Phase II Trial of Non-Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients with Relapsed Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response

BMT CTN PROTOCOL 0701
Version 5.0

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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute and National Cancer Institute

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7 Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin
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Cooperative Group participation will be facilitated by the Cancer Trials Support Unit (CTSU). Cooperative Group participation will be limited to approved transplant center sites affiliated with the following endorsing Cooperative Groups: Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), and Southwest Oncology Group (SWOG).

Core Study Participants:

City of Hope National Medical Center
Dana Farber Cancer Institute
Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Massachusetts General Hospital
Stanford Hospital and Clinics
University Hospitals of Cleveland/CWRU
Ohio State University Medical Center
Washington University, Barnes Jewish Hospital
University of California, San Diego Medical Center
University of Florida College of Medicine
University of Minnesota
University of Nebraska Medical Center
University of Texas, MD Anderson Cancer Center

Affiliate/Cooperative Study Participants:

Avera Hematology & Transplant Center
Baylor University Medical Center
Fox Chase, Temple University, BMT Program
H. Lee Moffitt Cancer Center
Loyola University Medical Center
Mayo Clinic, Phoenix
Medical College of Wisconsin
Montefiore Medical Center
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Wake Forest University Health Sciences
Weill Cornell Medical College, NY Presbyterian Hospital
West Virginia University Hospital
Wichita CCOP

This study is supported by the NCI Cancer Trials Support Unit (CTSU)

*Non-BMT CTN centers meeting the study criteria will participate through the CTSU mechanism.

*BMT CTN centers with Cooperative Group affiliation may choose to participate through the BMT CTN or through the CTSU mechanism.

CTSU Logistics are located in Appendix F of the protocol

Please note: This protocol does not follow the standard CTSU participation procedures for regulatory collection or patient enrollment. See Appendix F for protocol-specific details.

CTSU Contacts for BMT CTN 0701

To submit site registration documents listed in Appendix F TABLE 1:	To submit site registration documents listed in Appendix F TABLE 2:	For patient enrollments, data submission, and adverse event reporting:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 E-mail: CTSURegulatory@ctsu.org	Fax to BMT CTN Data and Coordinating Center (DCC)/EMMES 240-306-0963	Access the BMT CTN AdvantageEDC on-line system: https://secure.emmes.com/bmt/jsp/login.jsp

Questions?

Regarding:
- Registration requirements in Appendix F, Table 2
- BMT CTN AdvantageEDC system
- Patient eligibility, enrollment, or treatment

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Regarding:
- Registration requirements in Appendix F, Table 1
- Protocol and supporting documents posted on the members' section of the CTSU website located at www.ctsu.org

CTSU Regulatory Office Help Desk
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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL #0701

Phase II Trial of Non-Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients with Relapsed Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response

Study Chairperson: Ginna Laport, M.D.

Primary Objective: The primary objective of this study is to measure progression free survival at 2 years after non-myeloablative HSCT with a pre-transplant conditioning regimen of fludarabine, cyclophosphamide, and rituximab (FCR).

Secondary Objective: Secondary objectives for the study are two-year overall survival, time to progression/relapse, time to complete response (CR) and partial response (PR), time to off-study therapy, incidence and severity of acute and chronic GVHD, treatment-related mortality, incidence of primary and secondary graft failure, quality of life as measured by the SF-36 and the FACT-BMT, correlation of serum rituximab levels with development of acute GVHD, chronic GVHD, relapse and immune recovery, incidence of infections, incidence of toxicities, and immunologic reconstitution.

Study Design: The study is a Phase II, single arm, multicenter trial. It is designed to confirm the efficacy in a multi-center BMT CTN/inter-group study of a non-myeloablative allogeneic conditioning regimen of FCR. The study population is patients with relapsed follicular NHL receiving matched related or matched unrelated donor transplants.

Accrual Objective: A maximum of 65 patients will be enrolled and followed for two years post-transplant.

Accrual Period: The estimated accrual period is two years.

Eligibility Criteria: Eligible patients are $\leq$ 75 years of age with Karnofsky performance status $\geq$ 70% who have histologically confirmed recurrent follicular lymphoma (REAL classification follicle center follicular grades I and II or patients with histologically confirmed WHO classification follicular lymphoma grades 1, 2, or 3a). Patients must have chemosensitive disease by achieving reduction in lymph node axial diameter to $\leq$ 3cm or $\geq$ 50% reduction in estimated nodal diameter after their most

recent salvage therapy. Patients with stable disease are eligible if all lymph node masses are ≤ 3 cm and are smaller or unchanged in size to the most recent salvage regimen. Patients cannot have transformed follicular lymphoma, or have had prior allogeneic HSCT. Available donors must be either siblings with 6/6 –A, -B HLA and DRB1 match by DNA; or unrelated with 8/8 –A, B, C HLA and DRB1 by DNA. Donors must be willing to provide peripheral blood stem cells.

Treatment Description: All eligible patients will receive Rituxan 375 mg/m^2 on Day –13, Rituxan 1000mg/m^2 on Day –6, Fludarabine 30mg/m^2 on Days –5 to –3, and Cyclophosphamide 750mg/m^2 on Days –5 to –3, followed by HSCT, which will be followed by Rituxan 1000mg/m^2 on Day 1 and Day 8.

Study Duration: Patients will be followed for at least two years post-HSCT.

