BC Cancer Protocol Summary for Treatment of Philadelphia Chromosome (Ph)-Positive or Ph-Negative Refractory or Relapsed Pre-B-Cell Acute Lymphoblastic Leukemia with Blinatumomab

Protocol Code	*ULKBLIN*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr.Yasser Abou Mourad*

ELIGIBILITY:

Patients must have:
- Ph-positive or Ph-negative pre-B cell acute lymphoblastic leukemia (ALL),
- Relapsed or refractory disease after at least one of the following:
  - Refractory to induction or to salvage chemotherapy
  - Relapse within 12 months of first remission (CR1)
  - Relapse or refractory after second generation tyrosine kinase inhibitor (TKI), or intolerant to second or later generation TKI, or refractory or intolerant to imatinib
  - Relapse at any time after allo-HSCT; no active GVHD and no immunosuppressive medications,
- Treatment prescribed by Leukemia/BMT Program physicians and delivered at Vancouver General Hospital, and
- BC Cancer "Compassionate Access Program" approval prior to treatment (please refer to https://cap.phsa.ca/).

Patients should have:
- ECOG PS 0-2
- Available social support and ability to safely receive blinatumomab via an out-patient pump
- No clinically relevant CNS pathology or active CNS disease
- Alkaline Phosphatase, ALT <5 X ULN; Total Bilirubin < 1.5 ULN; Serum creatinine < 1.5 ULN.

Note:
- The sequential use of blinatumomab and inotuzumab ozogamicin is funded for relapsed or refractory Philadelphia chromosome negative (Ph-) patients. Patients can receive these agents in any order.

EXCLUSIONS:
- Prior treatment with blinatumomab for MRD (ULKMRDBLIN)

TESTS:
- Baseline: CBC & Diff, electrolytes, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, total bilirubin, albumin, LDH
- 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, HSV serology

Cycle 1:
- Daily: CBC & Diff, sodium, potassium, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, total bilirubin, albumin, LDH. Reassess blood work after Day 10.
- Amylase, lipase twice weekly
- INR, fibrinogen, serum CRP daily for 7 days
- For patients at risk of tumour lysis syndrome: sodium, potassium, uric acid, phosphate, calcium, urea, creatinine, LDH every 6 hours for 48 hours
  - If clinically indicated: HBV viral load (see protocol SCHBV)

Cycles 2 to 5:
- Before cycle 2: INR, fibrinogen, serum CRP
- Daily while an inpatient: CBC & Diff, electrolytes, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, total bilirubin, albumin, LDH.
- Twice weekly while an inpatient: amylase, lipase
- At each outpatient visit: CBC & Diff, electrolytes, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, total bilirubin, albumin, LDH, amylase, lipase
- If clinically indicated: HBV viral load (see protocol SCHBV)

SUPPORTIVE MEDICATIONS:
- cotrimoxazole DS 1 tablet PO BID every Monday and Thursday
- If HSV seropositive, valACYclovir 500 mg PO BID
- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

PREMEDICATIONS:
- dexamethasone 20 mg IV one hour before blinatumomab infusion
  - Day 1 and Day 8 on cycle 1
  - Day 1 on cycles 2 to 5
- acetaminophen 650 mg PO 30 minutes before blinatumomab infusion on Day 1
- diphenhydrAMINE 25 mg or 50 mg IV 30 minutes before blinatumomab infusion on Day 1

PREHYDRATION:
Cycles 1 and 2: NS IV at 100 mL/h starting on Day 1 and reassess after Day 3 *OR*
if at risk of tumour lysis syndrome D51/2NS IV at 3000 mL/m^2/day starting on Day 1 and reassess after Day 3

TREATMENT:
Each treatment cycle is 6 weeks. Hospitalization is recommended at a minimum for the first 9 days of cycle 1 and first 2 days of cycle 2. Subsequent cycles may be started as an outpatient.

Schema

Cycle 1	***Week 1***	***Week 2***	***Week 3***	***Week 4***	***Week 5***	***Week 6***
blinatumomab*	9 mcg/day for 7 days	28 mcg/day for 7 days	28 mcg/day for 7 days	28 mcg/day for 7 days	rest	rest
Cycles 2 to 5	***Week 1***	***Week 2***	***Week 3***	***Week 4***	***Week 5***	***Week 6***
blinatumomab*	28 mcg/day for 7 days	28 mcg/day for 7 days	28 mcg/day for 7 days	28 mcg/day for 7 days	rest	rest

*blinatumomab (fixed dose) is for patients greater than or equal to 45 kg

Cycle 1

Vital signs before blinatumomab infusion on Day 1, every hour for first 4 hours of infusion and every 2 hours for next 4 hours. If stable, then routine vital signs.

