Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative (CETI)

IL-15 Super Agonist ALT-803 to Treat Relapse Of Hematologic Malignancy After Allogeneic Stem Cell Transplantation

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Revision History

Revision #	Version Date	Revision Details	Consent Revision
	03/29/2013	Original	n/a
	04/18/2013	In response to CPRC stips; original to IRB	n/a
	07/29/2013	Original to FDA	n/a
	09/23/2013	In response to FDA review – not submitted to the IRB: Section 6.2.1.1 – refine the definition of dose limiting toxicity to include grade 3 hypotension that persists for > 4 hours, fever that persists > 24 hours (the definition of grade 4), and nausea or vomiting that persists for > 24 hours despite medical intervention; Schema and Section 11.4 – Add an early study stopping rule for mortality regardless of cause at day 60 after relapse and modify the excessive toxicity stopping rule definition to read grade 3 to 4, previously grade 3 to 5 non-hematologic, non-relapse and non-infectious toxicity (except for fevers alone) events; Sections 4.9 and 6.2 Monitoring section – further clarify monitoring requirements and admission requirement if >20% change in baseline vital signs Synopsis and Sections 6.2.1 and 11.1 – add that at least 72 hours must separate the 2nd and subsequent patients in a dose level (the 1st patient in a dose level must receive a minimum of 2 doses before the 2nd patient is enrolled)	n/a
1	09/25/3013	In response to FDA review, submitted to IRB: Synopsis, Schema, Sections 6.2 and 11.1: replace “treatment related” with ”treatment-emergent” when defining DLT; Section 9.1 add definition treatment-emergent adverse event; Section 6.2 – require 1st dose to be given as an inpatient however; if the first dose is well tolerated subsequent doses may be administered in an outpatient setting; Section 9.2 – adjust targeted toxicity time points to match dose 1 as inpatient; Appendix V – add nausea and vomiting Change infusion rate of ALT-803 from over 2-5 min to over 5-10 mins throughout protocol	n/a
2	11/15/2013	synopsis, sections 4.8 and 6.1, eligibility checklist – change time off immunosuppressants before dose of ALT-803 from 30 days to 14 days; section 6.5 – clarify use of hydroxyurea is permitted during the study as indicated to control blasts count section 7.2 – reduce blood volume for research related Immunogenicity test from 10ml to 5 ml per time point	yes
3	12/03/2013	section 6.2 – increase fever threshold for admission from 100.5° to 102.3° as a trigger for admission to correspond with CTCAE v4 grading categories	no

Revision #	Version Date	Revision Details	Consent Revision
		section 6.5 – allow topical steroid cream section 7.1 – add a footnote allowing several baseline tests to be done within 30 days of study registration in part to be consistent with eligibility criteria section 4.7; section 7.1 – clarify what is required for the neuro exam other minor edits	
	01/13/2014	interim version – emailed to the FDA for preliminary review section 6.2.1 –expand dose cohort 1 to six patients total to gain further experience before escalating to dose cohort 2 as planned section 6.2.1 – add a 48 hour timeframe to the definition of dose limiting toxicity, eliminate exceptions that are not applicable with new definition section 6.2 – admission to the inpatient unit will be required if any of the criteria occur (grade 3 fever, decreased 02 sat,etc.) and are present at the end of the 6 hour observation period	n/a
4	02/10/2014	Based on FDA's response to the proposed 01/13/2014 changes, also incorporates changes from WU's initial review: • schema, section 6.2.1 –expand dose cohort 1 to six patients total to gain further experience before escalating to dose cohort 2 as planned schema • schema, sections 6.2.1.1, 11.1 – revise and simplify definition of DLT • section 4.15, checklist – insert new exclusion criteria prohibiting concurrent chemotherapy (except hydroxyurea) or IL-2 therapy or anticipated need during the study treatment and for 1 week after the last dose of ALT-803 • section 6.2 – add the caveat to the criteria for admitting patients "and is still present at the end of the 6 hour observation" to avoid admissions for isolated events that quickly resolve (i.e. fever, hypotension) • section 6.2 – clarify treatment breaks • section 6.5 – clarify use of beta-blockers during ALT-803 section 8.4 – clarify stability testing	yes
5	05/13/2014	synopsis and section 1.2 – clarify acute GVHD by 4 weeks after the last dose of ALT-803 and delete late acute/chronic GVHD from the study endpoint section 7.1 and 6.7 – revise x chart for patients who have no benefit from ALT-803 and/or begin a new treatment – in general disease evaluations will not be required once no benefit is confirmed with follow-up ending at 4 weeks after the last dose of ALT-803. section 7.2 – add a 3 day post dose 1 research sample collection, clarify research samples are drawn while during treatment (even weeks with dose delays); add 1 more PK sample and adjust times section 7.2 – clarify day 5 research samples will only be done at UMN (Friday collection)	yes

Revision #	Version Date	Revision Details	Consent Revision
		section 4.21 and section 4.22 – add "known" before hepatitis and HIV section 6.2 – paragraph beginning with "Four to six hours after discharge" delete last sentence as it makes no sense. Section 11.3 – delete 'patients whose follow-up ends prior to day 42' from patient replacement criteria section 11.4 – update stopping rule calculations	
6	04/28/2015	Through-out protocol: change ALT-803 administration route from IV to SQ while retaining other aspects of the study design (dose escalation plan, treatment schedule, accrual and endpoints). Begin SQ enrollment at the current IV dose level 3 to ensure safety Synopsis/Schema, sections 6.2, 7 and 9: Allow up to 3 treatment cycles of ALT-803 (4 weekly treatments followed by a minimum of 2 weeks rest) in patients with stable disease and no unacceptable toxicity Schema, sections 4.24 and 7.1: Permit patients who received IV treatment to re-enroll as a "new" enrollment in the SQ cohort and allow to receive up to 3 additional cycles of ALT-803 Synopsis/Schema, section 7: shorten follow-up time from 5 years to 2 years Schema, sections 6.2.1.1, and 11: DLT and early stopping rule – redefine GVHD timeframe to account for up to 3 treatment cycles – previously based on time from last dose, now within 6 weeks after the 1st dose, updated secondary objective Correct section 4.1 and appendix I – MDS was inadvertently not included in the list of eligible disease in the inclusion criteria Section 10 – update to current U of MN IRB reporting requirements	yes
7	06/26/2015	Minor clarifications based on CPRC review: Schema page , table footnote for 3a: correct dose level as 3 and add that 3 to 6 patients will be enrolled at this level Synopsis, section 11.3: clarify enrollment numbers for the dose finding phase Other edit: appendix V – add febrile neutropenia Correction of header, Appendix IV (table of contents and appendix IV)	no
8	04/12/2016	Enroll a total of 6 patients in level 4 (ALT-803 10 mcg/kg) despite no dose limiting toxicity in the 1st patients treated at this dose level in order to collect additional toxicity data. The Synopsis/Schema and sections 3, 6, and 11 are updated Reduce the ALT-803 given at levels 5 and 6 from 20 and 30 mcg/kg to 15 and 20 mcg/kg to increase safety as it was questioned if doubling the dose with each dose level change was excessive Change duration of formal follow-up from 2 years to 1 year	yes

Revision #	Version Date	Revision Details	Consent Revision
		Delete re-enrollment option for patients treated with IV ALT-803 as no eligible patients remain Revisions related to skin rash seen in association with subcutaneous route of administration • Section 6.2 – add a proactive skin rash management plan initiating oral diphenhydramine 1 day prior to and continuing for 2 days after each ALT-803 dose plus a histamine given on treatment day • Section 6.2.2.1 – add "grade 3 skin rash not requiring systemic steroid therapy" to the list grade 3 toxicities that do not count toward DLT • Section 6.3.2 – add a skin rash section under Management of Selected Toxicity • Section 8.8 – ALT-803 Toxicity – add information regarding skin rash with SQ administration Updates to protocol to reflect other ALT-803 protocols (this protocol served as 1st in humans when written in 2013 and was written very conservatively) • Section 3 – Study design – remove rationale for outpatient treatment except keeping details of required stay during cycle 1 – remains mandatory during dose escalation • Section 4.8 and appendix I – delete dedicated caregiver requirement from inclusion criteria, change stay after last dose from 48 hours to 24 hours for 1st cycle only • Sections 6.2 and 8.2 – remove reference to caregiver and delete follow-up phone call 4 to 6 hours after discharge from clinic on each treatment day • Section 8.8 – update expected toxicity to match other ALT-803 studies sponsored by Altor – study was initially written as 1st in humans and used expected side effects based on IL-2 related toxicity Synopsis, Section 11.3 – extend planned enrollment period Section 4.7, 7.1, and appendix I – delete normal TSH as thyroid dysfunction is not associated with diseases under treatment, delete baseline PFTs Section 7.2 – revise to clarify which samples are drawn during cycle 1 only and those samples drawn during all treatment cycles Appendix III – add response criteria for MDS (previously missing) Minor clarifications and edits including: • Sections 9.2 and 9.4 – edit for clarity and to better define toxicity monitoring and documentation • Section 9.3 – simplify affiliate required expedited reporting • Section 10.4 – update link to the Cancer Center's DSMP, update language to current template • Appendix V – delete creatinine PI signature line from TT form	

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Synopsis

Study Design:

This is a multi-center, phase I/II clinical trial for patients who have relapsed more than 60 days after allogeneic transplant for a hematologic malignancy. The study consists of two phases. The dose finding phase is a modified version of a phase I trial and the extended phase is a modified version of a phase II trial.

The primary objective of the dose finding phase is to determine the maximum tolerated, minimum efficacious dose (MTD/MED) of a interleukin-15 (IL-15) super agonist complex (ALT-803) when given once weekly for 4 weeks. Effective with the April 2015 revision, patient may receive up to 3 treatment cycles. The study will follow a standard 3+3 design of dose escalation for toxicity with an added feature of stopping early if biologic activity is detected using absolute lymphocyte count as a surrogate marker. Up to six dose levels of ALT-803 will be tested to determine the MTD/MED.

The primary goal of the extended phase is to study the potential efficacy of ALT-803 in this patient population. Efficacy will be measured using rates of remission induction. An optimal Simon's two-stage design will be used in this phase. Stage 1 will enroll 14 patients, including the 6 patients treated at the MTD/MED during the dose finding phase. If 3 or more of these 14 patients respond to ALT-803, the trial will move to stage 2 and enroll an additional 23 patients.

The hypothesis is that ALT-803 will enhance allogeneic immunity through NK cells and CD8+ T cells capable of mediating a response without the need for lymphodepleting chemotherapy. A secondary aim is to achieve this goal without being limited by severe GVHD side effects.

Follow-up for overall response, toxicity, and survival through 1 year from the 1st dose of ALT-803.

Primary Objective:

Dose finding phase: To determine the maximum tolerated, minimum efficacious dose (MTD/MED) of ALT-803 when given weekly for 4 doses in patients with a hematologic malignancy who have relapsed after allogeneic transplant

Extended Phase: To study the potential efficacy of ALT-803 in this patient population as measured by the rates of remission induction

Secondary Objectives:

- To evaluate the safety of the ALT-803 when administered on this schedule
- To determine the incidence of acute GVHD within 6 weeks after the 1st dose of ALT-803

Correlative Objectives:

- To monitor the number and function of NK cells, T cells, and T regulatory cells pre- and post-therapy
- To quantify serum levels of ALT-803 and ALT-803 antibodies

Eligible Diseases:

- Relapse ≥ 60 days post allogeneic stem cell transplantation for one of the following hematologic malignancies:
  - Acute myelogenous leukemia (AML)
  - Acute lymphoblastic leukemia (ALL)
  - Myelodysplastic syndromes (MDS)
  - Lymphoma
  - Myeloma
  - Chronic Lymphocytic Leukemia (CLL)
  - Chronic myelogenous leukemia (CML) – failed or refused TKI and DLI

Inclusion Criteria:

- Minimum of 10% donor cell chimerism
- Age ≥ 18 years of age, Karnofsky performance status ≥ 70%
- Adequate renal, hepatic, and cardiac function
- Off prednisone and other systemic immunosuppressants for at least 14 days prior to 1st dose of study drug
- No indicators of acute or chronic GVDH requiring systemic treatment
- Prior DLI permitted but must be at least 30 days between DLI and 1st dose of ALT-803

Post-transplant lymphoproliferative diseases are not eligible

Endpoints: Dose Finding Phase: the Maximum Tolerated Dose (MTD) and/or Minimum Efficacious Dose (MED) for ALT-803 will be identified based on severity of treatment-emergent toxicity using CTCAE version 4 and/or biologic activity using a surrogate marker of absolute lymphocyte count (ALC)

Extended Phase: Potential efficacy will be measured by the rates of remission induction based on bone marrow examination 1 and 3 months after the last dose of ALT-803

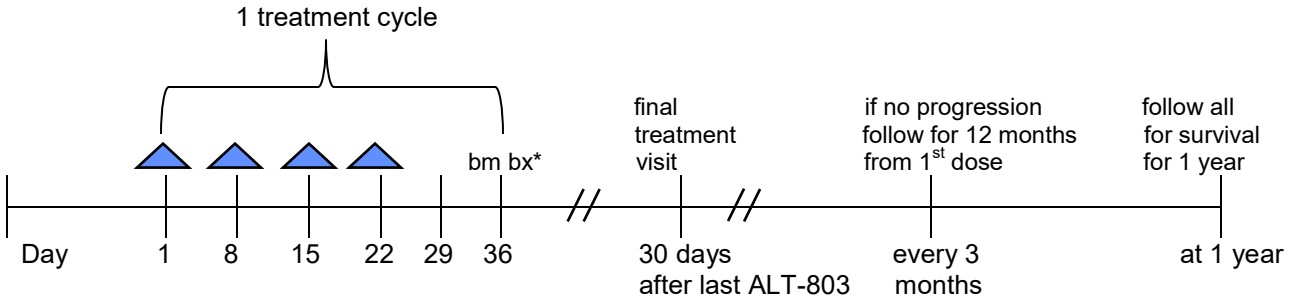
Sample Size: Dose Finding Phase: 16 patients were enrolled in the IV dosing cohort testing dose levels 1 through 4. With the change to SQ injection and enrollment re-starting at dose level 3 as required; the minimum additional enrollment during the dose-escalation phase will be 6 with a maximum additional 24 patients (6 each at the 4 remaining doses).

