STUDY NUMBER: CASE 10Z17

ClinicalTrials.gov #: NCT03342196

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STUDY TITLE: **A Phase II Study of Thiotepa added to Fludarabine and Melphalan as the Preparative Regime for Alternative Donor Transplantation**

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SUPPORT/FUNDING:	List any support/grants or any funding source (partial or full) here
IND #:	Exempt
OTHER AGENT***(S):***	Thiotepa / Melphalan / Fludarabine

SUMMARY OF CHANGES

Protocol Date	Section	Change
09/14/17		Initial IRB approval
12/19/17	Cover page	Added Clinical Trials.gov NCT #; updated version date and contact information for study coordinator
	Protocol Summary	Inclusion criteria revised to be consistent with Section 4.1.2
	11.1.2	Revised to indicate timing of follow-up tests and procedures
	11.2	Footnotes added to the Study Calendar to indicate timing of tests and procedures
03.22.18	Cover page	Updated version date
	Protocol Summary	Corrected typographical error
	4.2.1	Changed Pulmonary function: DLCOcorr < 40% normal to Pulmonary function: DLCOc <40% normal
	8.2.2	Corrected typographical error
04.13.18	Cover page	Updated version date
	8.2.3	Updated CTCAE version to 5.0
	11.1.2	Text has been added to clarify the timing of the bone marrow aspiration
	11.2	Footnotes have been revised to clarify the timing of the bone marrow aspiration
10.31.18	Cover page	Updated version date
	Cover page	KGF added to other agents
	Fig. 2	work
	Protocol summary	Added: KGF 60mcg/kg IV on day -11, -10, and -9 and 0, +1, and +2.
	3.4	Day -8 changed to day -11
	6.2	Added: Keratinocyte Growth Factor (Palifermin, Kepivance, K) will be given at a dose of 60mcg/kg IV on day -11, -10, and -9 and 0, +1, and +2 for both haplo-identical transplants and dUCBT.
	8.1.7	Added: 8.1.7 Palifermin (Kepivance) Palifermin may cause rash, itching, redness, or discoloration of the skin. It may cause edema, an increase in pancreatic enzymes. It may cause arthralgia. It may cause tongue discoloration or tongue edema.
	8.1.8	Renumbered from 8.1.7
	9.1.4	Added **Kepivance, Palifermin, KGF, Keratinocyte Growth Factor** Pharmacologic information

Protocol Date	Section	Change
	11.1.2	Added: **<u>T-11, -10, -9</u>** • Keratinocyte Growth Factor (Palifermin, Kepivance, K) will be given at a dose of 60mcg/kg **<u>T +0</u>** • Infusion of graft source: dUCBT or Haplo-Identical Donor • Keratinocyte Growth Factor (Palifermin, Kepivance, K) will be given at a dose of 60mcg/kg IV after the infusion of the hematopoietic stem cells **<u>T +1</u>** • Keratinocyte Growth Factor (Palifermin, Kepivance, K) will be given at a dose of 60mcg/kg IV **<u>T +2</u>** • Keratinocyte Growth Factor (Palifermin, Kepivance, K) will be given at a dose of 60mcg/kg IV
	11.2	Study calendar updated to include KGF
12.13.18	Figure 2 Protocol summary 6.2	Corrected dose of rabbit ATG (A) to 1 mg/kg on day -3 and 2 mg/kg on day -2
	11.2	Correct study calendar to indicate Palifermin on days -11, -10, -9 (not -8)
2.7.2020	Through out document	Minor grammatical & typographical corrections Updated protocol version date in footer Figures updated to correspond with text updates
	Title page	Updated version date Updated study nurse
	1.3	Added: Alternative donor transplant have acceptable clinical outcomes comparable to matched unrelated donors, therefore anyone without a matched related donor may be a candidate for this trial
	2.1	Changed leukemia-free survival to disease-free survival
	4.1.1	Added intermediate risk to inclusion criteria: Complete Remission (CR1) with poor or intermediate-risk cytogenetics or molecular markers (e.g. Flt 3 mutation, 11q23, del 5, del 7, complex cytogenetics)
	4.1.1	Added treatment related MDS to inclusion criteria: Myelodysplastic syndromes (MDS), Intermediate, High or Very High Risk by the revised international prognostic scoring system (IPSS-R; See Appendix B) or treatment related MDS.
	4.1.1	Added Intermediate one to inclusion criteria: Myelofibrosis (MF): Intermediate-1, Intermediate-2 or high risk by DIPSS-plus
	4.1.1	Added inclusion criteria: Chronic Myelomonocytic Leukemia

Protocol Date	Section	Change
	4.1.4	Removed unrelated from inclusion criteria: Patients without a matched related donor
	8.2.3	Added clarification: exempting those previously mentioned in section 8.2.2
	8.2.3	Added clarification: Attribution is required for the treatment as a whole, not individual components of the treatment.
	8.4	Added clarification: expected adverse events listed in Sec. 8.2.2 above (not collected at all).
	11.1	Added differential to Complete Blood Count and Differential
	11.1.2	Treatment Period corrected from day -8 to: Treatment time will begin the day -11
	11.2	Corrected study calendar to indicate testing window of 2 weeks Added clarifications to footer
5/13/20	Through-out document	Updated protocol version date in footer
	4.0	Added missing OR to inclusion criteria o Relapsed or Refractory Lymphoid Malignancies (including non-Hodgkin Lymphoma, Hodgkin Lymphoma) meeting the following criteria: ▪ Disease status: Stable Disease, Partial Remission or Complete Remission ***OR*** ▪ Have relapsed after autologous transplant or who have failed to collect for an autologous transplant.
7/22/20	Through-out document	Updated protocol version date in footer
	Cover page	Updated version date
	7.0	Revised to specify that the fludarabine dose may be reduced for patients at an increased risk for neurotoxicity, including those with impaired renal function, prior high dose cytarabine, intrathecal therapy, or cranial irradiation and prior HSCT with fludarabine conditioning.
1/8/2021	Through-out document	Updated protocol version date in footer
	Cover page	Updated version date; updated study staff
	7.0	Revised thiotepa dose modification to add *or has comorbidities that may increase the risk of morbidity or mortality with conditioning chemotherapy,* the dosage of thiotepa may be reduced to *7.5mg/kg or* 5mg/kg at the discretion of the treating physician.
	7.0	Added: If a patient develops a reaction to KGF that significantly impacts the care, health, and/or functionality of the patient, further doses may be omitted from the preparative regimen.

Protocol Date	Section	Change
3/31/21	Through-out document	Updated protocol version date in footer
	Through-out document	Minor corrections to spelling, grammar, and document formatting
	Study Schema	Figure 1: "Decision Tree on how donor sources are decided for patients enrolled in CASE 10Z17" revised
	Study Schema Study Summary	ATG for cord blood transplants removed as a treatment option for this protocol. We will not be utilizing ATG in cord blood transplants per ASTCT guidelines.
	Table of abbrevia-tions	Abbreviations added, table reorganized into alphabetical order for ease of use
	1.3	ATG for cord blood transplants removed as a treatment option for this protocol per ASTCT guidelines
	1.3	Removed ATG dosing, added We will not be utilizing ATG in cord blood transplants per ASTCT guidelines.
	3.4	Clarification: Added definition of treatment failure
	4.1.2	Upper age limit lowered from 75 years to 65 years
	4.2.1	Creatinine clearance changed from <30 to <50 ml/min AST(SGOT) & ALT(SGPT) changed from > 2X to >3X ULN DLCOc changed from <40 to < 60% normal Ejection fraction changed from < 35% to <50% KPS<80 Thus, revised section is: Patients with inadequate Organ Function as defined by: o Creatinine clearance < 50ml/min o BilirubinS ≥ 2X institutional upper limit of normal o AST (SGOT) ≥ 3X institutional upper limit of normal o ALT (SGPT) ≥ 3X institutional upper limit of normal o Pulmonary function: DLCOc < 60% normal o Cardiac: left ventricular ejection fraction < 50% o KPS < 80
	6.1	Figure 1: "Decision tree for choosing of a graft" revised
	6.2	Removed ATG dosing, ATG no longer utilized in cord blood transplants per ASTCT guidelines
	8.1.6	Removed ATG risks, ATG no longer utilized in cord blood transplants per ASTCT guidelines
	8.1	Sections re-numbered after deletion of section 8.1.6
	11.1.2	Removed ATG as treatment options, ATG no longer utilized in cord blood transplants per ASTCT guidelines
	Appendix A	Karnofsky Performance Status added
	Appendix B	Revised

