BC Cancer Protocol Summary for Treatment of Relapsed or Refractory Pre-B Cell Acute Lymphoblastic Leukemia with Inotuzumab Ozogamicin

Protocol Code	*ULKINOZ*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Yasser Abou Mourad* *Dr. David Sanford*

ELIGIBILITY:

Patients must have:

- Relapsed or refractory pre-B cell acute lymphoblastic leukemia (ALL) with positive CD-22 expression:
  - Philadelphia chromosome positive (Ph+): after at least one standard multi-drug chemotherapy induction and one second-generation or third-generation tyrosine kinase inhibitor
  - Philadelphia chromosome negative (Ph-): after at least one standard multi-drug chemotherapy induction
- Treatment prescribed by Leukemia/BMT Program physicians, and
- BC Cancer "Compassionate Access Program" approval prior to treatment (please refer to https://cap.phsa.ca/).

Patients should have:

- ECOG performance status 0-2
- Total bilirubin less than or equal to 1.5 x upper limit of normal (ULN), ALT less than or equal to 2.5 x ULN, serum creatinine less than or equal to 1.5 x ULN

Note:

- The sequential use of inotuzumab ozogamicin and blinatumomab (ULKBLIN) is funded for relapsed or refractory Philadelphia chromosome negative (Ph-) patients. Patients can receive these agents in any order.
- Patients are eligible for inotuzumab ozogamicin if previously treated with blinatumomab for MRD (ULKMRDBLIN), if all other eligibility criteria are met.
- For patients proceeding to hematopoietic stem cell transplant (HSCT), maximum of 3 cycles will be funded. For patients not proceeding to HSCT, maximum of 6 cycles will be funded.

EXCLUSIONS:

- Burkitt's lymphoma or mixed lineage leukemia
- Clinically significant liver disease such as history of venoocclusive disease (VOD)/ sinusoidal obstruction syndrome (SOS)
- Allogeneic-HSCT less than or equal to 4 months ago

TESTS:

- Baseline and before each treatment: CBC & differential, platelets, bilirubin (total and direct), ALT, alkaline phosphatase, LDH, GGT, albumin, sodium, potassium, magnesium, calcium, phosphate, urea, creatinine, uric acid, amylase, lipase
- Before Day 1: INR, PTT, fibrinogen
- Baseline and if clinically indicated: ECG, bone marrow biopsy, lumbar puncture
- 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

SUPPORTIVE MEDICATIONS:

- cotrimoxazole 1 DS tablet PO BID every Monday and Thursday
- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of inotuzumab ozogamicin treatment and for six months afterwards
- If HSV seropositive, start valACYclovir 500 mg PO BID
- Consider ursodiol for VOD/SOS prophylaxis in high risk patients

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)
- To prevent infusion-related reactions:
  - dexamethasone 20 mg IV 30 minutes prior to inotuzumab ozogamicin
  - diphenhydrAMINE 50 mg PO 30 minutes prior to inotuzumab ozogamicin
  - acetaminophen 650 mg PO 30 minutes prior to inotuzumab ozogamicin
- To prevent tumour lysis syndrome:
  - allopurinol 300 mg PO daily starting on Day 1

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
inotuzumab ozogamicin	<u>Cycle 1:</u> 0.8 mg/m^2 on day 1 0.5 mg/m^2 on days 8* and15* Cycle Length = 21 to 28 days†	IV in 25 to 50 mL NS over 60 minutes Observe for 60 minutes post-infusion
	<u>Cycles 2 - 6:</u>‡ *Patients who have not achieved CR or CRi:* 0.8 mg/m^2 on day 1 0.5 mg/m^2 on days 8* and15* *Patients who have achieved CR or CRi:* 0.5 mg/m^2 on days 1, 8* and 15* Cycle Length = 28 days	

* +/- 2 days (maintain at least 6 days between doses)

† Cycle 1 is 21 days but may extend up to 28 days if patient achieves complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) and/or to allow recovery from toxicity. All subsequent cycles are 28 days.

‡ For patients proceeding to HSCT, repeat for 2-3 cycles (2 cycles recommended; consider third cycle for patients who do not achieve CR/CRi and minimal residual disease (MRD) negativity after 2 cycles).
For patients not proceeding to HSCT, repeat up to 6 cycles maximum.
If CR/CRi not achieved after 3 cycles, discontinue treatment.

DOSE MODIFICATIONS:

- Inotuzumab ozogamicin doses within a treatment cycle (i.e. days 8 and/or 15) do not require interruption due to neutropenia or thrombocytopenia; dosing interruptions within a cycle are recommended for non-hematologic toxicities. If dose is reduced due to inotuzumab ozogamicin-related toxicity, dose should not be re-escalated.