Extended Phase: stage 1 – 14 patients (includes the 6 patients treated at the MTD/MED during the dose finding phase), if stage 2 is activated an additional 23 patients will be required

Enrollment Enrollment to dose level 1 is limited to University of Minnesota patients.
Affiliate sites may begin enrollment with dose level 2.

Enrollment is expected to take 24-36 months if all study components are completed.

Schema



*Patients with stable disease and meet the criteria in section 6.2 may receive up to 3 treatment cycles

Dose Finding Phase (refer to section 6.2.1):

ALT-803 at assigned dose SQ on days 1, 8, 15, and 22 of a 6 week cycle – up to 3 treatment cycles may be given in absence of disease progression. Refer to section 6.2 for additional re-treatment requirements

Dose escalation will stop for toxicity (MTD) or earlier if the efficacy goal (MED) of an absolute lymphocyte count (ALC) of > 25,000 cells/μl in ≥ 2 of 3 patients (or ≥ 4 of 6) within a cohort is achieved.

Dose Level	ALT-803 Weekly Dose	Route of Administration	Number of Patients	Enrolling Institutions
1	1 microgram/kg	IV	6*	U of MN
2	3 microgram/kg	IV	3 to 6	U of MN and affiliates
3	6 microgram/kg	IV	3 to 6	
3a#	6 microgram/kg	SQ	3 to 6	
4	10 microgram/kg	SQ	6&	
5	15 microgram/kg	SQ	3 to 6	
6	20 microgram/kg	SQ	3 to 6	

* with the Feb 10, 2014 protocol version - dose level 1 was expanded to 6 patients total after which dose escalation will continue as planned

with the April 28, 2015 protocol version ALT-803 dosing was changed from IV to SQ and dose level 3 was repeated with an additional 3-6 patients to confirm safety with the new route of administration – in the unlikely event of dose de-escalation to level 2 or 1, the route of administration will be SQ

&with the April 2016 protocol version Dose Level 4 (10 mcg/kg) was expanded to enroll 6 patients despite the absence of DLT to gain further toxicity information before making the decision to continue dose escalation or declare level 4 the optimal dose and proceed to the extended phase. Dosing cohorts 5 and 6 were lowered to increase safety.

Within a dose level, the 1st patient must receive a minimum of 2 doses before additional patients are enrolled. The 1st dose for subsequent patients within a dose level must be separated by at least 72 hours. Dose escalation to the next level cannot proceed until all patients in the current level have received at least 3 out of 4 planned doses of ALT-803.

Dose Limiting Toxicity (DLT) is defined as (during first treatment cycle only)**:**

- any treatment-emergent grade 3 non-hematologic toxicity lasting more than 48 hours (refer to section 6.2.1.1 for full definition)
- any treatment-emergent grade 4 or 5 non-hematologic toxicity of any duration
- grade III or IV acute GVHD within 6 weeks after the first ALT-803 dose

Maximum Tolerated Dose (MTD) is defined as the dose level where ≤ 1 out of 6 patients has DLT during the first treatment cycle

Minimum Efficacious Dose (MED) as a measure of biologic activity using absolute lymphocyte count (ALC) as a surrogate marker is defined as an ALC of > 25,000 cells/μl that is sustained for more than 24 hours in ≥ 2 of 3 patients (or ≥ 4 of 6) within a dose cohort.

Extended Phase:

ALT-803 at MTD/MED from Dose Finding Phase SQ on days 1, 8, 15, and 22 of a 6 week cycle
Up to 3 treatment cycles may be given if no disease progression or unacceptable toxicity

Stage 1: Enroll 8 additional patients at the MTD/MED dose
Activate Stage 2 if ≥ 3 responses are seen in the 1st 14 patients treated at MTD/MED (includes the 6 patients treated during the dose finding phase)

Stage 2: Enroll an additional 23 patients.

Extended Phase Early Study Stopping Rules:

- excessive toxicity defined as treatment related grade 3-4 non-hematologic, non-relapse, non-infectious events (except fever alone)
- overall mortality at day 60 post relapse
- grade III or IV acute GVHD within 6 weeks of the first dose of ALT-803

1.0 Objectives

1.1 Primary

Dose Finding Phase: To determine the maximum tolerated, minimum efficacious dose (MTD/MED) of ALT-803 when given weekly for 4 doses in patients with a hematologic malignancy who have relapsed after allogeneic transplant

Extended Phase: To study the potential efficacy of ALT-803 at the dose identified in the dose finding phase in this patient population as measured by rates of remission induction

1.2 Secondary Objectives

- To evaluate the safety of ALT-803 when administered on this schedule
- To determine the incidence of acute GVHD within 6 weeks after the first dose of ALT-803

1.3 Correlative Objectives

- To monitor the number and function of NK cells, T cells, and T regulatory cells pre and post therapy
- To quantify serum levels of ALT-803 and ALT-803 antibodies

2.0 Background and Significance

2.1 Introduction

Allogeneic bone marrow transplantation results in an approximately 40-60% disease-free survival in patients with acute or chronic leukemias and myelodysplastic syndromes. The effectiveness of allogeneic bone marrow transplantation depends in part on ablation of the malignant clone with a preparative regimen and reinfusion of benign stem cells to restore normal hematopoiesis. However, it is well established that the success of allogeneic transplantation is in part mediated by a graft-versus-leukemia effect induced by donor-derived T lymphocytes or NK cells. This graft-versus-leukemia effect is usually associated with acute and/or chronic graft-versus-host disease which are also mediated by donor-derived lymphocytes. In patients with leukemia and multiple myeloma there is a statistically significant correlation between the occurrence of acute graft-versus-host disease and freedom from relapse (1-4).

2.2 Relapse After Allogeneic Stem Cell Transplantation

The effectiveness of bone marrow transplantation for diseases such as CML, AML, MDS and ALL depends on the disease and the disease stage at the time of transplant. Relapse rates in patients undergoing transplantation with unmodified allogeneic donor grafts vary and are

approximately 15% for good risk patients and fully ablative preparative regimens and up to 50% for advanced leukemias and reduced intensity preparative regimens. Relapse rates are higher in those patients who receive lymphocyte depleted grafts, especially for CML where relapse rates are as high as 70% at 3 years (1-3). CLL numbers are small and often are not separated out from other miscellaneous lymphoid malignancies in the literature, however there definite long-term survivors after allogeneic transplant. If a patient relapsed after hematopoietic cell transplantation, prior to lymphocyte infusions, very few effective therapies were available.

In multiple myeloma, in a study of 17 patients with advanced stage disease, the rate of complete remission increased to 73% after a dose-reduced allograft increase from 18% after cytoreductive autografting. (5) For patients with AML and ALL, a second course of reinduction chemotherapy can be given with variable results. Between 12% and 70% of patients will achieve a second complete remission. However, the median survival of patients undergoing additional chemotherapy for relapse post-transplant in acute leukemia varies between 5.5 and 12 months. Long-term disease-free survival is very unlikely.

Table 1: Treatment for Relapse Post-Transplant - AML/ALL: Chemotherapy

Group (reference)	Number patients	CR	Median Survival
Westminster (ALL/AML)	88	7 (12%)	7 months
Minnesota (ALL) (6)	53	29 (56%)	5.5 months
EBMTR (ALL/AML) (7)	74	32 (40%)	12 months
Seattle (AML) (8)	62	20 (30%)	6 months
Seattle (ALL) (8)	94	52 (65%)	10.5 months

A second marrow transplant can be performed for AML, ALL, CML, or MDS but with significant mortality. Several studies demonstrate that continuous complete remission for greater than one year varies between 10 and 50%. A second bone marrow transplant is associated with very high early mortality (between 20 and 55%). IBMTR data evaluating second sibling transplants in 114 patients demonstrate that leukemia-free survival was 7% if undergoing transplantation within 6 months of first transplantation and 28% if second transplantation occurred greater than 6 months after the first (9). Hospitalizations for second transplants are lengthy, complicated and costly.

Table 2: Treatment for Relapse Post-Transplant - AML/ALL/CML: Second Transplant

Group (reference)	Number patients	CCR (> 1 year)	Acute Mortality (< 100 days)
Minnesota	23	38%	39%
Seattle (10)	77	15%	30%
MD Anderson	17	12%	24%
EBMTR (11)	90	12%	48%
Hopkins (12)	23	39%	---

Group (reference)	Number patients	CCR (> 1 year)	Acute Mortality (< 100 days)
Sidney	9	11%	44%
Duarte	5	20%	20%
Goldman (13)	16	50%	31%

2.3 Donor Lymphocyte Infusion After Relapse

Donor lymphocyte infusions (DLIs) can produce long lasting remissions after relapse for chronic myelogenous leukemia (CML), although it has proven less effective in non-CML blood disorders. As there are few treatment options available after relapse in this patient population, donor lymphocyte infusion (DLI) using the same donor as transplant or a close relative as the cell source is the fallback standard of care. Based on our experience, using a lymphodepleting chemotherapy compared to no lymphodepletion improved complete remission rate and improved 1 and 2 year survival in those who achieved a CR; however the incidence of grade 3-4 acute GVHD lead to morbidity (14). By reducing the DLI cell dose, the incidence of severe acute GVHD dropped the incidence of severe GVHD (25% for the lower cell dose vs 66% for the higher cell dose) while the CR rates were similar (45% and 53% respectively) and long term DFS is still limited by subsequent relapse (15).

2.4 Interleukin-15 (IL-15)

Interleukin-15 (IL-15) is a cytokine and growth factor capable of expanding activated T cells and NK cells. By broad consensus, the NCI Immunotherapy Workshop (2007) ranked IL-15 as the #1 agent with “high potential for immunotherapy.”(16). Based on preclinical non-human primate and early phase clinical trial data, IL-15 regimens can unquestionably be designed to prospectively and reproducibly increase T-cell and NK-cell counts. Increased T-cell and NK-cell counts are likely to expand the autochthonous T-cell response present in some patients with melanoma (17;18) and to augment the efficacy of other immunotherapy modalities. Other immune modalities that might work together with IL-15 include T-cell therapy, cancer vaccines, monoclonal antibody treatment, therapy with other immune response modifiers/T-cell growth factors such as IL-7, blockers of the programmed death 1 (PD-1)/programmed death ligand-1 axis and cytotoxic T-lymphocyte antigen-4 (CTLA-4), and agonistic antibodies to CD40 or OX40 costimulatory molecules.

2.4.1 rhIL-15

The NCI Biological Resource Branch has manufactured E. coli-expressed recombinant human IL-15 (rhIL-15), and testing is currently underway. Systemic administration of NCI rhIL-15 by daily intravenous (IV) bolus has been shown to increase the number of circulating CD8+ T and NK cells, but the cytokine has a very short half-life. In non-human primates, NCI rhIL-15 was most effective when administered by continuous IV infusion. To a lesser extent, daily subcutaneous injection

of NCI rhIL-15 was also effective at expanding the number of peripheral blood activated T cells and NK cells. These data strongly imply that low-dose continued presence of IL-15 in serum will be most effective at expanding T cells and NK cells.

2.4.2 rhIL-15 Experience at the University of Minnesota

To date 10 patients have treated on our investigator initiated, dose escalation, single institution clinical trial of intravenous rhIL-15 given daily for 12 days beginning the morning after the administration of haploidentical donor NK cells in adults with relapsed or refractory AML. This is after high dose cyclophosphamide and fludarabine but in a non-transplant setting. Initially 5 dose levels were proposed (0.25 mcg/kg to 3 mcg/kg daily for 12 doses); however; after one dose limiting toxicity (DLT - diffuse alveolar hemorrhage leading to respiratory compromise) and prolonged neutropenia experienced in 2 out of 4 patients at dose level 3 (1 mcg/kg/day), and after discussion with the FDA, dosing was dropped down to half way between dose level 2 and 3 (0.75 mcg/kg/day). This decision was based on no DLTs at dose level 2 and NK cell expansion at dose level 3. Enrollment continues at the 0.75 mcg/kg/day dose level with chills, febrile neutropenia and hypertension the most frequent side effects.

2.5 ALT-803

This trial will evaluate an alternative IL-15 construct designed to have a prolonged serum half-life. The novel IL-15 immunoconjugate, ALT-803 was developed by our collaborator, Altor BioScience Corporation (Altor, Miramar, FL), to overcome some of the biologic, regulatory, and commercial limitations of unmodified E. coli-derived rhIL-15. Under natural circumstances, IL-15 and IL-15 Receptor-alpha (IL-15R) are coordinately expressed by antigen-presenting cells (i.e., monocytes and dendritic cells) (19). During signaling by the IL-15 pathway, IL-15 bound to IL-15R is presented in trans to neighboring NK or CD8+ T cells expressing only the IL-2R receptor. At the immunologic synapse, IL15 trans-presentation appears to be a dominant mechanism for IL-15 action in vivo, providing tight physiologic control over the functions of IL-15 under homeostatic conditions and in response to immune stimuli (20). ALT-803 is a novel recombinant human superagonist IL-15 complex (ie, IL-15N72D:IL-15RαSu/IgG1 Fc complex) with a prolonged serum half-life in preclinical animal models. In addition, ALT-803 contains a novel IL-15 mutein with a single substituted amino acid (rhIL-15N72D) that has a 4-fold increase in biologic activity greater than wild-type IL-15 (IL-15 wt) (21).

