A Phase IIa Study of BL-8040 in Combination with Nelarabine for Relapsed or Refractory T-Acute Lymphoblastic Leukemia/ Lymphoblastic Lymphoma

Washington University School of Medicine
Section of BMT & Leukemia
660 South Euclid Avenue, Campus Box 8007
St. Louis, MO 63110

Protocol #: 201606146
Version Date: 01/17/2023

Coordinating Center:	**Washington University School of Medicine**
Principal Investigator:	**Geoffrey L. Uy, M.D.** **Phone: (314) 747-8439** **E-mail: guy@wustl.edu**

Sub-Investigators	**Institution**	
Daniel C. Link, M.D.	Washington University	Correlative Sciences
Bader Alahmari, M.D.	Washington University	Co-Investigator
Kathryn Trinkaus, Ph.D.	Washington University	Biostatistics

Study Drug(s):	**BL-8040** **Nelarabine**
IND #:	130875
ClinicalTrials.gov #:	NCT02763384

Protocol Revision History

Initial Approval Version	**06/29/16**
Amendment #1 Version	**10/25/17**
Amendment #2 Version	**01/17/23**

A Phase IIa Study of BL-8040 in Combination with Nelarabine for Relapsed or Refractory T-Acute Lymphoblastic Leukemia/ Lymphoblastic Lymphoma
Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

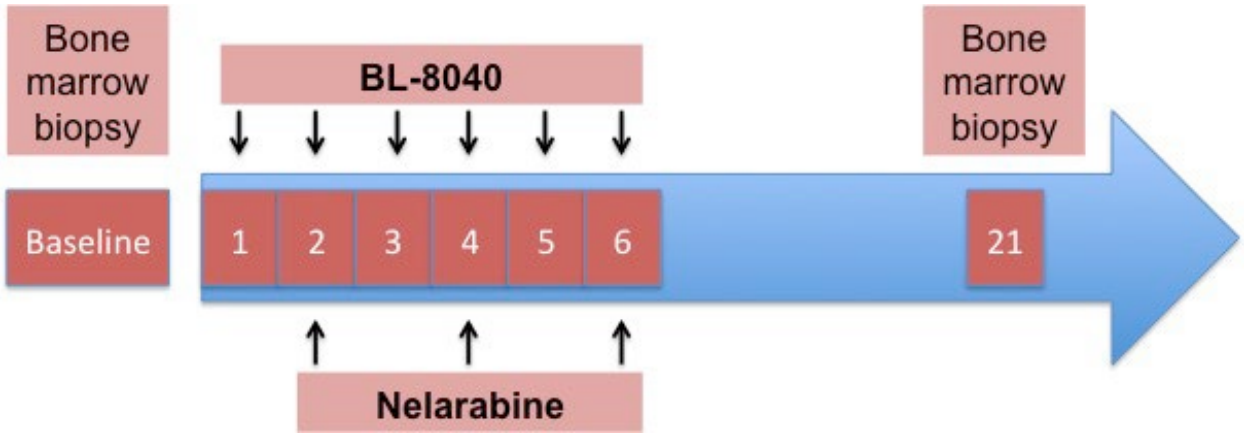
By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

SCHEMA

ELIGIBILITY (See section 3.0 for full criteria)

1. T-acute lymphoblastic leukemia/ lymphoblastic lymphoma which has relapsed or is refractory to chemotherapy.
2. Peripheral blood lymphoblasts ≤50,000 mcL.
3. Age ≥ 18 years
4. ECOG performance status ≤ 2.
5. Adequate organ function defined as:
   a. Calculated creatinine clearance ≥ 50 ml/min
   b. AST, ALT, total bilirubin ≤ 2 x institutional ULN

TREATMENT PLAN (See Section 7.0 for Details)



Treatment may be repeated every 21 days until disease progression for up to 4 cycles.
On days that both drugs are administered, BL-8040 will be administered approximately 2-4 hours prior to nelarabine.

<u>Cycle 1</u>
BL-8040: 1.5 mg/kg subcutaneous daily from Day 1 to Day 6.
Nelarabine: 1,500 mg/m2 intravenous over 2 hours on Days 2, 4 and 6.

<u>Cycle 2-4</u>
BL-8040: 1.5 mg/kg subcutaneous daily from Day 1 to Day 5.
Nelarabine: 1,500 mg/m^2 intravenously over 2 hours on Days 1, 3 and 5.

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 T-Acute Lymphoblastic Leukemia / Lymphoblastic Lymphoma

T-acute lymphoblastic leukemia (T-ALL), and the related disease T-lymphoblastic lymphoma (T-LBL), is an aggressive malignant neoplasm of the bone marrow. It accounts for 20% of all cases of ALL and is more common in adults than children [1]. With the use of modern therapy, 90% of people diagnosed with T-ALL and T-LBL will achieve first remission with 5-year overall survival (OS) of 48% [1]. Despite improvements to first-line therapy, the outcome of adult ALL (B-cell and T-cell subtype) after relapse, and in patients with failure to standard induction therapy, is extremely poor with 30% of the patients responding to first salvage therapy and long-term survival of only 10%[2-4]. These relapsed patients will have a chance of cure if they receive an allogeneic hematopoietic cell transplant (alloHCT) after first salvage therapy; however, only a small fraction of them will be candidates for such therapy due to refractory disease at time of relapse, and for those patients who fail the first salvage therapy, the outcome is dismal [5]. Novel therapies for ALL (including blinatumomab, inotuzumab, and CD19 chimeric antigen receptor T cells) have demonstrated significant promise in ALL but target only antigens specific to patients with B-ALL.[6] Therefore, novel therapies for patients with relapsed/refractory T-ALL/LBL represent an unmet clinical need.

