Very Low-dose Total Body Irradiation in Combination with Total Lymphoid Irradiation and anti-Thymocyte Globulin to Improve Donor Engraftment in Patients Undergoing Non-Myeloablative Hematopoietic Cell Transplantation

IRB-47407 **BMT330** **NCT03734601**

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Protocol Synopsis

TITLE	Very Low-dose Total Body Irradiation in Combination with Total Lymphoid Irradiation and anti-Thymocyte Globulin to Improve Donor Engraftment in Patients Undergoing Non-Myeloablative Hematopoietic Cell Transplantation for Leukemia and Lymphoma
STUDY PHASE	Phase 2

STUDY SITE	Stanford University Medical Center, CA 94305
INDICATION	Patients with leukemia and lymphoma who are not eligible for myeloablative transplantation
STUDY AGENT	The addition of low-dose total body irradiation to total lymphoid irradiation and anti-thymocyte globulin as transplant conditioning therapy
PRIMARY ENDPOINT and OBJECTIVE(S)	To determine the proportion of patients with full donor T-cell chimerism at Day 28 following hematopoietic cell transplantation
SECONDARY ENDPOINTS AND OBJECTIVE(S)	1. To determine the risk of disease progression, overall and event-free survival, and non-relapse mortality, following treatment with TLI/ATG/TBI 2. To determine the incidence of acute and chronic GVHD following treatment with TLI/ATG/TBI
STUDY OBSERVATION PERIOD	Patients will be followed for 1 year from the time of transplant
TREATMENT SUMMARY	The efficacy of non-myeloablative allogeneic transplantation is mediated in part by the establishment of an alloreactive donor T-cell compartment following transplant with minimal toxicity. The objective of this study is to evaluate whether a single administration of low-dose TBI to standard TLI/ATG non-myeloablative transplant conditioning will help to augment donor chimerism without reducing tolerability of this regimen or increasing the risk of GVHD. This is a single institution, open-label, single treatment study evaluating the efficacy of low-dose TBI added to TLI/ATG in adults with leukemia and lymphoma undergoing allogeneic HCT from sibling or unrelated donors.
SAMPLE SIZE	20 patients
SUMMARY OF SUBJECT ELIGIBILTY	Patients with the following histologically-confirmed disease: 1. Acute myeloid leukemia (AML) 2. Chronic lymphocytic leukemia (CLL) 3. Myelodysplastic syndrome (MDS) / Myeloproliferative disease syndrome (MPD) 4. Non-Hodgkin lymphoma (NHL) 5. Hodgkin lymphoma (HL) Patients not undergoing ablative transplant conditioning Patients with HLA-matched or single antigen/allele mismatched related or unrelated donors.
CONTROL GROUP	Not applicable. Single-arm study.

LIST OF ABBREVIATIONS and DEFINITION OF TERMS

AE	Adverse event	Kg	Kilograms
AML	Acute myeloid leukemia	KPS	Karnofsky performance status
ALT	Aspartate aminotransferase	LVEF	Left ventricular ejection fraction
AST	Alanine aminotransferase	MC	Mixed chimerism
ATG	Anti-thymocyte globulin	MDS	Myelodysplastic syndrome
BID	*bis in die* (twice-a-day)	MEP	Megakaryocyte erythroid progenitors
CFR	Code of Federal Regulations	MG	Milligrams
cGY	Centigray	MkP	Megakaryocyte progenitors
CLL	Chronic lymphocytic leukemia	MMF	Mycophenolate mofitel
CLP	Common lymphoid progenitors	MPD	Myeloproliferative disease syndrome
CML	Chronic myelogenous leukemia	MPPS	Multipotent progenitors
CMML	Chronic myelomonocytic leukemia	NCI	National Cancer Institute
CMP	Common myeloid progenitors	NHL	Non-Hodgkin lymphoma
CNS	Central nervous system	NK	Natural killer cells
CR	Complete remission / response	NRM	Non-relapse mortality
CRF	Case report / record form	OnCore	OnCore enterprise research system
CRi	CR + incomplete blood count recovery	OS	Overall survival
CTCAE	Common Terminology Criteria for Adverse Events	PAMPS	pathogen-associated molecular pattern
DAMP	Damage-associated molecular pattern	PBSC	Peripheral blood stem cells
DLCO	Diffusing capacity – lung for carbon monoxide	PB	Peripheral blood
DLI	Donor leukocyte infusion	PCR	polymerase chain reaction
DSMC	Data Safety Monitoring Committee	PD	Progressive disease, tumor progression
EFS	Event-free survival	PR	Partial response
EP	Electrophysiology	RIC	Reduced intensity conditioning
FACS	Fluorescence activated cell sorting	SAE	Serious adverse event
FDA	Food and Drug Administration	SCI	Stanford Cancer Institute
FDC	Full donor chimerism	SD	Stable Disease
FISH	Fluorescence *in situ* hybridization	SGOT	Serum glutamic oxaloacetic transaminase
GCP	Good Clinical Practice	SIN	Subject identification number
G-CSF	Filgrastim, granulocyte-colony stimulating factor	SRC	Scientific Review Committee
GVHD	graft-versus-host disease	STRs	Short tandem repeats
GVT	graft-versus-tumor	TAC	Tacrolimus
GMP	granulocyte macrophage progenitors	TBI	Total body irradiation
HCT	Hematopoietic cell transplant	TBili	Total bilirubin
HL	Hodgkin lymphoma	TCD	T-cell depleted
HLA	Human leukocyte antigen	TLI	Total lymphoid irradiation
HSC	Hematopoietic stem cell	ULN	Upper limit of normal
ICH	Int'l Conference on Harmonization	URD	Unrelated donor
IRB	Institutional Review Board		