Normal soluble IL-15R fragments, containing the “sushi” domain (Su) at the N terminus, have been shown to contain most of the structural elements responsible for cytokine binding, and IL-15R binds IL-15 with high affinity (Kd 100 pM). In addition, soluble IL-15R and IL-15 in solution

can form stable heterodimeric complexes capable of modulating (ie, either stimulating or blocking) immune responses via the IL-2R complex (22, 23, 24)). Previous studies have shown that the biologic activity of IL-15 could be increased 50-fold by administering preformed complexes of IL-15 and soluble IL-15R, which has a longer half-life than rhIL-15 (22, 24). The IL-15:IL-15R complex increases activity at lower concentrations, and the fusion with Ig-G1 Fc increases serum half-life, providing more ideal pharmacokinetics with prolonged cytokine function (25).

We hypothesize that ALT-803 will likely require only weekly or twice weekly injections to achieve a similar benefits to that provided by low-dose continuous rhIL15 exposure. This will allow a less complex administration schedule that should be preferred by patients and clinicians. Data from preclinical studies in mice and non-human primates support this hypothesis (26). Moreover, ALT-803 will provide a safe and effective method for increasing activated antigen-specific T cells and NK cells to benefit patients with hematologic malignancy who have relapsed after an allogeneic stem cell transplant.

ALT-803 has undergone good laboratory practice (GLP) pharmacology and toxicity studies in non-human primate models, to complete the investigational new drug (IND) requirements for the planned first time in humans testing. The preliminary results from the GLP toxicity study in non-human primates indicate that 4 weekly doses of ALT-803 are well tolerated at 0.1 mg/kg (100 mcg/kg), well above the highest dose level proposed in this study.

2.6 ALT-803 by Subcutaneous Injection (effective with the April 2015 protocol revision)

Emerging data from ongoing trials using the NCI's recombinant human IL-15 (rhIL-15) product and preclinical reports from Altor suggests that intravenous dosing likely is not optimal for IL-15 because it induces a high Cmax and secondary cytokine release (IL-6 and IFNγ) that affects its tolerability therefore limiting. Alternately, based on pre-clinical studies, other studies using rHIL-15, and published studies with IL-2, subcutaneous dosing is safer and provides much better tolerability. The increased tolerance of subcutaneous dosing is likely a result of a decreased Cmax compared with the same dose level administered intravenously and more sustained levels of the rIL-15 product in circulation. Lowering the Cmax allows for more drug delivery overall.

Waldmann and colleagues conducted the first in human solid tumor trial of rhIL-15 using daily intravenous bolus infusion for 12 consecutive days. (27) Dose limiting toxicities observed at the 3.0 and 1.0 mcg/kg per day cohort were grade 3 hypotension, thrombocytopenia, and elevations of ALT and AST. The maximum tolerated dose was declared at 0.3mcg/kg

per day. In contrast, the ongoing subcutaneous trial using the same rhIL-15 product being conducted through the Cancer Immunotherapy Trials Network ([Protocol CITN11-02: A Phase 1 Study of Recombinant IL15 (rhIL15) in Adults with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Head and Neck Cancer – Dr. Jeffrey Miller - PI] has successfully completed dose cohorts of 0.25, 0.5, 1.0, and 2.0 mcg/kg of rhIL-15 given as 10 daily doses out of 12 days (no dosing on days 6 and 7). The study is currently enrolling at 3 mcg/kg with no dose limiting toxicity. The major conclusion from this experience is that going from IV to subcutaneous dosing increases safety and allows for an MTD ≥ 6 times higher. In addition, research lab correlates show an increase in *in vivo* NK cell counts with this subcutaneous dose of rhIL-15 compared to what is reported with IV dosing.

Altor BioScience has also conducted pre-clinical studies to compare the pharmacokinetics, pharmacodynamics and antitumor efficacy of ALT-803 intravenous versus subcutaneous administration in mice. The results of these studies indicated that going to subcutaneous dosing decreases the Cmax compared to IV dosing, retains the immunostimulatory and antitumor efficacy without exaggerating toxicity. The main summary of the mice data (as no humor data) is that: when comparing IV to SQ, the peak concentration decreased by nearly 3-fold. We believe that peak concentration correlates with secondary cytokine release, such as IFNy and IL-6, which may be linked to fevers and low blood pressure, both of which are frequent and often treatment limiting side effects in this current clinical trial.

To date, potential efficacy was seen in two patients who received IV dosing. One subject had relapsed acute myeloid leukemia (AML) and had a pericardial chloroma (but no BM involvement) that decreased in size two months after treatment on CT scan. A second subject had 10% blasts associated with thrombocytopenia late after transplant. During treatment, his platelet count increased and two months later, his marrow blast count was still 10%. Although still with disease, stable disease is unusual in AML and untreated progression is usually rapid. Encouragement is seen with these two patients and switching to a SQ route of administration may allow more effective dosing with fewer limiting side effects.

3.0 Study Rationale

Relapse after allogeneic stem cell transplantation remains a clinical challenge. Donor Lymphocyte infusion (DLI) has been documented to induce varying levels of response depending on the underlying hematologic malignancy. CML remains the most clinically responsive with lymphoma, AML/MDS, CLL, and ALL showing decreasing levels of response and long term disease free survival. These studies establish proofs of concept that allogeneic immune responses can have direct anti-tumor responses but, how often these responses are inadequate.

A study is ongoing with r IL-15 at the University of Minnesota building on an ongoing trial at the NIH for melanoma and renal cell; however only a dosing schedule of 12 daily infusions is being tested. This current schedule requires either inpatient administration or daily visits (including weekends) by the patient imposing greatly on quality of life, as well as resulting in considerable expense in terms of resources and money.

ALT-803 is a recombinant human super agonist IL-15 complex with IL-15 presented with IL-15Rα and with the complex fused with Fc. Due to the higher affinity single amino acid substituted IL-15 and the presentation of IL-15 with IL-15Rα, ALT-803 is likely to be effective at low concentrations. Due to its longer half-life as a result of fusion with Fc, ALT-803 is likely to be effective using a practical regimen of weekly or biweekly injections. It is likely that low concentrations of ALT-803 will enhance allogeneic immunity through NK cells and CD8+ T cells capable of mediating a response without the need for lymphodepleting chemotherapy and with a safety profile appropriate for outpatient use.

If the first dose of ALT-803 as an inpatient is well tolerated, subsequent treatment may be offered in the outpatient clinic setting with the understanding that the patient will be admitted to the hospital if medically indicated. Given that relapse after transplant often leads to death, many patients prefer the opportunity of treatment/medical management in a full service outpatient setting over hospitalization to maximize quality of life. Patients who require admission for medical reasons will receive treatment in the hospital.

To be eligible for this study, the patient must agree to stay within a reasonable distance (i.e. 30 minutes travel time) of the study center for the duration of the first treatment cycle through 24 hours after the last dose. Patients enrolled in the dose escalation component will be required to remain in the area. Patients enrolled in the extension may have this requirement waived on an individual basis at the discretion of the treating physician.

Up to six dose levels of ALT-803 will be tested using a standard 3+3 design of dose escalation for toxicity with an added feature of stopping early if efficacy is confirmed using absolute lymphocyte count as a surrogate biomarker. The starting dose level of ALT-803 will be 1 mcg/kg. This dose is equivalent to the starting dose of a CITN trial under development for metastatic melanoma and based on allometric scaling to an equivalent human dose of pre-clinical mouse and cynomolgus monkey data (personal communication with Altor).

In April 2015 the protocol was revised to replace intravenous (IV) administration of ALT-803 with a subcutaneous (SQ) injection while maintaining the current dose escalation/enrollment plan. To ensure safety with the SQ dosing, a minimum of 3 patients will be enrolled in the highest dose level tested during

intravenous administration (dose level 3 - 6 mcg/kg). Enrollment will continue until the MTD/MED is identified or until dose level 6 (30 mcg/kg) is completed. The extended phase will be activated to complete study enrollment.

In addition in April 2015 the protocol was amended to provide additional treatment opportunities:

- With the change to SQ administration, the treatment plan was changed to permit the administration of up to 3 treatment cycles in patients with stable disease who meet the criteria found in section 6.2.
- patients who were previously treated with intravenous ALT-803 will be eligible to re-enroll in the protocol at the current ALT-803 dose level under the subcutaneous treatment plan provided they received at least 3 doses of IV ALT-803 without dose limiting toxicity and they meet the inclusion/exclusion criteria per section 4. (re-enrollment details deleted in the April 2016 version as there were no eligible patients remaining)

In April 2016 the protocol was amended to enroll a total of 6 patients in dose level 4 (ALT-803 at 10 mcg/kg) despite no dose limiting toxicity in the 1st 2 patients. As clinical activity has been observed in the dosing cohorts tested so far (at least one complete response and several subjects with stable disease) in the absence of unacceptable toxicity, this dose may prove to be the optimal level for the extended phase. The decision whether to continue dose escalation, or more likely, to declare ALT 803 at 10 mcg/kg the optimal dose for additional testing will be made after 6 patients are treated at dose level 4. If we decide to dose escalate further, dosing cohorts 5 and 6 have also been lowered to increase safety.

4.0 Patient Selection

Study entry is open to adults 18 years and older regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of allogeneic stem cell transplant studies at the University of Minnesota and other participating institutions.

Inclusion Criteria

4.1 Relapse after previous allogeneic stem cell transplant for one of the following hematologic malignancies - acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes (MDS), lymphoma, myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia meeting the following:

- For non-CML, relapse will be defined based on disease specific morphologic criteria from a bone marrow biopsy and aspirate or recurrence of disease specific cytogenetics. For disease specific definition of relapse, see appendix III. Relapse can be determined morphologically. Equivocal results for relapse should result in a

repeated test after an appropriate time interval (suggested 1 month) to determine eligibility.

- For CML, relapse will be defined as any cytogenetic evidence of a Philadelphia chromosome or persistence of BCR/ABL rearrangements by molecular testing on at least two measurements over a 6 month interval. If cytogenetics are normal and there is PCR evidence of a BCR/ABL fusion, patients will be eligible if they have evidence of a quantitative increase in CML measured either by quantitative PCR or by fluorescent in situ hybridization (FISH).
  For Chronic Phase CML patients only:
  - must have failed (no response in 3 months or incomplete response at 6 months) or refused treatment with a tyrosine-kinase inhibitor (TKI)
  - must have failed (defined as incomplete response or relapse) or refused DLI

4.2 Relapse must have occurred ≥ 60 days after transplant

4.3 Prior DLI is allowed, however not within the 30 days before the 1st dose of ALT-803

4.4 Minimum donor chimerism of 10%

4.5 ≥ 18 years of age

4.6 Karnofsky performance status ≥ 70% (appendix II)

4.7 Adequate organ function within 14 days (30 days for cardiac) of enrollment defined as:

- Creatinine: ≤ 2.0 mg/dL
- Hepatic: SGOT/SGPT < 5 x upper limit of institutional normal (ULN)
- Cardiac: LVEF by ECHO or MUGA > 40%

4.8 Ability to be off prednisone and other immunosuppressive drugs for at least 14 days before first dose of study drug

4.9 Patient agrees to stay within a reasonable distance (i.e. 30 minutes travel time) of the study site for the duration of the first treatment cycle through 24 hours after the last dose

4.10 Women of child bearing potential and men with partners of child bearing potential must agree to use effective contraception during therapy and for 4 months after completion of therapy

4.11 Voluntary written consent

Exclusion Criteria

4.12 Post-transplant lymphoproliferative diseases (often referred to as EBV-associated lymphomas)

4.13 Known active CNS leukemia or lymphoma – patients with previously treated CNS disease is permitted if neurologically stable with no ongoing or anticipated need for steroid therapy are eligible

4.14 Ongoing active acute or chronic GVHD requiring immunosuppressive therapy or signs of aGVHD or cGVHD requiring treatment

4.15 Concurrent chemotherapy (except hydroxyurea) or IL-2 therapy or anticipated need during the study treatment and for 1 week after the last

dose of ALT-803 – hydroxyurea is permitted at any time to control blast count

4.16 Pregnant or lactating – Women of child bearing potential must have a negative pregnancy test within 14 days of study treatment start

4.17 Class II or greater New York Heart Association Functional Classification criteria (appendix II) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)

4.18 Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval greater than 500 milliseconds)

4.19 New progressive pulmonary infiltrates on screening chest x-ray or chest CT scan for which evaluation with bronchoscopy is not feasible. Infiltrates attributed to infection must be stable/improving (with associated clinical improvement) after 1 week of appropriate therapy (4 weeks for presumed or documented fungal infections).

4.20 Active bacterial, fungal, or viral infections – all prior infections must have resolved following optimal therapy

4.21 Known positive hepatitis C serology or active hepatitis B infection because of the risk of hepatic inflammation and the possible confounding of drug toxicity assessment – chronic asymptomatic viral hepatitis is allowed

4.22 Known HIV positive because the effect of IL-15 viral loads, HIV immunity, and infectivity of proliferating T cells is unknown

4.23 History of severe asthma, presently on chronic medications (a history of mild asthma not requiring therapy is eligible)

5.0 Registration/Dose Assignment Procedures

Registration will occur after the patient has signed the subject consent and eligibility is confirmed, but before any study related procedures are performed.

To be eligible for registration to this study, the patient must meet each of the criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

A copy of the eligibility checklist is in appendix I and under attachments within this study in OnCore.

5.1 Registration and ALT-803 Dose Level Assignment

Upon completion of the screening evaluation, eligibility confirmation and obtaining written consent, study site coordinator or designee will enroll the patient into OnCore.

OnCore will automatically generate an email alerting key study personnel of the registration. The Masonic Cancer Center (MCC) Study Coordinator or designee will assign the ALT-803 dose level in OnCore to complete the

registration. An email with the dose level assignment will be sent to relevant study personnel.