1.2 Nelarabine for Relapsed / Refractory T-ALL/LBL

Nelarabine is a pro-drug of the nucleoside analog ara-G. In trials of patients with relapsed or refractory T-ALL/LBL, nelarabine results in a complete remission (CR) rate of 15-30% [7, 8]. One group reported on 126 patients treated with the regimen of 1.5 g/m^2 per day on Days 1, 3, and 5 in multiple 21-day cycles [8]. Forty-five patients achieved CR (36%) and 12 a partial remission (PR). Of the CR patients, 80% were able to proceed to alloHCT. The OS was 24% at 1 year and 11% at 6 years, with allo-HCT patients achieving an OS of 31% at 3 years. Nelarabine was granted accelerated approval by the FDA for treatment of patients who have been refractory to or relapsed after two chemotherapy regimens based on CR rates from two single arm phase 2 studies [9]. CR rates with single agent nelarabine lag behind what is already achieved with the use of immunotherapy alone in patients with relapse B-ALL. Thus, optimal combination regimens with nelarabine need to be evaluated.

1.3 Critical Role of CXCR4 and CXCL12 Interaction in T-ALL

CXCL12 (also known as stromal-derived factor-1, SDF-1) is a chemokine constitutively produced at high levels by bone marrow stromal cells. CXCL12, through interaction with its major receptor CXCR4, regulates many aspects of T cell biology, including proliferation, survival, and migration [10-13]. CXCR4 is expressed on most malignant hematopoietic cells, including T-ALL. Two recent studies provide strong preclinical evidence that CXCR4 signaling provides key signals that are required for T

ALL cell survival and expansion [14, 15]. Of particular interest, data suggest that CXCR4 signaling is required for T-ALL leukemia-initiating activity. Relevant to this proposal, treatment with a CXCR4 antagonist reduced the growth of primary human T-ALL in a xenotransplant mouse model. Of note, prior studies also have implicated CXCR4 signaling in resistance to chemotherapy [16]. A clinical trial investigating CXCR4 inhibition in combination with chemotherapy in patients with relapsed acute myeloid leukemia showed a higher response rate than expected in patients with advanced disease [17]. Based on these observations, we hypothesize that the addition of an inhibitor of CXCR4 to chemotherapy will improve the response rate of patients with T-ALL.

1.4 Study Agent: BL-8040

BL-8040 (developed by BioLineRx Ltd., formerly developed by Biokine Therapeutics and known as BKT140) is a novel selective inhibitor of the CXCR4 chemokine receptor. BL-8040 is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. It binds and inhibits the CXCR4 chemokine receptor with high affinity (IC_{50} 0.5-5.2 nM) and has been shown to be a specific antagonist of CXCR4 both *in vitro* and *in vivo* studies and to have a slow dissociation rate from the receptor [18, 19]. Compared to other inhibitors of CXCR4 such as plerixafor, BL-8040 is a more potent hematopoietic stem cell mobilizing agent and also induces apoptosis as a single agent against malignant hematopoietic cells [20]. Therefore, we propose to conduct a pilot study of BL-8040 in combination with nelarabine in adults with relapsed or refractory T-ALL/LBL. Two clinical trials with BL-8040 have been reported so far with promising safety and efficacy [21, 22]. In both studies the most common adverse events (AEs) seen are injection site reactions and systemic reactions: hives, pruritus, flushing, chills, rash and urticaria.

1.5 Study Rationale

The outcomes of patients with relapsed/refractory T-ALL/LBL are dismal and the only chance of cure is to undergo alloHCT soon after achieving second CR. However, with current strategies, only a small percentage of patients will respond to first salvage therapy. Recent data provide strong evidence that CXCR4 signaling plays a major role in T-cell leukemia cell maintenance and leukemia initiating activity, and targeting CXCR4 signaling in T-ALL cells reduces tumor growth in an animal model. Thus, we propose the addition of BL-8040 to nelarabine as a salvage therapy for patients with relapsed/refractory T-ALL/LBL. Our hypothesis is that such strategy will result in a higher CR rate than nelarabine alone without an increase in toxicity so that a higher percentage of patients with relapsed/refractory T-ALL/LBL will respond and proceed to alloHCT without delay.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the safety and tolerability of BL-8040 when administered with nelarabine in patients with T- ALL/LBL.

2.2 Secondary Objectives

1. To estimate the composite complete remission (CRc=CR+CRi) and the overall response rate (CR, CRi + PR) for patients with T-ALL/LBL treated with the combination of BL-8040 plus nelarabine.
2. To determine the time to response, duration of response, disease-free, event-free and overall survival of patients treated with BL-8040 plus nelarabine.
3. To estimate the rate of patients who proceed to alloHCT after treatment.