Hematological Toxicity If prior to inotuzumab ozogamicin treatment:	**Dose Modification**
ANC greater than or equal to 1.0 x 10^9/L	Delay next cycle until ANC recovers to greater than or equal to 1.0 x 10^9/L
Platelet count greater than or equal to 50 x 10^9/L*	Delay next cycle until platelet count recovers to greater than or equal to 50 x 10^9/L*
ANC less than 1.0 x 10^9/L and/or Platelet count less than 50 x 10^9/L*	Delay next cycle until at least one of the following: - ANC and platelet count* recover to at least baseline from prior cycle - ANC recovers to greater than or equal to 1.0 x 10^9/L and platelet count recovers to greater than or equal to 50 x 10^9/L* - Stable or improved disease** and ANC and platelet count decreases are due to underlying disease (not considered to be treatment-related)

* Platelet count used for dosing should be independent of transfusion

** Based on most recent bone marrow assessment

1. **Hepatic Toxicity:** Delay next dose until total bilirubin less than or equal to 1.5 x ULN and ALT less than or equal to 2.5 x ULN (unless due to Gilbert's syndrome or hemolysis). If VOD/SOS develops, permanently discontinue inotuzumab ozogamicin.

2. **Infusion-Related Reactions:** Follow SCDRUGRX for immediate clinical management. For life-threatening reactions, permanently discontinue inotuzumab ozogamicin.

3. **Other Non-HematologicToxicity:** If greater than or equal to Grade 2*, then interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.
   *Severity grading according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Duration of Dose Delay and Dose Modification

Duration of Dose Delay Within a Cycle	Dose Modification
Less than 7 days	Maintain a minimum of 6 days between doses
7 days to less than 14 days	Omit next dose within the cycle
14 days to less than 28 days	Reduce total dose by 25% for subsequent cycles; if further dose reduction is required, reduce to 2 doses per cycle
28 days or longer	Consider permanent discontinuation

4. **Renal Impairment:** No dose adjustment required in patients with mild to moderate renal impairment (CrCl greater than 30 mL/min). Limited data in patients with severe renal impairment (CrCl = 15-29 mL/min) – use with caution. No data on use in patients with end stage renal disease.

PRECAUTIONS:

1. **Venoocclusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS):** Fatal cases have been reported. Patients are at increased risk with current or prior history of active liver disease, prior HSCT, increased age, later salvage lines, and more inotuzumab ozogamicin treatment cycles. Patients are also at greater risk of VOD/SOS if they receive HSCT following inotuzumab ozogamicin, particularly if bilirubin is elevated prior to HSCT or a conditioning regimen with two alkylating agents is used. Monitor for signs/symptoms such as total bilirubin elevation, hepatomegaly, rapid weight gain, and ascites. Consider ursodiol for VOD/SOS prophylaxis in high risk patients, e.g. those with history of prior HSCT.
2. **Infusion-related reactions**: Symptoms such as fever, chills, rash and breathing difficulties are generally grade 2 or lower and usually occur shortly after the end of cycle 1 infusions. Premedication with corticosteroid, antihistamine, and antipyretic is recommended for all patients prior to each dose in all cycles of inotuzumab ozogamicin.
3. **Tumour Lysis Syndrome:** including electrolyte disturbances and acute renal failure may occur. Consider cytoreduction with combination of hydroxyUREA, steroids, and/or vinCRIStine prior to treatment with inotuzumab ozogamicin for patients with high peripheral lymphoblast count. Patients at risk of tumour lysis syndrome should receive adequate hydration, prophylaxis and be monitored closely. See BC Cancer Drug Manual inotuzumab ozogamicin drug monograph for more information.
4. **PR/QTc Prolongation:** Cases of PR interval prolongation and Grade 2 or lower QTc prolongation have been reported. Use caution in patients with history of QTc prolongation, conduction abnormalities (e.g. AV block), rhythm disturbances (e.g.

tachyarrhythmias) or cardiac disease and those receiving concurrent therapy with other medications associated with PR/QTc prolongation and/or medications that disrupt electrolyte levels. Correct electrolyte disturbances prior to inotuzumab ozogamicin 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.

5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Infection**: Consider anti-fungal prophylaxis with fluconazole or other antifungal for patients with neutropenia, prior HSCT, history of GVHD or prior invasive fungal infection. For patients who are HSV seronegative but have an indication for shingles prophylaxis (e.g. post HSCT, history of shingles, etc) give prophylaxis with valacyclovir. Consider antibiotic prophylaxis in neutropenic patients.
7. **Hepatitis B Reactivation:** All patients should be tested for HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during the chemotherapy and for six months afterwards. The 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.

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

References:

1. Kantarjian HM, DeAngelo DJ, Stelljes M et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375(8):740-753.
2. Pfizer Canada Inc. BESPONSA® product monograph. Kirkland, Quebec; 15 March 2018.
3. Kebriaei P, Cutler C, de Lima M et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant 2018;53(4):449-456.