SCHEMA

AML
MDS
MPD
CLL
NHL
HL
CMML

↓

Patient Screening / Eligibility

↓

- Age ≤ 80
- Not eligible for a myeloablative preparative regimen
- Available HLA-matched or single allele/antigen mismatched related or unrelated donor
- Estimated creatinine clearance ≥ 50 mL/min
- LVEF ≥ 30%
- DLCO ≥ 40% predicted (adjusted for Hgb)
- TBili < 3 mg/dL
- AST/ALT < 3 x ULN
- KPS ≥ 60

↓

HLA-matched or
single antigen/allele mismatched related or unrelated donor

↓

Donor: G-CSF 16 µg/kg x 5 days

↓

Collection of hematopoietic cells by apheresis,
desired goal of ≥ 5 x 10^6 $CD34^+$ cells/kg
recipient weight for infusion on Day 0

↓

Study Day	Radiation	ATG	Marrow, PBSC, & other
Day -11	TLI [1] 120 cGy	ATG [3] 1.5 mg/kg	
Day -10	TLI 120 cGy	ATG 1.5 mg/kg	
Day -9	TLI 120 cGy	ATG 1.5 mg/kg	
Day -8	TLI 120 cGy	ATG 1.5 mg/kg	
Day -7	TLI 120 cGy	ATG 1.5 mg/kg	
Day -4	TLI 120 cGy		
Day -3	TLI 120 cGy		Start oral Tac [4]
Day -2	TLI 120 cGy		
Day -1	TLI 120 cGy TBI [2] 80 cGy		
Day 0			Infusion of mobilized PBSC [5]
Days +28: + 56; +90; +180; +360			STRs [7]

1 TLI: Total lymphoid irradiation 2 TBI: Total body irradiation 3 ATG: Anti-thymocyte globulin 4 Tac: Tacrolimus (can be IV) See also Section 8 Study Calendar	5 PBSC: Peripheral blood stem cells. The PBSC infusion procedure is called a hematopoietic cell transplant (HCT) 6 MMF: Mycophenolate mofitel. 15 mg/k PO BID for PBSC from matched-related donors; 15 mg/kg PO q8 hours for PBSC from unrelated donors (URDs) or mismatched related donors. 7 STRs: Short tandem repeats for engraftment analysis

1. OBJECTIVES

1.1 Primary Objective

1. To determine the proportion of patients with full donor T-cell chimerism at Day 28 following hematopoietic cell transplantation

1.2 Secondary Objectives

2. To determine the risk of disease progression, overall and event free survival, and non-relapse mortality, following treatment with TLI/ATG/TBI
3. To determine the incidence of acute and chronic GVHD following treatment with TLI/ATG/TBI

2. BACKGROUND

2.1 Allogeneic Hematopoietic Cell Transplantation

Allogeneic hematopoietic cell transplantation (HCT) is proven effective therapy for patients with a variety of hematolymphoid malignancies. Following allogeneic HCT, a significant percentage of patients who were otherwise considered to have incurable cancers using best of care non-transplantation therapies have long-term disease free control and appear cured. These patients are characterized by developing donor type hematopoiesis and have complete resolution of all disease-related signs, symptoms and markers. Generally, patients who undergo allogeneic HCT are doing so as a “last ditch” effort for long-term disease control and possibly cure after exhausting all chemotherapy, and radiation therapy based treatment strategies. Often many of the patients who undergo allogeneic HCT for treatment of their lymphoma have had disease relapse even after high dose chemotherapy and autologous stem cell rescue (autologous HCT).

2.2 Relapse of Disease following Allogeneic HCT

The main cause for treatment failure following allogeneic HCT is disease relapse. Depending, in part, on the disease, disease status at the time of transplantation, and the intensity of the transplantation regimen, disease relapse occurs in roughly 25 to 80% of patients. For example, following a full dose transplant in younger patients with acute leukemia in 1^{st} or 2^{nd} complete remission (CR) and using a graft from a HLA-matched sibling, the 2-year risk of disease relapse was < 30% [1-8]. In contrast, the 2-year risk of disease relapse for younger patients with refractory acute leukemia who received a full-dose transplant was > 70% [9-11]. Older (> 55 years of age) patients or younger patients with medical co-morbidities that preclude full dose conditioning undergo reduced intensity conditioning (RIC) allogeneic HCT. The 2-year risk of disease relapse in patients with acute leukemia in CR who received RIC allogeneic HCT was > 50% [12, 13]. Similarly, disease relapse remains the major cause of treatment failure for patients with T-cell, large B-cell and Hodgkin lymphomas and chronic lymphocytic leukemia (CLL) and occurs in > 40% who undergo RIC allogeneic HCT with chemotherapy, sub-lethal total body irradiation (TBI), or total lymphoid irradiation combined with anti-thymocyte globulin (TLI/ATG) [13-18].

