A Phase II Study of Non-myeloablative Allogeneic Transplantation Using Total Lymphoid Irradiation (TLI) and Antithymocyte Globulin (ATG) In Patients with Cutaneous T Cell Lymphoma

Study Protocol and Statistical Analysis Plan

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BMT 206: A Phase II Study of Non-myeloablative Allogeneic Transplantation Using Total Lymphoid Irradiation (TLI) and Antithymocyte Globulin (ATG) In Patients with Cutaneous T Cell Lymphoma

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PROTOCOL SYNOPSIS

TITLE	A Phase II Study of Non-myeloablative Allogeneic Transplantation Using Total Lymphoid Irradiation (TLI) and Antithymocyte Globulin (ATG) In Patients with Cutaneous T Cell Lymphoma
STUDY PHASE	II
INDICATION	Advanced Stage Cutaneous T Cell Lymphoma
PRIMARY OBJECTVES	Clinical Response
SECONDARY OBJECTIVES	Engraftment and GVHD
HYPOTHESES	Graft versus Lymphoma effect provided by Non-myeloablative Allogeneic Transplantation will provide disease control
STUDY DESIGN	Single arm phase II
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS	Clinical response Incidence of GVHD, EFS, OS
SAMPLE SIZE BY TREATMENT GROUP	40 patients
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	Advanced stage cutaneous T cell lymphoma patients with HLA-matched related or unrelated donor
INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	Total lymphoid irradiation (TLI) 800 cGy and anti-thymocyte immunoglobulin
CONTROL GROUP	Not applicable
PROCEDURES	Not applicable
STATISTICAL CONSIDERATIONS	Clinical response and incidence of GVHD will be reported as percentage. EFS and OS will be determined using Kaplan-Meier estimation.

SCHEMA

ENROLLMENT

- Advanced stage cutaneous T cell lymphoma
- Relapse or refractory to conventional therapy
- HLA matched donor
- Signed Informed Consent

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TLI/ATG CONDITIONING AND ALLOGENEIC TRANSPLANTATION	
Day -35 to Day -2	TSEBT for extensive skin involvement Length of treatment and dose of TSEBT will be determined by the radiation oncologist
Day -11 to Day -7	TLI 800 cGy ATG 1.5 mg/kg & solumedrol 1 mg/kg
Day -4 to Day -2	TLI 800 cGy
Day -3	Start oral tacrolimus
Day -1	TLI 800 cGy x2
Day 0	Infusion of mobilized peripheral blood cells from donor, start oral MMF
Day +28	ECP weekly x4, then every two week x4, then monthly x4 in patients with persistent Sezary cells

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activity of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EFS	Event Free Survival
GVHD	Graft versus Host Disease
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
IV	Intravenous
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TSEBT	Total skin electron beam therapy
TTP	Time to progression
UNK	Unknown
WBC	White blood cell

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the graft versus lymphoma effect by monitoring rate of clinical response, event-free and overall survival.

1.2 Secondary Objectives

To evaluate the incidence and extent of acute and chronic GVHD and time to engraftment.

2. BACKGROUND

2.1 Study Disease

Mycosis Fungoides/Sezary Syndrome
MF is a mature T cell lymphoma that arises primarily from the skin. It is the major subtype of cutaneous T cell lymphoma (CTCL). Patients usually present initially with patch, plaque, tumor or erythrodermic involvement of their skin. MF has a long natural history (2). Many patients have non-specific skin manifestations for several years before a diagnosis is made. Although the initial lesions are usually limited skin patches or plaque, generalized plaques involving large body surface area and tumor lesions are common by the time patients seek medical attention. Extra-cutaneous dissemination may occur to lymph nodes, liver, spleen, lungs and blood (Sezary cells). SS is a leukemic form of MF in which patients have significant blood involvement with Sezary cells and diffuse erythroderma (3).

After the diagnosis is established, appropriate staging is important. Initial staging should include comprehensive skin examination, peripheral blood evaluation for Sezary cells, and appropriate imaging such as CT scan. The International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the EORTC has recently published a revised TNM staging for MF/SS (4). Several large studies have shown that overall clinical stage determines long-term outcome. Patients with limited stage IA disease have a very favorable outcome with life expectancy comparable to matched control population. Patients with IB/IIA disease have a median survival of 11-12 years after diagnosis, with fewer than 20% experiencing progression to higher stage. However, stage IIB/III disease carried a worse outcome with median survival of 4-5 years and higher chance to have large cell transformation. Patients with stage IV disease have the worst, <2 year median survival (Figure 1) (2).

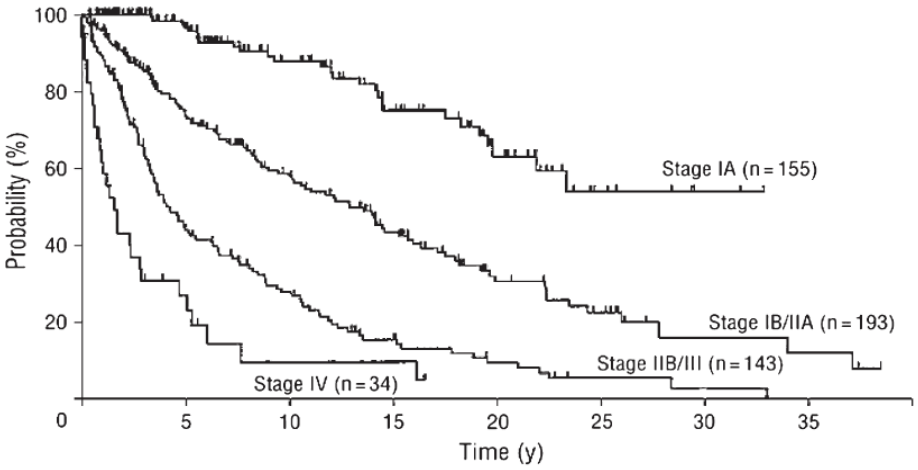

Figure 1 Actuarial overall survival of 525 patients at Stanford with MF/SS according to TNM stage at diagnosis.

Therapy for Mycosis Fungoides/Sezary Syndrome

Choosing appropriate treatment for individual patients is not easy. The most important consideration is the T (tumor) classification and overall clinical stage, with specific concerns for large cell transformation, acuity or severity of associated symptoms, and potential treatment related toxicities (5). In general, step-wise approach with first skin-directed therapy, then mild biological systemic therapy, and then systemic chemotherapy is the current strategy. Skin-directed therapies should be the first step to control skin lesions, which include topical steroids, topical nitrogen mustard, topical retinoids and phototherapy. Narrow-band UVB and Psoralen plus UVA are highly effective for thicker plaques. Total skin electron beam therapy, considered the most intensive skin-directed therapy, is reserved for patients with extensive generalized disease and severe skin symptoms (6). While clinical response is greater with more intensive skin-directed therapies, no improved progression free or overall survival has been shown.

For patients with refractory disease to skin-directed therapies or with advanced stage of MF (IIB-IV) and Sezary syndrome, systemic treatments should be included in the primary therapy strategy, with or without skin-directed treatments. The first category of systemic therapy is mild immunomodulating agents (biologics), such as systemic retinoids (bexarotene) (7), interferons (8,9), low dose methotrexate and newer reagents, histone deacetylase inhibitors (10), and denileukin diftitox (11). While these treatments have a slow time to response and generally provide partial response rates no greater than 50%, their lack of cumulative toxicity allows them to be used as maintenance treatment for long periods. Extracorporeal photopheresis (ECP) has been used as monotherapy or in combination with other systemic therapy and has been shown to be a very effective treatment, especially for disease control of SS (12). The next category of systemic therapy is more traditional cytotoxic chemotherapy. The most common reagents are liposomal doxorubicin, gemcitabine, chlorambucil and high dose methotrexate. Pegylated liposomal doxorubicin is effective as a single agent. In a prospective study, every 4 week infusions gave an overall response rate of 84% with 42% of the patients achieving complete response (13). However, these responses are usually short-lived and patients move from one agent to another agent, then proceed to combination chemotherapies, and eventually progress after multiple therapies.

Treatment with Hematopoietic Stem Cell Transplantation

Emerging data on allogeneic HSCT, particularly using non-myeloablative conditioning, suggest the existence of a graft-versus-T cell lymphoma effect. Allogeneic transplant should be considered in patients with advanced disease who fail to respond to all primary therapies or do not have durable response with salvage treatments.

Recently, we have performed a meta-analysis of studies treating MF/SS patients with HSCT in an attempt to understand its utility. In this analysis, 15 published reports with a total of 38 cases and 5 unpublished cases were included (14-28). Twenty three cases had high dose therapy followed by autologous HSCT and twenty cases had allogeneic transplant. The median age was relatively young of 42 years with an equal male/female distribution. All but one case had advanced stage ($\geq$IIB) disease at time of transplant. The median follow-up was 21 and 29 months for autologous and allogeneic transplant group, respectively. For autologous group, 12 cases received total body irradiation (TBI) and chemotherapy and 11 cases had only high dose chemotherapy. For allogeneic group, half of them received myeloablative preparative regimen with TBI plus chemotherapy; and the other half had non-myeloablative preparative regimen. As a whole group, the allogeneic transplant had a significantly longer event-free survival (EFS) than the autologous HSCT (Figure 2). In the autologous transplant group, 19 of 23 cases progressed/relapsed after transplant with median time to progression of 3 months. In contrast, only 5 of 20 cases progressed/relapsed with median time to progression not reached in allogeneic group.

The overall survival (OS) was also longer in allogeneic group than in autologous group (Figure 3). The estimated OS was 85% vs 65% at 1 year, 79% vs 56% at 2 year and 79% vs 36% at 5 year for the two groups. One hundred day post transplant mortality was 5% and 13% in allogeneic and autologous groups respectively. One year mortality was 15% and 35% for the two groups. While progressive disease caused 11 deaths in autologous group, none of the death in allogeneic cases was due to disease progression. The most interesting finding was that there was no difference in clinical outcome between the cases receiving myeloablative regimen and the cases having non-myeloablative approach in the allogeneic group.