Affiliate sites only: At the time of registration, a copy of the signed consent and completed eligibility checklist will be uploaded as an attachment into OnCore under the patient's record. Affiliates are responsible for fulfilling any local patient registration requirements.

5.2 Patients Who Are Registered and Do Not Receive Study Treatment

If a patient is registered to the study and is later found not able to begin ALT-803, for whatever reason, the patient will be removed from study and treated at the physician's discretion. Study staff will update OnCore of the patient's non-treatment status. Study data will be collected until the time the patient is taken off study. The reason for removal from study will be clearly indicated in OnCore. The patient will be considered unevaluable and replaced per section 11.3.

6 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.); however the use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided. Topical steroid cream is permitted.

6.1 At the Time of Relapse

At the time of relapse, patients should be tapered off immunosuppressive medications as soon as possible. To be eligible for this study, patients must be off prednisone and other immunosuppressive agents for at least 14 days before the first dose of ALT-803.

6.2 ALT-803 Administration

ALT-803 will be administered subcutaneously at the assigned dose level once a week (on day 1, 8, 15 and 22). Injection sites should be rotated per institutional guidelines and each injection site separated by at least 1 inch.

The first dose of ALT-803 of the 1st cycle will be given as an inpatient; however if the first dose is well tolerated, subsequent doses may be administered in an outpatient setting.

A window of +/- 2 days for the weekly ALT-803 dosing is allowed in the event of scheduling issues (i.e. holiday). All other tests and evaluations associated with that week's dose will be adjusted accordingly.

Recommended Skin Rash Management Plan (begins day before ALT-803 dose):
With the April 2016 protocol revision a skin rash management plan was added. Since the change to subcutaneous administration, an increase in the frequency and severity of skin rash has been noted.

The following is recommended for all patients with every dose of ALT-803. Adjustments to the plan are permitted without being a deviation. Refer to section 6.3.2 for management of skin rash despite these preventive measures.

- One day prior to each ALT-803 dose: Diphenhydramine 25-50 mg TID orally
- One hour prior to each ALT-803 dose: Diphenhydramine 25-50 mg orally with one of the following:
  Ranitidine 300 mg orally
  Cimetidine 300 mg orally
  Famotidine 20 mg orally
- After each ALT-803 dose: Continue Diphenhydramine 25-50 mg TID orally x 2 days

Pre-medication: Acetaminophen 650 mg PO and diphenhydramine 25 mg PO/IV thirty minutes before and 4 hours after each dose of ALT-803 is recommended. (adjust as needed if using skin rash prophylaxis)

Non-steroidal anti-inflammatory medication including acetaminophen, ibuprofen, or naproxen may be given per physician discretion following the recommended dosing thresholds:
Acetaminophen: not to exceed 3000 mg (3 grams) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

The use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided; however in the event of a life-threatening inflammatory reaction to ALT-803, the IV administration of dexamethasone or other steroid-based medication is warranted.

Monitoring:
During the Dose Finding Phase: Patients will be observed for a minimum of 6 hours after each dose of ALT-803 for immediate adverse events.

During the Extended Phase: Patients will be observed for a minimum of 6 hours after dose 1 of cycle 1 and a minimum of 2 hours after subsequent doses are the care team's discretion.

Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) for all patients will be documented prior to each ALT-803 dose and then at 15, 30, 60 and 120 minutes then hourly until discharge from clinic (minimum of 6 hours for Dose Finding Phase, minimum of 2 hours for Extended Phase).

For inpatients: continue vitals hourly (+/- 15 minutes) until 6 hours post dosing, then every 3 hours, or more often if indicated, beyond the first 6 hours until 24 hours post dosing.

For outpatients: Admission to the inpatient unit (or continued outpatient monitoring) should be considered if any of the following occurs and is still present at the end of required observation period:

- a new fever >102.3°F (39.0°C) develops or
- an oxygen saturation drops below 90% or
- there is a sustained changes in baseline vital signs by 20% for more than 1 hour or
- if there is any change in symptoms of concern

If vital signs remain within baseline and none of the changes above are present at the end of the observation period, the patient is eligible for continued outpatient monitoring:

Upon discharge from the outpatient infusion area on the day of each injection, it will be reiterated the need to contact the study staff or BMT physician on call with any questions or concerns. The patient will be given emergency access phone numbers and access to immediate hospital admission should be a clinical status change.

During week 1 of the first cycle, the patient will be discharged from the hospital after the 24 hour post injection assessment and lab work is done with a return to clinic at approximately 48, 72, and 96 hours post injection for a brief assessment and lab work, if scheduled.

During weeks 2, 3, and 4 of the first cycle and all doses of subsequent cycles, the patient will return to clinic approximately 24 hours post injection for a brief assessment and lab work. If ALT-803 is administered in the inpatient setting, the 24 hour post injection assessment and lab work will be done prior to discharge.

Refer to section 3 regarding requirements for staying close to the study site during the 1st treatment cycle.

Targeted toxicities (appendix VI) and unexpected adverse events will be collected at the time points listed in section 9.2.

Dose modification: No dose modifications are allowed. If a patient experiences toxicity that meets the definition used for dose limiting toxicity (DLT) at any time, ALT-803 will be permanently discontinued.

Dose delay: ALT-803 administration may be delayed by 1 week if on the day of the planned injection for any of the following situations:

- Grade 2 or greater acute GVHD is questioned (documented grade 3-4 GVHD will require discontinuing ALT-803)
- the patient has a fever of > 101°F (38.3 °C)
- treatment related side effects (except skin rash) have not resolved to grade 1 or better
- if in the opinion of the treating physician, a 1 week delay would be of benefit to the patient

If after a 1 week rest, the patient no longer meets any of the above criteria for dose delay, the patient may resume treatment with the intent of giving all 4 doses of ALT-803.

If after 1 week, the patient is still unable to be treated, the patient will be taken off treatment and followed per section 6.7.

Up to two separate 1 week delays will be permitted within a cycle potentially extending the treatment cycle to a maximum of 6 weeks.

If a delay is required in association with more than 2 of the injections within a treatment cycle, the patient will be taken off treatment and followed per section 6.7.

Patients who do not receive at least 3 out of 4 doses for reasons other than toxicity will be unevaluable and will be replaced in that dose level cohort per section 11.3.

Additional treatment cycles: A disease re-assessment will be done approximately 2 weeks after the 4^{th} dose of ALT-803. Patients with stable disease may be considered for an additional treatment cycle (up to 2 additional cycles) at the same dose of ALT-803 if all of the following criteria are met:

- received all 4 doses in previous cycle (exceptions may be made on an individual patient basis if no more than one dose was missed for reasons other than toxicity)
- patient had no unacceptable toxicity during previous cycle (i.e. did not experience the equivalence of dose limiting toxicity)
- treatment related side effects (except skin rash) have resolved to grade 1 or better
- no evidence of > grade 1 GVHD

Day 1 of each subsequent treatment cycle must be at least 2 weeks, but not more than 4 weeks after the last dose of the previous cycle.

6.2.1 ALT-803 Dose Level Assignment – Dose Finding Phase

ALT-803 dose level assignment will occur at the time of study registration based on the following Dose Level cohorts:

Dose Level	ALT-803 Weekly Dose	Route of Administration	Number of Patients	Enrolling Institutions
1	1 microgram/kg	IV	6*	U of MN
2	3 microgram/kg	IV	3 to 6	U of MN and affiliates
3	6 microgram/kg	IV	3 to 6	
3a#	6 microgram/kg	SQ		
4	10 microgram/kg	SQ	6[&]	
5	15 microgram/kg	SQ	3 to 6	
6	20 microgram/kg	SQ	3 to 6	

* with the Feb 10, 2014 dose level 1 was expanded to 6 patients total after which dose escalation will continue as planned

with the April 28, 2015 protocol version ALT-803 dosing was changed from IV to SQ and dose level 3 (6 mcg/kg) was repeated to confirm safety with the new route of administration – in the unlikely event of dose de-escalation to level 2 or 1, the route of administration will be SQ

&with the April 2016 protocol version Dose Level 4 (10 mcg/kg) was expanded to enroll 6 patients despite the absence of DLT to gain further toxicity data before making the decision to continue dose escalation or declare level 4 the optimal dose and proceed to the extended phase. Dosing cohorts 5 and 6 were lowered to increase safety.

Within a dose level, the 1st patient must receive a minimum of 2 doses before additional patients are enrolled. The 1st dose for subsequent patients within a dose level must be separated by at least 72 hours. Dose escalation to the next level cannot proceed until the following conditions are met:

- All patients at the current dose level have completed at least 3 of the 4 planned ALT-803 doses
- The maximum tolerated dose (MTD) has not been exceeded
- The minimum efficacious dose (MED) of ALT-803 dose has not been reached

In February 2014 dose level 1 was expanded to enroll 6 patients total. This was done to confirm the findings in the 1st 3 patients of possible immune activation (evidenced by a fever between 2 to 3 hours after each dose) and to gain additional experience before continuing the dose escalation plan described in section 11.1.

In April 2015, the protocol was revised to replace intravenous (IV) administration of ALT-803 with a subcutaneous (SQ) injection while maintaining the current dose escalation/enrollment plan. To ensure

safety with the SQ dosing, a minimum of 3 patients will be enrolled in the highest dose level tested during intravenous administration (dose level 3 - 6 mcg/kg).

In April 2016, dose level 4 (10 mcg/kg) was expanded to enroll 6 patients despite no dose limiting toxicity and dose levels 5 and 6 were reduced to 15 mcg/kg and 20 mcg/kg.

Intra-patient dose escalation is not allowed.

6.2.1.1 Definition of Dose Limiting Toxicity (DLT)

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE).

Dose limiting toxicity (DLT) is defined as (during first treatment cycle only):

- any grade 3 treatment-emergent, non-hematologic toxicity lasting more than 48 hours with exception to the following events which will not count toward DLT:
  - Grade 3 fatigue and/or anorexia
  - Grade 3 hypertension
  - Grade 3 fever without evidence of infection
  - Grade 3 diarrhea despite the use of adequate/maximal medical intervention and/or prophylaxis
  - Grade 3 skin rash not requiring systemic steroid therapy
- any grade 4 or 5 treatment-emergent, non-hematologic toxicity
- grade III or IV acute GVHD within 6 weeks of the 1st dose of ALT-803

Dose escalation will be done based on the schema found in section 11. DLT's will be counted based on the number of patients with DLT at a given dose level, not the absolute number of DLTs. No single patient can trigger more than one DLT event. No further treatment will be given to a patient experiencing a DLT.

6.2.1.2 Definition of Maximum Tolerated Dose (MTD)

The maximum tolerated dose is that level where no more than 1 out of 6 patients experience dose limiting toxicity during the first treatment cycle.

6.2.1.3 Definition of Minimal Efficacious Dose (MED)

Since the ultimate goal is to use ALT-803 as a component of a more complex therapy, it will be critical to "leave room" for additional agents by keeping toxicity to a minimum. With that respect and although the exact threshold for MED is unknown,

given the action of IL-15 to stimulate homeostatic expansion CD8+ T cells and NK cells, we will use the absolute lymphocyte count (readily available on a clinical CBC) as a surrogate biomarker of biologic activity to define the MED.

MED is defined as an absolute lymphocyte count (ALC) of > 25,000 cells/μl that is sustained for > 24 hours in ≥ 2 of 3 patients (or ≥ 4 of 6) within a cohort.

6.2.2 ALT-803 Dose Level Assignment – Extended Phase

All patients will be treated at the ALT-803 MTD/MED declared during the Dose Finding Phase while adhering to the study early stopping rules per section 11.4.

6.3 Management of Selected, Expected Adverse Events

6.3.1 Hypotension (systolic blood pressure < 90 mm Hg)

For hypotension with systolic blood pressure less than 90 mm Hg, AND greater than 20 mm Hg below baseline, AND clinically significant per investigator, ALT-803 should be held until the systolic blood pressure reading rises above 90 mm Hg OR to baseline OR is no longer clinically significant.

Since the regimen is intended for outpatient administration, the need for fluid support will be considered on a patient-by-patient basis and not count toward dose limiting toxicity (if phase I, cycle 1).

However, if urgent medical intervention, such as IV hydration in the emergency room or hospital admission for drug toxicities, is indicated, tALT-803 will be permanently stopped. If the patient is enrolled in the Dose Finding Phase and the event occurs during cycle 1, a DLT will be reported.

6.3.2 Skin Rash

Due to the increase in frequency and severity of skin rash with subcutaneous injection a proactive skin rash management plan was added to section 6.2 in April 2016.

If the skin rash area surrounding the ALT-803 injection site is > 6 cm, it should be treated with topical 0.05% clobetasol propionate (i.e. 0.05% Cormax) or 0.1% triamcinolone (i.e., Kenalog) cream.

A biopsy of skin rash should be considered to confirm or rule-out graft versus host disease (GVHD).
If systemic steroids are required, ALT-803 should be discontinued per section 6.5. If the patient is enrolled in the Dose Finding Phase

and the rash occurs in association with the 1st cycle, a DLT must be reported.

6.3.3 Pulmonary Changes

Pulmonary function will be monitored at each visit by clinical examination, assessment of vital signs and pulse oximetry. Patients with dyspnea or clinical signs of respiratory impairment (tachypnea or rales) must be further assessed if clinically indicated, including the need for hospitalization.

6.3.4 Cardiac Changes

Cardiac function should be monitored at each visit by clinical examination and assessment of vital signs. In addition, an EKG and troponin level will be done at study entry and, for patients enrolled in the Dose Finding Phase only before the 1st dose and at 6 and 24 hours post. Patients with signs or symptoms of chest pain, murmurs, gallops, irregular rhythm, or palpitations must be further assessed if clinically indicated, including the need for hospitalization. If there is evidence of cardiac ischemia or congestive heart failure, ALT-803 will be permanently discontinued.