2.3 Treatment for Disease Relapse Following Allogeneic HCT

Disease relapse following allogeneic HCT remains an ominous clinical event, which usually results in progressive disease and death. Treatment strategies of patients with relapse following

allogeneic HCT can often be further complicated by the overall general poor clinical status of the patient. Strategies for the treatment of disease relapse in these patients include the cessation of post-transplantation immune suppression medication, salvage chemotherapy with or without irradiation, a second allogeneic HCT, or the infusion of donor leukocytes (DLI). Despite these interventions few patients beyond those with chronic myelogenous leukemia (CML) can be returned to durable remissions and the overall survival (OS) at 2 years following disease relapse was < 20% [19, 20]. Given that disease relapse is relatively common after transplant, and that few if any patients can be returned to durable remission once relapse has occurred, a desired goal would be to improve the transplant strategy and avoid the serious problem of post-transplant disease relapse.

2.4 Graft Versus Tumor Reactions

A major mechanism of cancer eradication following allogeneic HCT is the immunological-based recognition of residual host tumor cells by donor-derived immune cells contained in the donor graft. This phenomenon, termed graft-versus-tumor (GVT) reactions, is supported by various lines of evidence. The initial observations in support of GVT reactions stemmed from studies that used T-cell depleted (TCD) donor grafts whereby graft-versus-host disease (GVHD) was eliminated; however, without donor T-cells in the donor inoculum patients suffered a high incidence of disease recurrence [21]. The importance of GVT reactions was further demonstrated by improved disease control and fewer relapses following HLA identical sibling (allogeneic) transplantation compared to syngeneic (identical twin) transplantation for patients with hematologic malignancies [22]. The three year probability for relapse of leukemia was substantially higher following syngeneic compared to allogeneic HCT in acute myelogenous leukemia (AML) (52% vs 16%) and CML (40% vs 7%) following treatment using full dose transplant conditioning regimens [22]. The increased risk of relapse in syngeneic transplants counterbalanced the beneficial effect of the lack of GVHD. Perhaps the most compelling evidence comes from the observation that the infusion of donor leukocytes obtained from the original donor in patients who have disease relapse following allogeneic HCT resulted in a GVT effect (23).

2.5 Reduced Intensity Transplant Conditioning

Following the recognition that a main mechanism of disease control after allogeneic HCT is by donor derived immune mediated GVT reactions, multiple groups, including our own at Stanford, developed reduced intensity transplant conditioning (RIC) regimens that shifted the burden of disease control from high doses of chemoradiotherapy to the donor immune system [23-25]). The low intensity transplant conditioning has allowed older patients and those with medical co-morbidities to proceed with transplant whereas, before these patients were excluded from allogeneic transplantation as the full dose conditioning regimens were associated with prohibitive toxicities. As a consequence of the low-dose conditioning, host hematopoietic and immune cells persist and result in a state of mixed hematopoietic and lymphoid chimerism (MC) that may convert to full donor chimerism (FDC) over a variable time course (13, 28-30). Importantly, the achievement of early (before Day 60) FDC appears to be a necessary precondition for disease control ([26, 27]. We and others have reported that irrespective of the specific type of RIC regimen used, the relapse risk is significantly higher in patients with persistent MC compared to those with FDC, and likely reflects tolerance of donor cells to recipient tissues (13, 28-30). In a report detailing the outcomes of 111 allogeneic HCT recipients from HLA-matched and single

antigen mismatch donors following TLI-ATG conditioning for leukemia and lymphoma there was a very low incidence of severe (Grade 2 to4) acute GVHD (< 5%), and a low incidence of non-relapse related mortality at 1 year (< 5%) (13). Whereas almost all patients who failed to achieve FDC experienced disease relapse, the actuarial event free survival was more than 55% in the patients who achieved > 95% donor type chimerism, with observations extending up to 6 years (13).

2.6 Rationale to include very low-dose TBI in NMA TLI-ATG conditioning

Low-dose TBI (doses of 50, 100, 150 and 200 cGy) is well established to improve donor hematopoietic stem cell (HSC) engraftment due to targeting of marrow HSC niches.[28] Engraftment is dose-dependent with more robust engraftment at higher doses. Yet increasing the dose of TBI is balanced by the risk of aggravating GVHD as higher doses (> 150 cGy) of TBI which may increase GVHD development by promoting intestinal inflammation with subsequent release of DAMPS and PAMPS.[29] It is hypothesized that in the current protocol the addition of one very low-dose (80 cGy) of TBI as a substitute for the last dose of TLI will help promote donor HSC engraftment due to its ability to help clear marrow niche space yet avoid the widespread intestinal inflammation typically associated with higher doses of TBI. Improved donor cell engraftment is associated with reduced rates of post-transplant disease relapse and improving donor cell engraftment without increasing GVHD is a significant goal of transplantation.