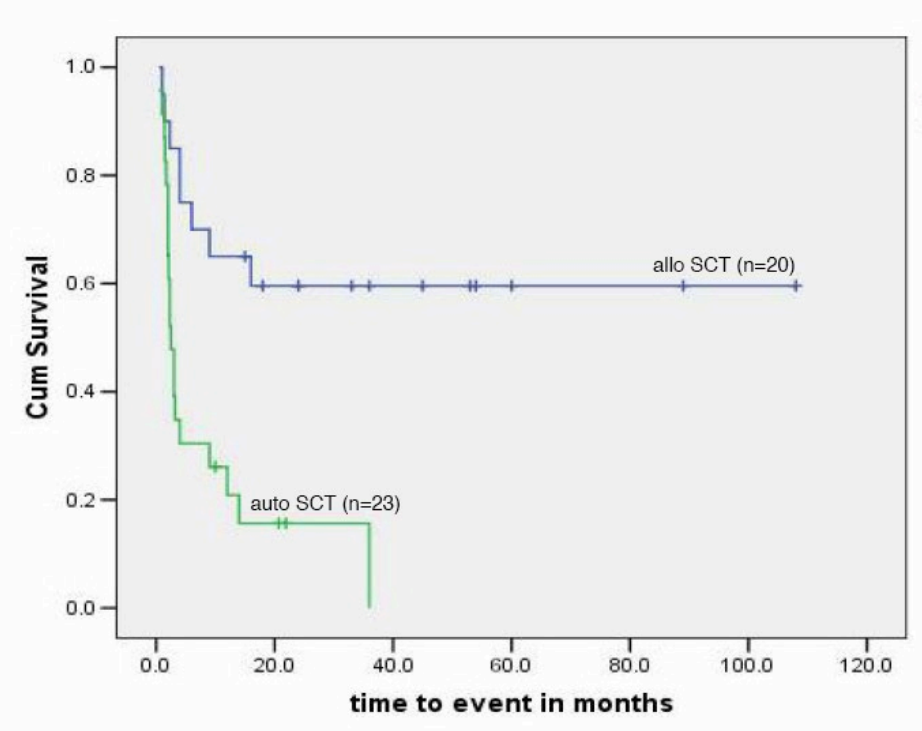

Figure 2 Post transplant event-free survival of MF/SS patients according to the type of transplant (*p < 0.0005*).

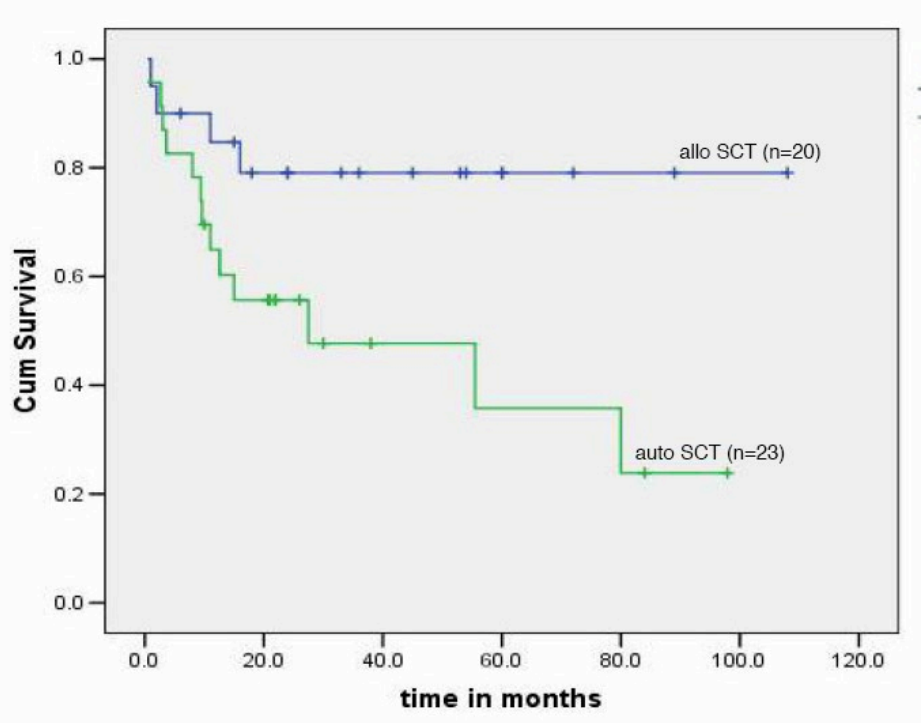

Figure 3 Post transplant overall survival (OS) of MF/SS patients according to the type of transplant (*p = 0.028*).

Although this is a very small sample size with many limitations, this meta-analysis suggests several important points related to the use of HSCT to manage MF/SS:

1) High dose therapy with either TBI or chemotherapy has not provided significant clinical benefit given the extremely short time to progression (3 months) in autologous transplant experience.

2) A significant fraction of cases remained in progression free status after allogeneic transplant, suggesting an effective graft-versus-MF/SS effect.
3) Non-myeloablative approach for allogeneic transplant is a reasonable option, especially given that the median age at diagnosis is 55-60 years and compromised skin is frequently present in these patients, which increases the risk of infection. Therefore, we propose a clinical study with allogeneic HSCT using a unique non-myeloablative preparative regimen, TLI/ATG, to treat advanced MF/SS.

2.2 Investigational Agent/Device/Procedure

Total lymphoid irradiation (TLI)/antithymocyte globulin (ATG) preparative regimen
One of the concerns using allogeneic HSCT is the toxicity related to transplantation process. While graft-versus-lymphoma is highly desired for a long-term disease control, the mortality and morbidity from preparative regimen, infections and graft versus host disease (GVHD) makes allogeneic transplant difficult to apply to patients with indolent lymphoma. To overcome this, preparative regimens of non-myeloablative radiotherapy, chemotherapy, or both to decrease early toxicity have been used (29-32). However, acute GVHD remains a major problem after non-myeloablative transplantation and is responsible for approximately 50 percent of the deaths that are not due to a relapse of the neoplasm (31-33).

A new approach to the prevention of acute GVHD takes advantage of the immune system's regulatory T cells. Two types of regulatory T (Treg) cells in mice, natural killer T cells and CD4+CD25+ T cells, can prevent acute GVHD (34-37). These Treg cells inhibit the proliferation of and cytokine secretion by CD4+ and CD8+ donor T cells that injure the intestines, liver, and skin in acute GVHD (34,37). Nevertheless, the direct tumor-killing activity mediated by donor CD8+ T cells remains unaffected (35). Thus, Treg cells can separate GVHD from the antitumor activity of the graft. Regulatory natural killer T cells of either donor or host origin have the unique capacity to prevent acute GVHD by secreting interleukin-4 (36-38). In a mice models, after repeated treatment with low-dose irradiation targeted to the spleen, thymus, and lymph nodes (total lymphoid irradiation, TLI), the proportion of these cells progressively increases until ultimately they constitute the majority of T cells in the spleen and bone marrow (37, 38). In preclinical studies, murine recipients of allogeneic bone marrow that underwent conditioning with anti–T-cell antibodies and TLI were fully protected from GVHD, whereas mice that underwent conditioning with anti–T-cell antibodies and a single dose of total-body irradiation were not protected (37, 38). Studies of the pattern of cytokine secretion by donor T cells in protected hosts showed a polarization toward a pattern of type 2 helper T (Th2) cells, with increased secretion of interleukin-4 (38). The Th2 cells assist B cells to produce antibodies and reduce the inflammation promoted by type 1 helper T cells.

To apply this novel non-myeloablative regimen of TLI and ATG for allogeneic HSCT, a clinical trial has been conducted in patients with hematological malignancies other than myelodysplasia or myeloproliferative disorders since December 2001. Analysis of the first 37 patients (last patient enrolled in 2004), 19 of whom had NHL, appeared in the New England Journal of Medicine (39). The regimen consisted of 800 cGy in 10 fractions over 11 days with ATG administered at 1.5 mg/kg/d from day -11 to -7. The median age was 56 (28-65) years and 35% had failed prior autologous HSCT. Multi-lineage chimerism was achieved within 56 days and sustained in 31 of 37 patients. Of the 6 who lost their grafts, 4 were in the setting of progressive disease. Minimal neutropenia was observed and more than half of patients did not require hospitalization. Remarkably and in agreement with the preclinical studies, 35 of 37 patients developed no acute GVHD. Among the 18 patients in partial remission at transplant, 10 achieved complete remission, strongly suggestive of retained graft versus tumor effect. Among the 17 patients in complete remission at transplant, 11 continued to be disease-free at 1.5 years. Transplant-related mortality in this study was just 5% at 180 days. To date, 4 deaths due to disease progression and 4 deaths related to the procedure have been recorded. Overall, these results indicate that preparation with TLI/ATG and allogeneic HSCT is well tolerated, associated with prompt multi-lineage engraftment and a markedly low incidence of acute GVHD, with a strong suggestion of retained graft versus tumor effect.

Update on experience in B cell lymphoma patients
Since the initial report, we continue to accumulate the experience using this novel non-myeloablative preparative regimen. To date, we have performed allogeneic HSCT using TLI/ATG preparative regimen in 111 patients. Sixty four of the patients had malignant lymphoma. The majority of the patients (83%) achieved full donor chimerism (> 95% donor cells) and the transplant was well tolerated.