Protocol Date	Section	Change
6/22/21	Through-out document	Updated protocol version date in footer References re-numbered as needed
	Cover page	Study coordinator updated
	decision tree	Updated
	1.3	Added: [9]. *Cord blood selection will be based on ASTCT guidelines as well*[10].
	4.1.3	ECOG performance status removed, Karnofsky Performance Status (KPS) added as protocol relies on KPS
	4.1.5	Inclusion criteria update to match ASTCT current guidelines
	11.2	ECOG performance status removed, Karnofsky Performance Status (KPS) added as protocol relies on KPS
	Appendix A	ECOG performance status removed as protocol relies on KPS
	References	References revised
10/26/22	4.1	Added inclusion criteria: Mixed Phenotypic Leukemia / Biphenotypic Leukemia in CR
2/21/23	Cover page Study Schema Protocol Summary Abbreviations 6.2 7.0 8.1.6 9.1.4 11.1 11.2	Palifermin (Kepivance or Keratinocyte Growth Factor (KGF)) is no longer manufactured, thus is no longer available and is being removed from the protocol.

STUDY SCHEMA

Figure 1. Decision Tree on how donor sources are decided for patients enrolled in CASE 10Z17

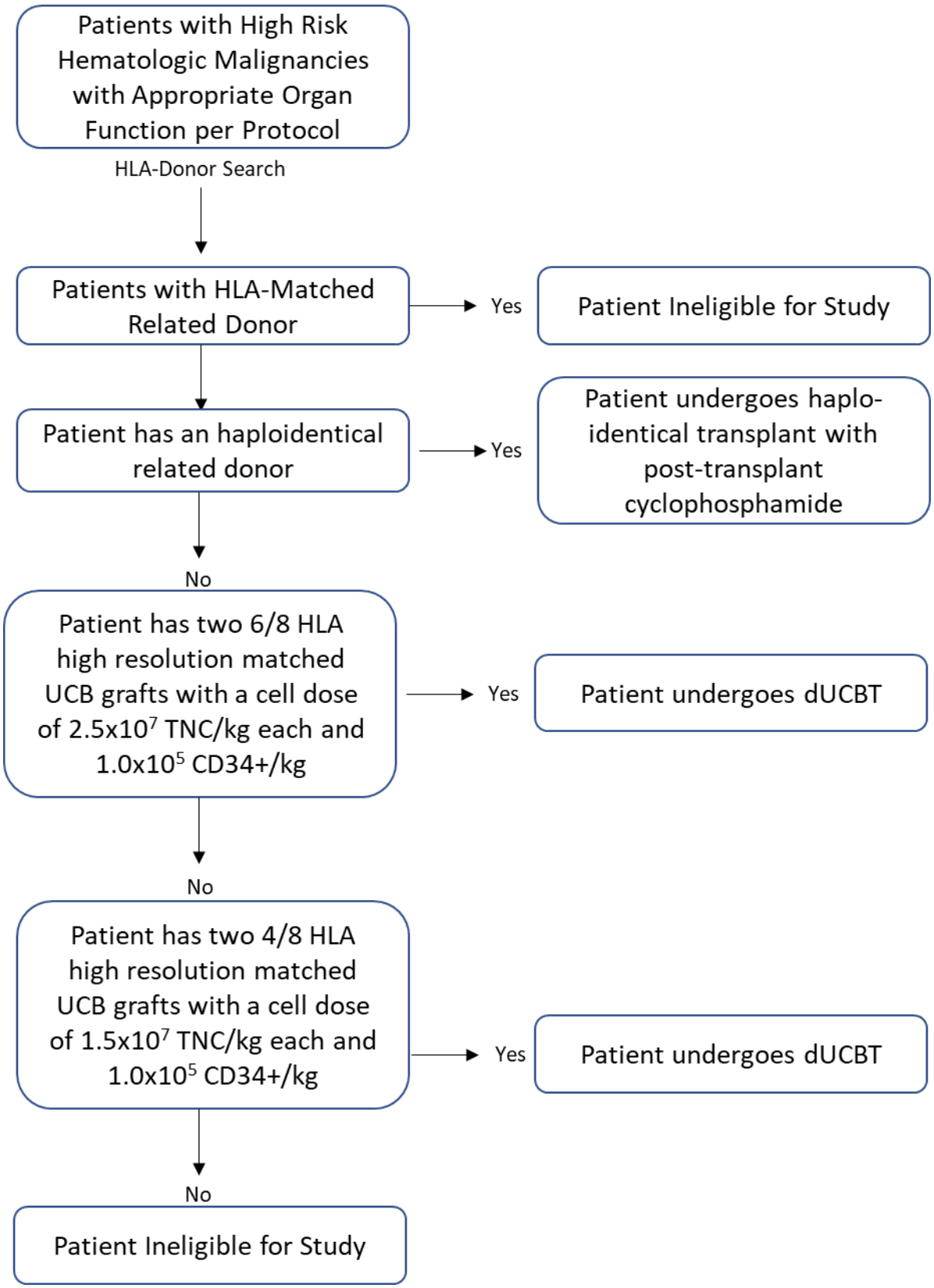


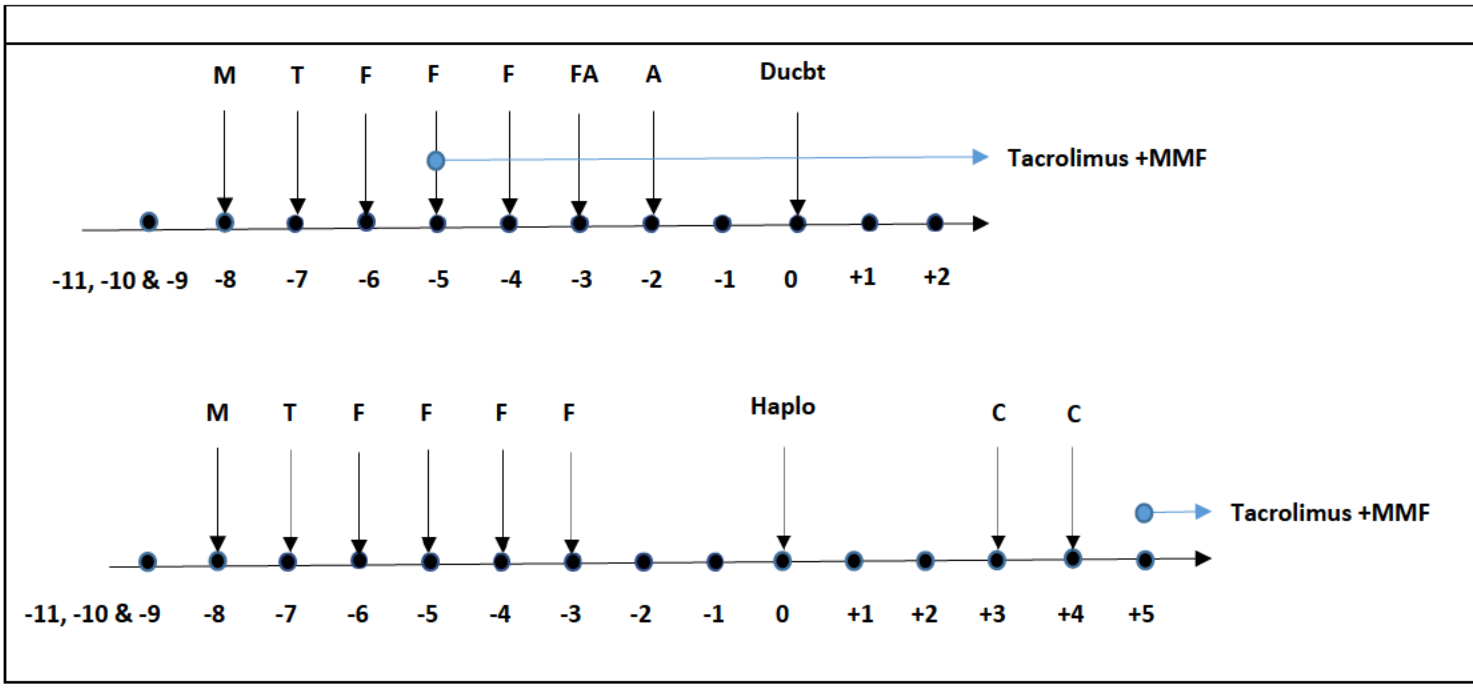
Figure 2. Preparative Regimen and Thiotepa Dosing for Double Umbilical Cord Transplant (dUCBT) and haplo-identical transplant (Haplo).