2.7 Study Rationale

The persistence of mixed hematopoietic cell chimerism is associated with a significantly high risk of disease relapse after allogeneic HCT [13, 28-30]. Once the patient's disease has relapsed after allogeneic HCT, the likelihood for long-term survival is poor. Therefore, a strategy that can help promote conversion of mixed to complete hematopoietic cell chimerism prior to disease relapse, and does not promote significant GVHD has the potential to help improve the outcomes of allotransplant recipients by reducing the risk of disease relapse. The goal of the current proposed trial will be to determine if the addition of very low-dose TBI to standard TLI-ATG conditioning therapy will increase the proportion of patients with FDC at Day 28 post-transplant, without reducing tolerability or increasing transplant morbidity. We **hypothesize** that the addition of very low-dose TBI at 80 cGy to TLI-ATG will result in at least a 30% increase in the proportion of patients with FDC in the CD3 subset at Day 28 post-HCT. This study will follow a single-arm Simon 2-stage trial principle. In Simon stage 1, we will enroll 11 patients, and if 5 or fewer patients respond, defined as ≥ 95% donor chimerism in the CD3 compartment at Day 28, we will stop for futility. If 6 or more respond in Simon stage 1, then in stage 2 we will continue to enroll a full sample of 20 patients and declare success if a total of 11 or more patients respond. The primary endpoint will be the determination of the rate of conversion from mixed to complete donor chimerism. Secondary endpoints will include the risk of acute and chronic GVHD, freedom from disease progression, event-free and overall survival, and the relapse rate. The goal is to improve the rate of attaining complete chimerism without increasing the risk of GVHD. If following the Simon 2-stage trial the results are encouraging, we will expand our experience to a broader trial to determine if the TLI/ATG/low-dose TBI is associated with significantly lower rates of disease relapse.

2.8 Study Design

This is a single institution open-labeled single treatment study evaluating the safety and efficacy of very low-dose TBI added to TLI-ATG conditioning in adults undergoing allogeneic HCT from related and unrelated donors. Enrollment of 20 patients is expected to be completed in less than 2 years. The study will involve a single non-randomized intervention arm of administering TBI 80 cGy on Day -1 of standard TLI ATG conditioning. The total duration of patient study participation is 12 months. Per regular medical care for HSC transplant patients, all recipients will be followed long term and tracked via the Stanford BMT patient database for overall survival; event-free survival; and late complications such as but not limited to relapse; late chronic GVHD; and infections.

3. PARTICIPANT SELECTION AND PRE-ENROLLMENT REQUIREMENTS

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist, following, and which may be extracted for use in screening potential subjects.

The following Participant Eligibility Checklist will be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist will be retained in the subject's study file, and the study's Regulatory Binder.

Pursuant to Stanford Medicine SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator); the Study Coordinator; and an Independent Reviewer will verify that the subject's eligibility is accurate; complete; and legible in source records. A description of the eligibility verification process will be included in the EPIC or other Electronic Medical Record progress note.

Participant Eligibility Checklist

For each prospective study participant that is screened, this checklist will be printed, the results recorded, and filed in the respective subject binder or file. It is anticipated that not all prospective study participants will be enrolled.

I. Protocol Information

Protocol Title:	Very Low-dose Total Body Irradiation in Combination with Total Lymphoid Irradiation and anti-Thymocyte Globulin to Improve Donor Engraftment in Patients Undergoing Non-Myeloablative Hematopoietic Cell Transplantation
eProtocol number: **OnCore number:**	IRB-47407 BMT330
Principal Investigator:	Robert Lowsky, MD

II. Subject Information

Subject name / Unique ID:	/	
Gender	☐ Male	☐ Female

III. Study Information

3.1 Patient Inclusion Criteria (patients must have all of the following).

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
1. ≥ 18 years old	☐	☐	
2. Has a HLA-matched or single allele-mismatched adult sibling donor or unrelated donor	☐	☐	
3. Has a myeloid or lymphoid malignant disease that will be treated with TLI and ATG reduced-intensity conditioning for allogeneic transplant [any of the following: acute myeloid leukemia (AML); myelodysplastic syndrome (MDS); myeloproliferative disease syndrome (MPD)]; chronic lymphocytic leukemia (CLL); B or T-cell non-Hodgkin lymphoma (NHL); Hodgkin lymphoma (HL); or chronic myelomonocytic leukemia (CMML)	☐	☐	
4. Patients who due to age, pre-existing medical conditions, or, prior therapy are considered to be at high-risk for regimen-related toxicity associated with fully ablative transplant conditioning, and therefore reduced intensity conditioning is recommended. Or patients for whom RIC allotransplant is recommended that is in keeping with standard of care in the transplant community	☐	☐	
5. Ability to understand and the willingness to sign a written informed consent document. Patients must have signed informed consent to participate in the trial.	☐	☐	

3.2 Patient Exclusion Criteria (excluded if any of the following)

Prospective Participants Must <u>NOT</u> Match <u>ANY</u> of These Exclusion Criteria	Yes	No	Supporting Documentation *
1. Uncontrolled bacterial, viral or fungal infection defined as currently taking medication and progression of clinical symptoms	☐	☐	
2. Progressive hemato-lymphoid malignancy despite conventional therapy	☐	☐	
3. Chronic myelogenous leukemia (CML)	☐	☐	
4. Active CNS involvement of the underlying malignancy if previously documented CNS involvement	☐	☐	
5. HIV-positive	☐	☐	
6. Pregnant or lactating	☐	☐	
7. Prior malignancy (EXCEPTION: diagnosed > 5 years ago without evidence of disease, OR treated ≤ 5 years ago but have a greater than 50% chance of life expectancy of ≥ 5 years for that malignancy).	☐	☐	