2.3 Exploratory Objectives

1. To describe the pharmacodynamic effects of BL-8040 on T-lymphoblasts in including inhibition of CXCR4 signaling on lymphoblasts, mobilization of lymphoblasts into the peripheral circulation, induction of apoptosis in lymphoblasts, and alterations in lymphoblast cell cycle status.
2. To describe the interaction of pretreatment disease and patient characteristics including morphology, CXCR4 expression on lymphoblasts, cytogenetics, immunophenotype, WBC, and performance status on clinical outcomes.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Diagnosis of T-acute lymphoblastic leukemia/ lymphoblastic lymphoma according to WHO criteria which has relapsed or is refractory to chemotherapy.
2. Peripheral blood lymphoblasts ≤ 50,000 mcL. Hydroxyurea and/or leukapheresis is permitted to reduce the peripheral blast count prior to enrollment and treatment.
3. Age ≥ 18 years
4. ECOG performance status ≤ 2.
5. Adequate organ function defined as:
   a. Calculated creatinine clearance ≥ 50 ml/min using the Cockroft-Gault formula
   b. AST, ALT, total bilirubin ≤ 2 x institutional ULN except for Gilbert's disease or when in the opinion of treating physician elevated levels are due to direct

involvement of leukemia (e.g., hepatic infiltration or biliary obstruction due to leukemia), in which case ALT and AST may be elevated up to ≤ 5 x IULN.

6. Women of childbearing potential and men must agree to use adequate contraception with a highly effective method (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Abstinence is acceptable if this is the established and preferred contraception for the subject.
7. Female subjects must have a negative urine or serum pregnancy test within 72 hours prior to start of study treatment if of childbearing potential or be of non-childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:
   a. ≥ 45 years of age and has not had menses for > 2 years
   b. Amenorrheic for > 2 years without a hysterectomy and oophorectomy and a FSH value in the postmenopausal range upon pretrial (screening) evaluation
   c. Post-hysterectomy, oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.
8. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

1. Previous treatment with nelarabine for relapsed or refractory disease.
2. Pregnant or nursing.
3. Received any other investigational agent or systemic cytotoxic chemotherapy within the preceding 2 weeks.
4. Active CNS involvement with leukemia
5. Active HIV or hepatitis B or C infection.
6. Any medical condition which, in the opinion of the clinical investigator, would interfere with the evaluation of the patient. Subjects with a clinically significant or unstable medical or surgical condition or any other condition that cannot be well-controlled by the allowed medications permitted in the study protocol that would preclude safe and complete study participation, as determined by medical history, physical examinations, laboratory tests, and according to the investigator's judgment.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Research coordinator name and contact information (telephone number, fax number, and email address)
2. Site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 STUDY CALENDAR

Tests & Observations	Baseline[1]	Cycle 1			Cycle 2-4			Follow-up
		D1	D8[2]	D15[2]	D1	D8[2]	D15[2]	
History	X							
Physical examination	X	X	X	X	X			
Performance status	X							
Adverse event assessment	X	X	X	X	X	X	X	
Follow-up								H
Laboratory Studies								
CBC with differential	X	A	X	X	A	X	X	
Basic metabolic panel (Na, K, Cl, CO_2, Ca, BUN, Creatinine, Glucose,)	X	B	X	X	X	X	X	
AST, ALT, Alk Phos, total bilirubin	X	X	X	X	X	X	X	
LDH, uric acid, phosphorus	X	B	X	X	X	X	X	
Pregnancy test for WOCBP	X							
BM biopsy /aspirate	X		C			C		
CT or PET/CT	X		D			D		
Lumbar puncture	E							
Research Studies								
BM biopsy /aspirate	F							
Peripheral blood			G					

Notes:

1 All baseline examinations are to be performed within 14 days of the start of therapy.

2 ± 2 days

A Performed prior to and 3 (± 1) hours post-dose of BL-8040 on C1, D1 to D5. From C2-4 prior to BL-8040 dosing.

B Performed daily on C1, D1-6

C For patients with marrow disease at baseline, a bone marrow biopsy and aspiration should be performed after every cycle until clearance of marrow leukemic blasts (<5%) is documented.

D For patients with measurable extramedullary disease at baseline, a CT scan should be performed at the end of Cycle 1, 2 and 4 for response assessment. A PET/CT scan should be used to confirm any response.

E For patients who have signs or symptoms of CNS involvement

F Bone marrow biopsy and aspirate 5-10 ml in EDTA containing tube at baseline

G Peripheral blood 30 ml in heparin containing tube on C1 D1 immediately prior to administration of BL-8040, 3 ± 1 hour after the first dose of BL-8040, and approximately 24 hours after the first dose of BL-8040 (prior to the second dose of BL-8040).

H Assessment at 30 +/-2 days post-treatment and for relapse and/or survival every 3 months for a maximum of 2 years.