The conditioning regimen would consist of melphalan (M) 100 mg/m^2 on day −8, thiotepa (T) 10 mg/kg on day -7, fludarabine (F) 160 mg/m^2 in divided doses given on days −6, −5, −4 and −3.

If the patient undergoes a haplo-identical transplant, post-transplant cyclophosphamide (C) will be added as 50 mg/kg given on each of days +3 and +4.

Graft-versus-host disease prophylaxis will consist of tacrolimus and mycophenolate mofetil (MMF), starting on day-5 for dUCBT.

Graft-versus-host disease prophylaxis will consist of tacrolimus and MMF starting on day+5 for haplo-identical transplant.



PROTOCOL SUMMARY

Protocol Number/Title	CASE 10Z17 A Phase II Study of Thiotepa added to Fludarabine and Melphalan as the Preparative Regime for Alternative Donor Transplantation
Study Phase	II
Brief Background/Rationale	In the United States, thiotepa has been utilized in reduced intensity conditioning regimens for alternative donor courses (double umbilical cord blood transplant (dUCBT) and haplo-identical transplants). Our hypothesis is that thiotepa at a dose of 10mg/kg, in combination with melphalan (100mg/m^2) and fludarabine (160mg/m^2) as a reduced intensity conditioning regimen for alternative donor transplant is safe and effective in patients with hematologic malignancies Given that this regimen has been investigated extensively, and the current study proposes to confirm those previous observations with a small modification (melphalan dose reduction due to previous mucositis rates with higher doses), this will be a phase II study designed to measure disease-free-survival.
Primary Objective	To assess the effectiveness of Thiotepa, Fludarabine, and Melphalan in alternative donor transplants as measured by leukemia free survival.
Secondary Objective(s)	To assess the 1- year OS, Relapse, TRM, aGVHD and cGVHD, rates of neutrophil and platelet engraftment.
Sample Size	Approximately 39 males and females 1 year to 75 years of age
Disease sites/Conditions	Acute Myelogenous Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Myelodysplastic syndrome (MDS), Myelofibrosis and Lymphoma
Interventions	Melphalan 100 mg/m^2 on day −8 Thiotepa 10 mg/kg on day -7 Fludarabine 160 mg/m^2 in divided doses given on days −6, −5, −4 and −3. If the patient undergoes a haplo-identical transplant, post-transplant cyclophosphamide will be added as 50 mg/kg given on each of days +3 and +4.

ABBREVIATIONS

AE	Adverse event
aGVHD	Acute Graft Versus Host Disease
AML	Acute Myelogenous Leukemia
ALL	Acute Lymphocytic Leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
cGVHD	Chronic Graft Versus Host Disease
CML	Chronic Myelogenous Leukemia
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CTCAE	NCI Common Terminology Criteria for Adverse Events
DCRU	Dahm's Clinical Research Unit
DFS	Disease Free Survival
DSTC	Data Safety and Toxicity Committee
dUCBT	Double Umbilical Cord Blood Transplant
FDA	Food and Drug Administration
ICF	Informed Consent Form
IPS	Idiopathic Pneumonia Syndrome
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
GVHD	Graft Versus Host Disease
GVL	Graft Versus Leukemia
KPS	Karnofsky Performance Statue
LFS	Leukemia Free Survival
MDS	Myelodysplastic Syndrome
MMF	Mycophenolate Mofetil
OS	Overall Survival
PRMC	Protocol Review and Monitoring Committee
RIC	Reduced Intensity Conditioning
SAE	Severe Adverse Event
SOC	Standard of Care
TBI	Total Body Irradiation
TRM	Transplant Mortality Rate
UCB	Umbilical Cord Blood
UH	University Hospitals
VOD	Veno-occlusive Disease of the Liver

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n/a

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Acute GVHD clinical assessment per Blood and Marrow Transplant Clinical Trials Network Manual of Operations (BMT MOP)

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1.0 Introduction

1.1 Study Diseases
Acute Myelogenous Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Myelodysplastic syndrome (MDS), Myelofibrosis and Lymphoma

1.2 Name and Description of Investigational Agents
Thiotepa / Melphalan / Fludarabine in Alternative Donor Transplants

1.3 Rationale
Reduced intensity conditioning (RIC) regimens have expanded availability of allogeneic transplantation and therefore cure to a greater number of patients who would not be otherwise eligible for myeloablative transplantation based on age or organ function[1]. However, the rates of relapse with such regimens remain high and thus there have been attempts to intensify RIC with a number of chemotherapeutic or immunologic agents[2,3]. Thiotepa, an alkylating agent with very good central nervous system penetration, has been studied in a number of phase II trials as a way to intensify RIC and achieve better outcomes for patients with hematologic malignancies[4,5].

Thiotepa has been shown to be safe and effective as an additional chemotherapeutic to conditioning regimens. In an European Society for Blood and Marrow Transplant (EBMT) retrospective analysis of the use of thiotepa as a part of the conditioning regimen in allogeneic transplant for AML, which included matched related donors, matched unrelated donors, and cord blood transplants, the majority of the conditioning regimens were myeloablative and consisted of: fludarabine, busulfan, and thiotepa; fludarabine and thiotepa (+/- TBI); and cyclophosphamide and thiotepa (+/- TBI)[6]. The overall leukemia free survival at 3 years was 41% in patients in CR1; non-relapse mortality at 3 years was 19%. The rates of mucositis were 47% and the rate of VOD was 4%, even with the high percentage of myeloablative conditioning within the cohort.

In the United States, thiotepa has been utilized in reduced intensity conditioning regimens for alternative donor courses (double umbilical cord blood transplant (dUCBT) and haplo-identical transplants). In a retrospective analysis of dUCBT for AML, thiotepa at 10mg/kg was added to melphalan 140mg/m^2 and fludarabine 160mg/m^2 [4]. Forty-three of 47 patients engrafted (91%); and 1-year treatment related mortality was 28%. One year overall survival was 59%. The major toxicity was GI (nausea / vomiting / mucositis / diarrhea) and there was no veno-occlusive disease diagnosed in this cohort. In a retrospective analysis of haplo-identical transplants for AML, thiotepa at 10mg/kg was added to melphalan 140mg/m2 and fludarabine 160mg/m2[5]. Haplo-identical grafts were CD34+ selected. Although there was a high rate of graft failure (22%), many patients had donor-specific antibodies (3 out of 22 patients). The major toxicity was GI (nausea / vomiting / mucositis / diarrhea) and there was no veno-occlusive disease diagnosed in this cohort. The non-relapse mortality was 32% and there was a high rate of relapse in these high risk patients (44% by day 72 post-transplant).