The one-year non-relapse mortality was 2% for patients receiving HLA-matched sibling donor graft and 8% for patients having HLA-matched unrelated donor graft. Acute GVHD only occurred in 4% of the patients, while the incidence of chronic GVHD is estimated to be around 35-45% at 2 years. For patients with lymphoma, the disease control was significantly better in patients who responded to salvage chemotherapy prior to transplantation than those who had refractory disease (Figure 4). One possibility is that graft-versus-lymphoma effect is a slow process after non-myeloablative allogeneic transplant and is unable to control high tumor burden or fast growing tumor in time. Therefore, we propose in this project to use non-myeloablative allogeneic HSCT in MF/SS patients after they achieve some degree of disease control with salvage therapy. One important observation was that patients who failed to achieve full donor chimerism had significant chance to relapse after transplant.

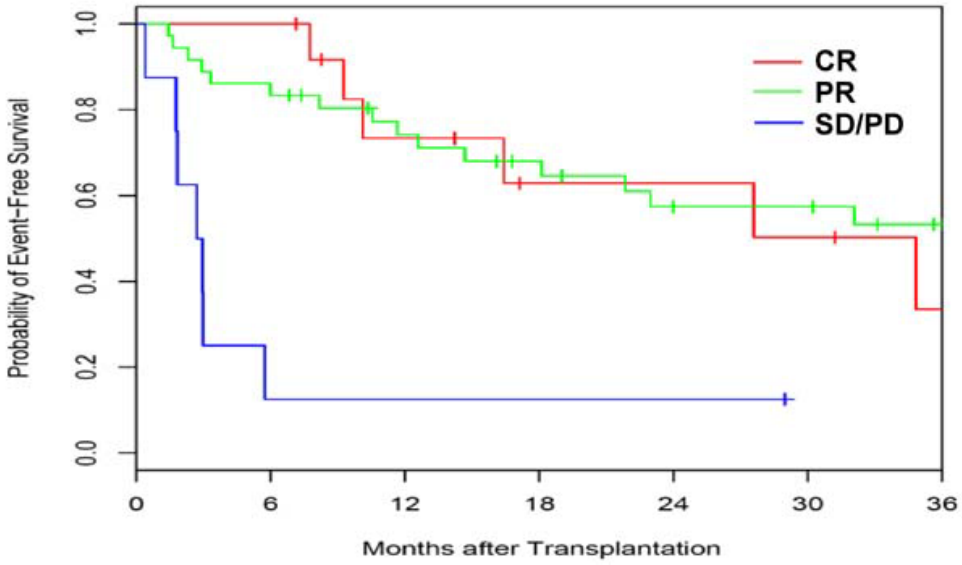

Figure 4 Actuarial event-free survival among patients with lymphoid malignancies (non-skin) stratified by disease status at transplant (N=64).

2.3 Rationale

Mycosis Fungoides (MF) and its leukemic variant, Sezary Syndrome (SS) is the most common type of cutaneous non-Hodgkin's lymphoma (NHL) in North America. Though most of the patients have an indolent course with median survival of 12-15 years, those with advanced diseases have a survival of 1-3 years after diagnosis, and there is no curative therapy (1). While localized skin treatment, novel biological therapies such as histone deacetylase inhibitors, or systemic chemotherapy can temperately control the diseases, none of these provide a long-term remission. Graft-versus-lymphoma effects after allogeneic hematopoietic stem cell transplantation (HSCT) have been demonstrated to provide a long-term disease control in B cell lymphoma, including low-grade B cell lymphoma and chronic lymphocytic leukemia. We propose a clinical trial using non-myeloablative allogeneic HSCT to treat patients with advanced stage MF/SS. The rationale is that graft-versus-lymphoma provided by this non-myeloablative approach will result in a clinical response and a prolonged progression free survival in these patients. The patient population enrolled in this clinical trial will be those with MF/SS who still have persistent or progressive disease after being treated with multiple lines of local and systemic therapies. When MF/SS reached this stage of their disease, the conventional chemotherapies will no longer provide any clinical benefit. Therefore, we proposed using this low toxicity allogeneic HSCT protocol to these patients.

2.4 Correlative Studies Background

2.4.1 Donor Cell Chimerism: The standard definition for full engraftment is that the percentage of donor cells in CD3 population rises above 95%. While most of our patients (83%) having undergone TLI/ATG preparative regimen reached full donor chimerism, the timing to achieving full chimerism varied significantly. It is of great interest to determine whether the full donor chimerism correlates to clinical response. In addition, donor chimerism of different cell populations may also have a significant impact on

clinical outcome. We will attempt to correlate the kinetics of donor chimerism of different cell populations to tumor response, disease progression, and GVHD. One prediction is that rising donor CD3/CD4/CD8 cells correlate to tumor response.

2.4.2 Profile of Grafting Immune Cells: To assess the T cells immune profile, intracellular cytokines with monoclonal antibodies against IL-2, IFN-g (Th1 pattern), IL-4 and IL-10 (Th2 pattern) will be assayed. In mouse models, TLI/ATG polarized T cells to a Th2 pattern, which has been thought to be critical for graft-versus-tumor effect. Therefore, it is of great interest to see whether this Th2 polarization can be recapitulated in humans and whether Th2 polarization may affect tumor response. In the case of MF/SS, it is more complicated as most of the tumor T cells express Th2 phenotype (44). Whether this will facilitate or hamper the graft-versus-tumor effect by the donor T cells is unknown.

2.4.3 Donor T Cell Trafficking: Engrafted donor T cells have to be in close contact with the tumor cells to help antigen-presenting cells (APC) to cross-prime cytotoxic CD8 T cells. Recently, chemokine receptors, CCR4, CCR10 and cutaneous lymphocyte antigen (CLA) have been shown to play a critical role in mediating CD4 T cell trafficking to skin in both mice and humans (45-49). We will first test whether the peripheral blood T cells express these skin homing receptors by using multi-color flow cytometry. In addition, CCR7 has been shown to mediate the homing of T or B lymphocytes to lymph nodes (50), which is an essential step after T cells being primed in the tumor sites. In addition, examining the skin tumor site after transplant will be extremely informative to determine whether donor T cells reach the tumor sites.

2.4.4 Regulatory T cell (Treg): Treg cells have been implicated in many important aspects of allogeneic transplant, such as modulating graft-versus-tumor effect and damping GVHD. Recent studies have also pointed a role for Treg in the progression of MF/SS and in immunomodulation in the skin (52,53). Therefore, monitoring the number and function of Treg will be performed. We will monitor the number of Treg in blood and their function using a mixed-lymphocyte-reaction (MLR) inhibition assay (39).

We will specifically monitor the number and function of Treg cells in patients who undergo ECP or TSEBT. The status of Treg cells in these patients becomes even more interesting because these treatments have been proposed to mediate their therapeutic effects via modulating Treg (54).

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

3.1.1 Stage IIB-IV mycosis fungoides or Sezary syndrome, who have failed at least 1 standard systemic therapy or are not candidates for standard therapy.

3.1.2 Pathology reviewed and the diagnosis confirmed at Stanford University Medical Center.

3.1.3 Age > 18 years and $\leq$ 75 years.

3.1.4 Karnofsky Performance Status $\geq$ 70%.

3.1.5 Corrected DLCO $\geq$ 40%.

3.1.6 Left ventricle ejection fraction (LVEF) $\geq$ 30%.

3.1.7 ALT and AST must be $\leq$ 3x normal.

3.1.8 Total bilirubin $\leq$ 2 mg/dL unless hemolysis or Gilbert's disease.

If AST and ALT are > 3 $\leq$5 x ULN, patient may be eligible if:

1) Liver biopsy performed within 60 days of HCT excludes active cirrhosis grade greater than 2/4 and bridging fibrosis.
2) No clinically evident ascites.
3) Patient with Hepatitis B or C are excluded if AST or ALT > 3 x UL.

3.1.9 Estimated creatinine clearance ≥ 50 ml/min.

3.1.10 Have a related or unrelated HLA-identical donor, or one antigen/allele mismatched in HLA-A, B, C or DRB1.

3.1.11 Signed Informed Consent.

3.1.12 Patients with prior malignancies diagnosed > 5 years ago without evidence of disease are eligible.

3.1.13 Patients with a prior malignancy treated < 5 years ago but have a life expectancy of > 5 years for that malignancy are eligible.

3.2 Exclusion Criteria

3.2.1 Uncontrolled active infection.

3.2.2 Uncontrolled congestive heart failure or angina.

3.2.3 Pregnant or nursing patients will be excluded from the study.

3.2.4 Those who are HIV-positive will be excluded from the study due to high risk of lethal infection after hematopoietic cell transplantation.

3.3 Donor Inclusion Screening Guideline

3.3.1 Age ≥17.

3.3.2 HIV seronegative.

3.3.3 No contraindication to the administration of G-CSF.

3.3.4 Willing to have a central venous catheter placed for apheresis if peripheral veins are inadequate.

3.4 Donor Exclusion Screening Guideline

3.4.1 Serious medical or psychological illness.

3.4.2 Pregnant or lactating women are not eligible.

3.4.3 Prior malignancies within the last 5 years, except for non-melanoma skin cancers.

3.5 Enrollment

Enrollment occurs when all eligibility criteria are met.

3.6 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. The attending physician will conduct the conference. All potential risks associated with the use of TLI, ATG, 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 at high risk of relapse or that will result in a significant decrease in life expectancies with conventional treatments. 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.

3.7 Randomization Procedures

No randomization process will be performed in this study.

4. TREATMENT PLAN

4.1 Investigational Agent or Device Administration

4.1.1 Pre-transplant Evaluation

a) Prior to initiating therapy, patients will have a complete history and physical examination performed. In addition, a bone marrow specimen and bone marrow aspirate will be obtained for the evaluation.
b) Patients will have the following laboratory tests performed: CBC with differential, HLA typing, comprehensive metabolic panel, urinalysis, hepatitis panel, HIV antibody, HIV p24 antigen, herpes simplex titer, herpes zoster titer, and CMV titer. Additional evaluation will include a chest radiograph, EKG and pulmonary function testing with spirometry and diffusing capacity. Other testing may be needed and will be determined based on the patients history and physical examination.
c) HLA typing of the donor will be confirmed at Stanford before beginning treatment.