6.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent	Prior to registration
On-Study Medical and Surgical History Treatment History	Prior to starting treatment
Treatment Record	Every cycle
CBC	C1D1 C1D2 C1D8 C1D15 C1D21 Days 1, 8, 15, and 21 of each cycle thereafter
Adverse Event	Continuous
Off Treatment	Completion of treatment
Follow Up	Every 3 months for 2 years
Response Assessment	Every cycle and at the end of treatment
MedWatch	See Section 12 for reporting requirements
Correlative Blood	Baseline Cycle 1 Day 1 Cycle 1 Day 2
Correlative Bone Marrow	Baseline
30-Day Mortality	Day 30
Death	Death

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

7.0 TREATMENT PLAN

7.1 Agent Administration

Cycle 1
BL-8040: 1.5 mg/kg subcutaneous daily from Day 1 to Day 6.
Nelarabine: 1,500 mg/m^2 intravenously over 2 hours on Days 2, 4 and 6.

Cycle 2-4
BL-8040: 1.5 mg/kg subcutaneous daily from Day 1 to Day 5.
Nelarabine: 1,500 mg/m^2 intravenously over 2 hours on Days 1, 3 and 5.

On days that both drugs are administered, BL-8040 should be administered approximately 2-4 hours prior to nelarabine. Treatment may be repeated every 21 days for up to 4 cycles or until disease progression, whichever occurs first.

7.2 Dose Modifications

The doses of nelarabine and BL-8040 will be calculated based on actual body weight. Nelarabine should be discontinued for grade ≥ 2 neurological events. BL-8040 should be held for a peripheral blood blast count which exceeds 50,000/mcL and upon clinical signs of leukostasis. Skipped doses of BL-804 will not be made up. No other dose modifications are permitted for either BL-8040 or nelarabine. Subsequent cycles of therapy should be delayed for clinically significant grade ≥ 3 nonhematologic toxicity until resolution to grade ≤ 2. For subjects achieving a morphologic leukemia free state (<5% BM blasts, no circulating lymphoblasts), nelarabine should be delayed until neutrophil recovery (ANC > 1,000/mcL). If dose delay is required beyond 28 days, the subject will be permanently discontinued from study treatment.

7.3 Response Evaluation

For patients with marrow disease at baseline, a bone marrow biopsy and aspiration should be performed after every cycle until clearance of marrow leukemic blasts (<5%) is documented.

For patients with measurable extramedullary disease at baseline, a CT scan should be performed at the end of Cycle 1, 2 and 4 for response assessment. A PET/CT scan should be performed to confirm any response.

7.4 Supportive Care

Hydroxyurea and/or leukapheresis is permitted to prevent or treat hyperleukocytosis. Concurrent intrathecal chemotherapy is permitted during treatment either as prophylaxis or treatment for CNS involvement of leukemia.

In case of TLS, subjects should be hydrated vigorously (urine output and fluid input should be monitored). Allopurinol, rasburicase, or any other treatment according to institutional practice should be considered.

Premedication and/or treatment with steroids and/or antihistamines is recommended in order to reduce the systemic reactions with BL-8040. Analgesics or local anesthetics (e.g. EMLA®) may be used for injection site pain management.

Supportive care including the use of antiemetics, antibiotic prophylaxis, and colony stimulating factors will be at the discretion of the treating physician and guided by institutional practices.

7.5 Women of Childbearing Potential

Women of childbearing potential should remain on birth control for 30 days after the last day of treatment, and men with partners who are of childbearing potential should use birth control for 90 days. Birth control method must be considered highly effective (hormonal or barrier method of birth control, abstinence).

Non-childbearing potential is defined as:

- ≥ 45 years of age and has not had menses for > 2 years
- Amenorrheic for > 2 years without a hysterectomy and oophorectomy and a FSH value in the postmenopausal range upon pretrial (screening) evaluation
- Post-hysterectomy, oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.

7.6 Duration of Treatment

If the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy must be discontinued and the reason(s) for discontinuation documented. All decisions regarding future therapy for both responding and refractory patients will be at the discretion of the treating physician.

Patients will be considered to have completed treatment upon completion of 4 cycles, disease progression, or administration of additional antileukemic therapy including alloHCT. All decisions regarding future therapy for both responding and refractory patients will be at the discretion of the treating physician.

7.7 Follow-up

Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed for a minimum of 30 days post-treatment for adverse events. Patients achieving a CR or CRi will be followed for disease relapse and/or death every 3 months following completion of treatment for a maximum of 2 years.

7.8 Removal from Study

Patients may be removed from the study at the discretion of the treating physician and / or Principal Investigator for any of the following reasons:

- Death
- Adverse event(s) that in the opinion of the investigator may cause severe or permanent harm or which rule out continuation of study drug
- Changes in the patient's condition that render him/her unacceptable for further treatment in the opinion of the investigator
- Suspected pregnancy
- Patient or investigator choice
- Major violation of the study protocol
- Lost to follow-up
- Study termination

8.0 RESPONSE EVALUATION

The following criteria will be used to assess the response to treatment.

Complete Remission (CR): A CR requires the following: an absolute neutrophil count (segs and bands) ≥ 1,000/mcL, no circulating lymphoblasts, platelets ≥ 100,000/mcL; and < 5% marrow leukemia blast cells with complete disappearance of all measurable disease as confirmed by physical examination, CT scan and/or FDG-PET (Deauville criteria score of 1, 2, or 3).