Besides utilizing chemotherapy to reduce relapse, another mechanism by which one can affect disease control is through the graft versus leukemia (GVL) effect. Recently Milano et al published data in support of superior GVL with cord blood grafts[7]. There is not similar data in regards to haplo-identical transplants.

Our hypothesis is that thiotepa at a dose of 10mg/kg, in combination with melphalan (100mg/m^2) and fludarabine (160mg/m^2) as a reduced intensity conditioning regimen for alternative donor transplant is safe and effective in patients with hematologic malignancies. Alternative donor transplant have acceptable clinical outcomes comparable to matched unrelated donors, therefore anyone without a matched related donor may be a candidate for this trial[8]. We have decided to reduce the melphalan dose to limit GI toxicity associated with the combination of melphalan (at 140mg/m^2), fludarabine (160mg/m^2) and thiotepa (10mg/kg). We will not be utilizing ATG in cord blood transplants per ASTCT guidelines[9]. Cord blood selection will be based on ASTCT guidelines as well[10]. Haplo-identical transplants will undergo post-transplant cyclophosphamide for GVHD prophylaxis.

Given that this regimen has been investigated extensively, and the current study proposes to confirm those previous observations with a small modification (Melphalan dose reduction due to previous mucositis rates with higher doses), this will be a phase II study designed to measure disease-free-survival.

2.0 Objectives

2.1 Primary Objective

To assess the effectiveness of Thiotepa, Fludarabine, and Melphalan in alternative donor transplants as measured by disease free survival.

2.2 Secondary Objective(s)

To assess the 1- year OS, Relapse, TRM, aGVHD and cGVHD rates and the rates of neutrophil and platelet engraftment.

3.0 Study Design

3.1 Study design

This is a Phase II study of Thiotepa, Fludarabine, and Melphalan in alternative donor transplants.

Subjects will be assessed for safety and tolerability (including adverse events, serious adverse events, and clinical/laboratory assessments) using a continuous monitoring approach. Subjects will be followed for up to 1 year or until progression of disease, relapse, or death.

3.2 Number of Subjects

Approximately 39 subjects will be enrolled in this trial.

3.3 Replacement of Subjects

There may be replacement of subjects if a patient is enrolled but does not start treatment before they come off study.

3.4 Expected Duration of Treatment and Subject Participation

Treatment time will begin the day -11 before transplant and continued until the conditioning regimen is completed; for dUCBT this is T+0 and for haplo-identical transplant this is T+4.

Patients will be followed for 12 months post-transplant, unless treatment failure. Treatment failure is defined by disease relapse, graft failure, or death. Patients will continue to be followed for safety for up to 30 days afterwards.

Patients will be followed for toxicity for 30 days after therapy has been completed or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

Subject's Name

_____

Medical Record #

_____

Research Nurse / Study Coordinator Signature:

_____ **Date** _____

Treating Physician [Print]

_____

Treating Physician Signature:

_____ **Date** _____

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Patients with the following hematologic malignancies:

- Acute myelogenous leukemia (AML): High-risk AML including:
  - Antecedent hematological disease (e.g., myelodysplasia (MDS))
  - Treatment-related leukemia
  - Complete Remission (CR1) with poor or intermediate-risk cytogenetics or molecular markers (e.g. Flt 3 mutation, 11q23, del 5, del 7, complex cytogenetics)
  - CR2 or CR3
  - Induction failure or 1st relapse with ≤ 10% blasts in the marrow
- Acute lymphoblastic leukemia (ALL)
  - High-risk CR1 including:
    - Poor-risk cytogenetics (e.g., Philadelphia chromosome t(9;22)or 11q23 rearrangements)
    - Presence of minimal disease by flow cytometry after 2 or more cycles of chemotherapy
  - No CR within 4 weeks of initial treatment
  - Induction failure with ≤ 10% blasts in the marrow
  - CR2 or CR3
- Myelodysplastic syndromes (MDS), Intermediate, High or Very High Risk by the revised international prognostic scoring system (IPSS-R; See Appendix B) or treatment related MDS.
- Mixed Phenotypic Leukemia / Biphenotypic Leukemia in CR
- Chronic Myelogenous Leukemia (CML) in second chronic phase after accelerated or blast crisis.
- Myelofibrosis (MF):
  - Intermediate-1, Intermediate-2 or high risk by DIPSS-plus (Appendix D) *OR*
  - Monosomal karyotype *OR*
  - Presence of inv(3)/i(17q) abnormalities *OR*
  - Other unfavorable karyotype OR leukocytes ≥40 × 10(9) /L *AND*
  - Circulating blasts =< 9%
- Chronic Myelomonocytic Leukemia
- Relapsed or Refractory Lymphoid Malignancies (including non-Hodgkin Lymphoma, Hodgkin Lymphoma) meeting the following criteria:
  - Disease status: Stable Disease, Partial Remission or Complete Remission ***OR***
  - Have relapsed after autologous transplant or who have failed to collect for an autologous transplant.

___ 4.1.2 Age ≥ 1 years, ≤ 65yrs

___ 4.1.3 KPS Performance status ≥80 [See Appendix A]

___ 4.1.4 Patients without a matched related donor

___ 4.1.5 Patient with either one or both:

- A related haplo-identical donor
- Two 4/8 HLA or better high resolution matched UCB grafts with a cell dose of $1.5x10^7$ TNC/kg each and $1x10^5$CD34+ cells/ kg each.

___ 4.1.6 Concurrent Therapy for Extramedullary Leukemia or CNS Lymphoma: Concurrent therapy or prophylaxis for testicular leukemia, CNS leukemia, and CNS lymphoma including standard intrathecal chemotherapy and/or radiation therapy will be allowed as clinically indicated. Such treatment may continue until the planned course is completed. Subjects must be in CNS remission at the time of protocol enrollment if there is a history of CNS involvement. Maintenance therapy after transplant is allowed.

___ 4.1.7 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Patients with inadequate Organ Function as defined by:

- Creatinine clearance < 50ml/min
- Bilirubin ≥ 2X institutional upper limit of normal
- AST (SGOT) ≥ 3X institutional upper limit of normal
- ALT (SGPT) ≥ 3X institutional upper limit of normal
- Pulmonary function: DLCOc < 60% normal
- Cardiac: left ventricular ejection fraction < 50%
- KPS < 80

___ 4.2.2 Patients with uncontrolled inter-current illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

___ 4.2.3 Pregnant or breastfeeding women are excluded from this study because chemotherapy involved with RIC have the significant potential for teratogenic or abortifacient effects.

___ 4.2.4 Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

___ 4.2.5 Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

___ 4.2.6 Presence of donor-specific antibodies against chosen graft source.

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

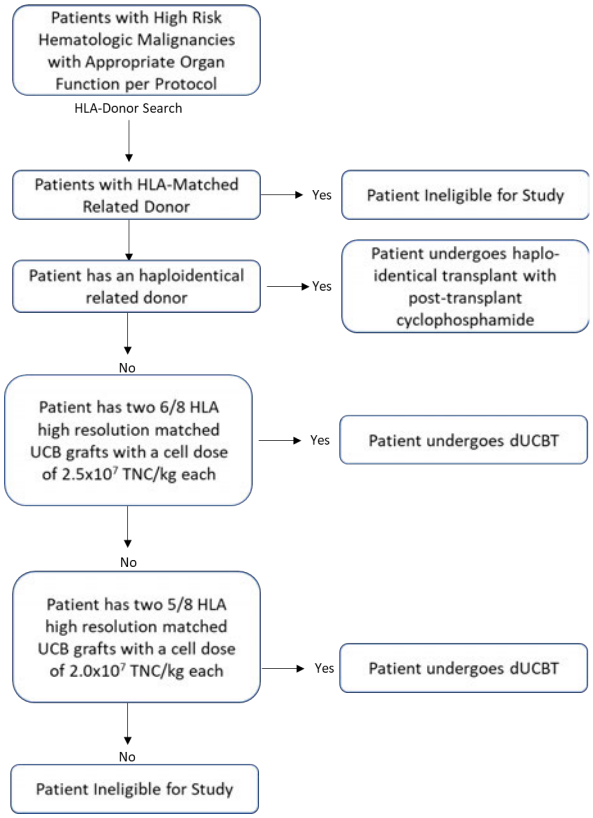
All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through University Hospitals Cleveland Medical Center and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Treatment Plan

6.1 Donor Selection

Figure 1: Decision tree for choosing of a graft



6.2 Conditioning Regimen

The conditioning regimen would consist of:
Melphalan 100 mg/m^2 on day −8
Thiotepa 10 mg/kg on day -7
Fludarabine 40mg/m2/day on days -6, -5, -4 and -3

If the patient undergoes a haplo-identical transplant, post-transplant cyclophosphamide will be added as 50 mg/kg given on each of days +3 and +4.All monitoring is done per standard of care.