4.1.2 Allogeneic Transplant: Preparative Regimen

d) Total Lymphoid Irradiation (TLI) Administration: TLI is administered ten times in 80c- 120c Gy fractions on day –11 through day –7 and day –4 through day –1 according to the above delineated schedule. TLI is administered from a 6 MeV linear accelerator (photon beam). The radiation field (four fields—two anterior and two posterior) will include all major lymphoid organs including the thymus, spleen and lymph nodes. A radiation oncologist will evaluate patients prior to conditioning to determine blocks and radiation ports. TLI will generally be administered between 10 a.m. and 1 p.m. Since TLI can cause nausea, premedication with antiemetic therapy is needed. TLI schedule may be adjusted based on schedule of radiation therapy department.
e) Anti-thymocyte Globulin (ATG) Administration: ATG will be administered five times intravenously at 1.5 mg/kg/day from day –11 through day –7 for a total dose of 7.5 mg/kg. ATG doses will be based on the adjusted ideal body weight. Premedication for ATG will include benadryl 25-50 mg, Tylenol 650 mg and solumedrol 1.0 mg/kg.
f) Total skin electron beam therapy (TSEBT) Administration: TSEBT will be given to patients who have extensive skin involvement such as wide spread plaques, tumors, or erythroderma with significant tumor infiltration, as part of cytoreduction prior to transplant. The length of therapy and dose of TSEBT will be determined by the radiation oncologist and individualized based on the patient's presentation and treatment history. In patients receiving TSEBT, TLI will begin during the last two week of TSEBT.
g) Extracorporeal Photopheresis (ECP) Administration: Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory therapy that has been approved by the US Food and Drug Administration for the treatment of cutaneous T cell lymphoma (CTCL) since 1988. ECP will be performed using the UVAR XTS Photopheresis System developed by Therakos, Inc (Exton, Pa). Blood (225 mL) will be passed through 3 cycles of leukapheresis, or 125 mL of blood will be passed through 6 cycles, depending on the patient's hematocrit value and body size. At the end of each leukapheresis cycle, the red blood cells and plasma are returned to the patient. The collected WBCs will be mixed with heparin, saline, and 8-methoxypsoralen (8-MOP), which intercalates into the DNA of the lymphocytes upon exposure to UVA light and makes them more susceptible to apoptosis when exposed to UVA radiation. The treated WBC mixture is returned to the patient.

4.1.3 Donor PBPC

h) Donors will receive G-CSF injections daily from day -5 to day 0. G-CSF will be administered

subcutaneously at a dose of 16 µg/kg/day. Collection of peripheral blood progenitor cells (PBPC's) will be performed by apheresis. Collections generally occur on day –1 and day 0 if needed. $CD34^+$ proportion will be evaluated by flow cytometry. Patients will receive all cells collected. The ideal cell doses (based on recipient body weight) for MRD and MUD transplants are > $5x10^6$ $CD34^+$ cells/kg. Cells collected on days –1 and 0 will be processed for infusion on day 0. Fresh cells (not frozen) are to be infused whenever possible. Patients will receive premedication approximately 1 hour prior to infusion using current standard of care or as recommended:

i) Acetaminophen: 650 mg p.o., Diphenhydramine: 50 mg i.v., Hydrocortisone: 100 mg i.v.,1 hour prior to infusion.

j) For MRD transplants, if the target cell dose is not achieved then a third apheresis procedure may be performed on day +1 and the cells infused on the same day. If after a third apheresis procedure the CD34 dose is <$3x10^6$/kg and the total CD3 cell dose does not exceed $5x10^8/CD3^+$ cells per kg, then a fourth apheresis procedure may be performed on day +2 and the cells infused on the same day. Total $CD3^+$ cell dose should not exceed $7x10^8$ $CD3^+$ cells/kg. Grafts that contain >$7x10^8$ $CD3^+$ cells/kg must first be evaluated by the Principal Investigator before infusion. Administration and premedication prior to cell infusion will be identical to those specified for day 0.

k) Collection of cells for the MUD transplants will be coordinated through the National Marrow Donor Program and subject to the rules of that Program, thus MUD collections will be limited to days –1 and 0 only. If mobilized PBPC is not available through certain NMDP collection centers then bone marrow will be considered.

l) ABO incompatibility: ABO incompatibility between donor and host will require red cell depletion only if bone marrow is used as the hematopoietic source. Red cell depletion is performed by Hetastarch sedimentation according to standard procedure.

m) Post-Transplant Growth Factors: Patients should not receive post-transplant growth factors while receiving MMF, particularly during the first month off MMF taper. Growth factors should not be given unless severe neutropenia develops or persists past day 27 post-transplant (ANC < 100/ml for > five days).

4.1.4 Immunosuppression for GVHD prophylaxis

n) Immunosuppression will include tacrolimus (Prograf) and mycophenolate mofetil (MMF)). Tacrolimus will be administered orally at a dose of 0.03 mg/kg/day bid from day -3 through day +56. MMF will begin at 15 mg/kg p.o. bid for MRD and Q 8 hours for MUD from the evening of day 0 to day +27 for MRD or day + 40 with a taper for MUD. Prograf dose adjustments will be made as clinically indicated. Trough levels will be monitored to keep the Tacrolimus level in the range of 8-10 ng/ml. MMF dose adjustments will be made if there is evidence of MMF-related GI toxicity or myelosuppression.

o) Tacrolimus (Prograf): Tacrolimus is given at 0.03 mg/kg p.o. b.i.d (9 am and 9 pm) from day –3 until after the day +56 chimerism studies have been obtained. Doses should be adjusted to maintain a high therapeutic Tacrolimus level to between 8-10 ng/mlng/ml, unless there is renal insufficiency (creatinine >2.0) or hyperbilirubinemia (bilirubin >2.0) in which case the Tacrolimus should be reduced to normalize these parameters. If there is nausea and vomiting at any time during FK506 treatment, Tacrolimus should be administered intravenously by continuous infusion at 3 mg/kg over 20 hours, and adjusted for the Tacrolimus blood level. Tacrolimus will be tapered per standard guideline of Stanford BMT program after the day +56 chimerism studies are obtained. If patient does not tolerate Tacrolimus, tacrolimus may be used and administered per standard guideline of Stanford BMT program.

p) Mycophenylate mofetil (MMF): Administration of MMF will begin at 15 mg/kg po on day 0, at 5-10 hours after mobilized PBPC infusion is complete. Thereafter, beginning on day +1 MMF is taken at 15 mg/kg po b.i.d. (30 mg/kg/day) if transplantation was using a matched related donor, and 15 mg/kg po Q8 hours if from a matched unrelated donor or a one antigen mismatched donor. Doses will be rounded up to the nearest 250 mg (capsules are 250 mg). MMF will be stopped on day +28 for matched related donors and for one antigen mismatched or unrelated donors beginning day +40. MMF will be tapered by 10% weekly till off, typically by day +96. If there is nausea and vomiting at any time preventing the oral administration of MMF, MMF should be administered intravenously.

q) Guidelines for MMF dose adjustment: If in the clinical judgment of the investigator, there is documented toxicity related to MMF administration, a dose adjustment will occur. Based on previous solid organ transplantation studies, dose adjustments are likely to occur because of hematopoietic or gastrointestinal adverse effects. Dose adjustments will not be made for hematopoietic toxicities unless severe neutropenia develops or persists until day +21 post-transplantation (ANC <100/ml for >5 days). In the event of gastrointestinal toxicity that requires medical intervention including

medication for control of persistent vomiting or diarrhea that is considered to be due to MMF, a 20% dose reduction or the drug will be given i.v. For severe gastrointestinal toxicity related to MMF (severe refractory diarrhea or overt gastrointestinal bleeding), MMF may be temporarily stopped.

4.1.5 Infection Prophylaxis

r) It is expected that patients on this protocol will be susceptible to opportunistic infections in the post-transplant period for at least 6 months. These expectations are based upon prior experiences with patients that have undergone treatment with TLI and/or ATG, as well as other non-myeloablative allogeneic transplantation procedures. Infectious disease prophylaxis will be according to the current standards of care of Stanford BMT program.

4.1.6 Engraftment and Disease Status Monitoring

s) Patients will be followed in the ITA for signs of infection or GVHD. Monitoring for engraftment and infection will be according to current standard of care of Stanford BMT program.
t) Chimerism: Microsatellite analysis (VNTR) of CD3, CD19, CD15, and CD56 peripheral blood cell subsets will be performed on days +28 ($\pm$ 5 days), +56 ($\pm$ 5 days), +90 ($\pm$ 14 days),+180 ($\pm$ 14 days), +270 ($\pm$ 14 days), and yearly ($\pm$ 4 weeks) to evaluate the degree of donor hematopoietic cell engraftment (donor chimerism), and on bone marrow on day +90 ($\pm$ 14 days), and yearly per physician's discretion.
u) Clinical response will be determined at 3, 6, 9, 12, 18, 24 months or until relapse or progression after transplant. The disease status and clinical response will be scored on a rigorous and multifactorial approach described before (41, appendix). This approach takes tumor burden in skin, lymph nodes and blood into consideration. To achieve this, patients will be evaluated at Cutaneous Lymphoma Clinic before transplant and at specified time points after transplant.

4.1.7 Therapeutic Interventions for Disease Progression

v) Early discontinuation of immunosupression (< day +120) should be considered the first therapeutic maneuver. However, neither MMF nor Tacrolimus should be stopped prior to reviewing chimerism results. If the donor T cell chimerism in blood is $\geq$ 50% and there is < grade II GVHD, MMF is to be stopped if still being taken, and Tacrolimus tapered over two weeks. Bone marrow aspirate and blood chimerism studies will be performed two weeks after discontinuation of immunosuppression.
w) For Sezary Syndrome patients, lymphoma cells in the blood (Sezary cells) will be monitored by flow cytometry on days +28, and then 3, 6, 9, 12, 18, 24 months after transplant as described for clinical response determination. Patients with persistent Sezary cells on day +28 will have the option to start extracorporeal photopheresis (ECP) on day +30 $\pm$ 5. The recommendation is to administrate four weekly treatments at the discretion of the investigator, followed by additional four monthly treatments, and to be re-evaulated.