STUDY CHART

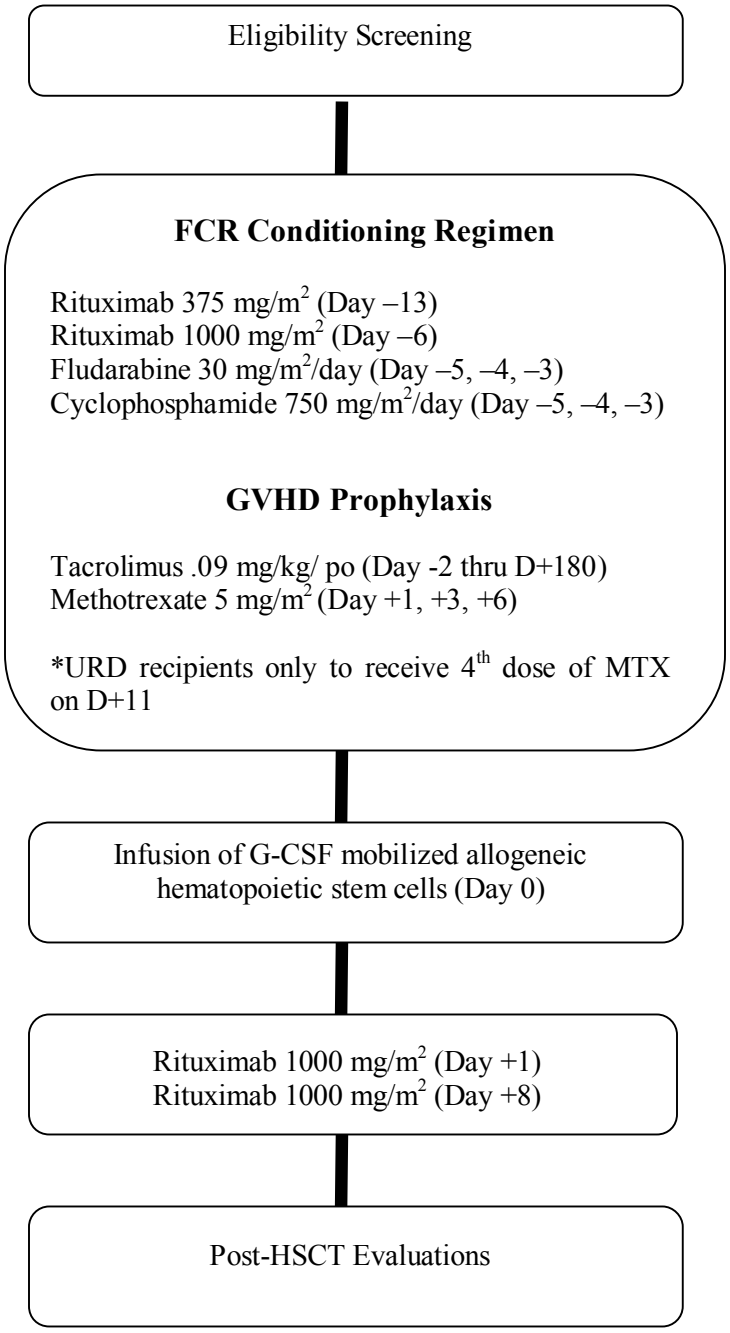
Eligibility Screening
FCR Conditioning Regimen
Rituximab 375 mg/m2 (Day –13)
Rituximab 1000 mg/m2 (Day –6)
Fludarabine 30 mg/m2/day (Day –5, –4, –3)
Cyclophosphamide 750 mg/m2/day (Day –5, –4, –3)
GVHD Prophylaxis
Tacrolimus .09 mg/kg/ po (Day -2 thru D+180)
Methotrexate 5 mg/m2 (Day +1, +3, +6)
*URD recipients only to receive 4th dose of MTX on D+11
Infusion of G-CSF mobilized allogeneic hematopoietic stem cells (Day 0)
Rituximab 1000 mg/m2 (Day +1)
Rituximab 1000 mg/m2 (Day +8)
Post-HSCT Evaluations

TABLE OF CONTENTS

LIST OF APPENDICES

CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Follicular NHL is the second most common type of non-Hodgkin's lymphoma with an incidence of ~15,000 new cases/year in the U.S. When treatment is indicated, most patients achieve a remission with initial chemotherapy. However, a continuous pattern of relapse typically follows resulting in progressively shorter remission durations. Patients with recurrent advanced follicular lymphoma have a median survival of 4-5 years[1, 2].

1.2. Autologous Hematopoietic Stem Cell Transplantation (HSCT)

In light of the discouraging results with conventional chemotherapy, high dose chemotherapy with autologous HSCT has been explored as an alternative approach in patients with relapsed follicular NHL. Several studies have shown improved disease-free survival (DFS) with 5 year survival rates ranging from 40%-63%[3, 4, 5, 6, 7]. One study demonstrated an advantage for overall survival in favor of autologous HSCT compared to conventional chemotherapy[6]. Relapse remains the predominant cause of treatment failure in recipients of autologous HSCT.

1.3. Allogeneic HSCT

High dose chemoradiotherapy with allogeneic hematopoietic stem cell/bone marrow transplantation has also been offered to patients with recurrent follicular NHL with the goal of harnessing a graft-versus-lymphoma effect and to circumvent the tumor cell contamination associated with autologous hematopoietic stem cell harvests[8, 9, 10]. Although no randomized trials have been performed, several studies have reported a significantly lower risk of relapse compared to autologous HSCT. However, this benefit has been invariably offset by the treatment-related mortality associated with myeloablative allogeneic HSCT.

An analysis from the CIBMTR compared the outcomes of 904 patients with follicular NHL who underwent either myeloablative allogeneic HSCT (n=176), purged autologous HSCT (n=131) or unpurged autologous HSCT (n=597). The risk for relapse was 54% lower in the allogeneic recipients (p<.001) and 26% lower in recipients of purged autotransplants (p=.04) than in recipients of unpurged autotransplants[11]. However, in a multivariate analysis, the risk of treatment-related mortality was 4.4 times higher after allogeneic than after autologous HSCT (p<.001), which resulted in comparable 5-year probabilities of overall survival (52% after allogeneic, 62% after purged autologous, 55% after unpurged autologous). The 5-year probabilities for DFS were 45%, 39% and 31%, respectively.

In a smaller retrospective study from the Netherlands, the results of 18 patients who underwent autologous HSCT were compared to 10 patients who received an allogeneic HSCT. The PFS rates after two years were 68% and 22% for the allogeneic and autologous patients, respectively.

Three of the allogeneic patients died from treatment-related mortality as opposed to none of the autologous patients[8].

1.4. Non-myeloablative Allogeneic HSCT

Non-myeloablative allogeneic HSCT incorporates a less intensive preparative regimen and relies primarily on the immunotherapeutic effects of the allograft to confer antileukemic activity rather than the cytoreductive effects of high dose chemotherapy.

Some of the most promising data employing non-myeloablative allogeneic (NMA) HSCT in relapsed follicular NHL patients was initially reported by the M.D. Anderson Cancer Center[12]. Twenty patients with indolent NHL received a conditioning regimen of fludarabine and cyclophosphamide $\pm$ rituximab. Tacrolimus and methotrexate were given for graft-versus-host disease (GVHD) prophylaxis. The median age was 51 years old (range 31-68) and all patients had advanced recurrent disease or were previously treated. The number of prior chemotherapy regimens ranged from 1-5 (median, 2). All had received salvage chemotherapy and had stable or responding disease. All patients achieved engraftment of donor cells with the median percentage of donor cells at one month being 80% (range, 10%-100%). These results were recently updated with a total accrual of 47 patients. All patients achieved a CR after HSCT. The incidence of grade 2-4 acute GVHD was 11% and extensive cGVHD was 36%. With a median follow-up of 60 months(range 19-94 months), the five year OS and PFS were 85% and 83%, respectively[13].

The EBMT described the use of reduced-intensity conditioning for 188 patients with low-grade lymphoma including 52 patients with follicular and small lymphocytic NHL[14]. The median age of the low-grade NHL patients was 46 (range, 27-65). The median number of prior chemotherapy regimens was three (range, 1-5) and 29% had previously received an autologous HSCT. Forty-four patients (85%) demonstrated chemosensitive disease at the time of transplant. Most patients received a fludarabine-based preparative regimen with 10% of patients receiving BEAM (BCNU, etoposide, cytarabine, melphalan), a myeloablative regimen. Of the low-grade NHL patients, the two year PFS and OS was 54% and 65% respectively with a 21% progression rate. Treatment-related mortality was 31%, which was considerably higher than the previously mentioned M.D. Anderson study. The use of a more intensive conditioning regimen may have contributed to toxicity.