CTCAE v 5.0 will be used as the criteria for evaluating infusion-related events. We will attribute acute toxic effects noted during and within 60 minutes of the infusion to administration of that cellular product.

6.3 General Concomitant Medications and Supportive Care Guidelines

6.3.1 Graft versus host disease prophylaxis

1. For dUCBT:

a. Tacrolimus will be initiated on the day –5 before the transplant. Tacrolimus will be administered IV at 0.02 mg/kg/dose over 24 hours. Subsequently doses will be adjusted according to trough levels monitored at least biweekly and/or upon symptoms or alteration in renal function. When appropriate, the treating physician may transition the patient to oral tacrolimus. The target range for serum tacrolimus levels will be 7 ng/mL to 15 ng/mL, or as clinically indicated. This dose of tacrolimus will continue until day +100, and then will be tapered as long as the severity of GVHD is less than grade II.

b. Mycophenolate mofetil (MMF) will be given at 1g intravenously or orally twice daily from day -5 to +100, or as clinically indicated.

2. For haplo-identical transplants:

a. Tacrolimus will be initiated on the day + 5 after the transplant. Tacrolimus will be administered IV at 0.02 mg/kg/dose over 24 hours. Subsequently doses will be adjusted according to trough levels monitored at least biweekly and/or upon symptoms or alteration in renal function. When appropriate, the treating physician may transition the patient to oral tacrolimus. The target range for serum tacrolimus levels will be 7 ng/mL to 15 ng/mL, or as clinically indicated. This dose of tacrolimus will continue until day +100, and then will be tapered as long as the severity of GVHD is less than grade II.

b. Mycophenolate mofetil (MMF) will be given at 1g intravenously or orally twice daily from day +5 to +35, or as clinically indicated.

6.3.2 Growth factor support: Per standard of care.

6.4 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

• Disease progression,
• The investigator considers it, for safety reasons, to be in the best interest of the subject.
• Subject decision to withdraw from treatment (partial consent) or from the study (full consent),
• Pregnancy during the course of the study for a child-bearing participant
• Death, or
• Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.5 Duration of Follow Up

Patients will be followed as outpatient per standard of care with their transplant physician. Patients will be followed for this study for 1 year following the allogeneic transplant, relapse, or death, whichever comes first.

The clinical course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Maintenance therapy post hematopoietic stem cell transplant is allowed if clinically indicated or patient is eligible for another trial.

Serious adverse events, such as chronic infection or grade III-IV GVHD, that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 Dose Delays/Dose Modifications

If patient is over the age of 60 or has comorbidities that may increase the risk of morbidity or mortality with conditioning chemotherapy, the dosage of thiotepa may be reduced to 7.5mg/kg or 5mg/kg at the discretion of the treating physician.

In patients with an increased risk for neurotoxicity, including those with impaired renal function, prior high dose cytarabine, intrathecal therapy, cranial irradiation, or prior HSCT with fludarabine conditioning, the fludarabine dose may be reduced to 30 mg/m^2 on days -6, -5, -4 and -3 instead of 40mg/m^2.

If a patient develops toxicity attributed to the chemotherapy the nurse and physician will adhere to institutional guidelines for infusion toxicity / reaction.

8.0 Potential Risks, Adverse Events, Reporting Requirements

8.1 Potential Risks

8.1.1 Thiotepa

Thiotepa may cause a lowering of the white blood cell, red blood cell, or platelet counts, leading to an increased risk of infection and frequent bruising or bleeding. It may cause damage to the GI tract causing mouth sores, nausea, vomiting, and diarrhea. Other side effects may include loss of appetite, liver abnormalities, hair loss, swelling, fatigue, sleepiness, skin rash.

8.1.2 Melphalan

Melphalan may cause a lowering of the white blood cell, red blood cell, or platelet counts, leading to an increased risk of infection and frequent bruising or bleeding. It may cause damage to the GI tract causing mouth sores, nausea, vomiting, and diarrhea. Other side effects may include loss of appetite, liver abnormalities, hair loss, swelling, fatigue, sleepiness, skin rash.

8.1.3 Fludarabine

Fludarabine may cause a lowering of the white blood cell, red blood cell, or platelet counts, leading to an increased risk of infection and frequent bruising or bleeding. Other side effects may include loss of appetite, liver abnormalities, hair loss, swelling, fatigue, sleepiness, skin rash, and lower limb weakness.

8.1.4 Mycophenolate Mofetil (MMF, Cellcept)
MMF may cause a lowering of the white blood cell, red blood cell, or platelet counts. This may lead to an increase in the risk of infections or bleeding. Other side effects include headache, rash, fever, nausea, vomiting, allergic reaction, liver abnormalities, kidney abnormalities, thyroid dysfunction, fatigue, and swelling.

8.1.5 Tacrolimus
Tacrolimus may cause a lowering of the white blood cell, red blood cell, or platelet counts. This may lead to an increase in the risk of infections or bleeding. Other side effects include headache, rash, fever, nausea, vomiting, allergic reaction, high blood pressure, high blood sugar, mental status changes, liver abnormalities, kidney abnormalities, thyroid dysfunction, fatigue, and swelling.

8.1.7 Risks of Transplant
Risks of Transplant include fever, nausea and vomiting, fatigue, weakness, malaise, diarrhea, dark stools, sores in the mouth, headache, low blood counts, cough, swelling, rash, hives, allergic reaction, muscle pain, loss of appetite, painful urination, red urine, kidney damage, liver damage, serious infection, and death. Specific risks discussed below:

Graft rejection: First, the UCB or Haplo-Identical cells may not grow after they are infused. This problem is termed graft rejection, occurs rarely, and is reduced by giving high-dose chemotherapy. The high-dose chemotherapy is not only given to get rid of the cancer cells, but it will get rid of the immune system and prevent graft rejection.

Graft-versus-host disease (GVHD): GVHD is the most common complication following allogeneic stem cell transplant. Development of GVHD can result in damage to the skin, intestine, liver, immune system, and occasionally bone marrow. Following an allogeneic stem cell transplant UCB, the risk of GVHD is roughly between 20 and 30%. Methotrexate, and/or prednisone and/or mycophenolate mofetil, and/or cyclosporine/tacrolimus may be given to prevent the development of GVHD. On the other hand, there is some benefit to the development of GVHD; the T-lymphocytes present in the cells obtained from an HLA matched UCB may kill any remaining cancer cells**,** a process called the graft-versus-tumor (GVT) effect. GVHD and GVT can occur despite the preventative medications. GVHD can be serious enough to cause death. Most common symptoms are skin rash diarrhea, yellowing of the skin, and also dry eyes, mouth sores and changes of the finger and toe nails. GVHD may also affect the lung, tendons and joints.