4.2 General Concomitant Medication and Supportive Care Guidelines

4.2.1 Supportive care measures will be consistent with standard practice of the Stanford BMT Program. Standard care measures are included by not limited to measures for skin care, mucositis, nausea, diarrhea, constipation, pain control, infection prevention and patient and family education.
4.2.2 Transfusion support for red blood cells and platelets will be consistent with standard practice of the Stanford BMT Program.

4.3 Duration of Therapy

4.3.1 See table below for time lines.

Non-Myeloablative Allogeneic Transplant

Day – 11	Day - 10	Day - 9	Day -8	Day - 7

TLI ATG	TLI ATG	TLI ATG	TLI ATG	TLI ATG

Day - 4	Day - 3	Day - 2	Day - 1	Day 0
TLI	TLI Begin Tacrolimus	TLI	TLI x 2	Allogeneic Transplant

4.3.2 Active treatment continues post-allogeneic transplant for approximately 3 – 4 months and then care is transitioned back to the BMT clinic for ongoing monitoring and care.

4.4 Duration of Follow Up

Patients will be followed for 2 years after transplant. Subsequent follow-up will be consistent with standard practice of the Stanford BMT program.

4.5 Criteria for Removal from Study

4.5.1 Patients who develop severe adverse reaction to ATG infusion, such as serum sickness that result end-organ damage will be removed from study.

4.6 Alternatives

4.6.1 Alternatives may include continued standard therapies, other investigational therapies or no therapy.

4.7 Compensation

Subjects will not be paid for their participation in the study.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

5.1.1 Non-myeloablative allogeneic transplant using total lymphoid irradiation (TLI) and anti-thymocyte globulin (ATG):

As discussed earlier, using a non-myeloablative preparation regimen for allogeneic transplant preserves the benefit of graft versus tumor effect but decreases the toxicity. However, one major complication found in our previous approach using TBI/fludarabine regimen is GVHD. Recently, Lowsky et al. (32) have extended the preclinical model of Strober and colleagues to the clinic using a novel conditioning strategy of total lymphoid irradiation (TLI) and anti-thymocyte globulin (ATG) prior to allogeneic HCT. In this recent report, the incidence of acute GVHD was just 5%, prompt multi-lineage engraftment was demonstrated, and promising efficacy was reported in hematologic malignancies, including mantle cell lymphoma and DLBCL(32). Since this report, we have performed allogeneic transplant with both related and unrelated donors using TLI/ATG in over 150 patients who have a variety of hematological malignancies including mantle cell lymphoma, transformed lymphoma, follicular lymphoma, chronic lymphocytic leukemia, acute myelobalstic leukemia, myelodysplastic syndrome and myelofibrosis. The overall experience has re-demonstrated the low incidence of acute GVHD and preserved graft versus tumor effect.

5.2 Availability

All agents used in this study are commercially available. Total lymphoid irradiation is part of standard care provided by Stanford Radiation Oncology department.

5.3 Agent Ordering

All agents used in this study are commercially available and will be ordered accordingly.

5.4 Agent Accountability

The agents will be kept and monitored by Stanford central pharmacy.

6. DOSING DELAYS/DOSE MODIFICATIONS

No dose modifications will be made.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Tacrolimus

- Human Toxicology: Nephrotoxicity is the most frequent side effect of tacrolimus. Other frequently observed side effects include hypertension, hirsutism, tremors, paresthesias, hepatotoxicity, hypomagnesemia, and hyperkalemia. Transient gastrointestinal symptoms have also occurred, to include anorexia, nausea and ileus. The drug has demonstrated a relative lack of myelotoxicity.

- Pharmaceutical Data Formulation: Tacrolimus is available for oral and intravenous administration. The intravenous solution is available as 1 ml ampules containing 5 mg/ml. Tacrolimus should be administered intravenously over 2-6 hours. Longer infusion times are acceptable and sometimes better tolerated. The contents of the ampules should be diluted 0.9% NaCl injection or 5% dextrose injection

- Supplier: This drug is commercially available.

Mycophenolate Mofetil

- Human Toxicology: The principal side effects include diarrhea, leukopenia, vomiting and infection. The drug is also associated with abdominal pain, nausea, hypertension and anemia.

- Pharmaceutical Data: Mycophenolate Mofetil is available in 250 mg capsules and 500 mg tablets. Mycopenolate Mofetil should be taken on an empty stomach.

- Supplier: Mycophenolate Mofetil is commercially available.

Granulocyte-Colony Stimulating Factor

- Human Toxicology: The primary side effect of G-CSF is bone pain and is more common with higher doses of G-CSF.

- Pharmaceutical Data: G-CSF is available in vials containing 300µg or 480µg at a concentration of 300µg/ml. G-CSF should be refrigerated. G-CSF is given as a daily subcutaneous injection.

- Supplier: G-CSF is commercially available.

Anti-thymocyte Globulin (ATG)

- Thymoglobulin® is a rabbit-thymocyte globulin. It is the purified, sterile, IgG fraction of immune serum of rabbits immunized with human thymus lymphocytes. ATG is a lymphocyte-selective immunosuppressant. It is believed to act by modifying the number and function of lymphocytes.

- Administration: Thymoglobulin® is diluted in 0.9% NaCl. Thymoglobulin® is given intravenously as a 4-

6 hour infusion into a central vein.

- Potential Toxicities: Thymoglobulin® may cause:
  Cytopenia of any cell line

  Pyrogenic action (ATG causes chills and fever in a high proportion of patients treated)

  Fluid retention

  Allergic reactions (rash, pruritus, urticaria, wheal and flare reactions are reported, as well as bronchospasm and anaphylactic shock)

  A serum sickness-like syndrome may develop. This is best prevented by steroid co-administration.

  EBV lymphoproliferative disorders have been associated with administration of anti-thymocyte globulin in highly immunosuppressed patients.

- Because of the potential for anaphylaxis, resuscitation equipment should be available during administration. After an anaphylactic reaction, infusion should not be resumed. A central line should be established and oxygen, as well as resuscitation equipment should be available.

Total Lymphoid Irraditaion (TLI)

- TLI may cause nausea, vomiting, diarrhea, temporary hair loss and painful swelling of the salivary glands for a few days. The TLI in this protocol is approximately one-fifth of that used in standard NHL treatments. Therefore, these side effects most likely will be milder and severe acute side effects are not expected. The risk of secondary malignancies after the low dose TLI is yet to be determined.

Total Skin Electron Beam Therapy (TSEBT)

Acute side effects can include a skin burn that is much like a moderate to severe sun burn (worse in patients who burn but do not tan when exposed to sun), deep tanning (in those who tan after sun exposure), itching and fatigue. Although these acute side effects are occasionally severe, they are self-limited if appropriate supportive therapy is administered in a timely fashion.

Long-term side effects can include generalized dry skin and permanently decreased secretion of sweat and oil on much but not all of the skin, scattered dilated blood vessels (telangectasias), pigmentation changes, and partial or complete scalp hair loss which is more severe in males with signs of thinning hair than in females.

Extracorporeal photopheresis (ECP)

ECP is a very well-tolerated procedure. Transient hypotension may occur in some patients during the collection phase of the treatment, but this is asymptomatic. Some patients may experience low-grade fevers a few hours after ECP.

Some patients with CTCL may experience an increase in pruritus or redness during the course of ECP.

In all of the various patient groups treated, no immunosuppression, opportunistic infections, or neoplasia has been associated with ECP. The risk of secondary malignancies after the low dose TLI is yet to be determined.

Finally, although patients with hypertriglyceridemia do not experience further adverse events during ECP, they may have a less efficacious treatment because of the inability of the UVAR machine to separate the WBCs from the lipid-rich blood. Because of this, patients should have triglyceride levels of less than 300 mg/dL and should eat a very low fat or non-fat diet starting the evening before the procedure.

7.2 Adverse Event Reporting

Appendix C outlines AE and SAE reporting Guidelines.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

8.1.1 Donor Cell Chimerism

8.1.1.1 Collection of Specimens
Peripheral blood will be drawn on day +28, +56, +90, and +180.
Bone marrow biopsy will be performed on day +90.

8.1.1.2 Handling and Shipping of Specimens
Per standard BMT guidelines.

8.1.1.3 Site(s) Performing Correlative Study
Stanford HLA Typing Laboratory will be responsible for performing the donor chimerism study.

8.1.1.4 Coding of specimens for privacy protection
Specimens will be coded for privacy protection.

8.1.2 Profile of Grafting Immune Cells

8.1.2.1 Collection of Specimens
Peripheral blood will be drawn before preparative regimen and on day +30, +60, +90, and +180 post transplant.

8.1.2.2 Handling and Shipping of Specimens
Per standard BMT guidelines.

8.1.2.3 Site(s) Performing Correlative Study
Study of T cell cytokine and chemokine receptor profile will be performed in the Stanford Cellular Therapy Facility (CTF).

8.1.2.4 Coding of specimens for privacy protection
Specimens will be coded for privacy protection.

8.1.3 Donor T Cell Trafficking

8.1.3.1 Collection of Specimens
Two 5 mm punch skin biopsy of target lesions will be performed in Stanford Cutaneous Lymphoma Center on day +90 and at the time of tumor regression/progression.