Investigators from Seattle reported the results of 45 patients with relapsed FL who received a NMA regimen with fludarabine and low dose TBI[15]. Twenty-two patients received G-CSF mobilized peripheral blood allograft from matched related donors (MRD) and 23 patients were recipients of unrelated donor (URD) grafts. With a median follow-up of 24 months, the PFS was 51% and the OS was 58% with a relapse rate of 15%. Donor type did not significantly affect PFS and OS. The cumulative probabilities of acute grades II-IV, III-IV and chronic GVHD were 60%, 18%, and 51%, respectively. The United Kingdom Collaborative Group reported the outcomes of 88 patients with NHL including 29 patients with FL. Both MRD and URD grafts were conditioned with a regimen of alemtuzumab, fludarabine and melphalan[16]. For the FL patients, the three year PFS and OS were 65% and 73%, respectively with a 2% nonrelapse mortality at 100 days. When examining donor source among the FL patients, there was no

significant difference in OS (MRD vs URD, 78% vs 56%, *p=.09*) but a significant difference was seen in PFS, 71% vs 44%, favoring MRD (*p=.04*). Donor type did not affect relapse incidence or non-relapse mortality.

1.5. Rituximab

Rituximab Background

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG_1 κ immunoglobulin containing murine light-and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analaysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

Rituximab Pharmacokinetics

Some of the earlier phase I and II trials detailing the use of rituximab (RTX) measured the pharmacokinetics (PK) of this chimeric IgG1 kappa monoclonal antibody. The IDEC-C2B8 Study Group measured serum levels of RTX using ELISA (enzyme-linked immunosorbent assay) in 11 patients with relapsed B cell lymphoma who received 4 weekly doses of 250 mg/m^2 or 375 mg/m^2 [17]. The PK parameters fluctuated widely even among the patients treated with the same dose but the median elimination half life (T ½) was 445 hrs +/- 361 hours. In most patients, the serum levels were still detectable at 3 months after the last infusion. The mean values of maximum concentration (Cmax) were higher in the 375 mg/m^2 group compared to the 250 mg/m^2 group (92 +/134.3 ug/ml and 64 +/- 21 ug/ml, respectively). When the Cmax, T ½ and AUC were compared between the responders and non-responders, no significant differences were found.

In contrast, two published series did find an association between serum RTX concentration and anti-tumor response. In an analysis from a phase III trial of 166 patients with recurrent low-grade NHL, a statistically significant correlation was found between the median RTX concentration and response for multiple time points during the treatment and follow-up[18]. Interestingly, the mean serum RTX antibody concentration was also inversely correlated with tumor bulk and with number of circulating B cells at baseline. The median serum RTX levels were 20.3 ug/ml (range 0.0 – 9.7) and 1.3 ug/ml (range 0.0 – 29) at 3 months and 6 months post-treatment, respectively. The T ½ also increased with subsequent infusions which was a mean of 76 hours after the first infusion and 206 hours after the fourth infusion. A phase II trial of 37 patients with low-grade lymphoma also observed a correlation between clinical response and median serum RTX concentrations[19]. The increase in T ½ after subsequent doses is most likely related to elimination of circulating CD20+ B cells, which serve to clear serum antibody with the initial RTX infusions. Additionally, saturation or reduction of involved nodal sites by RTX would also result in decreased antibody clearance. Both of the above reports also found a correlation between dose infused and serum levels.

Rituximab and Graft-vs.-Host Disease

There is growing amount of evidence implicating B cells in the pathogenesis of acute and chronic GVHD which suggests that the pathogenesis of GVHD stems from a coordinated response of both B and T cells[20, 21, 22]. The largest series comes from the Dana Farber Cancer Institute in which RTX was administered to 21 patients with steroid-refractory chronic GVHD. A 70% overall clinical response rate was reported including two patients with complete remissions. Interestingly, a correlation was found between a reduction in allogeneic H-Y antibodies and clinical response, which supports the role of B cells in the pathogenesis of chronic GVHD. There also is a report of 3 patients with steroid-refractory acute GVHD who responded to RTX[23]. In summary, these studies implicate the role of B cell activity in both acute and chronic GVHD and thus lend support to investigating the impact of RTX on the incidence of acute and chronic GVHD.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

All patients will undergo a non-myeloablative allogeneic HSCT. Pre-transplant conditioning will consist of fludarabine 30 mg/m^2/day and cyclophosphamide 750 mg/m^2/day on Days –5, –4, and –3. Rituximab 375 mg/m^2/day will be administered on Days –13 and Rituximab 1000 mg/m^2/day on Day –6 pre-HSCT, and Days +1 and +8 post-HSCT. Graft-versus-host disease prophylaxis will consist of tacrolimus and methotrexate (MTX).

2.2. Study Objectives

2.2.1. Primary Objective

To measure progression free survival at two years after non-myeloablative HSCT with a transplant conditioning regimen of fludarabine, cyclophosphamide, and rituximab (FCR) in patients who are less than or equal to 75 years of age.

2.2.2. Secondary Objectives

- 2-year overall survival
- Time to progression/ relapse
- Time to Complete Response and Partial Response
- Time to off study therapy
- Grade II-IV and III-IV acute GVHD
- Chronic GVHD
- Incidence of primary and secondary graft-failure
- QOL measurements
- Correlation of serum rituximab levels with development of acute GVHD, chronic GVHD, relapse and immune recovery
- Treatment-related mortality
- Infections
- Toxicities
- Immune reconstitution

2.3. Patient Eligibility

2.3.1. Initial Inclusion Criteria

1. Patients with confirmed CD20+ follicle center lymphoma that meet the following:
   a. Histologically confirmed recurrent REAL classification $CD20^+$ follicle center lymphoma, follicular grades I and II, OR
   b. Histologically confirmed WHO classification $CD20^+$ follicular lymphoma grades 1, 2, or 3a

   For either classification, the diffuse component of large cleaved cells (if present) cannot be > 50% of cellularity. Patients do not have to express t(14;18) to be eligible.
2. Age ≤ 75 years of age at time of first registration.
3. Any number of prior regimens (including autologous HCT). The most recent prior regimen must have occurred > 28 days before study enrollment.
4. Patients must demonstrate chemosensitive or radiosensitive disease to most recent prior regimen and meet one of the following:
   a. Patients in 2nd or subsequent CR
      OR
   b. Patients in 1st or subsequent PR
   c. Patients experiencing a relapse that demonstrates a response as defined below:

      Response is defined as largest nodal mass ≤ 3cm or ≥ 50% reduction in estimated lymph node volume measured as a product of bi-dimensional measurements (see Chapter 3 for detailed definition).
   d. Patients with stable follicular lymphoma are eligible if all lymph node masses are ≤ 3 cm and are smaller or unchanged in size to the most recent salvage regimen.