6.4 Supportive Care

Supportive care will be provided per institutional guidelines. Guidelines may be updated based on current data/drugs without requiring a protocol amendment or be considered a protocol deviation.

Due to the similarity of this agent to IL-2, which can inhibit neutrophil chemotaxis and increase the risk of complications from bacterial infections, patients who require or who have a pre-existing venous access device will receive prophylactic antibiotics (i.e. levofloxacin 250 mg daily or other appropriate prophylaxis) for the duration of the study treatment.

Patients with a diagnosis of multiple myeloma may receive additional therapy (e.g. lenalidomide, bortezomib) at the discretion of the treating physician after a minimum of 14 days have passed from the last dose of ALT-803.

6.5 General Concomitant Medications Guidelines

Concurrent chemotherapies (except hydroxyurea) and interferon-alfa treatment with ALT-803 are prohibited. Hydroxyurea may be used to control blasts count.

Administration of glucocorticoids is prohibited during the ALT-803 treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. They should be avoided except in the event of a severe toxicity or unrelated condition requiring

steroid and there use will be an indication to stop ALT-803. Topical steroid cream is permitted.

Beta-blockers and other antihypertensives may potentiate the hypotension and extra caution should be used during ALT-803 regimen treatment period. It is recognized, that ALT-803 treatment, like IL-2 and IL-15, may be associated with low blood pressure especially if the patient is not well hydrated.

Due to the similarity to IL-2 the potential drug interactions associated with IL-2 listed below may occur with ALT-803 treatment:

- Central nervous function: interactions could occur with concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquilizers).
- Kidney and liver function: concomitant nephrotoxic (e.g., aminoglycosides, indomethacin), myelotoxic (e.g., cytotoxic chemotherapy), cardiotoxic (e.g., doxorubicin), or hepatotoxic (e.g., methotrexate, asparaginase) medications should be avoided during ALT-803 regimen treatment period.
- Hypersensitivity reactions: reported in some patients receiving combination regimens of sequential high dose Proleukin and antineoplastic agents, specifically, dacarbazine, cisplatin, tamoxifen and interferon-alfa. Reactions including erythema, pruritus, and hypotension occurred within hours of administration of chemotherapy.
- Autoimmune and inflammatory disorders: exacerbation or initial presentation of crescentic IgA glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, and Stevens-Johnson syndrome has been observed following concurrent use of interferon-alfa and Proleukin.
- Delayed Adverse Reactions to Iodinated Contrast Media: 11–28% of patients treated with various Proleukin containing regimens and subsequently administered radiographic iodinated contrast media experienced acute, atypical adverse reactions. The onset of symptoms usually occurred within 1 to 4 hours following the administration of contrast media. Most events occurred when contrast media was given within 4 weeks after the last dose of Proleukin, but reactions were also reported when contrast media was given several months after Proleukin treatment. Reactions included fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, and oliguria. Similar conditions may occur with ALT-803 treatment.

6.6 Duration of Treatment

Patients may receive up to 3 treatment cycles (4 weekly injections of ALT-803 followed by at least 2 weeks, but not more than 4 weeks of no treatment) unless one or more of the following occurs:

- consent is withdrawn or patient is noncompliant

- patient requires a change in therapy
- patient experiences dose limiting toxicity (DLT) or other unacceptable toxicity
- patient requires more than a 1 week delay in the administration of an ALT-803 dose
- patient requires more than two separate 1 week delays from the planned ALT-803 administration day
- patient requires GVHD therapy

6.7 Duration of Study Participation

Evaluable patients will be followed for overall remission response, toxicity, and survival for 12 months from the 1st injection unless one of the following occurs:

- consent is withdrawn
- the patient is unevaluable per section 11.3 – if a patient is not evaluable, he/she will be followed only until the resolution or stabilization of treatment related toxicity. Unevaluable patients will be replaced to complete enrollment.
- the patient has no benefit from ALT-803 and/or begins other treatment in attempt to control the disease
- the patient enters hospice care – is this case date and cause of death will be recorded upon knowledge
- data collection on the study ends

All patients, regardless of circumstances, must be followed for a minimum of 4 weeks after the last dose of ALT-803 for incidence of acute GVHD (DLT event/early study stopping rule event and study endpoint) and any ongoing ALT-803 treatment related toxicity. If a clinic visit is not reasonable, follow-up may be done by an alternate means including via communication with the patient, family and/or local medical provider.

7 Clinical Evaluations and Procedures

Scheduled evaluations during the treatment cycles may be performed +/-2 day from the targeted date. The final treatment visit may be done +/-7 days of the targeted date. During follow-up, schedule assessments may be done +/- 30 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

The 24, 48, 72, and 96 hour follow-ups post dosing may be performed +/- 2 hours.

7.1 Standard of Care Clinical Evaluations

	Screening Within 14 days of enrollment unless o/w indicated	Each Treatment Cycle (up to a maximum of 3 cycles)												Final Treatment visit 4 weeks after final dose	Follow-up every 3 months from 1st dose until PD then survival only until 1 year
		Dose #1					Dose #2		Dose #3		Dose #4		Day 29 or 1 week after last dose	After each treatment cycle (~2 weeks after last dose)	
		Day1	Day 2 (~24 hours post)	Cycle 1 only: Day 3 (~48 hours post)	Cycle 1 only: Day 4 (~72 hours post)	Cycle 1 only: Day 5 (~96 hours post)	Day 8	Day 9 (~24 hours post)	Day 15	Day 16 (~24 hours post)	Day 22	Day 23 (~24 hours post)				
Consent	X															
Medical History	X															
Physical Exam	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]
Vitals and pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X															
Performance Status	X	X					X		X		X		X	X	X	X[4]
Survival Status														X	X	X
Assessment/query for reportable event(s)																X[4]
GvHD Surveillance refer to appendix IV for scoring	X												X[5]	X[5]	X[5]	X[4]
CBC, diff, plt	X	X	X	X			X	X	X	X	X	X	X	X	X	X[4]
BUN, creat, glucose, Na, K, Cl	X	X	X	X			X	X	X	X	X	X	X	X	X	X[4]
AST, ALT, bili, alk phos	X	X	X				X		X		X		X	X	X	X[4]
Troponin	X															
PT/PTT	X															
Pregnancy test[2]	X															
BM biopsy and aspirate	X[3]													X		X[4]
BM chimerism	X[3]													X		X[4]
CXR or chest CT scan	X[3]															
EKG	X[3]															
Ejection Fraction	X[3]															

1 – Neurological assessment at baseline only including basic motor (gait), coordination (steadiness) and cognitive function (alert and oriented) - any abnormalities should be followed up with a detailed neurologic exam.
2 - serum or urine, women of childbearing potential
3 - within 30 days of enrollment
4 – perform only if ongoing stable disease or benefit from ALT-803 (not required if disease progression after ALT-803 was previously documented or suspected).
5- grade III or IV acute GVHD within 6 weeks of the first dose of ALT-803 is a DLT event or early study stopping rule event based on which component the patient is enrolled

7.2 Research Related Evaluations

	protocol section	All Cycles			Cycle 1 Only (in addition to samples under "all cycles")							4 weeks after final dose[5] at final treatment visit
					Week 1 (Dose 1)							
		Before or on Dose 1	Weekly during dosing period[4]	1 week after final dose within a cycle[5]	Day 1 (inpatient) pre-dose	Day 1 (inpatient) time after dose	Day 2	Day 3 (+/- 1 day)	Day 5 (+/- 1 day) (U of MN only)	Pre-dose 3	1 week post final dose	
Toxicity Notation	9.2	Refer to section 9.2 for time points and documentation requirements										
EKG (Dose Finding Phase only)	n/a				X	6 hours	X					
Troponin (Dose Finding Phase only)	n/a				X	6 hours	X					
50 ml of heparinized blood (5 green top tubes)[1]	7.2.1	X	X	X				X	X			X
10 ml of serum (1 red top tube)[1]	7.2.1	X	X	X				X	X			X
Immunogenicity of ALT-803 5 ml red top tube	7.2.2				X[2]					X	X	
Pharmacokinetics (PKs) 5 ml red top (a minimum of 2 ml blood needed) per time point	7.2.2				X[2]	30 min, 2, 4,and 8 hours	X[3]					

1 Collect prior to day's ALT-803 dosing, if applicable
2 For cycle 1, the baseline PK and immunogenicity sample can be collected into the same tube
3 Final PK sample 24 hours (+/- 2 hours) post dose 1
4 Collect research blood samples weekly (i.e. prior to doses 2, 3, and 4, and on any weeks where dosing is delayed per protocol section 6.2)
5 Do not collect any additional research samples once a patient is off treatment for disease progression

7.2.1 Assessment of Immune Activation (TTL)

Samples to evaluate lymphocyte number, phenotype and function will be collected as detailed above for the Masonic Cancer Center Translational Therapy Lab (TTL).

Samples are shipped the day of collection to the University of Minnesota Masonic Cancer Center's Translational Therapy Lab (TTL) by overnight delivery in an insulated container with a frozen gel pack Monday-Thursday. Refer to the Affiliate Manual for additional details.

Translational Therapy Core Facility
University Of Minnesota
420 Delaware St. SE
Room A410 Mayo Building
Minneapolis, MN 55455
Phone: 612-625-6165
Fax: 612-625-9631

Flow cytometry analysis of a fraction of the PBMC will detect surface markers that define lymphocyte subsets (NK, NKT, B, and T cells, both CD4 and CD8), as well as intracellular markers that define regulatory T cells (Foxp3) and proliferating cells (Ki67). All remaining PBMC will be cryopreserved in 10% DMSO and stored in liquid nitrogen for future testing, if subject agreed to future storage at the time of initial consent.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples may be drawn at additional time points that are not specified above.

7.2.2 Pharmacokinetics and Antibodies (ALTOR)

The pharmacokinetics profile of ALT-803 levels will be assessed by ELISA using blood collected at the following time points:

ALT-803 dose	Pharmacokinetic Time Points for ALT-803
All cohorts	Immediate Pre-dose ALT-803
All cohorts	30 minutes after (± 5 minutes) ALT-803 injection is completed
All cohorts	2 hours after (± 15 minutes) ALT-803 injection is completed
All cohorts	4 hours after (± 60 minutes) ALT-803 injection is completed
All cohorts	8 hours after (± 60 minutes) ALT-803 injection is completed (omit if outpatient)
All cohorts	24 hours after (± 2 hours) ALT-803 injection is completed

NOTE: The precise ALT-803 administration time and the precise pharmacokinetic draw time must be recorded on the pharmacokinetic flow sheet.

Whole blood will be collected into 5 ml red top tubes (collect a minimum of 2 ml blood) to obtain serum for assays for quantifying serum levels of ALT-803.

Patients will be monitored for the presence and development of auto-antibodies to ALT-803 on day 1 pre-treatment (the baseline PK sample can be taken from this sample) and 1 week after the second dose (day 15) and 1 week after the final dose.

The tubes will be allowed to clot at room temperature and clinical sites will separate serum from cells within 4 hours of blood draw. Serum aliquots will be stored frozen at -20°C. Samples (ideally every 2 patients) will be batched and shipped overnight directly from the clinical site on dry ice to the Altor Bioscience's central laboratory.

Assays for quantifying serum levels of ALT-803 and ALT-803 antibodies will be conducted in the laboratory at Altor Bioscience, Miramar, FL.

8 ALT-803 Formulation, Supply, and Potential Toxicity

ALT-803, a recombinant human superagonist IL-15 complex, is the working name of the drug under investigation. Its active ingredient is ALT-803 and its pharmacologic class is as a targeted anticancer immunotherapeutic.

ALT-803 has been referred to as IL-15N72D:IL-15RαSu/IgG1 Fc complex in various preclinical study reports, publications, and other related documents. No other names exist for this product, as it is a novel investigational biologic.

8.1 Formulation and Composition

The biological drug product, ALT-803, is formulated in a phosphate buffered saline solution. The drug substance is produced by a recombinant mammalian cell line and is manufactured without the use of animal derived components. The vialed quantitative composition of ALT-803 is listed in the table below.

Quantitative Composition of ALT-803

Component	Concentration	Amount/Vial
ALT-803	1 mg/mL	1.2 mg
Phosphate Buffered Saline (PBS)	QS	1.2 mL

PBS Formulation: Sodium Chloride (USP) 8.18 g/L; Sodium Phosphate Dibasic (USP) 2.68 g/L; Potassium Phosphate Monobasic (NF) 1.36 g/L pH 7.4.

8.2 Structural Formula

ALT-803 is a soluble complex consisting of 2 protein subunits of a human IL-15 variant associated with high affinity to a dimeric IL-15R sushi domain/human IgG1 Fc fusion protein. The IL-15 variant is a 114 aa polypeptide comprising the mature human IL-15 cytokine sequence with an Asn to Asp substitution at position 72 of helix C (N72D).6. The human IL-15R sushi domain/human IgG1 Fc fusion protein comprises the sushi domain of the IL-15R subunit (aa 1-65 of the mature human IL-15Rα protein) linked with the human IgG1 CH2-CH3 region containing the Fc domain (232 amino acids). Aside from the N72D substitution, all of the protein sequences are human. Based on the amino acid sequence of the subunits, calculated molecular weight of the complex comprising 2 IL-15N72D polypeptides and a disulfide linked homodimeric IL-15RαSu/IgG1 Fc protein is 92.4 kDa. Each IL-15N72D polypeptide has a calculated molecular weight of approximately 12.8 kDa and the IL-15RαSu/IgG1 Fc fusion protein has a calculated molecular weight of approximately 33.4 kDa. Both the IL-15N72D and IL-15RαSu/IgG1 Fc proteins are glycosylated resulting in an apparent molecular weight of ALT-803 as approximately 114 kDa by size exclusion chromatography. The isoelectric point (pI) determined for ALT-803 range from approximately 5.6 to 6.5. Thus, the fusion protein is negatively charged at pH 7. The calculated molar extinction coefficient at A280 for ALT-803 is 116,540 M-1, or 1.26 OD280 for a 1 mg/mL solution of ALT-801, or one OD280 is equivalent to 0.79 mg/mL solution of ALT-803.