Prospective Participants Must NOT Match ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
8. Have a psychiatric disorder(s) or psychosocial circumstance(s) which in the opinion of the primary physician would place the patient at an unacceptable risk from transplant.	☐	☐	
9. Organ dysfunction defined as follows: i. Left ventricular ejection fraction (LVEF) < 30%, or uncontrolled cardiac failure ii. Diffusing capacity of lung for carbon monoxide (DLCO) < 40% predicted iii. Total bilirubin > 3 mg/dL iv. SGOT or SGPT > 4 x ULN v. Creatinine > 2 mg/dL and an estimated creatinine clearance < 40 mL/min vi. Poorly-controlled hypertension despite multiple antihypertensive medications	☐	☐	
10. Karnofsky Performance Status (KPS) < 60%	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is: ☐ eligible / ☐ ineligible for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the IRB of record, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator printed name:	Date:
Signature:	

Investigator printed name:	Date:
Signature:	

Triple-check reviewer printed name:	Date:
Signature:	

3.3 Informed Consent Process

A conference will be held with the patient and family to discuss this study and alternative treatments available for treatment of the underlying disease. All potential risks associated with the use of TLI; ATG; , low-dose TBI; immunosuppressive drugs; and allogeneic hematopoietic cell infusions will be discussed as objectively as possible. It will be explained that patients offered this protocol have an underlying malignancy that render them either at high risk of relapse or that will result in life expectancies of several months to no more than one to two years with conventional treatments. These patients would be unlikely to benefit from, or tolerate an autologous transplant, and are at high risk of early transplant mortality from conventional allogeneic transplant. Informed consent from the patient will be obtained using a form approved by the Administrative Panel on Human Subjects in Medical Research of the Stanford University Medical Center. The participant will receive a copy of the signed and dated consent document. The original signed copy of the research consent document must be retained in the subject's research file.

3.4 Study Timeline

It is expected the study will accrue 10 to 15 patients per year and therefore the target goal of 20 patients will be completed within 2 years of the study opening.

Patients will be followed for 12 months after the mobilized PBSC infusion on Day 0. Patients' End-of-Study Visit will be scheduled for approximately Day 360 post-PBSC infusion, +/- 8 weeks. Therefore, it is expected the study will be complete within 48 months of opening. Per regular medical care for HSC transplant patients, all recipients will be followed long-term and tracked via the Stanford BMT patient database for overall survival; event-free survival; and late complications such as but not limited to relapse; late chronic GVHD; and infections.

4. TREATMENT PLAN

The full procedure schedule is described in Section 7 Study Calendar.

4.1 Study Treatment Schedule

Transplant Schedule (See also Section 7 Study Calendar)

Week 1

Monday Day -11	Tuesday Day -10	Wednesday Day -9	Thursday Day -8	Friday Day -7	Saturday Day -6	Sunday Day -5
TLI 120 cGy	TLI 120 cGy	TLI 120 cGy	TLI 120 cGy	TLI 120 cGy	Rest	Rest
ATG **** 1.5 mg/kg + solumedrol 1.0 mg/kg	ATG 1.5 mg/kg + solumedrol 1.0 mg/kg	ATG 1.5 mg/kg + solumedrol 1.0 mg/kg	ATG 1.5 mg/kg + solumedrol 1.0 mg/kg	ATG 1.5 mg/kg + solumedrol 1.0 mg/kg		

Week 2 and beyond

Monday Day -4	Tuesday Day -3	Wednesday Day -2	Thursday Day -1 *	Friday Day 0	Saturday Day +1	Day 28 +/- 5 days	Day 56 +/- 5 days	Day 90 +/- 5 days
TLI 120 cGy	TLI 120 cGy	TLI 120 cGy	TLI 120 cGy	Mobilized PBMC				
	Start Tac 0.05 mg/kg oral BID***		TBI 80 cGy	Start MMF **				
						PB STRs	PB STRs	PB STRs

* As a guideline 5 hour interval will be provided between TLI and TBI on Day -1. No lung blocks will be used for TBI. The dose rate with be ≤ 2 Gy/minute. The Pre-HCT radiation oncology consultation will include simulation for both TLI and TBI and should be scheduled as such

** MMF 15 mg/kg PO BID for matched related donors; 15 mg/kg PO q8 hours for unrelated donors (URDs) or mismatched related donors. Physician discretion can round up or round down MMF to the nearest 250m/dose.

*** Tac starting dose is a recommended guideline yet based on Physician/APP discretion this start dose can be modified, typically lowered due to concern about drug-drug interaction and possible Tac toxicity.

**** ATG dosing is based on actual weight yet if >15kg above ideal body weight the ordering MD has the discretion to dose ATG based on actual weight or dose based on adjusted weight, both are acceptable.