Morphologic complete remission with incomplete blood count recovery (CRi): Defined as CR with the exception of neutropenia < 1,000/mcL or thrombocytopenia <100,000/mcL.

Partial Remission (PR): A PR requires all of the CR criteria except that marrow may still contain 5-25% leukemia blast cells. An absolute neutrophil count (segs and bands) ≥ 1000/mcL, no circulating blasts, and platelets ≥ 100,000/mcL are requires as for a CR. For patients with measurable disease, a reduction of 50% or more in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements and with no new or enlarging lesions.

Refractory Disease: Failure to achieve a CR/CRi with persistence of leukemia cells after treatment.

Relapsed Disease: The reappearance of unequivocal leukemia blasts cells in the blood or the bone marrow (>5%) or in any other extramedullary site after a CR/CRi.

Time to neutrophil recovery: Defined as the date of the first dose of study drug to the date that the absolute neutrophil count is ≥1,000/mcL.

Time to platelet recovery: Defined as the date of the first dose of study drug to the date that the platelet count is ≥100,000/mcL in the absence of platelet transfusions.

Overall survival: Defined as the date of first dose of study drug to the date of death from

any cause.

Event-free survival: Defined as the interval from the date of first dose of study drug to date of treatment failure, recurrence, or death due to any cause.

Duration of remission: Defined as the interval from the date CR/CRi is documented to the date of recurrence.

Relapse-free survival: For patients achieving a complete remission, defined as the interval from the date of first documentation of CR/CRi to the date of recurrence or death due to any cause.

9.0 PHARMACEUTICAL INFORMATION

9.1 BL-8040

Mechanism of action:
BL-8040 (developed by BioLineRx Ltd., formerly developed by Biokine Therapeutics and known as BKT140) is a novel selective inhibitor of the CXCR4 chemokine receptor. BL-8040 is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. It binds and inhibits the CXCR4 chemokine receptor with high affinity (IC_{50} 0.54-5.2 nM) and has been shown to be a specific antagonist of CXCR4 both *in vitro* and *in vivo* studies and to have a slow dissociation rate from the receptor.

Availability
BL-8040 drug product is formulated as a sterile and non-pyrogenic lyophilized powder containing 73mg/vial BL-8040 (free base, on dry basis). Reconstitution instructions will be provided separately in a pharmacy manual. Lyophilized BL-8040 is filled and packed in clear Type I glass vials (DIN 6R) with 20 mm rubber stoppers and sealed with 20 mm aluminum caps. BL-8040 can be injected within 24 hours after reconstitution if stored in the refrigerator, 5°C ± 3°C (36 to 46°F).

Storage & Stability
Vials of BL-8040 for injection should be stored in the refrigerator (5°C ±3°C) in their original package, protected from light. BL-8040 is to be injected within six hours after reconstitution.

Administration
BL-8040 will be administered by slow SC injection. Injection sites should be rotated daily.

Toxicity
Preclinical Studies
The nonclinical development of BL-8040 has encompassed a large number of

pharmacodynamic, pharmacokinetic (PK), safety pharmacology, and single and repeated dose toxicity studies.

BL-8040 exhibits CXCR4-dependent selective cytotoxicity toward malignant cells both in vivo and in vitro and induces apoptotic cell death in cancer cells [20, 23-25][3–6]. BL-8040 leads to phospharidylserine externalization, decreased mitochondrial membrane potential, caspase activation, subsequent sub-G1 arrest and DNA double-stranded breaks in leukemic and Multiple Myeloma cells [20]. These effects were shown to be specific; BL-8040 did not affect the viability of human keratinocytes and normal human hematopoietic cells [20]. This property of direct apoptotic effects on top of the mobilization capacity, distinguishes BL-8040 from other CXCR4 antagonists such as Mozobil/Plerixafor[20]. In addition, administration of BL-8040 induces the mobilization of NK cells, T cells and B-cells from the BM and lymph nodes into the periphery. Using a syngeneic cancer model in mice it was demonstrated that BL-8040 may eliminate the immunological barrier and allow the accumulation of immune cells within the tumor microenvironment (unpublished data).

BL-8040 exhibited very high binding to human plasma proteins (99.2%) and high binding to the proteins in rat and dog plasma (94.9-96.9%) in the range of tested concentrations.

The subcutaneous injection (SC) of BL-8040 was tested in GLP toxicology studies in dogs, and Rats with the main identified AE's being a transient and local erythema at the injection site and peripheral edema. These reactions were noticed from a few minutes up to approximately 2 hours following the injection. There were no significant changes in terms of histopathology, Electrocardiogram (ECG), ophthalmological findings, blood chemistry or hematological variables. No target organ for toxicity could be identified.