8.3 Storage and Handling

Study medication is provided in a 2 mL vial containing 1.2 mL of ALT-803 at a concentration of 1 mg/mL. Vials are packaged in cartons and shipped to the clinical site. Study medication must be maintained at a temperature between 2°C and 8°C.

8.4 Stability

Stability studies are ongoing and will be continued throughout the clinical study. Based on previous lots, the study drug is expected to be stable for at least 2 years. The site will be periodically updated on the stability of the drug and will be immediately informed if there is evidence that the drug no longer meets its stability specifications.

8.5 Agent Ordering and Agent Accountability

ALT-803 is produced in the USA by Altor Biosciences Corporation, Miramar, FL. After manufacturing, the product is stored at Altor Biosciences Corporation for clinical supply, packaging, and labeling. The label indicates the product name, strength, manufacturing date, and the study requirement information. ALT-803 will be shipped from Altor Biosciences Corporation to each participating site. (See the Study Procedures Manual for instructions on how to order ALT-803.)

8.6 Study Drug Preparation and Administration

ALT-803 dose calculation will be based on actual body weight. The calculated amount of ALT-803 will be drawn into a syringe for subcutaneous injection. The stock concentration is 1 mg/ml. Doses will be drawn directly into the syringe for injection. If the total subcutaneous dose is greater than 1.5 mL, the dose will be divided into 2-3 subcutaneous injections as needed. Each injection site should be separated by at least 1 inch.

8.7 Agent Inventory Records

The investigator, or a responsible party designated by the investigator (e.g. institutional investigational pharmacy), must maintain a record of the inventory and disposition of all agents received from Altor Biosciences Corporation using the Study Agent Drug Accountability Record. (See the Study Procedures Manual for the form to use and instructions on how to complete it.)

8.8 Toxicity

There is no previous safety and effectiveness experience of ALT-803 in humans. The ALT-803 protein complex comprises a variant of iL-15, a common γ chain cytokine that may have similar immunostimulatory properties as IL-2.

The study drug ALT-803 can cause many side effects which may be similar to the side effects of interleukin-2 (IL-2), which has been used for more than 20 years.

Risks of ALT-803		
Most likely (greater than 10% - 1 in 10 patients)	**Less likely (3% to 10% - 1 in 30 to 1 in 10 patients)**	**Rarely (< 3% - 1 in 30 patients)**
• weight gain with swelling of hands and feet due to fluid retention • feeling tired or short of breath due to a low red blood count (anemia) • increase in blood pressure • flu-like symptoms such as fever, chills, shaking, headache, stiffness, aching muscles and joints • increased risk of infection due to a low white blood count • increased risk of bruising and bleeding due to a low	• heart problems - causing low blood pressure, dizziness, chest pain or changes in heart rhythm (heart beat) • pain and redness at the injection site • changes in liver and kidney function as detected on routine blood tests • cough and shortness of breath • mouth sores • confusion, sleepiness and depression especially in older persons or persons with a history of depression	• allergic reaction • temporary thinning of hair

Risks of ALT-803		
Most likely (greater than 10% - 1 in 10 patients)	**Less likely (3% to 10% - 1 in 30 to 1 in 10 patients)**	**Rarely (< 3% - 1 in 30 patients)**
platelet count • skin rash • weakness, headache, dizziness • vomiting, nausea, loss of appetite • lower the levels of electrolytes as detected by routine blood tests		

To prevent or reduce the severity of the anticipated fever and chills, all patients will receive medications before and after each dose of ALT-803.

The most common side effects seen on this study with subcutaneous (under the skin) injections have been change in blood pressure (increase or decrease), a reaction at the injection site, and skin rash, which at times has been widespread. These localized skins reactions are expected to be common (up to 20% [one in 5 patients]). A biopsy of skin rash should be considered to confirm or rule-out graft versus host disease (GVHD).

Refer to the ALT-803 Investigator Brochure for additional details.

9 Adverse Event Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Note: throughout this section the generic term “study drug” refers to ALT-803.

9.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Treatment-Emergent Adverse Event: Any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment. A

treatment emergent AE refers to an event temporally related to the study treatment regardless of the causality assessment by the investigator.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Serious Adverse Event Or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Event Attribution Categories:
CTCAE does not define an AE as necessarily 'caused by a therapeutic intervention.' The clinical investigator must assign attribution for an adverse event after naming and grading of the event.

Attribution with 2 Options	Attribution with 5 Options	Description
Not related	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, as defined by the FDA

adverse events that occur as part of the disease process or underlying medical conditions are considered *unexpected;* however, for the purposes of this study they will not be documented or reported.

9.2 Adverse Event Monitoring and Documentation

9.2.1 Monitoring Period

Patients will be monitored for toxicity beginning with the 1st dose of ALT-803 through the final treatment visit approximately 4 weeks after the last dose of study drug. After the final treatment visit, only those events that meet the definition of serious, are felt to be at least possibly related to ALT-803,and are unexpected will be documented upon knowledge and, if applicable, reported in an expedited manner. Affiliate sites follow section 9.3 for expedited reporting requirements.

9.2.2 Event Documentation

As this study enrolls a medically complicated patient population adverse event documentation will be limited to ALT-803 “targeted” toxicities (side effects expected with this treatment to document the frequency and severity) and unexpected suspected adverse events (reactions).

Targeted adverse events and unexpected suspected adverse reactions will be documented using the form in appendix V at the following time points:

<u>First cycle only:</u>

- Before the 1st dose of ALT-803
- After the 1st dose (cycle 1 only)
  - 1-4 hours post
  - 6 hours +/- 1 hour
  - 24 hours +/- 2 hours
  - 48 hours +/- 2 hours
  - 96 hours +/- 2 hours
- Before the 2nd, 3rd, and 4th doses of ALT-803
- After the 2nd, 3rd, and 4th doses of ALT-803
  - At time of discharge from clinic (or 6 hours +/- 1 hour post dose if inpatient)
  - 24 hours +/- 2 hours
- 1 week after the last dose of ALT-803

<u>Subsequent cycles:</u>

- Before each dose
- At time of discharge from clinic (or 6 hours +/- 1 hour post dose if inpatient)
- 24 hours +/- 2 hours
- 1 week after the last dose of ALT-803 of each treatment cycle

Final Treatment Visit

- 4 weeks after the last dose of ALT-803 (final treatment visit)

At each of these time points the worst grade of the targeted toxicity since the previous assessment will be recorded in addition to any unexpected toxicities felt at least possibly related to ALT-803. If it has been greater than 24 hours since the last assessment (i.e. before each dose, 1 week after 4th dose) toxicities will be assessed for the previous 24 hours.

After the final treatment visit, monitoring for adverse events will become less frequent based on the follow-up schedule in section 7.1 and only events that meet the definition of serious, are at least possibly related to ALT-803, and are unexpected will be documented in OnCore and, if occurring at an affiliate site, reported to the MCC Study Coordinator per section 9.3.

In addition, although not always a reportable event, date and cause of death will be recorded in OnCore upon knowledge in the follow-up tab.

9.3 Affiliate Event Reporting to the U of MN MCC

Serious events:

Study Time Point	Beginning with the first dose of ALT-803 through the final treatment visit		After the final treatment visit
Reporting Requirements	any event meeting the definition of serious, regardless of attribution or expectedness		any event that is serious, unexpected and felt to be at least possibly related to ALT-803

Reports are to be submitted to the Study Coordinator at the University of Minnesota Masonic Cancer Center (MCC) within 24 hours of knowledge using the SAE reporting form found in OnCore. The MCC Study Coordinator will facilitate reporting to the University Of Minnesota IRB, Altor Bioscience, and the FDA as required.

Dose Limiting Toxicity (DLT) – Dose Finding Phase cycle 1 only:
Events counting toward dose limiting toxicity (DLT) as defined in section 6.2.1.1 must be reported to the MCC Study Coordinator within 24 hours of knowledge using the Event Form found OnCore under the reports tab.

Stopping Rule Events – Extended Phase only:

Events counting toward a study early stopping rule per section 11.4 must be reported to the MCC Study Coordinator within 24 hours of knowledge using the Event Form found OnCore under the reports tab.

Events that count toward a DLT or an early stopping rule do not necessarily constitute an adverse event requiring expedited reporting and should be reported as such only if they meet the criteria for expedited reporting as defined in section 9.1.

Affiliate institutions will be responsible for submitting adverse events to their institutional IRB and any other required local regulatory entities.

9.4 Required Reporting by the U of MN to the U of MN IRB, the FDA, and Altor BioScience

Note: Affiliate sites report adverse events to the Study Coordinator at the University of Minnesota per section 9.3. The Study Coordinator and personnel at the University of Minnesota are responsible for reporting to the entities in the below table.

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy AE to:
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm. refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xral0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu with a copy to Altor BioScience and each institutional PI	SAE Coordinator mcc-saes@umn.edu
FDA	Unexpected and fatal or life threatening suspected adverse reaction	As soon as possible but no later than 7 Calendar-Days	UMCC SAE form	Submit as an amendment to IND with a copy to Altor BioScience and each institutional PI	
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	As soon as possible but no later than 15 Calendar-Days			
	All other events per CFR 312.33	At time of IND annual report	Summary format	Submit as part of the IND annual report	Altor BioScience
	Note: Events due to the disease under treatment or an underlying medical condition will not require expedited reporting to the FDA for the purposes of this study				
Cancer Center SAE Coordinator	Any event that counts toward a DLT (cycle 1 dose finding phase) or stopping rule (extended phase)	Upon reporting	Event Form	SAE Coordinator mcc-saes@umn.edu	Altor Bioscience

10 Study Status Updates, Data Collection, and Monitoring

10.1 Study Status Updates

At least monthly teleconferences will be held between the PI (Dr. Miller) and key representatives of the affiliate sites to discuss enrollment, treatment tolerability and toxicity, disease response, and sample collection, as well as other relevant issues. Depending on the speed of enrollment and the level of patient issues, these teleconferences may be held more frequently or cancelled if there are no issues to discuss.

10.2 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms. Key study personnel will be trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore forms. Patient demographics, patient specific study treatment calendars, targeted adverse events, reporting of deaths, and other information required for IND annual reporting will be placed in OnCore and other research databases maintained by MCC IT.

10.3 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for completing e-CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

10.4 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://www.cancer.umn.edu/prod/groups/ahc/@pub/@ahc/@mcc/documents/content/ ahc_content_487799.pdf

For the purposes of data and safety monitoring, this study is classified as high risk (investigator initiated protocol under an IND). Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least quarterly (a copy pf the Progress Report will be provided to each affiliate site).
- The PI will comply with at least twice yearly monitoring of the clinical protocol by the Masonic Cancer Center monitoring services.
- The PI with the MCC CTO has oversight responsibility for trial monitoring at affiliate sites
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 9.4 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, FDA, and Altor BioScience.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the IND sponsor (Dr. Miller) will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect. A copy of the IND annual report will be provided to Altor BioScience and each affiliate institution.

10.5 Monitoring

The PI (Dr. Miller) with the MCC CTO has oversight responsibility for trial monitoring at affiliate sites. Affiliate sites must self-monitor following the University of Minnesota Masonic Cancer Center Data and Safety Monitoring Plan (http://www.cancer.umn.edu/prod/groups/ahc/@pub/@ahc/@mcc/documents/content/ahc_content_487799.pdf) and the CTO Affiliate and Satellite Site Monitoring SOPs.

10.6 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

In addition, the University of Minnesota Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the U of MN CTO before destroying any study related records.

11 Statistical Considerations

This phase I/II clinical trial includes two phases. The dose finding phase is a modified version of a phase I trial and the extended phase is a modified version of phase II trial.

11.1 Dose Finding Phase

The primary objective of this phase is to define the “maximum tolerated, minimum efficacious dose” (MTD/MED) of interleukin-15 (IL-15) super agonist complex (ALT-803) when given once weekly for 4 weeks in patients with hematologic malignancy who have relapsed after allogeneic transplant. The study will follow a standard 3+3 design of dose escalation for toxicity with an added feature of stopping early if efficacy is confirmed. The reason for using this modified 3+3 design is because it is possible for the MED to be below the MTD. Although the exact threshold for MED is unknown, given the action of IL-15 to stimulate homeostatic expansion

CD8+ T cells and NK cells, we will use the absolute lymphocyte count (readily available on a clinical CBC) as a surrogate biomarker of biologic activity to define the MED. We would like to identify MTD or MED whichever is encountered first at the dose finding phase and start the extended stage with the identified MTD or MED.

There are six dose levels of ALT-803 to determine the MTD/MED: 1, 3, 6, 10, 20, and 30 mcg/kg (in April 2016, the two highest dose levels were reduced to 15 and 20 mcg/kg as it was questioned if doubling the dose with each dose level change was excessive). Within a dose level, the 1st patient must receive a minimum of 2 doses before additional patients are enrolled. The 1st dose for subsequent patients within a dose level must be separated by at least 72 hours. Dose escalation to the next level cannot proceed until the following conditions are met:

- All patients at the current dose level have completed at least 3 of the 4 planned ALT-803 doses
- The maximum tolerated dose (MTD) has not been exceeded
- The minimum efficacious dose (MED) of ALT-803 dose has not been reached

Intra-patient dose escalation is not allowed.

Dose limiting toxicity (DLT) is generally defined as

- any treatment-emergent non-hematologic grade 3 toxicity lasting more than 48 hours with the exceptions detailed in section 6.2.1.1
- any treatment-emergent non-hematologic grade 4 or 5 toxicity
- grade III or IV acute GVHD within 6 weeks of the 1st dose of ALT-803

Efficacy is defined as an absolute lymphocyte count (ALC) of > 2500 cells/μl sustained for more than 24 hours in ≥ 2 of 3 patients (or ≥ 4 of 6) within a cohort.