Veno-occlusive disease of the liver (VOD): VOD is damage to the blood vessels of the liver that can be caused by the chemotherapy given before stem cell transplant. In VOD the flow of blood into the liver is impaired. This causes a painful enlargement of the liver, an increase in body fluid and weight, and an increase in blood bilirubin. In severe cases the liver fails, which can result in death.

Damage to the kidneys: Kidney damage may occur due to medicines used as part of the transplant and to prevent GVHD. Kidney function will be monitored carefully during and after the transplant procedure.

Damage to the lungs: Lung damage may occur due to the chemotherapy used prior to stem cell transplant or as a result of the transplant itself. Lung inflammation that occurs early after transplant, in the absence of infection, is known as *idiopathic pneumonia syndrome or IPS*. IPS occurs in less than 10% of patients that received allogeneic stem cell transplant. However, if/when it occurs, IPS can be fatal. Prednisone will be given to reduce the inflammation should IPS occur. Other IPS treatment options may be used at the discretion of the treating physician.

Serious infections: Infections in the blood stream or other organs are more likely to occur because the immune system is weakened for a period of time by the stem cell transplant and the medicines used to prevent GVHD. These infections are sometimes fatal.

These side effects, alone or in combination with other problems, may be severe enough to cause death.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation

of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:

  - The admission results in a hospital stay of less than 24 hours OR
  - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
  - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

Neutropenic fever, thrombocytopenia and anemia, electrolyte disturbances, elevations of enzymes, LDH, gamma GT, alkaline phosphatase are expected side effects of stem cell transplantation and will not be considered regimen-related toxicity.

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all reportable adverse events (both serious and non-serious, exempting those previously mentioned in section 8.2.2) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5.0** will be utilized for AE reporting.

GVHD grading scales and assessment forms are included in Appendices C-F.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.
Attribution is required for the treatment as a whole, not individual components of the treatment.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For this study, only grade 3 and greater (according to CTCAE 5.0) AEs will be collected and reported, with the exception of infusion site reactions (all grades will be collected) and the expected adverse events listed in Sec. 8.2.2 above (not collected at all).

For the purposes of safety reporting, serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- All serious adverse events must be reported to the Sponsor-Investigator within **24 hours** of discovery or notification of the event.
    - Leland Metheny, 216-844-0139, Leland.Metheny@uhhospitals.org
- The Sponsor-Investigator will review the SAE and report the event to external collaborator(s), and IRB as applicable.

Institutional Review Board Reporting Requirements:

- Adverse events will be reported to the IRB of record according to the local IRB's policies and procedures in reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the completed SAE form (FDA Form 3500A) is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

ALL SAEs occurring on this trial must be reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with OnCore™.

The Sponsor-Investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

9.1 Agents

9.1.1 Thiotepa

Product description: Thiotepa is an alkylating agent which produces cross-linking of DNA strands leading to inhibition of DNA, RNA, and protein synthesis; thiotepa is cell-cycle independent.

Solution preparation: Thiotepa for Injection, USP, for single use only, is available in vials containing 15 mg of nonpyrogenic, sterile lyophilized powder.

Thiotepa for injection should be reconstituted with 1.5 mL of sterile water for injection resulting in a drug concentration of approximately 10 mg/mL. The reconstituted solution is hypotonic and should be further diluted with sodium chloride injection (0. 9% sodium chloride) before use. When reconstituted with sterile water for injection, solutions of thiotepa should be stored in a refrigerator and used within 8 hours.

Reconstituted solutions further diluted with sodium chloride injection should be used immediately. In order to eliminate haze, filter solutions through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

Storage requirements: As for other antineoplastic agents Thiotepa should be handled by trained personnel using procedures for proper handling. The use of gloves and protective glasses is recommended to avoid exposure upon accidental spillage.

Route of administration: intravenous infusion over 30-60 minutes

Drug Procurement: Thiotepa must be obtained from commercial sources.

9.1.2 Melphalan

Product description: Alkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.

Solution preparation: ALKERAN for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. ALKERAN for Injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and Water for Injection to a total of 10 mL.

As for other antineoplastic agents Melphalan should be handled by trained personnel using procedures for proper handling. The use of gloves and protective glasses is recommended to avoid exposure upon accidental spillage.

Route of administration: intravenous infusion over 30-60 minutes

Drug Procurement: Melphalan must be obtained from commercial sources.

9.1.3 Fludarabine

Product description: Antineoplastic fluorinated nucleoside analog. After phosphorylation to fluoro-ara-ATP [adenosine triphosphate] the drug appears to incorporate into DNA and inhibit DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The half-life of the activated compound is approximately 10 hours but the pharmacology is incompletely understood. Excretion is impaired in patients with impaired renal function.

Solution preparation: Each vial contains 50 mg lyophilized drug, to be reconstituted with 2 mL sterile water to a solution that is 25 mg/mL for intravenous administration. Solution Preparation: mix each vial with 2 mL sterile pyrogen-free water to a clear solution, which is 25 mg/mL for intravenous administration only. Reconstituted solution should be used within 8 hours.

As for other antineoplastic agents Melphalan should be handled by trained personnel using procedures for proper handling. The use of gloves and protective glasses is recommended to avoid exposure upon accidental spillage.

Route of administration: intravenous infusion over 30-60 minutes

Drug Procurement: Fludarabine must be obtained from commercial sources.

10.0 EXPLORATORY or CORRELATIVE STUDIES

N/A

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

Laboratory Studies:

- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, SGOT [AST], SGPT [ALT], sodium.
- Complete Blood Count and Differential
- Additional lab studies (Screening only)
    - PT, PTT.
    - Urinalysis
    - CMV IgG and IgM, EBV panel, Hep B sAg, Hep B sAb, Hep B cAb, Hep C Ab, HIV I/II, HSV I/II, HTLV I/II, Syphilis, Toxo IgG (and if positive IgM), VZV IgG

Vital signs include: blood pressure, pulse, respiratory rate, percent oxygen saturation and temperature

Bone marrow aspiration; flow cytometry, cytogenetics, and molecular studies as clinically appropriate

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed $\leq$ 60 days **prior** to administration of protocol therapy.

11.1.2 Treatment Period

Treatment time will begin the day -11 before transplant and continued until the conditioning regimen is completed; for dUCBT this is T+0 and for haplo-identical transplant this is T+4.

If the patient undergoes a haplo-identical transplant, post-transplant cyclophosphamide will be added as 50 mg/kg given on each of days +3 and +4.

T-8

- Melphalan 100 mg/m^2

T-7

- Thiotepa (T) 10 mg/kg

T-6

- Fludarabine 40mg/m^2

T -5

- Fludarabine 40mg/m^2

T -4

- Fludarabine 40mg/m^2

T -3

- Fludarabine 40mg/m^2

T +0

- Infusion of graft source: dUCBT or Haplo-Identical Donor

T +6 to +30

- Continue GVHD prophylaxis per standard of care
- Bone Marrow Aspiration may be performed following between T+6 and T+30 if engraftment has not been demonstrated or if loss of graft is suspected; flow cytometry, cytogenetics, and molecular studies as clinically appropriate

T +30 to +60

- Bone Marrow Aspiration may be performed following T+30 bone marrow if engraftment has not been demonstrated or if loss of graft is suspected; flow cytometry, cytogenetics, and molecular studies as clinically appropriate. If a bone marrow aspiration has been already performed between T+6 and T+30, this does not need to be repeated.

Follow up: Outpatient, up to T+100, 6, 9, and 12 months post-transplant (+/- 2weeks)

Bone marrow aspiration; flow cytometry, cytogenetics, and molecular studies as clinically appropriate.

Acute GVHD
Acute GVHD will be graded and staged according to the BMT CTN Manual of Operations (BMT CTN MOP) (Appendixes C, D, and E).

Chronic Graft Versus Host Disease
Chronic GVHD is scored according to the BMT CTN MOP (Appendix F). The first day of cGVHD onset will be used to calculate cumulative incidence curves.

