cumulative high-dose anthracycline therapy, or

other medications that may induce QT prolongation (please also refer to the section under Exclusions).

7) **Pregnancy:** Women of childbearing potential must be advised to use highly effective contraception during treatment.
8) **Peripheral Arterial Occlusive Disease (PAOD):** There have been recent reports suggesting an increased incidence of PAOD in patients receiving niLOtinib therapy. Patients with symptoms of peripheral vascular disease (claudication, stroke, MI, etc.) should be promptly evaluated and if PAOD is confirmed, niLOtinib therapy should be discontinued.
9) **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.
10) **Drug interactions**: Nilotinib inhibits CYP3A4 enzyme, which may result in a reduction in the clearance of CYP3A4 metabolized drugs (e.g., quinidine). Similarly, *CYP3A4 inhibitors* (e.g., erythromycin) may increase niLOtinib's concentration. *Concomitant Strong CYP3A4 Inhibitors*: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g.,ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit products may also increase serum concentrations of niLOtinib and should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with niLOtinib be interrupted. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, 400 mg once daily (a dose reduction to 1/2 of the original daily dose) is predicted to adjust the niLOtinib AUC to the AUC observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the niLOtinib dose is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors.Conversely, *coadministration of CYP3A4 inducers* (e.g., phenytoin) may reduce niLOtinib's concentration and lead to a subtherapeutic effect

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

References:

1. TASIGNA® product monograph. Dorval, Quebec: Novartis; 5 September 2009.
2. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood 2007;110(10):3540-6.
3. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. Blood 2008;111(4):1834-9.