The **specific dose finding procedure** based on traditional 3+3 design to determine MTD or MED is listed in the following table. The basic idea is that:

- If the current dose level is neither too toxic nor very effective, escalate to the next higher dose level;
- If the current dose level is toxic to a certain degree, further evaluate the current dose level for both toxicity and efficacy. If it turns out the current dose is neither too toxic nor very effective, escalate to the next higher dose level; if the current dose is very effective, stop and declare the current dose the MED (below MTD); if the current dose is too toxic, regardless of its efficacy, de-escalate to the next lower dose level.

- If the current dose level is too toxic, regardless of its efficacy, de-escalate to the next lower dose level.

The number of patients required in this dose finding phase would range from 6 patients at minimum to 36 patients at maximum.

Note: In February 2014 dose level 1 was expanded to 6 patients total to gain additional experience before continuing with the dose escalation plan (refer to section 6.2.1 for rationale).

Note: with the April 28, 2015 version of the protocol the administration route was changed from intravenous to subcutaneous and dose level 3 (6 mcg/kg) was repeated to ensure safety.

Note: with the April 2016 version of the protocol, dose level 4 was expanded to enroll 6 patients despite the absence of dose limiting toxicity in the 1st couple of patients treated at this dose level. Clinical benefit (at least 1 complete response and several patients with stable disease) has been noted in the absence of unacceptable toxicity. Therefore rather than continuing the dose escalation plan and moving to dose level 5 (ALT-803 at 20 mcg/kg), it was decided to enroll 6 at dose level 4 to gain additional toxicity data. Once 6 evaluable patients are treated at the ALT-803 10 mcg/kg level a decision will be made to either continue dose escalation, or more likely, proceed to the extended phase using dose level 4.

Dose-finding procedure of 3+3 design for determining MTD or MED, whichever is encountered first

# of patients with DLT at current dose level	Step 1 Decision Rule	# of patients with efficacy at current dose level	Step 2 Decision Rule
0/3 with DLT →	check efficacy →	≤ 1/3 with efficacy →	Escalate to current dose level+1 for the next 3 new patients.
		≥ 2/3 with efficacy →	• When 6 patients have been treated at current dose level, if ≥ 4/6 patients with efficacy, declare current dose level the MED; otherwise, escalate to current dose level +1. • When only 3 patients have been treated at dose level i, enter 3 new patients at dose level i. If ≥ 4/6 patients with efficacy, declare dose i the MED; otherwise, escalate to dose level i+1.
1/3 with DLT	Add 3 new patients at current dose level. If 0/3 with DLT (i.e. 1/6 with DLT) →	≤ 1/3 with efficacy →	Escalate to current dose level +1 for the next 3 new patients.
		≥ 2/3 with efficacy →	6 patients have been treated at current dose level. If ≥ 4/6 with efficacy, declare current dose level the MED; otherwise, escalate to current

# of patients with DLT at current dose level	Step 1 Decision Rule	# of patients with efficacy at current dose level	Step 2 Decision Rule
			dose level +1.
	Add 3 new patients at current dose level. If ≥ 1/3 with DLT (i.e. ≥ 2/6 with DLT) →	Regardless of efficacy →	Current dose level is above the MTD. De-escalation starts: • If 6 patients have been treated at current dose level -1, declare current dose level -1 the MTD; • If only 3 patients have been treated at current dose level -1, add 3 new patients at this dose level. If ≤ 1/6 with DLT and ≥ 4/6 with efficacy, declare current dose level -1 both the MTD and MED; if ≤ 1/6 with DLT and ≤ 3/6 with efficacy, declare current dose level -1 the MTD; if ≥ 2/6 with DLT, regardless of efficacy, dose de-escalation continues according to the same scheme.
≥ 2/3 with DLT	→	Regardless of efficacy →	Current dose level is above the MTD. De-escalation starts: • If 6 patients have been treated at current dose level -1, declare current dose level -1 the MTD; • If only 3 patients have been treated at current dose level -1, add 3 new patients at this dose level. If ≤ 1/6 with DLT and ≥ 4/6 with efficacy, declare current dose level -1 both the MTD and MED; if ≤ 1/6 with DLT and ≤ 3/6 with efficacy, declare current dose level -1 the MTD; if ≥ 2/6 with DLT, regardless of efficacy, dose de-escalation continues according to the same scheme.

11.2 The Extended Phase

The primary objective of this phase is to study the potential efficacy of IL-15 super agonist complex, ALT-803, in patients with hematologic malignancy who have relapsed after allogeneic transplant. The ALT-803 MTD/MED identified during dose finding will be the dose used during this enrollment. **Efficacy** of ALT-803 will be measured using rates of remission induction.

An **optimal Simon's two-stage design** will be used in this phase to test the null hypothesis of ≤ 10% remission induction versus the alternative hypothesis of ≥ 30% remission induction. For sample size estimation, we set the power (the probability of concluding efficacy of ALT-803 given it is truly effective) at 80%, and significance level (the probability of concluding efficacy of ALT-803 given it is actually not effective) at 0.05. If 2 or fewer of the first 14 patients (including the 6 patients treated at the same dose level from the dose finding phase) respond to ALT-803, we will conclude ALT-803 is unworthy of further study and terminate the trial early.

Otherwise, the trial goes on to the second stage, and an additional 23 patients will be studied. If the total number of patients responding to ALT-803 is ≤ 5, we will conclude ALT-803 is not effective.

11.3 Enrollment Plan

With the change in April 2016 and enrollment of 2 additional patients at dose level 4, the minimum additional enrollment during the dose-escalation phase will be 2 with a maximum additional 14 patients (2 at dose level 4 and 6 each at the 2 remaining doses). After completion of the dose escalation phase, a minimum of 8 additional patients with a maximum of 31 additional patients will be required to complete the trial. The maximum total additional patients with both phases will be 45 with 37 evaluable at the end of the phase II trial.

Based on enrollment in this protocol over the past year (N=17), our goal is to complete this study in 24 to 36 months.

A patient will be replaced and the ALT-803 dose level cohort reassigned if:

- the patient does not start ALT-803
- if more than 1 dose of ALT-803 is missed for a reason other than DLT
- patient requires more than two separate 1 week delays from the planned ALT-803 administration day

11.4 Stopping Rules

Excessive Toxicity

Because of severity of the diseases, toxicity of ALT-803 needs to be evaluated carefully. The hypothesized rate of having grade 3-4 non-hematologic, non-relapse and non-infectious toxicity (except for fevers alone) based on the NCI's CTCAE version 4 is encountered is 5%.

The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the true toxicity is equal to 5% and our sample size is at most 31 patients. This means enrollment will be stopped and the study re-evaluated if there are 2 patients with a grade 3-4 non-hematologic, non-relapse and non-infectious toxicity (except for fevers alone) occurring out of the first 7 patients, 3 out of 16, 4 out of 29, or 5 at any time.

Overall Mortality At Day 60 Post Relapse

The hypothesized rate of overall mortality at day 60 is 20%.

The goal is to construct a boundary based on mortality such that the probability of early stopping is at most 10% if the true mortality rate is equal to 20% and our sample size is at most 31 patients. This means

enrollment will be stopped and the study re-evaluated if there are 3 patients with an event out of the first 4 patients, 4 out of 6, 5 out of 10, 6 out 13, 7 out of 16, 8 out of 20, 9 out of 23, 10 out of 27 or 11 at any time.

Grade III-IV Acute GvHD
The hypothesized rate of having grade III-IV Acute GvHD is 5%.

The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the true toxicity is equal to 5% and our sample size is at most 31patients. This means enrollment will be stopped and the study re-evaluated if there are 2 patients with GVHD occurring within 6 weeks of the 1st dose of ALT-803 out of the first 7 patients, 3 out of 16, 4 out of 29 or 5 at any time. The stopping rules were developed using Pocock stopping boundaries.(28)

Note: these stopping rules are based on a per patient count, not the absolute number of events experienced by an individual patient. No single patient can count more than once toward these stopping rules.

11.5 Statistical Analysis Plan

Descriptive statistics will be calculated for correlative outcomes such as number and function of NK cells, T cells, and T regulatory cells. The changes in these correlates pre and post therapy will be evaluated using either nonparametric Wilcoxon signed rank test or parametric paired t test. For time-to-event data, Kaplan-Meier curves will be generated if no competing risk is presented for the event, otherwise cumulative incidence will be calculated for the event.

12 Conduct of the Study

12.1 Good Clinical Practice

The study will be conducted in accordance the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the

patients, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

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Appendix I –Patient Eligibility Checklist
IL-15 Super Agonist ALT-803 to Treat Relapse Of Hematologic Malignancy After Allogeneic Stem Cell Transplantation (HM2013-12)

Eligibility Checklist – page 1 of 2

Patient initials ☐☐☐☐ Patient ID☐☐☐-☐☐

1st 2 initials of first name + 1st 2 initials of last name — 3 letter site code – Seq # (i.e. 01, 02, 03, etc.)

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Relapse after previous allogeneic stem cell transplant for one of the following hematologic malignancies - acute myelogenous leukemia, acute lymphoblastic leukemia, lymphoma, myelodysplastic syndrome, myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia meeting the following: ○ For non-CML, relapse will be defined based on disease specific morphologic criteria from a bone marrow biopsy and aspirate or recurrence of disease specific cytogenetics. For disease specific definition of relapse, see appendix III. Relapse can be determined morphologically with < 5 percent blasts if definitive relapse can be determined. Equivocal results for relapse should result in a repeated test after an appropriate time interval (suggested 1 month) to determine eligibility. ○ For CML, relapse will be defined as any cytogenetic evidence of a Philadelphia chromosome or persistence of BCR/ABL rearrangements by molecular testing on at least two measurements over a 6 month interval. If cytogenetics are normal and there is PCR evidence of a BCR/ABL fusion, patients will be eligible if they have evidence of a quantitative increase in CML measured either by quantitative PCR or by fluorescent in situ hybridization (FISH). ○ For Chronic Phase CML patients only: • must have failed (no response in 3 months or incomplete response at 6 months) or refused treatment with TKI therapy • must have failed (defined as incomplete response or relapse) or refused DLI	☐	☐
2.	Relapse must be ≥ 60 days after transplant	☐	☐
3.	Prior DLI is allowed, however not within the 30 days before the 1st dose of ALT-803	☐	☐
4.	Minimum donor chimerism of 10%	☐	☐
5.	≥ 18 years of age	☐	☐
6.	Karnofsky performance status ≥ 70% PS = ☐☐☐%	☐	☐
7.	Adequate organ function within 14 days (30 days for cardiac) of enrollment defined as:	☐	☐

AST (SGOT)	< 5 x UNL	☐☐☐☐	☐☐/☐☐/☐☐
ALT (SGPT)	< 5 x UNL	☐☐☐☐	☐☐/☐☐/☐☐
creatinine	≤ 2.0 mg/dl	☐.☐	☐☐/☐☐/☐☐
Cardiac	LVEF > 40%	☐☐☐%	☐☐/☐☐/☐☐

		Yes	No
8.	Ability to be off prednisone and other immunosuppressive drugs for at least 14 days before first dose of study drug	☐	☐
9.	Patient agrees to stay within a reasonable distance (i.e. 30 minutes travel time) of the study site for the duration of the first treatment cycle through 24 hours after the last dose	☐	☐
10.	Women of child bearing potential and men with partners of child bearing potential must agree to use effective contraception during therapy and for 4 months after completion of therapy	☐	☐
11.	Voluntary written consent	☐	☐

IL-15 Super Agonist ALT-803 to Treat Relapse Of Hematologic Malignancy After Allogeneic Stem Cell Transplantation (HM2013-12)

Eligibility Checklist – page 2 of 2

Patient initials ☐☐☐☐

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
12.	Post-transplant lymphoproliferative diseases (often referred to as EBV-associated lymphomas)	☐	☐
13.	Known active CNS leukemia or lymphoma – patients with previously treated CNS disease is permitted if neurologically stable with no ongoing or anticipated need for steroid therapy are eligible	☐	☐
14.	Ongoing active acute or chronic GVHD requiring immunosuppressive therapy or signs of aGVHD or cGVHD requiring treatment	☐	☐
15.	Concurrent chemotherapy (except hydroxyurea) or IL-2 therapy or anticipated need during the study treatment and for 1 week after the last dose of ALT-803	☐	☐
16.	Pregnant or lactating – Women of child bearing potential must have a negative pregnancy test within 14 days of study treatment start	☐	☐
17.	Class II or greater New York Heart Association Functional Classification criteria (appendix II) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy	☐	☐
18.	Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval greater than 500 milliseconds)	☐	☐
19.	New progressive pulmonary infiltrates on screening chest x-ray or chest CT scan for which evaluation with bronchoscopy is not feasible. Infiltrates attributed to infection must be stable/improving (with associated clinical improvement) after 1 week of appropriate therapy (4 weeks for presumed or documented fungal infections).	☐	☐
20.	Active bacterial, fungal, or viral infections – all prior infections must have resolved following optimal therapy	☐	☐
21.	Known positive hepatitis C serology or active hepatitis B infection because of the risk of hepatic inflammation and the possible confounding of drug toxicity assessment – chronic asymptomatic viral hepatitis is allowed	☐	☐
22.	Known HIV positive because the effect of IL-15 viral loads, HIV immunity, and infectivity of proliferating T cells is unknown	☐	☐
23.	History of severe asthma, presently on chronic medications (a history of mild asthma not requiring therapy is eligible)	☐	☐

Date consent form signed: _____

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is:

☐ Eligible ☐ Ineligible Date registered _____

_____ _____

Signature of person verifying eligibility Date

Appendix II – Karnofsky PS and NYHA Classification

Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Ref: Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), *Evaluation of Chemotherapeutic Agents.* Columbia Univ Press. Page 196.