Clinical Studies

BL-8040 has demonstrated safety and initial clinical efficacy in several Phase I and II studies:

- A Phase IIa, non-randomized, open-label, single dose, dose escalation, safety study of BL-8040 in multiple myeloma subjects on top of G-CSF has been completed (NCT01010880, study BKTSC001).
- A clinical trial for the treatment of adult relapsed/refractory Acute Myeloid Leukemia (AML) with a combination of BL-8040 and cytarabine (Ara-C) is currently ongoing (NCT01838395; BL-8040.01).
- A Phase I, Two Part Study Exploring the Safety, Tolerability, Pharmacodynamic and Pharmacokinetic Effect of Ascending Doses of BL-8040 in Healthy Subjects (NCT02073019, study BL-8040.02).
- An Investigator Initiated Phase II study termed the "BLAST study" (Study No. UKH062014) is ongoing in Germany. This is a double-blind placebo controlled study that will assess the efficacy of BL-8040 as an add-on therapy to Ara-C for

consolidation therapy in AML patients in first complete remission.

In general, the most common AEs seen in all studies conducted with BL-8040 are injection site reactions, including: pain, erythema, pruritus and inflammation, and systemic reactions including among others: hives, pruritus (not at the injection site), flushing, chills, rash and urticaria. Other isolated AEs reported among others were paresthesia, musculoskeletal pain, headache, constipation, tingling, and elevation of liver function tests.

For details concerning these studies please refer to the BL-8040 IB.

9.2 Nelarabine

Mechanism of action:
Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G), a nucleoside metabolic inhibitor. Nelarabine is demethylated by adenosine deaminase (ADA) to ara-G, mono-phosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and subsequently converted to the active 5'-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic blasts allows for incorporation into deoxyribonucleic acid (DNA), leading to inhibition of DNA synthesis and cell death. Other mechanisms may contribute to the cytotoxic and systemic toxicity of nelarabine.

Availability
The commercially available supply of nelarabine will be used for this study. Nelararbine is supplied as a clear, colorless, sterile solution in glass vials. Each vial contains 250 mg of nelarabine (5 mg nelarabine per mL) and the inactive ingredient sodium chloride (4.5 mg per mL) in 50 mL Water for Injection, USP.

Preparation, Storage, Stability and Administration
Please refer to the FDA-approved package insert for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Toxicity
Likely >10%: Peripheral edema, Fatigue, fever, somnolence, dizziness, headache, hypoesthesia, Petechiae, Hypokalemia, Nausea, diarrhea, vomiting, constipation. Anemia, neutropenia, thrombocytopenia, leukopenia, neutropenic fever. Transaminases increased. Peripheral neuropathy, weakness, paresthesia, myalgia, Cough, dyspnea.

Less likely 1% to 10%: Hypotension, sinus tachycardia, chest pain, Ataxia, confusion, insomnia, depressed level of consciousness, depression, seizure, motor dysfunction, amnesia, balance disorder, sensory loss, aphasia, attention disturbance, cerebral hemorrhage, coma, encephalopathy, hemiparesis, intracranial hemorrhage, lethargy, leukoencephalopathy, loss of consciousness, mental impairment, nerve paralysis,

neuropathic pain, nerve palsy, paralysis, sciatica, sensory disturbance, speech disorder. Hypocalcemia, hyper-/hypoglycemia, hypomagnesemia, stomatitis, taste perversion. Albumin decreased, bilirubin increased, AST increased. Arthralgia, back pain, muscle weakness, rigors, limb pain. Blurred vision, nystagmus, Creatinine increased. Pleural effusion, pneumonia, sinusitis, Infection.

<1% (Limited to important or life-threatening): Craniospinal demyelination, neuropathy (peripheral) (similar to Guillain-Barré syndrome), opportunistic infection, pneumothorax, progressive multifocal leukoencephalopathy (PML), respiratory arrest, rhabdomyolysis, tumor lysis syndrome.

10.0 CORRELATIVE STUDIES

A bone marrow biopsy and aspirate will be obtained at baseline for correlative studies. Approximately 1 cm of the core biopsy should be placed in saline. Approximately 5 mL of aspirate should be collected in a heparin containing tube.

In addition, 30 ml of peripheral blood will be collected in a heparin containing tube on cycle 1, day 1 immediately before and approximately 3 hours ± 1 hour after dosing of BL-8040. On day 2 of cycle 1, and additional 30 ml of peripheral blood will be collected in a heparin containing tube prior to the administration of BL-8040 or nelarabine. A separate 1 mL sample collected in an EDTA containing tube at the same time points will be used for a complete blood count.

Samples should be maintained at room temperature and delivered or sent by overnight mail to the laboratory of Daniel C. Link located at Room 613 Southwest Tower of the Washington University Medical Center.

Shipping address:
Washington University
Division of Oncology
Attn: Link Lab, SWT 7th fl
4940 Parkview Place
St. Louis, Mo 63110
(314) 362-8771

Preclinical studies predict that treatment with a CXCR4 antagonist will induce T-ALL apoptosis through mobilization from perivascular niches in the bone marrow and through decreased c-Myc expression. To test these predictions, bone marrow and peripheral blood will be obtained from patients at baseline. Peripheral blood will also be obtained 3 ± 1 hour after the first dose of BL-8040 and approximately 24 hours after the first dose of BL-8040 (prior to the second dose of BL-8040). The following assays will be performed on these samples.