11.2 Calendar

Study Days	Screening	T -11, -10, -9	T -8	T -7	T -6	T -5	T -4	T -3	T -2	T -1	T +0	T +1, T +2	T +6 to T +30	T +30 to T +60	T+100, 6, 9, and 12mo f/u
Required Assessments															
Informed Consent	X														
Demographics	X														
Medical History	X														
Height	X														
Weight	X		X[1]												
Vitals (section 11.1)	X		X[1]	X[1]											
Physical exam	X			X[1]											
Con Med Assessment	X														
KPS	X														X[2]
Baseline Symptoms Assessment	X														
Adverse Events Assessment			X	X							X	X	X	X	X[‡]
CBC/diff/Platelets	X		X[1]	X[1]											X[2]
Chemistries (section 11.1)	X		X[1]	X[1]											X[2]
Additional Lab Studies (section 11.1)	X														
ß-HCG for women of childbearing potential[3]	X														
2-D ECHO or MUGA	X														
Pulmonary function testing (including DLCO)	X														
CT, PET, for lymphoma	X														
Cardiology consult	X														
Bone Marrow Aspiration (see section 11.1)	X													X*	X[2] (T+100 only)
Treatment															
Melphalan			X												
Thiotepa				X											
Fludarabine					X	X	X	X							

***** Bone Marrow Aspiration may be performed following T+30 bone marrow if engraftment has not been demonstrated or if loss of graft is suspected; flow cytometry, cytogenetics, and molecular studies as clinically appropriate**.** It may be repeated as clinically appropriate

‡ Follow-up of adverse events that are still ongoing after the 30 day reporting period
[1]These studies may have a window to +/-3 days.
[2] These studies may have a window of 2 weeks.
[3] ß-HCG test should be performed within 7 days before admission.

12.0 MEASUREMENT OF EFFECT

Disease Free Survival (DFS) at 1 year is the percentage of patients alive and without evidence of hematologic malignancy at 1 year after transplant.

Overall Survival (OS) at 1 year is the percentage of patients alive at 1 year after transplant.

Relapse incidence at 1 year is the percentage of patients who experience relapse of their hematologic malignancy up to 1 year after transplant.

Treatment Related Mortality (TRM) at 1 year is the percentage of patients who expire from treatment related toxicity attributed to transplant up to 1 year after transplant.

Acute graft versus host disease (aGVHD) 1 year cumulative incidence is the percentage of patients who experience any aGVHD up to 1 year after transplant.

Chronic graft versus host disease (cGVHD) 1-year cumulative incidence is the percentage of patients who experience any cGVHD up to 1 year after transplant.

Neutrophil engraftment will be calculated as the days from transplant where the absolute neutrophil count (ANC) reaches >500cells/ul x 3 days.

Platelet engraftment will be calculated as the days from transplant where the platelet count reaches 20,000 platelets /ul without the need of transfusion of platelets for 7 days.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. A calendar of events and required forms are available in OnCore™.

This study will utilize electronic Case Report Form completion in the Overture database system, a part 11 compliant electronic data capture system. Approved users will received access independently from the OnCore™ system used for clinical trial management.

13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

14.1 Design and Sample Size:

The one year leukemia free survival (LFS) is the primary endpoint for the phase II study. One year LSF is measured is the percentage of patients alive and without evidence of hematologic malignancy at 1 year after transplant. We are particularly interested in the rate of LFS within one year after transplant. The 1-year LFS rate for this study population under standard care is about 40% ($P_0 = 0.4$). We expect the target 1-year LFS rate of the investigation therapy to be 60% ($P_1 = 0.60$). R. Simon's minimax two-stage phase II design[11] with type I error of 0.05 and power of 80% will be used on 1-year LFS. Thirty-four patients will be enrolled on stage one. If there are 17 or less alive without relapse beyond 1 year, the trial will be stopped and the treatment will be considered not effective for this patient population. If there are 18 or more alive without relapse after 1 year, 5 additional patients will be enrolled. If 20 or fewer are alive without relapse after 1 year are observed in the total 39 patients, then the trial will be considered to be not effective. On the other hand, if there are more than 20 patients alive without relapse after 1 year, then the treatment will be considered to be effective.

14.2 Analysis Plan

AEs and SAEs from this phase II study will be tabulated. For time-to-event endpoints, such as overall survival, the Kaplan-Meier method[12] will be used to estimate survivor function. The cumulative incidence of acute GVHD, chronic GVHD, and the rate of neutrophil and platelet engraftment will be estimated by the method that accommodates competing risks[13]. As part of exploratory data analysis, the predictive value of laboratory correlates on time-to-event data will be estimated using Cox models[14].

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APPENDIX A

Karnofsky Performance Scale		
General category	**%**	**Specific criteria**
• Able to carry on normal activity • No special care needed	**100**	Normal general status - No complaint - No evidence of disease
	90	Able to carry on normal activity - Minor sign of 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 • Various amount of assistance needed	**70**	Able to care for self, unable to carry on normal activity or do work
	60	Requires occasional assistance from others, frequent medical care
	50	Requires considerable assistance from others; frequent medical care.
• Unable to care for self • Requires institutional or hospital care or equivalent • Disease may be rapidly progressing	**40**	Disabled, requires special care and assistance
	30	Severely disabled, hospitalization indicated, death not imminent
	20	Very sick, hospitalization necessary, active supportive treatment necessary
• Terminal states	**10**	Moribund
	0	Dead

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

APPENDIX B
Revised International Prognostic Scoring System (IPSS-R)

IPSS-R Cytogenetic risk groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

IPSS-R Prognostic Risk Categories/Scores*

RISK CATEGORY	RISK SCORE
Very Low	<=1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.

**Schanz J et al, J Clin Oncology 2012; 30:820

APPENDIX C
Acute GVHD Staging per BMT CTN Manual of Operations (BMT MOP).

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500ml/d or persistent nausea	Bilirubin 2-3mg/dl
2	25-50%	> 1000 ml/d	Bilirubin 3-6 mg/dl
3	> 50%	> 1500 ml/d	Bilirubin 6-15 mg/dl
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dl

APPENDIX D
Acute GVHD Grading per BMT CTN Manual of Operations (BMT MOP).

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stage 2-4	Stage 2-3
IV	Stage 4	—	Stage 4

APPENDIX E
Acute GVHD Clinical Assessment per BMT CTN MOP

Clinical Acute GVHD Assessment

Date _____ Patient ID _____ Karnofsky/Lansky _____

	Code						Differential Diagnosis						
	0	1	2	3	4	5		GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	☐	☐	☐	☐	☐		% body rash:____	☐	☐	☐		☐		_____
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____	☐	☐	☐	☐	☐		_____
Upper GI	☐	☐						☐	☐	☐	☐	☐		_____
Liver	☐	☐	☐	☐	☐		Max bili: _____	☐	☐	☐	☐	☐	☐	_____

Treatment: ☐ CSA ☐ Tacrolimus ☐ Pred ☐ Methylpred ☐ Ontak
☐ Pentostatin ☐ MMF ☐ Etanercept ☐ Other _____

Code Definitions:

Skin:
0 No rash
1 Maculopapular rash, <25% of body surface
2 Maculopapular rash, 25-50% of body surface
3 Generalized erythroderma
4 Generalized erythroderma with bullous formation and desquamation

Lower GI (Diarrhea):
0 None
1 ≤500 mL/day or <280 mL/m^2
2 501-1000 mL/day or 280- 555 mL/m^2
3 1001-1500 mL/day or 556- 833 mL/m^2
4 >1500 mL/day or >833 mL/m^2
5 Severe abdominal pain with or without ileus, or stool with frank blood or melena

Upper GI:
0 No protracted nausea and vomiting
1 Persistent nausea, vomiting or anorexia