5. Patients with HLA-matched donors that meet the following criteria:

   a. 6/6 HLA-matched related donor. HLA typing must be performed by DNA methods for HLA-A and B at intermediate (or higher) resolution, and DRB1 at high resolution. The donor must be willing to donate peripheral blood stem cells and meet institutional criteria for stem cell donation. The donor must be medically eligible to donate stem cells according to individual transplant center criteria. **OR**

   b. 8/8 HLA-matched unrelated donor. HLA typing must be performed by DNA methods for HLA-A, B, Cand DRB1 at high resolution. The donor must be willing to donate peripheral blood stem cells and meet NMDP criteria for stem cell donation. The donor must be medically eligible to donate stem cells according to NMDP criteria.
6. Patients with adequate organ function as measured by:
   a. Cardiac: Left ventricular ejection fraction at rest ≥ 45%.
   b. Pulmonary: DLCO, FEV1, FVC > 50% of predicted (corrected for hemoglobin). For patients where pulse oximetry is performed, baseline O2 saturation > 85% (when pulmonary function testing cannot be performed due to age restrictions).

c. Hepatic: Bilirubin < 2x the upper limit of normal for age as per local laboratory; ALT and AST < 3x the upper limit of normal as per local laboratory.
d. Renal: Calculated or measured creatinine clearance ≥ 40 mL/min; if creatinine ≥ 1.5 mg/dL then 24 hour urine for measured creatinine clearance should be performed.

7. Signed informed consent form.

2.3.2. Exclusion Criteria

1. Patients in 1st CR.
2. Karnofsky performance score < 70%.
3. Patients with follicular lymphoma that demonstrates evidence of histologic transformation. In the presence of B symptoms, rapid growth of a single dominant site, or prolonged (> 2 yrs) interval since last tissue diagnosis, investigators are encouraged to consider re-biopsy of nodes prior to enrollment.
4. Patients with uncontrolled hypertension.
5. Patients with uncontrolled bacterial, viral, or fungal infection (currently taking medication and progression of clinical symptoms).
6. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent < 5 years will not be allowed unless approved by the Medical Monitor or Protocol Chair. Cancer treated with curative intent > 5 years will be allowed.
7. Pregnant (βHCG+) or breastfeeding.
8. Seropositive for human immunodeficiency virus (HIV).
9. Fertile men or women unwilling to use contraceptive techniques from the time of initiation of conditioning until six-months post-transplant.
10. Prior allogeneic HSCT.
11. Known anaphylactic reaction to rituximab.
12. Seropositive for any of the following: HIV ab, hepatitis B sAg or PCR+ or hepatitis C ab or PCR+.

2.4. HSCT Donor Criteria

2.4.1. Donor Inclusion Criteria

The donor must be medically eligible and consent to donate stem cells according to individual transplant center criteria for related donors or NMDP criteria for unrelated donors.

2.4.2. Donor Exclusion Criteria for Matched Related Donors

1. A sibling donor cannot be an identical twin of the patient.
2. Infection with HIV, viral hepatitis (B or C).

3. Donors receiving experimental therapy or investigational agents.
4. Donors with cancer other than treated basal cell or carcinoma in situ of cervix. Cancer treated with curative intent < 5 years will not be allowed unless approved by the Medical Monitor or Protocol Chair. Cancer treated with curative intent > 5 years will be allowed.

2.5. Study Treatments

2.5.1. Body Weight Formulas

All chemotherapy, rituximab and tacrolimus should be dosed based on actual body weight (ABW) for patients who weigh < 100 to 120% of their ideal body weight (IBW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

Ideal Body Weight (IBW) Formulas:
Males IBW = 50 kg + 2.3 kg/inch over 5 feet
Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet
For patients less than 5 feet, subtract 2.3 kg/inch

Adjusted Ideal Body Weight (AIBW) Formula:
AIBW = IBW + [(0.25) x (ABW – IBW)]

2.5.2. HSCT

Pre-HSCT conditioning and hematopoietic stem cell infusion may be administered on an outpatient basis. Patients must comply with all scheduled study visits whether receiving their transplants as an inpatient or outpatient.

TABLE 2.5.2: FCR REGIMEN

	Day									
	-13	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**8**
Fludarabine 30 mg/m^2			**X**	**X**	**X**					
Cyclophosphamide 750 mg/m^2			**X**	**X**	**X**					
Rituximab 1000 mg/m^2		**X**							**X**	**X**
Rituximab 375 mg/m^2	**X**									
PBSCT								**X**		

2.5.3. Conditioning Regimen

Dosing is based on the body weight formulas in Section 2.5.1.

1. **Fludarabine:** 30 mg/m^2 IV x 3 doses total to be administered daily over 30 minutes on Days –5, -4, and –3 pre-HSCT.
2. **Cyclophosphamide:** 750 mg/m^2 IV x 3 doses total to be administered daily over 1 hour on Days –5, -4, and -3 pre-HSCT. Administer cyclophosphamide approximately 4 hours after start of fludarabine infusion.
3. **Rituximab:** 375 mg/m^2 IV to be administered on Day –13, and 1000 mg/m^2 IV on Day –6, pre-HSCT and Days +1 and +8 post-HSCT. Mix rituximab in either 0.9% NS or D5W according to institutional practice. Rituximab may be infused through an infusion pump and should not be mixed or diluted with any other solutions or drugs. Do not administer Rituximab as an IV push or bolus. See Appendix D for recommended infusion guidelines.

Rituximab will be provided free of charge by Genentech and Biogen IDEC. The Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements."

Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Second, Third and Fourth Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 100 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. (See Appendix D for "Suggested Guidelines for Rituximab Infusion.")

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy

Rituximab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be

resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions.

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Day 0 will be the day of HSCT.

2.5.4. Graft-versus-host Disease (GVHD) Prophylaxis

TABLE 2.5.4: GVHD PROPHYLAXIS SCHEDULE

	Day													
	-2	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Tacrolimus 0.09 mg/kg PO	**X** ----------► Daily until Day +180, then start taper													
Methotrexate 5 mg/m^2 IV				**X**		**X**			**X**					**X***

*URD recipients receive a 4th dose of Methotrexate on Day +11

1. **Tacrolimus:** 0.09 mg/kg/day PO, based on body weight formulas in Section 2.5.1, will start on Day –2 and continue until Day +180 post-HSCT. Tacrolimus may be administered orally either qd or twice daily per institutional practice. Tacrolimus dosing should be based on actual body weight – see Section 2.5.1 for body weight formulas. Doses should be adjusted to maintain whole blood "trough" levels at 5-15 ng/mL, with a preferred target of 10ng/mL. Tapering of tacrolimus doses should commence starting at Day +180. . An equivalent dose of IV tacrolimus may be used as per local institutional preference.
2. **Methotrexate:** 5 mg/m^2 IVP will be administered on Days +1, +3, and +6 post-HSCT. URD recipients are to receive a 4th dose on Day +11. In the event of renal/hepatic impairment, dose changes should be made according to the following guidelines:

Bilirubin mg/dL	% Dose	Creatinine mg/dL	% Dose
< 2.0%	100	< 1.5	100
2.1 – 3.0	50	1.5 – 1.7	75
3.1 – 5.0	25	1.8 – 2.0	50
> 5.0	Hold dose	> 2.0	Hold dose

2.5.5. Collection and Infusion of Allogeneic HSC

2.5.5.1. G-CSF administration to donors

All donors will receive G-CSF dosed per institutional guidelines. G-CSF will be administered by daily subcutaneous injections. If necessary, based on volume, the G-CSF can be given in multiple injection sites. It is recommended that these doses will be administered before 10:00 AM each day. G-CSF can be rounded based on donor weight and available G-CSF vial sizes.