New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Ref: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix III – Disease Specific Response Criteria

CHRONIC MYELOGENOUS LEUKEMIA (CML) RESPONSE CRITERIA

In chronic phase CML, a hematologic response was defined as a 50% reduction in WBC counts from baseline sustained for at least 2 weeks. A Complete Hematologic Response (CHR) was defined as WBC < 10,000 per mm^3 and platelet count < 450,000 per mm^3 maintained for at least 4 weeks.

In blast crisis CML, a hematologic response is defined as a decrease in bone marrow blast count to < 5%, the disappearance of blasts in the peripheral blood, an absolute neutrophil count > 1000 cells/mm^3 and platelet count > 100,000 cells/mm^3. Patients who did not meet the criteria for a complete hematologic response may be categorized according to marrow response.
A marrow response is defined as either a decrease in the blast count to < 5% or between 5-15% regardless of peripheral blood cell counts.

- Disease progression is defined as an increase in marrow blasts > 15%, increase in peripheral blood blasts > 5% or WBC > 20,000 cells/mm^3.
- A relapse is defined as evidence of disease progression or death.

Cytogenetic Response
Cytogenetic responses (CR) were defined in terms of percentage of cells in metaphase existing within the bone marrow that were Philadelphia (Ph) chromosome positive. These responses were based upon a sample size of twenty cells in metaphase.

- A Complete Cytogenetic Response (CCR) was defined as no Ph(+) cells.
- A partial CR was defined as < 35% cells that were Ph(+).
- A minor CR was defined as 35-65% cells that were Ph(+).
- A lack of CR was identified when >65% cells were Ph(+).
- A major cytogenetic response (MCR) is comprised of complete and partial responses.

Molecular response
Standardization studies are ongoing and definition of molecular response currently varies.

- Complete molecular response: no detectable bcr-abl transcripts by RT-PCR.
- Major molecular response: ≥ 3-log reduction in the level of bcr-abl transcripts or bcr-abl/abl ratio ≤ 0.05%.

ACUTE MYELOGENOUS LEUKEMIA (AML) RESPONSE CRITERIA

Modified RECIST

Complete Remission (CR)

CR requires that all of the following be present.

- Peripheral Blood Counts
  - ANC count > 1,000/mm^3
  - Platelet count > 100,000/ mm^3
  - Reduced hemoglobin concentration or hematocrit has no bearing on remission status.
  - Leukemic blasts must not be present in the peripheral blood
- Marrow Aspirate and Biopsy
  - Bone marrow biopsy must demonstrate trilineage hematopoiesis with maturation of all cell lines.
  - < 5% blasts
- Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

Morphological Remission (MR)

MR requires that the following be present:

- Patient meets all peripheral blood and bone marrow criteria for CR, except that platelet count is < 100,000/mm3 but > 50,000/mm3.

Relapse

Relapse following CR is defined as:

- Peripheral Blood Counts
  Presence of peripheral blasts. A bone marrow examination must be performed to confirm relapse. However, please note that the date of relapse is the first date at which the relapsed patient had: leukemic blasts in the peripheral blood smear, **or** >5% blasts in the bone marrow.
- Bone Marrow Aspirate or Biopsy
  Presence of more than 5% blasts, not attributable to another cause (e.g., bone marrow regeneration).

ACUTE LYMPHOCYTIC LEUKEMIA (ALL) RESPONSE CRITERIA

Bone Marrow:
A1.Maturation of all cell lines: and <5% blasts and no Auer rods.
A2. Same as A1, except blasts ≥ 5% and < 25%.
A3. Failure to meet the criteria for A1 or A2.

Peripheral Blood:
B1. Neutrophils > 1,000/mcl; and platelets > 100,000/mcl; and no leukemia blasts in the peripheral blood.
B2. Failure to meet the criteria for B1.

Extramedullary Disease:
C1. None
C2. Any

CR	Attainment of A1 marrow status and B1 peripheral blood status and C1 extramedullary disease status for a period of at least 28 days.
CRi	CR with incomplete blood count recovery: Same as CR but platelets ≤ 100,000/mcl and/or neutrophils ≤ 1,000/mcl.
PR	Partial Response: All of the above criteria for CR must be met, except that the bone marrow may contain ≥ 5% but less than 25% blasts, or ≤ 5% blasts in the presence of Auer rods or abnormal morphology
Failure – resistant disease	Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course with persistent leukemia in the last peripheral blood smear or bone marrow, or with persistent extramedullary disease.
Failure – aplasia	Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow aplastic or hypoplastic (i.e. < 20% cellularity) and without leukemia blasts.
Failure - indeterminate	Indeterminate: (a) Patient survives < 7 days after completion of initial treatment course; or (b) patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.
relapse from CR	Relapse: Reappearance of leukemia blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); or appearance or reappearance of extra-medullary disease.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) RESPONSE CRITERIA

Complete Remission

CR requires all of the following criteria as assessed at least 3 months after completion of therapy:

- Absence of clonal lymphocytes in the peripheral blood.
- Absence of significant lymphadenopathy (e.g., lymph nodes > 1.5 cm in diameter) by physical examination or CT scan.
- No hepatomegaly or splenomegaly by physical examination or by CT scan.
- Absence of constitutional symptoms.
- Blood counts above the following values:
    - Polymorphonuclear leukocytes 1.5 x 10^9/L or more.
    - Platelets more than 100 x 10^9/L
    - Hemoglobin more than 11.0 g/dL; untransfused.

A bone marrow aspirate and biopsy should be performed at least 3 months after the last treatment if clinical and laboratory results demonstrate a CR. The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B-CLL cells. Cases with residual CLL cells by conventional flow cytometry or immunohistochemistry are defined as partial remission (PR).

In some cases, lymphoid nodules can be found (formerly used to define nodular PR), which often reflect residual disease. Therefore, these nodules should be assessed by immunohistochemistry to define whether they are comprised of CLL cells.

CR with Incomplete Bone Marrow Recovery (CRi)

For the definition of this category, CRi, the marrow evaluation should be performed with scrutiny and not show any clonal infiltrate.

Partial Remission

PR is defined by at least one of these parameters and needs to be documented for a minimal duration of 2 months:

• A decrease in the number of blood lymphocytes by less than 50% or more from the value before therapy.

• A decreased lymph node size by 50% or more in the sum products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node was present before therapy, as assessed by CT scan.

• No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant.

• A decrease in the size of the liver and/or spleen by 50% or more as defined by CT scan.

• The blood count should show one of the following results:

- Polymorphonuclear leukocytes at 1.5 x 10^9/L or more or 50% improvement over baseline without granulocyte colony-stimulating factor (G-CSF) support.
- Platelet counts greater than 100 x 10^9/L or 50% improvement over baseline.
- Hemoglobin greater than 11.0 g/dL or 50% improvement over baseline without red blood cell transfusions or erythropoietin support.

Progressive Disease

Progressive disease is characterized by at least one of the following:

- Constitutional symptoms persisting for more than 1 month.
- Progression of lymphadenopathy.
- Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site.
- A lymph node of 1 to 1.5 cm must increase by 50% or more to a size greater than cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
- An increase of 50% or more in the sum of the product of diameters of multiple nodes.
- An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (e.g., Richter syndrome).

Whenever possible, this diagnosis should be established by lymph node biopsy.
After treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease
Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease.

REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA (Cheson, 2007)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Cheson B, Pfistner B, Juweid, ME, et al. Revised Response Criteria for Malignant Lymphoma. JCO February 10, 2007 vol. 25 no. 5 579-586.

MULTIPLE MYELOMA RESPONSE CRITERIA

International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (BGM Durie 2006)

Response	IMWG Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence[3]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[2]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hour
PR	> 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 hour If the serum and urine M-protein are unmeasurable,[4] a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
MR	Not applicable
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	Increase of > 25% from lowest response value in any one or more of the following: •Serum M-component and/or (the absolute increase must be > 0.5 g/dL)[5] •Urine M-component and/or (the absolute increase must be > 200 mg/24 h) •Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL •Bone marrow plasma cell percentage; the absolute percentage must be > 10%[6] •Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas •Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse from CR[4] (To be used only if the end point studied is DFS)[7]	Any one or more of the following: •Reappearance of serum or urine M-protein by immunofixation or electrophoresis •Development of > 5% plasma cells in the bone marrow[6] •Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7. Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

1. Confirmation with repeat bone marrow biopsy not needed.
2. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
3. All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

4. For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
5. Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.
6. For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

MDS RESPONSE CRITERIA

Based on International Working Group 2006 Modified Criteria (BLOOD, 15 JULY 2006 VOLUME 108, NUMBER 2)

- Complete Remission (CR): ≤ 5% myeloblasts with normal maturation of all cell lines
  - Persistent dysplasia will be noted
  - Peripheral Blood:
    - Hgb ≥ 11g/dl
    - Platelets ≥ 100 X 10^9 /L
    - Neutrophils ≥ 1000
    - Blasts = 0%
- Partial Remission (PR): all CR criteria if abnormal before except:
  - BM blasts decreased by ≥ 50% over pre-treatment but still >5%
- Marrow CR: Bone marrow with ≤ 5% myeloblasts and decrease by ≥50% over pretreatment with incomplete peripheral blood count normalization
- Hematologic Improvement (HI):
  - Hgb: Increase by ≥ 1.5g/dl or decreased PRBC transfusions by at least 4/8 week period (only PRBC given for Hgb<9.0g/dl)
  - Platelet Response: Absolute increase of ≥ 30 X 10^9/L for those starting at >20 X 10^9/L For those < 20 X 10^9/L at baseline increase by 100%.
  - Neutrophil Response: at least 100% increase and an absolute increase of >0.5 X 10^9/L
- Stable Disease: Failure to achieve at least a PR but no evidence of disease progression for >8 weeks
- Failure: Death during treatment or disease progression characterized by worsening cytopenias, increase percentage of marrow blasts, or progression to a more advanced MDS FAB subtype
- Cytogenetic Response:
  - Complete: Disappearance of any pre-treatment chromosomal abnormalities without the appearance of new ones
  - Partial: At least 50% reduction of chromosomal abnormality
- Disease Progression: Compared to pre-treatment values
  - Less than 5% blasts: greater than 50% increase to >5% blasts
  - 5-10% blasts: greater than 50% increase to >10% blasts
  - 10-20% blasts: greater than 50% increase to >20% blasts

Appendix IV - GvHD Scoring

Acute GVHD
Organ involvement will be staged using the criteria outlined in the table below. Biopsy of each organ site at diagnosis or major change in disease activity will be performed unless clinical circumstances make it impossible.

Consensus Clinical Stage and Grade of Acute GVHD (Przepiorka *et al*, 1995)

Stage	Skin	Liver	Lower Gastrointestinal Tract	Upper Gastrointestinal Tract
1	Maculopapular rash <25% of body surface	Bilirubin 2.0 – 3.0 mg/dl	Diarrhea 500 – 1000 mL/day or 280 – 555 mL/m^2	No protracted nausea and vomiting
2	Maculopapular rash 25-50% body surface	Bilirubin 3.1 – 6.0 mg/dl	Diarrhea 1000 – 1500 mL/day or 556 – 833 mL/m^2	Persistent nausea, vomiting or anorexia
3	Generalized erythroderma	Bilirubin 6.1 – 15.0 mg/dl	Diarrhea >1500 mL/day or >833 mL/m^2	
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/dl	Severe abdominal pain, with or without ileus, or stool with frank blood or melena	

Grading for Treatment Criteria:

Mild GVHD Skin stage I-II only (Equivalent to Seattle Grade I).

Moderate GVHD Skin stage I-III and/or liver I-IV and/or Gastrointestinal tract (GI) I-III and/or Upper GI (UGI). (Equivalent to Seattle Grade II, III).

Severe GVHD Any stage IV along with severe clinical illness.

Late Acute and Chronic GVHD
Late acute and chronic GVHD will be assessed using the National Institutes of Health (NIH) Consensus Criteria.

Appendix V –Targeted Toxicity Form (CTCAE 4.0)

See section 9.2 for time points HM2013-12 (shade events may meet definition of DLT)

Patient Initials: _____ Date of Assessment: _____ Assessment Time Point: _____

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Dyspnea	None or no change	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypoxia	None	……	Decreased O_2 saturation with exercise (e.g., pulse oximeter < 88%) intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or $PaO_2 \leq 55$ mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Fever	None	38.0 - 39.0 °C (100.4 - 102.2 °F)	> 39.0 - 40.0 °C (102.3 - 104.0 °F)	> 40.0°C (>104.0 degrees F) for ≤ 24 hours	> 40.0 °C (>104.0°F) for > 24 hours
Febrile neutropenia	None	……	……	ANC <1000/mm with a single temperature of >38.3°C (101 °F) or sustained temp ≥38 °C (100.4°F) for > 1 hour	Life-threatening consequences; urgent intervention indicated
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	……
Hypertension	None	Pre-hypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent ≥ 24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.	Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
Hypotension	None	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Edema	None	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	……
Pneumonitis	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation or tracheotomy)
Injection Site Reaction	None	Tenderness with or without associated symptoms	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Rash	None	Covering < 10% body surface area (BSA)	Covering 10-30% body surface area (BSA)	>30% body surface area (BSA)	Generalized exfoliative, ulcerative, or bullous dermatitis
Weight Gain	None	5 - <10% from baseline	10 - <20% from baseline	≥20% from baseline	……
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	……
Vomiting	None	1 - 2 episodes (separated by 5 minutes) in 24 hours	3 -5 episodes (separated by 5 minutes) in 24 hours	≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization	Life-threatening consequences; urgent intervention indicated
Other record on AE log CRF in Oncore		Mild	Moderate	Severe	Life- threatening

Person Completing Form: _____ ADL = activities of daily living

All Events are Expected and Attributable Except: _____