1. Quantification of T-ALL cell number in blood and bone marrow at each time to assess T-ALL mobilization.
2. Assessment of T-ALL CXCR4 cell surface expression by flow cytometry using monoclonal antibodies that are (clone 12G5) and are not (1D9) sensitive to BL-8040 binding.
3. Assessment of T-ALL migration in response to CXCL12 using a transwell assay.
4. Assessment of T-ALL apoptosis in the blood before and after BL-8040 administration using flow cytometry to measure cell activated caspase 3 expression.
5. Assessment of T-ALL cell cycle status in the blood using flow cytometry to assess Ki67 and DAPI staining.
6. Assessment of T-ALL c-Myc mRNA and c-Myc target gene mRNA expression using real time RT-PCR of RNA obtained from sorted T- ALL cells.
7. Assessment of CXCL12 and other niche factor expression in the bone marrow at baseline.

Specimens will also be retained for future research, including possible future genetic research. Blood, bone marrow, and data will be retained indefinitely in a coded fashion in Dr. Link's lab. In order for these specimens and this data to be accessed in the future for additional research, the study PI must provide formal permission after reviewing a written request, and other appropriate approvals must be obtained by the investigator.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is an open label pilot study consisting of up to 20 patients. Demographic and clinical characteristics will be summarized using mean ± SD or median, IQR and extreme values for continuous values. Frequencies, percentages and confidence intervals will be reported for counts and proportions. Adverse events will be graded using NCI CTCAE v4.03 and summarized by patient, grade, frequency and time of occurrence. Kaplan-Meier product limit estimators will be used to estimate median and time-specific disease-free and overall survival. Cox proportional hazards regression will be used to describe time to neutrophil and platelet engraftment with early death treated as a competing risk. Additional Cox models may be used for time to event modeling to explore the effect of covariate adjustment. Pharmacodynamic data will be analyzed using descriptive statistics as described above, and plots. Differences between baseline and BL-8040 treated marrow will analyzed for significance using paired T-tests or Wilcoxon signed rank tests, as appropriate.

Futility: No inferential procedures are planned, so futility cannot be defined as loss of power or inability of reject null hypotheses. With respect to safety, futility will be

addressed by the monitoring rule described below. With respect to tolerability, futility will be defined as the loss of no more than 4 patients, or 20% (6%, 44%) of the planned sample size, due to delayed hematologic recovery as defined in section 7 or death occurring within the first 30 days of treatment or.

11.2 Monitoring Rule for Excess Mortality

The estimated 30-day mortality in a population of patients with relapsed or refractory ALL is approximately 10%. Toxicity will be reviewed on a continuous basis.

Thirty day mortality will be monitored using a continuous toxicity monitoring rule:

Suspend the study for review of the # deaths on or before 30 days due to toxicity is **greater than:**	In the following number of enrolled patients:
1	6
2	14
3	20

The probability is low (.055) of inappropriate early suspension if the true rate is 5% and remains low (.27) if the true rate is 11%. The probability is high (.68) of correct early suspension if the true rate is 20%.

12.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 12.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 12.6. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

BioLineRx requires that all events described in Section 12.7 be reported as outlined in that section.

12.1 Definitions

12.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP) available at http://www.hhs.gov/ohrp/policy/advevntguid.html

12.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

12.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

12.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it

does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

12.1.5 Unanticipated Problems

Definition:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

12.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

12.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington

University IRB approval is not required for protocol exceptions occurring at secondary sites.

12.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

12.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

12.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

12.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

12.6 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 12.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 12.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

Secondary sites must submit a completed MedWatch form to the Washington University PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

12.7 Notification of Serious Adverse Events to BioLineRx

Initial notification of SAEs
An initial SAE report form must be completed and sent by fax/email to the BioLineRx Medical Monitor within 24 hours of the Investigator's knowledge of the event. Any fatal or life-threatening event should be reported immediately, by phone, fax or email.

Medical Monitor
Dr. Anna Emde
Mobile +972 54 2802352
Email: safety8040@biolinerx.com
Fax: + 972-8-642-9137

The initial SAE report will be followed within 24 hours by a completed SAE report including a sufficiently detailed narrative, as well as copies of hospital case reports, results of applicable diagnostic tests, laboratory results, biopsy results, autopsy reports and other documents when requested and applicable.

Minimum criteria for a valid initial SAE case:
For regulatory purposes, initial SAE reports should be submitted to BioLineRx immediately and should include:

- Protocol identification
- A suspected investigational medicinal product,
- An identifiable subject (e.g. study subject code number),
- An AE with the Investigator's assessment of seriousness and relationship to any the study drugs,
- An identifiable reporting source i.e. Investigator contact details.

Follow-up of SAEs
A Follow-up SAE Report Form must be completed by the site (marked as "Follow-up report") and sent to the Medical Monitor within a reasonable timeframe (an SAE Follow-up report is required whether or not there is any additional information to the initial report).

The contact information for Follow-up SAE reporting is the same as for initial SAE reports (see above Section).

12.8 Timeframe for Reporting Required Events

Adverse events will be collected from first dose of study treatment through 30 days after the last study treatment.

12.9 Exceptions in the Reporting of AE and SAE

According to EU and FDA detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, regarding clinical trials in high morbidity or mortality diseases, it is acceptable to define some exceptions in the immediate reporting of specific SAEs. Refer to EU guidance ENTR/CT3, 5.1.9 and FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" (Dec 2012).