Week 1

Drug	Dose	BC Cancer Administration Guideline
blinatumomab	9 mcg on days 1 to 7	IV in NS 250 mL over 24 hours at 10 mL/h

Weeks 2 to 4

Drug	Dose	BC Cancer Administration Guideline
blinatumomab	28 mcg on day 8	IV in NS 250 mL over 24 hours at 10 mL/h
	112 mcg on days 9, 13, 17, 21, 25*	IV in NS 250 mL over 96 hours at 2.5 mL/h

*Patients need to return to clinic on day 29 for bag removal

Cycles 2 to 5

- Cycle 2: Vital signs before infusion starts on Day 1, every hour for first 4 hours of infusion and every 2 hours for next 4 hours. It stable, then routine vital signs.
- Cycles 3 to 5: Vital signs routine.

Drug	Dose	BC Cancer Administration Guideline
blinatumomab	112 mcg on days 1, 5, 9, 13, 17, 21, 25*	IV in NS 250 mL over 96 hours at 2.5 mL/h

* Patients need to return to clinic on day 29 for bag removal

Special notes on preparation and administration

1. Prepare with non-DEHP bag and administer via CADD pump with non-DEHP tubing and 0.2 micron in-line filter.
2. Infuse ONLY 240 mL because each bag is prepared with excess drug.
3. Prime IV line with blinatumomab only via CADD pump. Do not prime with NS. Do not prime using gravity.
4. Change bag at the same time each day. Discard any remaining IV solution.
5. Use a dedicated IV line. Do not flush the infusion line for any reason.

DOSE MODIFICATIONS

If the interruption after an adverse event is 7 days or less, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

1. Infusion interruption

Interruption	Management
1 to 4 hours	May resume at physician's discretion
More than 4 hours	Repeat dexamethasone 20 mg IV 60 minutes prior to restarting the infusion. Lower dose may be considered but not required.

2. Cytokine release syndrome

	Management
Grade 3	Hold until Grade 1. Resume at 9 mcg/day and increase to 28 mcg/day after 7 days if toxicity does not recur
Grade 4	Discontinue blinatumomab

3. Neurologic events

	Management
Grade 3	Hold until Grade 1 or baseline and for at least 3 days. Resume at 9 mcg/day and increase to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with up to 24 mg of dexamethasone with a 4-day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab.
Grade 4 or more than one seizure	Discontinue blinatumomab

4. Other adverse reactions

	Management
Grade 3	Hold until Grade 1 or baseline. May resume at 9 mcg/day or 28 mcg/day. Discontinue if toxicity takes more than 14 days to resolve.

Grade 4	Consider discontinuing blinatumomab permanently.

PRECAUTIONS:

1. **Cytokine release syndrome:** patients with significant burden of disease may require dexamethasone (10 to 24 mg/m^2/day) for 5 days prior to blinatumomab treatment. For treatment, consider dexamethasone IV 8 mg q8h for 3 days, then 8 mg q12h for 2 days, then 8 mg once daily for 1 day, then 4 mg once daily for 1 day.
2. **Infusion Reactions,** including anaphylaxis, may occur within 24 hours of infusion, usually with the first infusion and decreasing with subsequent infusions. Risk factors include a high tumour burden. Infusion reactions may require rate reduction, interruption of therapy, or treatment discontinuation. Hospitalization is recommended at a minimum for the first 9 days of cycle 1 and for the first 2 days of cycle 2.
3. **Tumour Lysis Syndrome** including acute renal failure can occur within 12-24 hours after the first infusion. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely. See BC Cancer Drug Manual blinatumomab drug monograph for more information.
4. **Neurologic events:** Elderly patients (65 years and older) are at higher risk of developing neurological events, including cognitive impairment, encephalopathy, and confusion.
5. **Infections:** Consider anti-fungal prophylaxis with fluconazole or other antifungal for patients with neutropenia, prior stem cell transplant, 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.
6. **CNS prophylaxis:** Intrathecal chemoprophylaxis is recommended prior to starting blinatumomab and following each cycle of blinatumomab.
7. **Hepatitis B Reactivation:** See SCHBV protocol for more details.

Call Dr. Yasser Abou Mourad (Leukemia/BMT) or tumour group delegate at (604) 875-4337 with any problems or questions regarding this treatment program.

References:

1. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47.
2. Amgen Canada Inc. Blinatumomab Product Monograph. Mississauga, Ontario; 28 April 2017.