2.5.5.2. HSC collection and evaluation

Donors will preferably undergo vein-to-vein collections but may receive an appropriate central venous catheter inserted on or before the day of apheresis. HSCs will be collected on Day –1 pre-HSCT and stored in the refrigerator at 2-8°C overnight. If necessary, a second collection will be performed the following day and both collections will be infused. Each collection will be separately evaluated in the laboratory for cellular composition in keeping with the BMT CTN MOP for graft characterization.

A minimum dose of 2.0 x 10^6 CD34+ cells/kg will be collected (according to institutional practices) and given. If ≥ 5.0 x 10^6 CD34+ cells/kg are collected on Day –1, a second collection will not be necessary. If < 2.0 x 10^6 CD34+ cells/kg are collected after 2 aphereses, a 3rd collection must be performed on Day +1. If a 3rd collection occurs on Day +1, the post-transplant methotrexate and rituximab administrations will be adjusted by one day to ensure at least 24 hours between the time of last stem cell infusion and the first dose of methotrexate. All cells collected should be infused. Cryopreservation of donor hematopoietic stem cells is acceptable per institutional guidelines.

If < 1.0 x 10^6 CD34+ cells/kg are collected from the donor after three collections, patients may proceed to transplant at the discretion of their attending physician and subsequent management of these patients is at the discretion of their attending physician. However, these patients will now be considered off-study, but continued to be followed for relapse, progression and survival.

If > 10 x 10^6 CD34+ cells/kg are collected, follow local institutional guidelines for freezing the cells. For unrelated donors, the NMDP must be notified if cells are frozen.

Unrelated donors will be managed and mobilized following the procedures of the unrelated donor registry. The transplant center should request a target CD34+ cell dose of 5 x 10^6/kg of recipient weight. Cryopreservation must follow the registry's policies.

TABLE 2.5.5: TREATMENT SCHEDULE FOR DONOR

	Days					
	-4	**-3**	**-2**	**-1**	**0**	**1**
G-CSF (per institutional guidelines)	**X**	**X**	**X**	**X**	**X**	**X****
HSC Collection				**X**	**X***	**X****
HSC Administration					**X***	**X****

* The 2nd HSC collection can be cancelled only if > 5.0 x 10^6 CD34+ cells/kg are collected with the 1st apheresis. G-CSF administration is not required on Day 0 if the second collection is cancelled.

** A 3rd collection is required if < 2.0 x 10^6 CD34+ cells/kg are collected with the 2 previous aphereses.

** If a 3rd collection occurs on Day +1, the post-transplant methotrexate and rituximab administrations will be adjusted by one day to ensure at least 24 hours between the time of last stem cell infusion and the first dose of methotrexate..

2.6. Supportive Care

2.6.1. Post-HSCT

All supportive care will be given in keeping with BMT CTN MOP and local institutional guidelines.

2.6.1.1. Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the post-HSCT period according to the BMT CTN MOP. Additional specifications/requirements for this study are summarized below.

Infectious prophylaxis will include prophylaxis for:

1. Bacteria: In keeping with the BMT CTN MOP and local institutional standards.
2. Pneumocystis jiroveci: Prophylaxis will start at the time of engraftment or at 4 weeks post-HSCT according to institutional preference. Prophylaxis should be continued until at least 1 month after the patient is off all immunosuppressive medications.
3. Fungi: Anti-fungal prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.
4. HSV/VZV: Antiviral prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.

5. CMV: Monitoring and preemptive treatment strategy will be in accordance with the BMT CTN Technical Committee (Infectious Diseases) MOP and local institutional practice. The duration of monitoring is recommended for at least 100 days post-HSCT and longer if the patient is on immunosuppressive medications.

2.6.1.2. Blood products

Transfusion thresholds for blood product support will be in keeping with BMT CTN MOP and standard institutional guidelines. All blood products will be irradiated. Transplant candidates who are CMV negative will receive CMV negative or filtered blood products from study entry.

2.6.1.3. Post-HSCT growth factors

If neutropenia occurs (ANC < 500/mm^3) post-HSCT, the decision to use hematopoietic growth factors will be guided by the institutional practice of the transplant center.

2.6.1.4. Post-HSCT immunization schedule

Once a patient is off all immunosuppressive therapy or has evidence of T-cell function (approximately one year post-HSCT), immunizations may be given in keeping with the BMT CTN MOP and local institutional practice.

2.6.1.5. Post-HSCT donor cellular infusions (DCI)

At the discretion of the investigator, DCI may be given to patients for tumor progression. Patients receiving DCI will be considered a failure for the primary study endpoint. DCI will not be given (on protocol) for low donor or dropping donor chimerism.

2.7. PCR Monitoring for t(14;18)

Quantitative PCR analysis for t(14;18) from peripheral blood will be performed on all patients at the time of registration. Samples will be collected and quantitative PCR will be performed at the individual transplant centers as per institutional standards. If patient was known to be t(14;18) negative prior to registration, this test still must be performed once at the time of registration for documentation purposes. Patients with any positive test for t(14;18) since the time of diagnosis must have the subsequent t(14;18) PCR assessment samples collected 3 months, 6 months, 1-year and 2-years post-transplant (see Section 4.2.4.3 and Appendix C).

2.8. Serum Rituximab Levels

Serum rituximab levels will be performed pre-HSCT within 4 weeks prior to the initiation of the conditioning therapy of the start of conditioning, then on 1 month, 3 months, 6 months, and 1-year post-HSCT. Samples will be sent to a central lab. See Section 4.2.4.5 and Appendix C for schedule of samples and details on collection, processing, storage and shipment.