4.2 Criteria for Removal from Study

All adverse events will be reviewed by Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) and patients will be removed from the study for the following reasons:

- Non-compliance with the protocol (defined as inability to receive all scheduled treatments, follow-up appointments, and tests)
- Patient request to withdraw from the study

4.3 Alternatives

Alternative therapies will be discussed with each patient and would potentially include allogeneic transplantation using TLI and ATG conditioning without TBI or allogeneic transplantation using

other transplant conditioning or other investigational therapies, or best of care non-transplantation therapy.

4.4 Compensation

There will be no compensation for participation on study.

5. ADVERSE EVENTS AND REPORTING PROCEDURES

5.1 Adverse Events

Hematopoietic cell transplantation (HCT) is an aggressive therapy for the treatment of a number of life threatening disorders, including cancer. In this setting, a very large number of Grade 1, 2 and 3 adverse events (AEs) are expected to occur, regardless of whether or not a patient is participating in a research study. In order to minimize the "background noise" and to focus on clinically significant, meaningful adverse events useful in the assessment of proposed trial the following AE reporting schema is proposed. This schema is intended to capture all AEs that are clinically significant and/or impactful, but minimize "not informative" AE collection.

- Grade 4 and higher AEs will be collected and documented with causality attribution on an adverse event log (AE log), and all AEs meeting the criteria of "serious" as defined at 21CFR§312.32(a), including any that are otherwise Grade 1, 2 or 3 will be collected; identified as serious; and documented on an AE log, including causality attribution.
    - An adverse event is considered serious if it fulfills one of the following criteria per 21CFR§312.32(a):
        - Results in death.
        - Life threatening (patient at risk of death at the time of the event).
        - Requiring new inpatient hospitalization or prolongation of existing hospitalization.
        - Resulting in persistent or significant disability.
        - Other medical events that may not be immediately life threatening or result in death or hospitalization by may jeopardize the patient or require intervention to prevent one of the outcomes listed above
- Laboratory values without a clinical consequence or outcome will not be tracked as adverse events, unless deemed serious.
- Grade 1-3 AEs not meeting these criteria will not be collected, except as follows. Grade 1 to 3 AEs resulting in subject termination or withdrawal from the study will be collected.

All Serious Adverse Events (SAEs) will be tracked until resolution or at least 60 days after the study treatment.5.2 Adverse Event Reporting

All serious adverse events (SAEs) as outlined in section above and meeting the criteria specified in 21CFR§312.32(c)(1) that occur from start of transplant conditioning through to day +90 post transplant will be collected. SAEs related to study treatment will be collected through the Week 52 follow up visit. All SAEs will be reported to in accordance with the established practices of the Stanford Division of Blood and Marrow Transplantation, as well the IRB and DSMC. The collected AEs will be documented in the adverse event log.

6. DATA CAPTURE

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study, in accordance with the established practices of the Stanford Division of Blood and Marrow Transplantation.

The trial completed enrollment and is closed to patient accrual. The trial remains open for patient observation and determination of the trial's secondary outcomes.

Time is needed for patients to complete this period of observation. Once all the patients have passed the last time point of observation the study PI will analyze the data in context of BMT Core Group B which includes Drs. Ying Lu and John Tamaresis. The outcomes will be uploaded to Clinical trials.gov.

There is no data specific for this trial that extends beyond what the extensive and comprehensive bmt database already collects. This data will be reviewed by the study PI and Core B for accuracy before it is finalized in BMTcore.

7. STUDY CALENDAR

	Pre-enrollment requirements		Day -11, -10, -9, -8, -7	Day -4	Day -3	Day -2	Day -1	Day 0	Day 28 +/- 7 days	Day 56 +/- 14 days	Day 90 +/- 14 days	Day 180 +/- 4 weeks	Day 360 +/- 8 weeks
	Day-180 to -13	Day -42 to -12											
Informed consent	X												
Demographics	X												
Donor evaluation	X												
B-HCG [a]		X											
Height		X											
Weight		X						X	X	X	X		
Medical history	X							X	X	X	X		
Concurrent meds		X						X	X	X	X		
Physical exam		X						X	X	X	X		
Vital signs [b]		X						X	X	X	X		
Performance status		X						X	X	X	X		
Central venous catheter		X											
Blood sample for:		↓						↓	↓	↓	↓	↓	↓
CBC w/diff		X						X	X	X	X		
Serum chemistry [c]		X						X	X	X	X		
STR analysis [k]									X	X	X	X	X
TLI [e]			X	X	X	X	X						
TAC [f]					X								
ATG [g]			X										
TBI [h]							X						
PBSC Infusion								X					
MMF [i]								X					
SAE evaluation								X - Weekly from Day 0 through Day 90					
Disease Status Assessment [j]	X										X	X as indicated	X as indicated

a: Pregnancy test for women of childbearing potential only.
b: Temperature, blood pressure, and pulse.
c: Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium
e: TLI: Total lymphoid irradiation, 120 cGy.
f: TAC: Tacrolimus
g: ATG: Anti thymocyte globulin, 1.5 mg/kg with solumedrol 1.0 mg/kg.
h: TBI: Total body irradiation, 80 cGy.
i: MMF: Mycophenolate mofitel, by mouth.
j Response assessment as per disease histology, and may include CT, PET, and/or MRI imaging, and bone marrow biopsy or aspiration (refer to Appendix B), and is typically performed around Day 90 post-transplant (Day 0).
k: Short tandem repeat (STR) analysis (by comparison to subject's pre-study HLA analysis) on Day 28 +/- 7 days; Day 56 +/- 14 days; Day 90 +/- 14 days; Day 180 +/- 4 weeks; Day 360 +/- 4 weeks, and thereafter as per standard of care.