8.1.3.2 Handling and Shipping of Specimens
Per standard BMT guidelines.

8.1.3.3 Site(s) Performing Correlative Study
Stanford Cellular Therapy Facility (CTF)

8.1.3.4 Coding of specimens for privacy protection
Specimens will be coded for privacy protection.

8.1.4 Regulatory T Cell (Treg)

8.1.4.1 Collection of Specimens
Peripheral blood will be drawn on day +30, +60, +90, and +120 post transplant.

8.1.4.2 Handling and Shipping of Specimens
Per standard BMT guidelines.

8.1.4.3 Site(s) Performing Correlative Study
Study of Treg will be performed in the Cellular Therapy Facility (CTF).

8.1.4.4 Coding of specimens for privacy protection
Specimens will be coded for privacy protection.

8.1.5 Tumor Immune Response

8.1.5.1 Collection of Specimens
Peripheral blood will be drawn on day +60, +90, and +180.

8.1.5.2 Handling and Shipping of Specimens
Per standard BMT guidelines.

8.1.5.3 Site(s) Performing Correlative Study
Stanford Human Immune Monitoring Center (HIMC) Laboratory will be responsible for serum storage. The testing of antibody against patients' tumor cells will be performed by Dr. Weng in HIMC laboratory.

8.1.5.4 Coding of specimens for privacy protection
Specimens will be coded for privacy protection.

9. STUDY CALENDAR

		Post-Transplant Day							
	BS	±5 days	±5 days	±10 days	± 2 wks	± 2 wks	± 2 wks	± 4 wks	± 4 wks
		d+30	d+60	d+90	d+180	d+270	d+365	d+540	d+730
Informed Consent	X								
Path Review	X								
H&P/KPS	X								
PFT	X								
Echo	X								
CBC with diff	X								
Chemistry: BMT I	X								
HLA confirmed	X								
BMT Panel (serologies)	X								
CXR	X								
EKG	X								
STR subsets: PB		X	X	X	X	X	X**		X
BM bx/asp**	X			X			X		X
Research Samples		X	X	X	X				
Skin Biopsy	X			X					
Flowcytometry** (SS only)		X		X	X	X	X	X	X
Disease Status/Response**	X			X		X	X	X	X
GVHD assessment	X	X	X	X	X	X	X		X

** Per Attending Physician's discretion

Correlative Study Calendar

	Donor Chimerism	Chemokine Receptor Profile	Th1/Th2 Phenotype	Treg Cell Quantity	Treg Cell Function	Skin Biopsy Pathology	Skin Biopsy T Cell Trafficking	Derm Clinical Assessment	Bone Marrow Biopsy	CTL Assay	Tumor Cell Banking
Pre TSEBT		X		X		X		X	X	X	Sezary only
Pre TLI/ATG		X		X		X	First 5 pt	X			
Pre Infusion		X		X							
+ 30 day	X	X	X	X	First 5 pt			X			
+ 60 day	X	X	X	X				X			
+ 90 day	X	X	X	X	First 5 pt	X	First 5 pt	X	X	X	
+ 180 day	X	X	X	X	First 5 pt		First 5 pt	X	X	X	
+ 270 day	X	X	X	X				X			
+ 1 year	X	X	X	X	First 5 pt		First 5 pt	X	X	X	
+ 2 year	X							X	X		
Cell Product		X	X	X							
Pre ECP		X	X	X							
Post ECP		X	X	X							
Disease Regression						X		X			
Disease Progression						X		X			
Sample		Up to 5 GGT				5 mm punch	5 mm punch		Routine	2 GTT for effector	2 GTT
Site	HLA Lab	HIMC	CTF	CTF	CTF	Path	CTF	Cut Lym Clinic		HIMC	HIMC
Assay	Chimerism: CD3, CD19, CD56, CD15	Skin: CCR4, CCR10, CLA; LN: CCR7	Th1: IL-2, IFN γ; Th2: IL-4, IL-10	FoxP3 positive	Inhibition of MLR	Monitoring Residual Disease	Lymphocyte Donor Chimerism, Chemokine receptor			FAM-VAD Assay	Use as Target Cell for CTL

10. MEASUREMENT OF EFFECT

The measurement of effect is determined by clinical response to non-myeloablative allogeneic HSCT. The clinical response will be assessed by a rigorous and multifactorial approach described before (41, appendix). This approach takes tumor burden in skin, lymph nodes and blood into consideration. To achieve this, patients will be evaluated at Cutaneous Lymphoma Clinic before transplant and at specified time points after transplant.

10.1 Anti-tumor Effect

10.1.1 Definitions

Disease status will be evaluated right before non-myeloablative allogeneic transplants and at 3, 6, 9, 12, 18, 24 months after allogeneic transplant or up to 1st recurrence or progression.

10.1.2 Disease Parameters

Measurable diseases include skin, lymph node, viscera and blood Sezary cells.

10.1.3 Methods for Evaluation of Measurable Disease

Please refer to Appendix C.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Please refer to appendix.

10.1.4.2 Evaluation of Non-Target Lesions

N/A

10.1.4.3 Evaluation of Best Overall Response

Clinical response will be determined at different time points after allogeneic transplant.

10.1.5 Duration of Response

Duration of overall response is time measurement between first compete response and the first recurrent documentation.

10.1.6 Progression-Free Survival (or other parameters)

Event-free survival (EFS) is the time measurement between the day of allogeneic transplant and the first documented recurrence or death from any cause. Overall survival (OS) is the time measurement between the day of allogeneic transplant and death from any cause.

10.1.7 Response Review

No external review of clinical response is planned.

10.2 Other Response Parameters

N/A

11. DATA REPORTING / REGULATORY CONSIDERATIONS

11.1 Monitoring plan

Research team will meet monthly to review the adverse events. Any severe adverse events will be reported to principal investigator immediately. The stopping rule is described below.

11.2 Stopping rules for the individual patient and for the study as a whole

Individual patient:
Patients who develop severe adverse reaction to the ATG infusion, such as serum sickness that result end-organ damage, will be removed from study.

For the study as a whole: There is no interim analysis for efficacy (PFS), but the study may stop early for safety. The safety monitoring is by means of two rules, one for Grade II-IV acute GVHD and the other for 100 day mortality. The rules call for assessing observed counts after every 5 patients and stopping as follows:

For 100 day mortality

after.pt	5	10	15	20	25	30	35	40
stop.if.reach	2	3	3	4	5	5	6	7

For Grade II-IV acute GVHD

after.pt	5	10	15	20	25	30	35	40
stop.if.reach	2	3	4	5	6	7	8	9

For example, if there are 3 deaths in the first 15 patients, the study will stop at 15 patients or earlier, or if there are 3 Grade II-IV acute GVHD cases in the first 10 patients, the study will stop at 10 or earlier, and so on. The usual 'look ahead' principle will apply: as soon as it is known that a stopping boundary will surely be reached (such as 3 deaths in the first 9 patients) the study will stop. These rules guarantee stopping if the lower 80% one-sided confidence limit for the true rate exceeds 10% for 100 day mortality or 15% for Grade II-IV acute GVHD.

11.3 Data management

All the clinical data from this study will be maintained by BMT data management team.

11.4 Confidentiality

All patients undergoing hematopoietic cell transplantation at Stanford are assigned a SPN (Stanford Patient Number) and data is entered into a secure database. Access to the database is limited to study personnel and password protected. Research records are maintained in a secure office of the data management staff.

12. STATISTICAL CONSIDERATIONS

The primary goal of this study is to provide proof-of-concept evidence for the safety and efficacy of non-myeloablative allogeneic transplant with TLI/ATG conditioning for patients with MF/SS as described above. Safety will be measured at the end of study by rates of GVHD, other measures of side effects, and overall survival (see above for safety monitoring methods). The primary efficacy endpoint is PFS at 180 days. The historical control for safety is the acute GHVD and mortality rates of myeloablative allogeneic treatment. The rationale for this study is based on the expectation that the new non-myeloablative allogeneic transplant will achieve response rates (and subsequent disease control) that is comparable to myeloablative allogeneic transplant, but with a great reduction in GVHD and TRM.

12.1 Endpoints

12.1.1 Primary endpoint

The primary efficacy endpoint is PFS at 180 days (defined above). The safety endpoints include GVHD and other treatment related events, including mortality.

12.1.2 Secondary endpoints

We will report OS, EFS, cumulative incidence of cancer and treatment-related mortality.

12.2 Analysis Populations

We will report outcomes on all patients who begin the preparative protocol (corresponding to the intent-to-treat principle) as the primary analysis, and also on those who actually receive transplant and those who successfully engraft (subset analyses).

12.3 Plan of Analysis

12.3.1 Background and Demographic Characteristics

Tabulate summary statistics with measures of variation.

12.3.2 Evaluation of Efficacy

Efficacy will be evaluated by calculating the Kaplan-Meier estimates of progression-free survival (PFS, i.e., probability of remaining alive and free of progression). We will also calculate the cumulative incidence estimate of the progression rate, using non-relapse mortality as a competing risk.

12.3.3 Methods for handling missing data and non-adherence to protocol

We do not expect to have missing data on key outcome variables, and non-adherence to protocol presumably is limited to failure to complete the entire process of preparation and transplant; this will be handled by subgroup analyses as described.

12.3.4 Evaluation of Conduct of trial (including accrual rates, data quality)

Accrual and progress of patients through the regimen will be monitored by the PI, and data quality will be monitored by the BMT data coordinators.

12.3.5 Pharmacokinetics/Pharmacodynamics

N/A

12.3.6 Methods for Correlative Studies

Analyses of the correlation of response and other outcomes with measures of chimerism and other markers will be done with standard methods, including fixed and time-varying Proportional Hazards models and graphical methods. Given the small sample size, we do not expect to have power to do more than explore such correlations.

12.4 Sample Size

12.4.1 Accrual estimates

12-15 patients per year over 3 years for a maximum of 40 patients, subject to stopping rules above.

12.4.2 Sample size justification

The study sample size is based on expected accrual of 12-15 patients per year, up to a maximum of 40 patients over 3 years, with at least 1 year of follow-up in all patients. With 180 day PFS measure and assuming a target rate of 75%, the 95% confidence interval half-width (the precision estimate) will be 15% (e.g., from 58% to 88% if we observe 27/36 PFS). If the PFS is substantially closer to 50%, the results will not be considered encouraging, while if the PFS is even better than 75% the half-width is never greater than 17%.