2.9. Participant Risks

Recipients of HSCTs incur risks from pre-HSCT conditioning and post-HSCT therapy, which must be weighed against the risk of the disease for which the HSCT is prescribed. Major risks following transplantation include: 1) Infection which can be bacterial, viral, parasitic, or fungal. Often, these infections are life threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 2) GVHD, either acute or chronic in nature, may occur following allogeneic transplantation. The degree of GVHD varies from mild cutaneous reactions to extensive widespread and systemic involvement of skin, liver, and gastrointestinal tract. Probably due to a direct association, the incidence of fatal infection is greater in patients developing GVHD; 3) Graft Failure can occur and is associated with a high risk of mortality; 4) End Organ Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., chemotherapy, antibiotics, anti-fungal medications, tacrolimus, cyclosporine, etc.), and as a result of destructive processes (e.g., infection, GVHD, etc.), and may have a fatal outcome; 5) Relapse or progression of lymphoma may occur, especially in patients with advanced disease status at time of treatment; 6) Unknown toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain. Brain damage can result in some loss of cognitive or neurologic function; and, 7) Death.

2.10. Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. All of the following listed agents are commercially available. Please refer to www.fda.gov for full adverse event information regarding the agents listed below. All of the following agents should be administered per institutional standards, and stored per package insert instructions.

2.10.1. Fludarabine

Fludarabine is a purine analog. Toxicities include hemolytic anemia, neutropenia or thrombocytopenia, low blood counts secondary to bone marrow suppression, nausea, vomiting, diarrhea, stomatitis, skin rash, pneumonitis, edema, fever, chills, fatigue, blurred vision, decreased immunity and rarely encephalopathy (in very high doses).

2.10.2. Cyclophosphamide

Cyclophosphamide is an alkylating agent as well as an immunosuppressant. Likely side effects include nausea, vomiting, myelosuppression, alopecia, and possible sterility. Less likely side effects include mucositis, cardiomyopathy and jaundice. Uncommon side effects include hemorrhagic cystitis.

2.10.3. Rituximab

Rituximab is a chimeric human/mouse monoclonal antibody directed against CD20+, an antigen expressed on all cells of the B cell lineage. It consists of a murine antigen binding region and a human Fc region. The likely side effects include infusion reactions such as rigors, fevers, and itching. Uncommon side effects include hypotension, dyspnea, rash, and nausea/vomiting. Rare non-infusion toxicities include myelopsupression, thrombocytopenia, fatigue, and tumor pain. No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

2.10.3.1. Fatal infusion reactions

Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

2.10.3.2. Cardiac events

Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

2.10.3.3. Tumor lysis syndrome

Tumor lysis syndrome has been reported and is characterized in patients with a high number of circulating malignant cells (≥25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

2.10.3.4. Renal events

Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has lead to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (≥25,000/mm^2) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

2.10.3.5. Mucocutaneous reactions

Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

2.10.3.6. Hematologic events

In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

2.10.3.7. Infectious events

Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulin in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

2.10.3.8. Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

2.10.3.9. Other serious viral infections

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

2.10.3.10. Progressive multifocal leukoencephalopathy (PML)

PML is a rare and demyelinating disease of the brain caused by infection with the JC virus that usually leads to death or severe disability. JC virus infection resulting in PML and death has been reported rarely in patients with hematologic malignancies receiving rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported in

patients with systemic lupus erythematosus (SLE) treated with rituximab. These patients with SLE had longstanding disease, history of prior immunosuppressant therapy, and were diagnosed with PML within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

2.10.3.11. Bowel obstruction and perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1−77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

2.10.3.12. Additional safety signals

The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

Hepatitis B reactivation with fulminant hepatitis, hepatic failure and death is a risk in patients who have ever been infected with the hepatitis B virus and/or are carriers of hepatitis B. The risk of hepatitis B reactivation may continue for several months after rituximab administration.

2.10.4. Tacrolimus

Tacrolimus is a macrolide antibiotic that is a potent immunosuppressant. Toxicities include predisposition to infection, renal insufficiency, hypertension, cholestatic hepatic toxicity, gingival hyperplasia, seizures, tremors, hirsutism, anorexia, nausea and possibly later B-cell lymphomas. To reduce the risk of toxicity, blood pressure, tacrolimus levels, renal function and liver enzymes will be monitored closely and vital signs aggressively maintained at baseline.

2.10.5. Methotrexate

Methotrexate is an antimetabolite that inhibits DNA synthesis and cell reproduction in malignant cells. Toxicities include mucositis, hyperuricemia, elevated liver function tests, leucopenia, thrombocytopenia, nausea, vomiting, diarrhea, anorexia, malaise, fevers, chills, rash, nephrotoxicity and penumonitis.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Definition of Disease Status

Patients at each data collection period are classified into one of the following stages. Until relapse/progression, all disease classifications are relative to the patient's pre-HSCT disease status. Once the patient has relapsed/progressed, these states are relative to the patient's best disease state. Tests used for evaluation of disease status will be physical examination, laboratory testing, bone marrow biopsy and aspirate, PET scans, and CT scans of the neck, chest, abdomen and pelvis as indicated.

Segments of this section are excerpts from the Bruce Cheson, et al, article "Revised Response Criteria for Malignant Lymphoma," JCO, 2007.

TABLE 3.1: RESPONSE DEFINITIONS

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

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously 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

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

Complete Remission (CR):

The designation of CR requires the following (Table 3.1):

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0cmin their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical exam and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged

spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

- If bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Complete Remission Undetermined (CRu):

- The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial Remission (PR):

The designation of PR requires all of the following:

- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver or spleen.
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma, a PET scan is only indicated with one, or at

most two, residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD):

Stable disease (SD) is defined as the following:

- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
- Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD, after CR)/ Progressive Disease (PD after PR, SD):

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes $\leq 1.0 \times \leq 1.0$cm will not be considered as abnormal for relapse or progressive disease.

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes or in a single involved node, or the size of other lesions (e.g, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cmin its short axis
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g. pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found

to be histologically negative. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use, response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

3.2. Primary Endpoint

The primary endpoint is a two-year progression-free survival. Patients are considered a failure for this endpoint if they die, or if they relapse/progress or receive anti-lymphoma therapy not including planned post-transplant radiation. The time to this event is the time from enrollment on study until death, relapse/progression, receipt of anti-lymphoma therapy, or last follow-up, whichever comes first.

3.3. Secondary Endpoints

3.3.1. Two Year Overall Survival

The event is death from any cause. The time to this event is the time from enrollment to death or last follow-up. Surviving patients are censored at the time of last observation.

3.3.2. Time to Progression/Relapse

The event is progression/relapse. The time to this event is measured from study enrollment. Deaths without relapse/progression are considered as a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up.

3.3.3. Time to CR and PR

The event is achieving CR (or PR and CR). The time to event is measured from the time of study enrollment to the time to CR (or PR). Patients who die in a state other than CR (PR) are considered as failing from a competing risk. Patients alive and not in CR (PR) are censored at the time of last observation.

3.3.4. Incidence and Time to Acute GVHD

The event is the incidence of grades II-IV and grades III-IV acute GVHD from day of transplant. The first day of acute GVHD onset at a certain grade will be used to calculate a cumulative incidence curve for that acute GVHD grade. An overall cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant with death considered as a competing risk.

3.3.5. Time to First Clinical Onset of Chronic GVHD

The event is the incidence and severity of chronic GVHD from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at two years post-transplant. Death prior to occurrence of chronic GVHD will be considered as a competing risk.

