BC Cancer Protocol Summary for Therapy of Relapsed or Refractory FLT3+ Acute Myeloid Leukemia using Gilteritinib

Protocol Code	*ULKAMLGIL*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. David Sanford*

ELIGIBILITY:

- Relapsed or refractory acute myeloid leukemia (AML) with FLT3 mutation confirmed on most recent bone marrow biopsy with active disease:
  - Mutations in internal tandem duplication (FLT3-ITD), or
  - Mutations in the tyrosine kinase domain (FLT3-TKD/D835, FLT3- TKD/I836)
- A BC Cancer "Compassionate Access Program" request with appropriate clinical information for each patient must be approved prior to treatment.

EXCLUSIONS:

- Therapy-related AML (t-AML)
- Acute promyelocytic leukemia
- Pregnancy

TESTS:

- Baseline: CBC & Diff, sodium, potassium, calcium, magnesium, phosphate, urea, creatinine, bilirubin (total and direct), GGT, alkaline phosphatase, LDH, ALT, albumin, creatine kinase, lipase, serum HCG (for women of child bearing potential)
- 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
- Bone marrow aspirate and biopsy is recommended on cycle 2 day 1 to assess response. In patients who are not in CR at this time, this should be repeated every 1-2 months to assess remission status until CR is documented and also if there is suspicion of disease relapse or progression.
- Cycle 1 - weekly: CBC & Diff, sodium, potassium, calcium, magnesium, phosphate, urea, creatinine, bilirubin (total and direct), GGT, alkaline phosphatase, LDH, ALT, albumin, creatine kinase

- Cycle 2 - prior to cycle and on day 15: CBC & Diff, sodium, potassium, calcium, magnesium, phosphate, urea, creatinine, bilirubin (total and direct), GGT, alkaline phosphatase, LDH, ALT, albumin, creatine kinase
- Cycle 3 onwards – prior to each cycle: CBC & Diff, sodium, potassium, calcium, magnesium, phosphate, urea, creatinine, bilirubin (total and direct), GGT, alkaline phosphatase, LDH, ALT, albumin, creatine kinase
- If clinically indicated: lipase, HBV viral load (see protocol SCHBV)
- ECG for QTc monitoring:
  - Cycle 1: Baseline, Days 8 and 15
  - Cycles 2 and 3: before each cycle
  - Cycles 4 onwards: as clinically indicated

PREMEDICATIONS:
- None

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
gilteritinib	120 mg once daily May increase to 200 mg once daily if no response after 1 cycle	PO

One cycle is 28 days

- Consider stopping gilteritinib if no response (PR or better) observed after 6 cycles
- Continue treatment until disease progression or unacceptable toxicity
- Stop gilteritinib one week prior to administration of conditioning chemotherapy for hematopoietic stem cell transplant. Gilteritinib maintenance can be restarted after day +30 following hematopoietic stem cell transplant if engrafted and no severe graft-versus-host-disease (GVHD).

DOSE MODIFICATIONS:

Starting Dose	Dose level -1	Dose level +1
120 mg	80 mg	200 mg

1. Differentiation Syndrome:

Symptoms	Gilteritinib dosing
Fever, dyspnea, rapid weight gain, hypotension, rash, pleural or pericardial effusion, pulmonary or peripheral edema, renal dysfunction	▪ Initiate corticosteroids and hemodynamic monitoring until symptom resolution. ▪ Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. ▪ Resume gilteritinib at same dose when signs and symptoms improve to Grade ≤ 2.

2. QTc Prolongation:

QTc interval*	Gilteritinib dosing
500 ms or higher	▪ Interrupt gilteritinib. ▪ Review patient medications and consider stopping or substituting other QTc prolonging medications where feasible. ▪ Resume gilteritinib at reduced dose when QTc returns to within 30 ms of baseline or below or equal to 480 ms.
Increased by greater than 30 ms on Day 8 of Cycle 1	▪ Repeat ECG on Day 9. ▪ If confirmed, consider reducing dose by one level.

* calculated using the Fridericia formula.

3. Pancreatitis:

Hold gilteritinib until pancreatitis is resolved, then resume at reduced dose level.

4. Other Adverse Reactions:

Grade 3/4 toxicity	Hold gilteritinib until toxicity resolves or improves to Grade ≤ 2, then resume at reduced dose level

PRECAUTIONS:

1. **Differentiation syndrome** may be fatal and can include symptoms and clinical findings such as fever, dyspnea, rapid weight gain, hypotension, rash, pleural or pericardial effusion, pulmonary or peripheral edema, and renal dysfunction. Patients may have concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome with gilteritinib has been observed with or without concomitant leukocytosis, occurring as early as day 1 and up to day 82 of therapy. Management includes corticosteroid therapy and hemodynamic monitoring until symptom resolution or therapy interruption for persistent symptoms.
2. **Posterior Reversible Encephalopathy Syndrome (PRES):** PRES has been uncommonly reported with gilteritinib and has resolved with discontinuation. If patients present with headache, seizure, lethargy, confusion, altered mental function, blindness, or other visual or neurological disturbances, hold gilteritinib and other potential culprit medications. Request brain imaging, preferably MRI, to confirm the diagnosis. Discontinue gilteritinib in patients who develop PRES.
3. **QTc interval prolongation:** Increased frequency of QTc prolongation has been observed. ECG monitoring of QTc interval should be undertaken at baseline and periodically during gilteritinib therapy as described above. Use caution in combination with other medications known to prolong the QTc interval. Keep electrolytes within normal limits.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Consider antimicrobial prophylaxis if ANC below 0.5 x 10^9/L.
5. **Drug Interactions:**
   - Strong CYP3A4 inducers (e.g., rifampin) or P-glycoprotein inducers can decrease gilteritinib exposure and concomitant use should be avoided.
   - Strong CYP3A4 inhibitors (e.g. voriconazole, posaconazole) or P-glycoprotein inhibitors can increase gilteritinib exposure and alternatives should be considered where possible. If concomitant use is required, patients should be closely monitored for gilteritinib toxicity, especially during the first week of gilteritinib treatment.
6. **Hepatitis B Reactivation:** See SCHBV protocol for more details.

Call Dr. David Sanford or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or Chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019;381(18):1728-40.
2. Astellas Pharma Canada Inc. XOSPATA® product monograph. Markham, Ontario; 23 December 2019.