12.4.3 Criteria for future studies

See above.

12.5 Interim analyses

The trial may also stop early for safety at any time, based on unexpected high rates of acute GVHD or mortality. Specifically, the stopping rule (every 5 patients) will guarantee stopping if

the lower one-sided confidence limit for the rate exceeds 10% for 100 day mortality or 15% for acute GVHD.

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APPENDICIES

A. Participant Eligibility Checklist
B. AE and SAE reporting Guidelines
C. Response Criteria in Mycosis Fungoides and Sezary Syndrome

Appendix A

I. Participant Eligibility Checklist

Protocol Title:	**A Phase II Study of Non-myeloablative Allogeneic Transplantation Using Total Lymphoid Irradiation (TLI) and Antithymocyte Globulin (ATG) In Patients with Cutaneous T Cell Lymphoma**
Protocol Number:	**BMT 206 / IRB # 16213**
Principal Investigator:	**Dr. Wen-Kai Weng, MD PhD**
Study Coordinator:	[redacted]

II. Subject Information:

Subject Name/MRN:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Stage IIB-IV mycosis fungoides or Sezary syndrome, who have failed at least 1 standard systemic therapy or are not candidates for standard therapy.	☐	☐	
2. Pathology reviewed and the diagnosis confirmed at Stanford University Medical Center.	☐	☐	
3. Age > 18 years and ≤ 75 years.	☐	☐	
4. Karnofsky Performance Status ≥ 70%.	☐	☐	
5. Corrected DLCO ≥ 40%.	☐	☐	
6. Left ventricle ejection fraction (LVEF) ≥ 30%.	☐	☐	
7. Total bilirubin ≤ 2 mg/dL unless hemolysis or Gilbert's disease.	☐	☐	
8. ALT and AST must be ≤ 3x ULN.	☐	☐	
9. If AST and ALT are > 3 ≤ 5 x ULN, patient may be eligible if: 1) Liver biopsy performed within 60 days of HCT excludes active cirrhosis grade greater than 2/4 and bridging fibrosis. 2) No clinically evident ascites. 3) Patient with Hepatitis B or C are excluded if AST or ALT > 3 x UL.	☐	☐	
10. Estimated creatinine clearance ≥ 50 ml/min.	☐	☐	

11. Have a related or unrelated HLA-identical donor or one antigen/allele mismatched in HLA-A, B, C or DRB1.	☐	☐	
12. Signed Informed Consent.	☐	☐	
13. Patients with prior malignancies diagnosed > 5 years ago without evidence of disease are eligible.	☐	☐	
14. Patients with a prior malignancy treated < 5 years ago but have a life expectancy of > 5 years for that malignancy are eligible.	☐	☐	

Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Uncontrolled active infection.	☐	☐	
2. Uncontrolled congestive heart failure or angina.	☐	☐	
3. Pregnancy or nursing patients will be excluded from the study.	☐	☐	
4. Those who are HIV-positive will be excluded from the study due to high risk of lethal infection after hematopoietic cell transplantation.	☐	☐	

IV. 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 Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Appendix B
AE and SAE Reporting Guidelines

ADVERSE EVENT MONITORING AND REPORTING

Definitions:

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), a symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to medicinal product or treatment.

Life Threatening Adverse Event
Any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction.

Unexpected Adverse Event
An adverse event, the nature or severity of which is not consistent with the applicable product information (Investigator's Brochure, product insert). For studies that do not involve investigational products or devices, an unexpected adverse event is an adverse event that is not described in the transplant medical literature or consent form.

Serious Adverse Event (SAE)
Any adverse event occurring that results in any of the following outcomes: death, a life threatening adverse event, a persistent or significant disability/incapacity, a congenital anomaly, requires intervention to prevent permanent impairment or damage. Unless the Principal Investigator is using an investigational agent, s/he is not bound by the definition in Title 22 CFR 312.32. The PI is bound by Title 45 CFR 46, Subpart A which is the "Common Rule" for the Protection of Human Subjects, therefore, the Stanford IRB definition applies (report "unanticipated problems" involving risks to study participants or others).

Distinction between Serious and Severe
The term severe is used to describe the intensity (severity) of a specific event, for example mild, moderate or severe. The event itself however, may be of relatively minor medical significance, for example a severe headache. This is not the same as serious, which is based on the patient/event outcome and is usually associated with events that pose a threat to the patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

Hematopoietic cell transplantation (HCT) is an aggressive therapy for the treatment of a number of life threatening malignant and non-malignant disorders. Individuals presenting for HCT generally have exhausted other avenues of therapy that will result in any lasting benefit. The treatment related mortality (TRM) of autologous transplantation is approximately 5%. The TRM of a sibling myeloablative allogeneic transplant is approximately 20% and the TRM for an unrelated myeloablative allogeneic transplant ranges from 20-50%. In the setting of a non-myeloabative allogeneic transplant from a sibling donor the TRM is approximately 10% and ranges from 20-50% for unrelated donors.

As an aggressive therapy HCT is associated with a large number of AEs and SAEs. The toxicities associated with HCT are related to the following: 1) the underlying disease, 2) therapy antecedent to HCT, 3) the health status of the transplant recipient including co-exiting

conditions, 4) the high dose preparative regimen employed in preparation for transplant, 5) therapies directed at reducing transplant related complications (e.g. immunosuppressants for the prevention of GVHD), and 6) the treatment of complications of HCT.

The use of toxicity grading scales such as the NCI CTC is a standard in the medical community for the reporting of AEs and SAEs in the investigation of new drugs or devices. The use of this type of scale is less helpful in the evaluation of AEs and SAEs associated with a treatment, such as HCT. In an effort to report to regulatory agencies the toxicities that are relevant and meaningful for the evaluation of risks and benefits to potential HCT recipients the following guidelines will serve to determine what is reported as AEs and SAEs.

The following SAEs require reporting to the CCTO. If the event is unexpected, it will also require reporting to the IRB:

1) Deaths
All deaths

- while the patient is receiving treatment on a protocol
- up to 60 days (autologous) or 90 days (allogeneic) after last dose of protocol treatment
- or any death that occurs more than 60 days (autologous) or 90 days (allogeneic) after protocol treatment has ended that is felt to be treatment related.

This includes deaths from the common and expected grade 4 toxicities noted below. Deaths that occur outside of Stanford will be reported whenever possible. It must be noted that obtaining detailed information on the cause and circumstances of a death occurring at another institution can be difficult. This excludes deaths related to relapse of underlying disease, which will be reported at the time of protocol renewal.

2) All serious and unexpected toxicities.
Defined as those toxicities not identified in the transplant literature, product inserts or in the consent form.

The following will generally not be reported as AEs or SAEs:

1) Hospitalizations
Approximately 70% of autologous transplants are readmitted to the hospital for management of HCT related events. The most common indication for readmission of an autologous transplant recipient is neutropenic fever. Approximately 50% of allogeneic transplant recipients will be readmitted to the hospital. The most common indications for readmission of an allogeneic HCT recipient are fever, failure to maintain nutritional status and graft versus host disease.

2) Relapse of disease
Relapse unfortunately remains a significant problem following both autologous and allogeneic transplantation. The risk of relapse is influenced by both patient and disease variables. In general, the risk of relapse following autologous transplant is approximately 50%. The risk of relapse following allogeneic transplant is extremely dependent on the disease being treated but ranges from 10% (for patients with severe aplastic anemia) to 80% (for patients with refractory acute leukemia).

3) Common and expected grade 4 toxicities of HCT that are well described in the transplant literature, the product inserts or stated in the consent form and do not result in death.
This includes but is not limited to neutropenia, thrombocytopenia, anemia, thrombotic microangiopathy, bleeding requiring transfusions, edema, hypertension, hypotension, gastritis, mucositis, nausea, vomiting, diarrhea, hematuria, central venous catheter infections, febrile

episodes, sepsis, mental status changes, infections, insomnia, mood alterations, seizures, tremor, pain, hypoxia, pleural effusion, pneumonitis, incontinence, infertility, laboratory abnormalities, veno-occlusive disease, graft failure, cardiac arrhythmias and graft versus host disease.

4) Secondary Maligancies.
The occurrence of secondary malignancies and associated mortality is a known risk of cancer therapies. The occurrence of secondary malignancies will be reported at the time of the protocol annual review.

Appendix C
Response criteria for Mycosis fungoides and Sezary Syndrome

Clinical Endpoints and Response Criteria in Mycosis Fungoides and Sezary Syndrome: a Joint Consensus Statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Consortium for Cutaneous Lymphomas (USCCL) and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC)

The global response criteria uses scoring system for the following four organ involvement systems: skin, lymph node, blood and viscera. Based on the response score of individual systems, a global response score will be given for individual patient. The skin disease burden will be measured using the modified severity weighted assessment tool (mSWAT); the skin responses are recorded and assessed as changes of the mSWAT score.

Response in Skin*

Complete response (CR)	100% clearance of skin lesions[#]
Partial response (PR)	50-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease (SD)	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Progressive disease (PD)♦	(1) ≥25% increase in skin disease from baseline or (2) New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or (3) Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with CR

*Based on mSWAT score.

[#] A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease where otherwise a CR would exist. If histologic features are suspicious or suggestive of MF/SS (see histologic criteria for early MF[7]), the response should be considered a PR only.

♦ Whichever criterion occurs first.