Liver (Bilirubin):
0 <2.0 mg/dl
1 2.1-3.0 mg/dl
2 3.1-6.0 mg/dl
3 6.1-15.0 mg/dl
4 >15.1 mg/dl

Signature _____

University Hospitals
Seidman Cancer Center

Acute GVHD Staging and Grading*

T "0": _____ T "+": Current Weight: _____

Karnofksy Score (Age > 16 yrs)
☐ 100 Normal, no complaints; no evidence of disease
☐ 90 Able to carry on normal activity
☐ 80 Normal activity with effort
☐ 70 Cares for self; unable to carry on normal activity or do active work
☐ 60 Requires occasional assistance but is able to care for most needs
☐ 50 Requires considerable assistance and frequent medical care
☐ 40 Disabled, requires special care
☐ 30 Severely disabled
☐ 20 Hospitalization necessary
☐ 10 Fatal process progressing

GVHD Target Organ	0	1	2	3	4	*Biopsy Proven* BX	
Skin	☐	☐	☐	☐	☐	☐	% body rash:
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____
Upper GI	☐	☐				☐	(3 Day Average)
Liver	☐	☐	☐	☐	☐	☐	Max bili:

Differential Diagnosis	GVHD	Drug Rxn	Cond Reg	TPN	Infect	SOS	Other
	☐	☐	☐		☐		
	☐	☐	☐	☐	☐		
	☐	☐	☐	☐	☐		
	☐	☐	☐	☐	☐	☐	

Other:
☐ Treatment ☐ Cyclosporin ☐ Mycophenolate mofetil ☐ Infliximab ☐ Photopheresis
☐ Prophylaxis ☐ Tacrolimus ☐ Antithymocyte Globulin ☐ Etanercept ☐ Sirolimus
☐ Prednisone ☐ Pentostatin ☐ Methylprednisolone ☐ Other

Lansky Score (Age < 16 yrs)
☐ 100 fully active, normal
☐ 90 Minor restriction in physically strenuous play
☐ 80 Restricted in strenuous play, tires more easily, otherwise active
☐ 70 Both greater restrictions of, and less time spent in active play
☐ 60 Ambulatory up to 50% of the time, limited activity play with assistance
☐ 50 Considerable assistance with active play, able to engage in quiet play
☐ 40 Able to initiate quiet activity
☐ 30 Needs assistance with quiet play
☐ 20 Limited to passive activity
☐ 10 Disabled, no passive activity

Organ Staging of GVHD

Skin:	Lower GI (Diarrhea):	Upper GI:	Liver (Bilirubin):
0 No Rash	0 < 500mL/day or < 280 mL/m^2	0 No protracted nausea and vomiting	0 < 2 mg/dL
1 Maculopapular rash <25% of body surface	1 500-1000 mL/day or 280-555 mL/m^2	1 Persistent nausea, vomiting or anorexia	1 2–3 mg/dL
2 Maculopapular rash, 25-50% of body surface	2 1001-1500 mL/day or 556-833 mL/m^2		2 3.1–6 mg/dL
3 Maculopapular rash, >50% of body surface	3 1501-2000 mL/day or >833-mL/m^2		3 6.1–15 mg/dL
4 Generalized erythroderma with bullous formation and desquamation	4 > 2000 mL/day or severe abdominal pain with or without ileus, or stool with frank blood or melena		4 > 15 mg/dL

Overall Clinical Grading of Severity Acute GVHD

Grade \ Degree of Organ Involvement
0 ☐ No Stage 1-4 of any organ
1 ☐ Stage 1-2 skin & no liver or GI involvement
2 ☐ Stage 3 skin or stage 1 liver involvement or stage 1 GI involvement
3 ☐ Stage 2-3 liver involvement, or stage 2-4 GI
4 ☐ Stage 4 skin, or stage 4 liver involvement

Signature: _____ Print Name Date:

AGSG 12/1/2011 V6
Revised: 02/02/2017
Owner: SCT Clinical Program
*Przepiorka D1, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. Bone Marrow Transplant. 1995 Jun;15(6):825-8. 1994 Consensus Conference on Acute GVHD Grading

APPENDIX F

Chronic GVHD severity scoring per BMT CTN MOP

	0	1	2	3
Skin	❑ No changes	❑ < 18% BSA lichenoid, sclerodermatous, or icthyotic involvement ❑ Eczema hypo or hyperpigmentation	❑ 18-50% BSA lichenoid, sclerodermatous, or icthyotic involvement	❑ > 50% BSA involved ❑ Interference with ADLs due to impaired mobility ❑ Skin ulcerations
Hair Loss	❑ None	❑ Mile (<50%)	❑ >50%	
Joints	❑ No contractures ❑ Arthralgias ❑ Migratory arthritis	❑ Persistent arthritis in 1-2 joints	❑ Mild joint contractures (do not affect ADL) ❑ Polyarticular arthritis	❑ Severe joint contractures (interfere with ADLs)
Oral	❑ No changes	❑ Symptomatic but no change in diet	❑ Able to eat most foods, although some dietary changes due to oral chronic GVHD	❑ Unable to eat most foods due to oral chronic GVHD
Ocular	❑ No changes	❑ Dry eyes but not requiring therapy ❑ Keratoconjunctivitis, asymptomatic	❑ Dryness of eyes requiring artificial tears, lacrimal plugging, or Schirmer's < 5 mm ❑ Keratoconjunctivitis, symptomatic	❑ Pseudomembranes ❑ Corneal ulcerations ❑ Loss of vision
Esophagus	❑ No changes	❑ Symptomatic but can eat regular diet	❑ Dysphagia or odynophagia requiring dietary changes	❑ Need for parenteral nutrition ❑ Web/stricture formation
Pulmonary	❑ Asymptomatic	❑ 75-90% FEV1/FVC ❑ Asthma	❑ Dyspnea with exertion ❑ 50-74% FEV1/FVC ❑ Desaturation with exercise	❑ Dyspnea with normal activities ❑ < 50% FEV1/FVC ❑ Requires supplemental oxygen
KPS	❑ Asymptomatic and fully active (ECOG 0, KPS 100%) ❑ Lansky = 90-100%	❑ Symptomatic; fully ambulatory; restricted in physically strenuous activity (ECOG 1, KPS 80-90%) ❑ Lansky = 70-80%	❑ Symptomatic; ambulatory, capable of self-care, > 50% of waking hours are spent out of bed (ECOG 2, KPS 60-70%) ❑ Lansky = 50-60%	❑ Symptomatic; limited self care, spends > 50% of waking hours in bed but, not bedridden (ECOG 3, KPS 40-50%) ❑ Lansky = <50%

	0	1	2	3
GI Manifestations	❑ None	❑ Anorexia or malabsorption ± <5% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant	❑ Anorexia or malabsorption ± 5-10% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant	❑ Anorexia or malabsorption ± >20% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant
Hematologic	❑ Thrombocytopenia not attributable to other causes >100K	❑ Thrombocytopenia not attributable to other causes >75K	❑ Thrombocytopenia not attributable to other causes >50K	❑ Thrombocytopenia not attributable to other causes <50K
Autoimmune (e.g., IPT, AHA)	❑ None	❑ Positive laboratory tests, clinically not requiring treatment	❑ Requires <6 months additional immunosuppressive therapy to control symptoms	❑ Requires transfusions (AHA) or splenectomy (ITP) or >6 months of increased immunosuppression to control disease

Laboratory and clinical variables **(Please complete for this visit date)**	Platelets ___ ___ ___ x 10^9/L Total bilirubin __ __ . __ mg/dl Alkaline phosphatase __ __ __ mg/dl Weight __ __ __ . __ kg or lb (circle unit of measure)	
Specific manifestations **(Please circle Yes, No, or Not applicable)**	Serositis Y / N Myositis Y / N Fasciitis Y / N	Scleroderma Y / N Steatorrhea Y / N Vaginitis/vaginal stricture Y / N / NA

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