3.3.6. Treatment-Related Mortality (TRM)

The event is death occurring in patients in continuous complete remission. The TRM distribution will be estimated by the Kaplan-Meier curve at two years post-transplant.

3.3.7. Correlation of Serum Rituximab Levels

The incidence of relapse, acute GVHD, chronic GVHD, quantitative immunoglobulin levels, and lymphocyte analysis will be compared between patients with detectable levels of serum rituximab and no detectable levels at the specified time-points.

3.3.8. Incidence of Primary and Secondary Graft Failure

Donor engraftment is defined as >5% donor peripheral blood T cell chimerism by Day +30 post-HSCT in the setting of ANC recovery (ANC >500 for 3 consecutive days). Primary graft failure is defined as a donor peripheral blood T cell chimerism < 5% at Day +30 post-HSCT. Methodological requirements for chimerism are outlined in the BMT CTN MOP.

Secondary Graft Failure is defined as documented engraftment followed by loss of graft as defined by donor peripheral blood T cell chimerism < 5% as demonstrated by a chimerism assay.

3.3.9. Time to Off-Study Therapy

The event is the initiation of anti-lymphoma therapy other than those defined by the protocol. The time to this even is measured from study enrollment. Patients who die without initiation of an off-study therapy will be considered as experiencing a competing risk. Patients who are alive and have not received an off-study therapy are censored at the time of the last observation.

3.3.10. Incidence of Infections

Microbiologically documented infections will be reported by site of disease, date of onset, severity, and resolution, if any. This data will be captured via an event-driven case report form and will be collected from Day 0 until two years post-transplant.

3.3.11. Incidence of CTCAE Version 3.0 > Grade 3 Toxicities

See the BMT CTN MOP for the CTCAE grading scales.

3.3.12. Quality of Life (SF-36)

Health Related Quality of Life will be described prior to the initiation of conditioning therapy for English and Spanish-speaking patients utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. The questionnaires will be scored according to standard procedures. This will be compared to the Health Related QOL for patients at 2-years post-transplant.

3.3.13. Immunologic Reconstitution

This will be measured in all patients prior to the initiation of the conditioning therapy (baseline), at Day +100, and at 1 year post-transplant. This will also be measured at 2 years post-transplant if the 1 year assessment is abnormal. Tests to be performed on peripheral blood at those time points include CD3, CD4, CD8, CD19, CD20, CD56, and quantitative immunoglobulins (IgM, IgG and IgA).

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

All patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). Centers participating through the Cancer Trials Support Unit (CTSU) should follow the CTSU instructions for pre-approval and registration in Appendix F **prior** to following the instructions below.

4.1.1. Screening and Eligibility Procedures

The following procedures should be followed:

1. At least 2 days prior to initiation of conditioning therapy, an authorized user at the transplant center completes the eligibility screening by entering patient demographics, and the Enrollment Form in AdvantageEDC. The eligibility screening includes questions that will verify eligibility, capture the proposed start date of conditioning, HLA typing information, and a question confirming that the patient signed the informed consent form.
2. If the patient is eligible, a study number is generated.

4.2. Study Monitoring

4.2.1. Follow-Up Schedule

The follow-up schedule for scheduled study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide. The Data Management Handbook, including the Forms Submission Schedule is available on the homepage of the Internet data entry system.

TABLE 4.2.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day (± 7 Days Prior to Day 100 Post-HSCT) (± 28 Days After Day 100 Post-HSCT)
1 week	7 days
2 week	14 days
3 week	21 days
4 week	28 days
5 week	35 days
6 week	42 days
7 week	49 days

Study Visit	Target Day (± 7 Days Prior to Day 100 Post-HSCT) (± 28 Days After Day 100 Post-HSCT)
8 week	56 days
9 week	63 days
10 week	70 days
11 week	77 days
12 week	84 days
13 week	91 days
14 week	98 days
6 month	180 days
12 month	365 days
18 month	540 days
24 month	730 days

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data and Coordinating Center's (DCC) master database or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Recipient Death Information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

Center for International Blood and Marrow Transplant Research (CIBMTR) Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #0701 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post-transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.2.2. Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of

knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule. See Appendix E for detailed reporting guidelines.

4.2.2.1. Adverse event reporting to Genentech

Unexpected grade 3-5 adverse events (AE) will be reported by the Data and Coordinating Center, by password-protected e-mail attachments, to Genentech Drug Safety twice per year (Tel: 888-835-2555; Fax: 650-225-4682 or 650-225-4683). Annual reports listing expected toxicities will be reported by password-protected e-mail attachments.

See Appendix E for detailed reporting guidelines.

4.2.3. Weekly GVHD Monitoring Post-HSCT

GVHD should be monitored in accordance with BMT CTN guidelines as specified in the MOP. Patients should be assessed weekly until Day 100 post-HSCT for GVHD. After Day 100, patients will be assessed at each study visit for the presence of GVHD.

4.2.4. Patient Assessments

4.2.4.1. Evaluations prior to HSCT

The following observations will be done ≤ 4 weeks prior to initiation of the HSCT conditioning therapy.

1. History, physical examination, height and weight.
2. Karnofsky performance score.
3. CBC with differential, platelet count, creatinine, bilirubin, LDH, alkaline phosphatase, AST, ALT, sodium, magnesium, potassium, chloride, and CO_2.
4. Creatinine clearance (measured or calculated)
5. CMV titer, hepatitis panel (HepA Ab, HepB sAb, HepB sAg, HepB Core Ab, HepC Ab), herpes simplex titer, syphilis, HIV and HTLV1 antibody.
6. EKG.
7. Left ventricular ejection fraction.
8. DLCO, FEV1 and FVC.
9. HLA typing of heparanized peripheral blood sample to determine availability of HLA-matched sibling or HLA-matched unrelated donor (may be completed at any time prior to conditioning). Minimum HLA typing for related donors must be performed by DNA methods for HLA-A and -B at intermediate resolution and DRB1 at high resolution. Minimum HLA typing for unrelated donors must be performed by

DNA methods for HLA-A, -B, -C, and -DRB1 at high resolution consistent with NMDP standard procedures.