Response in Lymph Nodes*

CR	All lymph nodes are now <1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma. In addition, lymph nodes that were N_3 classification and <1.5 cm in long axis diameter at baseline, must now be ≤1 cm in diameter of the short axis or biopsy negative for lymphoma.
PR	(1) Cumulative reduction ≥50% of the SPD sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis) of each abnormal lymph node at baseline and no new lymph node ≥1.5 cm or >1.0 cm in the short axis if long axis 1-1.5cm diameter.
SD	Fails to attain the criteria for CR, PR and PD
PD ♦	(1) >50% increase in SPD from baseline of lymph nodes or (2) Any new node ≥1.5 cm in greatest transverse diameter or >1 cm in short axis diameter if 1-1.5 cm in long axis that is proven to be N_3 histologically or (3) Loss of response: in those with PR or CR, >50% increase from nadir in SPD of lymph nodes
Relapse	Any new lymph node ≥1.5cm in long axis diameter in those with CR

* Peripheral and central lymph nodes.

♦Whichever criterion occurs first.

Response in Blood*

CR**	B_0
PR[#]	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR or PD
PD⬥	(1) B_0 to B_2 or (2) >50% increase from baseline and at least 5,000 neoplastic cells/μL[42] or (3) Loss of response: 1. in those with CR who were B_1 or B_2 at baseline, increase in neoplastic >1000 neoplastic cells/ μL or 2. in those with PR who were originally B_2 at baseline, >50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

* As determined by absolute numbers of neoplastic cells/uL.
** If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
[#] There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
⬥ Whichever occurs first.

Response in Viscera

CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging. No nodules should be present on imaging of liver or spleen. Any post treatment mass must be determined to be biopsy to be negative for lymphoma.
PR	≥50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline. No increase in size of liver or spleen and no new sites of involvement.
SD	Fails to attain the criteria for CR, PR or PD
PD⬥	(1) >50% increase in size (SPD) of any organs involved at baseline or (2) New organ involvement or (3) Loss of response: in those with PR or CR, >50% increase from nadir in the size (SPD) of any previous organ involvement
Relapse	New organ involvement in those with CR

*Use of FDG-PET scan in this instance is compatible with other NHLs but there is a paucity of data in clinical trials of MF/SS to document its utility.
⬥Whichever criterion occurs first.

Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any other category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR or PD representative of all disease	PR	No category has a PD and if any other category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence disease in prior CR	Relapse in any category			

NI = non-involved

*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation.

Record of Changes

Date	Protocol Changes	IRB

		Approval Date
March 11, 2009	Original protocol	April 21, 2009
April 29, 2009	Request of the SRC for clarifications in the statistical section	May 19, 2009
June 29, 2009	Changed eligibility criteria related to prior malignancies. Clarified collection goals and processing. Changed CSA taper to begin when chimerism studies obtained. Added timeframes for chimerism evaluations. Added tumor assessments to study calendar. Updated study calendar. Added research sample calendar. Changed fasting before ECP to a low fat diet.	July 14, 2009
March 30, 2010	Decreased TLI from 1200 cGy to 800 cGY. Length of treatment and dose of TSEBT will be determined by the radiation oncologist.	April 20, 2010
October 27, 2010	Clarified stopping rule for acute GVHD to Grade II-IV acute GVHD. Clarified minimum number of research GGT.	November 09, 2010
October 5, 2011	Modified Study calendar for BM Bx	October 18, 2011
February 24, 2012	Modified verbiage	April 17, 2012
May 31, 2012	Updated Investigators and Appendix D (response criteria)	June 19, 2102
February 28, 2013	Modified eligibility criteria 3.1.8 ALT and AST must be < 3X ULN previously </= to 3X Normal. Total bilirubin </= 2 mg/dL previously <3 unless hemolysis or Gilbert's disease. If AST and ALT are <5 x ULN, patient may be eligible if: 1 Liver biopsy performed within 60 days of HCT excludes active cirrhosis gradd greater than 2/4 and bridging fibrosis 2 No clinically evident ascites 3 Patientwith Hepatitis B or C are excluded if AST or ALT > 3 x ULN Deleted BM STR subset on section 9 of the study calendar. Deleted bone marrow biopsy on Day 90 for chimerism study in section 8.1.1.1	March 19, 2013
March 7, 2014	Changed from cyclosporine to tacrolimus Section 3 PARTCIPANT SELECTION AND ENROLLMENT PROCEDURES 3.1 Inclusion Criteria. Modified section 3.1.4 from Age > 18 years and < 75 years. to Age >18 Section 4.1.4 Immunosuppression for GVHD prophylaxis. Modified Immunosuppresant from Cycloporine to Tacrolimus Section 4.3 Duration of Therapy: Day -3;Modified from Cyclosporine to Tacrolimus Section 7.ADVERSE EVENTS AND REPORTING PROCEDURES 7.1 Potential Adverse Events: Human Toxicology section: from cyclosporine to tacrolimus Pharmaceutical Data: Formulation: from cyclosporine to tacrolimus	March 18, 2014
June 13, 2014	Consent form: Modified the footer to add patient name and MRN Medical Record Number Protocol body Updated Schema Page 6 to reflect: "Length of treatment and dose of TSEBT will be determined by the radiation oncologist". Has been approved in April 10,2010 but was not change in the protocol body. Moved the "Record of Revision" from page 38 to page 42 where all the list of revisions are located. Updated the list of revisions.	June 17, 2014
November 18, 2014	Added Dr. Lori Muffly as listed personnel Protocol body: Modified section 4.1.4 Immunosuppression for GVHD prophylaxis in section n and o: Tacrolimus dose from 0.12 to 0.05 mg/kg 4.1.4 Immunosuppression for GVHD prophylaxis	June 21, 2016

	n) Immunosuppression will include tacrolimus (Prografand mycophenolate mofetil (MMF). Tacrolimus will be administered orally at a dose of 0.05 mg/kg/day bid from day -3 through day +56. o) Tacrolimus (Prograf): Tacrolimus is given at 0.05 mg/kg p.o. b.i.d (9 a.m and 9 p.m.) from day –3 until after the day +56 chimerism studies have been obtained. Updated the verbiage to reflect the change previously submitted on March 7,2014 from cyclosporine to Tacrolimus on section 4.1.1 section n and o: n) Trough levels will be monitored to keep the Tacrolimus level in the range of 8-10 ng/ml. MMF dose adjustments will be made if there is evidence of MMF-related GI toxicity or myelosuppression. o) Tacrolimus should be administered intravenously by continuous infusion at 3 mg/kg over 20 hours	
February 17, 2017	**Protocol edits** Page 1 – adjusted version # in footer Page 1- Added BMT # to protocol title Page 1 - formatting- added spaces after Dr. Meyer and Dr. Rezvani names, added date to footer Page 1 - Removed italics from PIs name to make consistent with rest of document Page 2 - Adjusted alignment to match page 2 Page 2 – updated study personnel to CJG as study coordinator, added revision #12 Page 2 - Added missing space between February 6,2014 Page 3- corrected page #s so reflected actual page #s in document Page 3-4 – added spaces after section numbers for formatting Page 5 – adjusted font to be consistent Page 5 - Added missing letter a to “GVHD will be reported as a percentage” Page 5 – removed bold lettering from subject titles Page 5 - Changed Non-Myeloablative hypothesis section to lowercase Non-myeloablative to match how it is lowercase in protocol title Page 6 – added missing space between Day-2 Page 6 - Added missing space to Day-7 Page 6 – added spaces between days for clarification, added border formatting to schema table Page 6 - Removed space to cGy x2 to be consistent with rest of schema Page 8 - removed dash between T-cell to be consistent with how written in protocol title Page 8 - Made arise plural so now reads “MF is a mature T cell lymphoma that arises primarily” Page 9 – added missing a to “is effective as a single agent” Page 9 – correct word “withour” to “without” Page 11 – added dash to non-myeloablative to reflect how it is written in protocol title Page 11 – changed “a effective” to “an effective,” bullet formatting unbolded, added missing word is to sentence “compromised skin is frequently present” Page 12 – changed year to years Page 12- added missing word “with” so now reads “The patient population enrolled in this clinical trial will be those with MF/SS who” Page 13- changed since to as Page 14 – added missing punctuation Page 15 - Added missing comma after “Since TLI can cause nausea, premedication” Page 15 - Added missing parenthesis in (ECP) Page 16 – removed space between – 5 so matches schema Page 16- Added missing period after day +40 Page 16 – made font consistent Page 17- add windows to ECP treatments (+/- 3 days) Page 17 – removed duplicate comma Page 18 – made footnote formatting consistent with rest of document, made font consistent Page 19 – corrected spacing, added punctuation Page 20 – correct on-fifth to one-fifth, added missing period Page 21 – spacing Page 21- changed name of Stanford Therapeutics and Transplantation (SCTT) Laboratory to new name of Stanford Cellular Therapy Facility (CTF) Page 22 – removed extraneous chart	

	Page 34- made appendix B heading bold to match Appendix A Page 23 – adjusted table settings of Correlative Study Calendar so all fits on one page Page 24 – added missing word “to” Page 25 – added missing word “the,” changed “see below” to “see above,” removed unnecessary italics Page 27- added missing period Page 29 – spacing Page 34 – changed “patient or subject” to subject to be consistent with above paragraph Page 35 – added missing word be to “disease, which will be reported” Page 35 – adjusted spacing Page 36 – removed duplicate summary of changes log Page 37 - Adjusted spacing in Adverse Event Reporting, added missing period after lymphoma Page 41 – corrected spelling of revisions to revisions Page 42 – added above changes to summary of changes log, added last IRB approval date to Summary of Changes Log, adjusted spacing of table **Informed Consent edits:** Entire document- Added hyphen to Dr. Wen-Kai’s name Page 1- Added word have to “you were selected as a possible participant because you have a T cell” Page 8 – added comma after “If your donor is a sibling,” Page 9 – added missing word start to “cells will not start growing” Page 11- changed “Web site” to “website” Page 15 – tabbed final bullet point so in proper alignment with rest of experimental subjects bill of rights **Eligibility Checklist edits** Added period after UL in item #10 Added date consent signed to footer Adjusted spacing in Exclusion criteria #1 from center to left alignment **Donor Eligibility Checklist** Changed Donor Screening criteria to CCTO eligibility checklist format	
January 7, 2019	**Protocol edits**	