8. MEASUREMENTS and STATISTICAL METHODS

Our extensive experience with the TLI ATG conditioning for allogeneic HCT in cancer patients showed a 30 to 40% incidence of FDC at Day 90, with a 95% confidence interval of 10 to 49%. The non-relapse mortality (NRM) was 3% (95% CI: 0 to 14%) at 100 days and 6% (95% CI: 1 to 28%) at 1 year. The incidence of acute GVHD by Day 100 was 6% (0.7 to 22%).

8.1 Primary and Secondary Outcome measures

The primary outcome is to determine the proportion of patients with full dose donor chimerism (FDC) at Day 28 following TLI/ATG/TBI conditioning. FDC is defined as achieving ≥ 95% donor type in the CD3+ lineage within 28 days of donor cell infusion.

The secondary outcome measures include time-to-disease progression assessed at 1 year after hematopoietic cell transplantation (HCT); overall survival (OS) at 1 year; and event-free survival (EFS) at 1 year; and non-relapse mortality at 1 year. The incidence of acute and chronic GVHD following the infusion of allogeneic CD8+ memory T-cells will be assessed at 1 year after HCT.

Recipients will be monitored for HCT toxicities and the rates of GVHD as per the study calendar. STR analysis will be performed on Day 28 +/- 7 days and per the study calendar thereafter. The level of tumor burden will be evaluated at 3 months after transplant and at 6 and 12 months as clinically indicated by standard imaging and blood evaluation procedures specific for the patient disease (refer to Appendix B).

Beyond 12 months and per regular medical care for HSC transplant patients, all recipients will be followed long-term and tracked via the Stanford BMT patient database for overall survival; event-free survival; and late complications such as but not limited to relapse; late chronic GVHD; and infections.

9. REGULATORY CONSIDERATIONS

This study evaluates an approved therapy (anti-thymocyte globulin, ATG) and an established radiotherapy procedure (low-dose total body irradiation, TBI). The study therapy is considered to not represent an increase in risk over that described in the ATG labeling, and on this basis, is considered to be an IND-exempt investigation.

9.1 Institutional Review of Protocol

The protocol, the informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Center Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

9.2 Data and Safety Monitoring Plan

The Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to

ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9.3 Data Management Plan

The Protocol Director, or his designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. The Stanford BMT data monitoring team along with the study coordinator will collect the information required in the Study calendar of events and maintain records for data analysis. The data will be reviewed by the study PI for accuracy against source document data.

9.4 Confidentiality

Patient records will be kept in a secure location at Stanford University Medical Center accessible only to research authorized personnel. Patient identity will be kept as confidential as possible as required by law. The patient will not be identified by name, social security number, address, telephone number, or any other personal direct identifier. Study patients will be assigned an identification code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this study may be presented at scientific or medical meetings or published in scientific journals, however patient identity will not be disclosed. Personal data included in the investigators' database will be maintained in compliance with all applicable laws and regulations.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis

The sample size determination for the clinical trial will follow a single arm Simon 2-stage trial principle. The null hypothesis that the true response rate is $p_u = 0.40$ will be tested against a one-sided alternative ($p_d = 0.7$). In the first stage, $n_1 = 11$ patients will be accrued. If there are [illegible] or fewer responses in these $n_1 = 11$ patients, the study will be stopped. Otherwise, $n - n_1 = 9$ additional patients will be accrued for a total of [illegible]. The null hypothesis will be rejected if $r + 1 = 11$ or more responses are observed in $n = 20$ patients. This design yields a type I error rate of $\alpha = 0.10$ and power of $1 - \beta = 0.90$ when the true response rate is $p_d = 0.70$.

We plan to use a dose of 80 cGy of TBI on Day -1 of HCT. It is fully expected that this low-dose will be safe and not provoke or increase the risk of GVHD or other complications. Patients will be evaluated for toxicities, defined as new Grade 3 to 4 toxicities, according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5 and Grade 3 to 4 GVHD (Appendix A) during the 90 days following HCT.

10.2 Stopping Rule

Based on preclinical data, we do not believe the TBI at such a low-dose will aggravate GVHD, and we do not expect additional regimen-related toxicities at this dose. Patients will not be enrolled into Stage 2 until all patients in Stage 1 have reached 90 days post-transplant. Patients will not be enrolled into Stage 2 until all patients in Stage 1 have reached 90 days post-transplant.