These AEs will be thoroughly handled and followed up through the CRF (AE form) and will be reviewed by the medical safety officer and could be re-qualified for reporting if necessary.

Each event must be carefully analyzed by the Investigator's or designee to decide whether the SAE could be considered as an exception or if it must be immediately reported.

Exceptions for AE/SAE reporting are:
All myelosuppression related adverse events: anemia, neutropenia, lymphopenia, leukopenia, leukocytosis.

Grade 1-2 fatigue, weakness, nausea, alopecia, bone, joint or muscle pain, electrolyte abnormalities (sodium, potassium, carbon dioxide, calcium, magnesium, phosphorus) and glucose.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least once every 6 months following activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator

name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 12.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source

documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation.

1. Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
2. Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
3. Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.

4. Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

16.0 REFERENCES

1. Marks, D.I., et al., *T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993).* Blood, 2009. **114**(25): p. 5136-45.
2. Fielding, A.K., et al., *Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study.* Blood, 2007. **109**(3): p. 944-50.
3. Tavernier, E., et al., *Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial.* Leukemia, 2007. **21**(9): p. 1907-14.
4. Oriol, A., et al., *Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group.* Haematologica, 2010. **95**(4): p. 589-96.
5. Gokbuget, N., et al., *Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation.* Blood, 2012. **120**(10): p. 2032-41.
6. Frey, N.V. and S.M. Luger, *How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia.* Blood, 2015. **126**(5): p. 589-96.
7. DeAngelo, D.J., et al., *Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801.* Blood, 2007. **109**(12): p. 5136-42.
8. Gokbuget, N., et al., *High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation.* Blood, 2011. **118**(13): p. 3504-11.
9. Cohen, M.H., et al., *FDA drug approval summary: nelarabine (Arranon) for the treatment of T-cell lymphoblastic leukemia/lymphoma.* Oncologist, 2008. **13**(6): p. 709-14.
10. Peled, A., et al., *Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4.* Science, 1999. **283**(5403): p. 845-8.
11. Levesque, J.P., et al., *Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide.* J Clin Invest, 2003. **111**(2): p. 187-96.
12. Lapidot, T., *Mechanism of human stem cell migration and repopulation of NOD/SCID and B2mnull NOD/SCID mice. The role of SDF-1/CXCR4 interactions.* Ann N Y Acad Sci, 2001. **938**: p. 83-95.
13. Lapidot, T. and I. Petit, *Current understanding of stem cell mobilization: the roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells.* Exp Hematol, 2002. **30**(9): p. 973-81.
14. Pitt, L.A., et al., *CXCL12-Producing Vascular Endothelial Niches Control Acute T Cell Leukemia Maintenance.* Cancer Cell, 2015. **27**(6): p. 755-68.
15. Passaro, D., et al., *CXCR4 Is Required for Leukemia-Initiating Cell Activity in T Cell Acute Lymphoblastic Leukemia.* Cancer Cell, 2015. **27**(6): p. 769-79.
16. Nervi, B., et al., *Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100.* Blood, 2009. **113**(24): p. 6206-14.
17. Uy, G.L., et al., *A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia.* Blood, 2012. **119**(17): p. 3917-24.

18. Zhang, W.B., et al., *A point mutation that confers constitutive activity to CXCR4 reveals that T140 is an inverse agonist and that AMD3100 and ALX40-4C are weak partial agonists.* J Biol Chem, 2002. **277**(27): p. 24515-21.
19. Tamamura, H., et al., *Synthesis of potent CXCR4 inhibitors possessing low cytotoxicity and improved biostability based on T140 derivatives.* Org Biomol Chem, 2003. **1**(21): p. 3656-62.
20. Beider, K., et al., *CXCR4 antagonist 4F-benzoyl-TN14003 inhibits leukemia and multiple myeloma tumor growth.* Exp Hematol, 2011. **39**(3): p. 282-92.
21. Peled, A., et al., *The high-affinity CXCR4 antagonist BKT140 is safe and induces a robust mobilization of human CD34+ cells in patients with multiple myeloma.* Clin Cancer Res, 2014. **20**(2): p. 469-79.
22. Borthakur, G., et al., *The Peptidic CXCR4 Antagonist, BL-8040, Significantly Reduces Bone Marrow Immature Leukemia Progenitors By Inducing Differentiation, Apoptosis and Mobilization: Results of the Dose Escalation Clinical Trial in Acute Myeloid Leukemia.* Blood, 2015. **126**(23): p. 2546-2546.
23. Fahham, D., et al., *In vitro and in vivo therapeutic efficacy of CXCR4 antagonist BKT140 against human non-small cell lung cancer.* J Thorac Cardiovasc Surg, 2012. **144**(5): p. 1167-1175 e1.
24. Beider, K., et al., *Targeting the CD20 and CXCR4 pathways in non-hodgkin lymphoma with rituximab and high-affinity CXCR4 antagonist BKT140.* Clin Cancer Res, 2013. **19**(13): p. 3495-507.
25. Beider, K., et al., *Combination of imatinib with CXCR4 antagonist BKT140 overcomes the protective effect of stroma and targets CML in vitro and in vivo.* Mol Cancer Ther, 2014. **13**(5): p. 1155-69.