The study will be terminated if the number of subjects who experience a "stopping event" (*defined as Grade 4 GVHD*) is 2, 3 or 4 among (respectively) the first 6, 12, or 18 patients. This rule is based on stopping if the lower 80% confidence limit for the true probability of a "stopping event"

exceeds 12% (the maximal acceptable rate) at any look. The rule is implemented with a forward-looking interpretation, so that if the number of events hits the boundary for the current look at any time, the study will stop. Subjects will not be enrolled into Stage 2 until all subjects in Stage 1 have reached 90 days post-transplant without triggering the stopping rule, and enrollment will be delayed if necessary at each stopping rule milestone, to ensure that subject 7, 13, and 19 are not enrolled until the stopping rule at (respectively) 6, 12, and 18 is cleared (for example, if there has been one stopping event in the first 5 subjects, enrollment is paused until patient 6 reaches 90 days without an event.

The stopping rule described above, which we have used in many studies, controls the "false alarm" rate. We do not generally calculate the "true alarm rate" at probabilities exceeding the max acceptable rate, because we do not think it is informative. It is well-understood that the small samples in phase 1 and 2 generally do not provide precise upper bounds for the probability of unwanted effects, so the purpose of stopping rules is to protect the patients enrolled in the study, as far as possible, consistent with the inherent risks of early phase studies and the potential benefit. If the stopping rule is not triggered even though the true risk is substantially greater than the max acceptable rate, then the actual harm has been limited to the extent possible in an early phase trial.

10.3 Sample Size

Twenty patients will be required to complete the study.

10.4 Accrual estimates

Approximately 10 to 15 patients will be enrolled annually. Time to complete enrollment will be 2 years. Overall time to initiate, conduct, and complete the trial will be about 4 years.

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APPENDIX A: Glucksberg clinical stage and grade of acute GVHD

Stage	Skin	Liver	Intestinal tract
1	Maculopapular rash < 25% of body surface	Bilirubin 34–50 μmol/l	> 500 ml diarrhoea/d
2	Maculopapular rash 25–50% body surface	Bilirubin 51–102 μmol/l	> 1000 ml diarrhoea/d
3	Generalized erythroderma	Bilirubin 103–225 μmol/l	> 1500 ml diarrhoea/d
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 255 μmol/l	Severe abdominal pain, with or without ileus

Grade	Degree of organ involvement
I	Stage 1–2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance
II	Stage 1–3 skin rash; stage 1 gut involvement or stage 1 liver involvement (or both); mild decrease in clinical performance
III	Stage 2–3 skin rash; stage 2–3 gut involvement or 2–4 liver involvement (or both); marked decrease in clinical performance
IV	Similar to Grade III with stage 2–4 organ involvement and extreme decrease in clinical performance

APPENDIX B. RESPONSE CRITERIA by DISEASE HISTOLOGY

AML Response Criteria (Cheson, *et al*. 2003)

Response Criterion	Time of Assessment	Neutrophils (μL)	Platelets (μL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	7-10 days after therapy	NA	NA	< 5	
Morphologic leukemia-free state	Varies by protocol	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	Varies by protocol	> 1,000	> 100,000	< 5	Transfusion EMD
Cytogenetic CR	Varies by protocol	> 1,000	> 100,000	< 5	Cytogenics – normal, EMD
Molecular CR	Varies by protocol	> 1,000	> 100,000	< 5	Molecular – negative, EMD
Partial remission	Varies by protocol	> 1,000	> 100,000	> 50 or decrease to 5-25	Blasts < 5% if Auer rod positive

In this study Day of assessment is 12 weeks and 24 weeks post stem cell infusion. For patients who are in a pathologically confirmed remission prior to infusion, a bone marrow biopsy and/or aspirate are not required; disease can be followed by confirmatory CBCs

NHL Response Criteria (Cheson, *et al*. 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 measurable 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 PDT 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 identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

In this study, the day of assessment is 12 weeks and 24 weeks after stem cell infusion.

CLL Response Criteria (Hallek, *et al*. 2008)

Parameter	CR	PR	PD	SD
Lymphadenopathy[1]	None above 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%	Change of -49% to +49%
Liver and/or spleen size	Normal size	Decrease ≥ 50%	Increase ≥ 50%	Change of -49% to +49%
Constitutional symptoms	None	Any	Any	Any
Polymorphonuclear leukocytes	> 1500/μL	> 1500/μL or > 50% improvement over baseline	Any	Any
Circulating clonal B-lymphocytes	Nil	Decrease ≥ 50% from baseline	Increase ≥ 50% from baseline	Change of -49% to +49%
Platelet count	> 100,000/μL	> 100,000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	> 11.0 g/dL (untransfused and without erythropoietin)	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi.	≥ 30% lymphocytes, or B-lymphoid nodules, or not done	Increase of lymphocytes to more than 30% from normal	No change in marrow infiltrate

[1] sum of the products of multiple lymph nodes (as evaluated by CT scans, physical exam or ultrasound).
CR: complete remission, all of the criteria have to be met, with a marrow aspirate and biopsy performed at least 3 months after last treatment; PR: partial remission, at least one of the criteria has to be met; PD: progressive disease, at least one of the above criteria has to be met; SD: stable disease, all of the above criteria have to be met. Note that it is not necessary to assess bone marrow to confirm SD and determination of circulating clonal B lymphocytes is only necessary if other criteria are insufficient to define a response.

In this study day of assessment is 12 weeks and 24 weeks post stem cell infusion.

MDS Response Criteria (Cheson, *et al*. 2006)

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100×10^9/L
	Neutrophils ≥ 1.0×10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.