10. Baseline Disease Evaluation:
    a) Bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics. Flow cytometry is not required.
    b) CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease. PET is strongly recommended if PET scans were initially used to diagnose disease.
11. Flow cytometry analysis of allogeneic graft per the Graft Characterization section of the BMT CTN MOP.
12. Two vials (20 cc) of nucleated cells from patient's peripheral blood for future testing (see the Table C-1 in Appendix C for processing/shipping instructions).
13. Quality of life assessment.
14. ABO Rh Blood typing.
15. Blood samples for evaluation of immune reconstitution by flow cytometry (CD3, CD4, CD8, CD19, CD20 and CD56) and quantitative immunoglobulins (IgM, IgG, and IgA) (see Appendix C for details).
16. PCR for presence of t(14;18)
17. Peripheral blood for serum Rituximab levels collected and sent per Appendix C.
18. Signed informed consent

4.2.4.2. Post-HSCT evaluations

1. CBC at least three times a week from Day 0 until ANC > 500 for 3 days after nadir reached. Thereafter twice per week until Day 28 (or 4 weeks), then at 8 weeks, 3 months, 6 months, one year and two years post-HSCT.
2. Comprehensive chemistry panel defined as creatinine, LDH, bilirubin, alkaline phosphatase, AST, ALT, magnesium, sodium, potassium, chloride, CO_2 twice a week until Day 28 (or four weeks) and then at 8 weeks, 3 months, 6 months, one year and two years post-HSCT.
3. Toxicity assessments at 4 weeks, 8 weeks, 3 months, 6 months, one year and two years post-HSCT.
4. Disease restaging at 3 months, 6 months (6-month disease restaging only if clinically indicated), 1 year and 2 years post-HSCT.
    a. Bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics. Flow cytometry is not required. Post-HCT bone marrow assessments are not required unless the original diagnostic marrow or the baseline marrow documented abnormal morphology/cytogenetics.

b. CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease. PET is strongly recommended, if PET scans were initially used to diagnose disease.

c. In patients with known t(14;18), peripheral blood samples will be drawn for t(14;18) analysis by quantitative PCR. These samples will be processed and analyzed locally per institutional guidelines

d. Quality of life assessment at 2 years post-HSCT.

5. Peripheral blood for immune reconstitution studies by flow cytometry (CD3, CD4, CD8, CD19, CD20 and CD56) and quantitative immunoglobulin levels (IgM, IgG, and IgA) should be determined at 3 months, 6 months and 1 year (see Appendix C for details).

In addition, all patients are required to have a history and physical exam to assess GVHD weekly until Day 100 post-HSCT, then at 6 months, one year and then yearly until two years post-HSCT. GVHD evaluation and grading is to be in keeping with BMT CTN MOP.

4.2.4.3. Quantitative PCR sampling

Below is the sampling schedule for quantitative PCR of t(14;18) from peripheral blood sample:

1. At study entry.
2. For patients with positive PCR at any time since diagnosis. These samples will be processed and analyzed locally per institutional guidelines. Post-HSCT:
   - 3 months post-HSCT
   - 6 months post-HSCT
   - 1 year post-HSCT
   - 2 years post-HSCT

4.2.4.4. Chimerism analysis sampling

Below is the sampling schedule for **chimerism analysis** of peripheral blood for all patients:

1. 4 weeks post-HSCT
2. 8 weeks post-HSCT
3. 3 months post-HSCT
4. 6 months post-HSCT
5. 1 year post-HSCT

4.2.4.5. Serum rituximab levels sampling

Sampling schedule for serum rituximab levels for all patients:

1. Pre-HSCT
2. 4 weeks post-HSCT
3. 3 months post-HSCT
4. 6 months post-HSCT
5. 1 year post-HSCT

4.2.4.6. Donor assessments

1. Donor assessments for matched related donors are performed per institutional guidelines, to include peripheral blood draw for chimerism and infectious disease markers.
2. Donor assessments for matched unrelated donors are performed per NMDP guidelines.

TABLE 4.2.4a: BASELINE EVALUATIONS

Required Studies/Testing	Baseline[1]
History, Physical Examination, Height and Weight	X
Karnofsky Performance Score	X
CBC with differential, Platelet Count, Creatinine, Bilirubin, Alkaline Phosphatase, AST, ALT, LDH, Sodium, Magnesium, Potassium, Chloride and CO_2	X
ABO Rh Typing	X
Creatinine Clearance	X
CMV Titer, Hepatitis Panel (A,B,C) Herpes Simplex, Syphilis	X
HIV/HTLV1 Antibody	X
EKG	X
Left Ventricular Ejection Fraction	X
DLCO, FEV1, FVC	X
β -HCG Serum Pregnancy Test for Females of Childbearing Potential	X
Toxicity Assessment	X
CT Neck, Chest, Abdomen and Pelvis	X[2]
Bone Marrow Aspirate and Biopsy[4]	X
Peripheral Blood for t(14;18) PCR	X
Peripheral Blood for HLA Typing	X
Blood Samples for Rituximab levels	X
Nucleated Cells	X[3]
Immune Reconstitution Assays[5]	X
Health Quality of Life	X
Consent Review	X

Notes:

[1] To be performed within 4 weeks of starting conditioning therapy.

[2] Neck CT only required if previous site of disease.

[3] Two vials (20 cc) of nucleated cells from peripheral blood for future testing (see Table C-1: Schedule of Laboratory Evaluations for processing/shipping instructions).

[4] Bone marrow aspirate and biopsy samples to pathology, aspirate for cytogenetic analysis.

[5] Immune reconstitution assays to include CD3, CD4, CD8, CD19, CD20, CD56, and quantitative immunoglobulin (IgM, IgG and IgA) levels.

Table 4.2.4b: Summary of Patient Clinical Assessments

Study Assessments/ Testing	Baseline	Days Post-Transplant																
		7	14	21	28	35	42	49	56	63	70	77	84	91	98	180	365	730
History, physical exam, weight, height[11], and Karnofsky/Lansky performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GVHD assessments[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC[2], differential, platelet count, and blood chemistries[3]	X	X	X	X	X				X				X			X	X	X
ABO Rh Typing	X																	
Creatinine Clearance	X																	
Infectious disease titers[4]	X																	
EKG	X[5]																	
Left ventricular ejection fraction	X[5]																	
DLCO, FEV1 and FVC	X																	
Bone marrow aspirate for pathology and cytogenetics[5]	X												X			X[10]	X	X
Bone marrow biopsy for pathology[5]	X												X			X[10]	X	X
ß-HCG serum pregnancy test (females only)	X																	
Toxicity Assessment	X				X				X				X			X	X	X
CT Neck, Chest, Abdomen and Pelvis	X[6]												X			X	X	X
Peripheral Blood for t(14;18) PCR	X												X[7]			X[7]	X[7]	X[7]
Peripheral Blood for HLA typing	X																	
Blood Samples for Chimerism Assays					X				X				X			X	X	
Blood Samples for Rituximab levels	X				X								X			X	X	

Study Assessments/ Testing	Baseline	Days Post-Transplant																
		7	14	21	28	35	42	49	56	63	70	77	84	91	98	180	365	730
Nucleated Cells[8]	X																	
Flow Cytometry analysis of allogeneic graft	X																	
Immune Reconstitution Assays[9]	X												X			X	X	
Health Quality of Life	X																	X
Consent Review	X																	

Notes:

[1] GVHD performed weekly until Day 100 post-transplant.

[2] CBC performed three times weekly from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28.

[3] Blood chemistries include: differential, platelet count, creatinine, LDH, bilirubin, alkaline phosphatase, AST, ALT, magnesium, sodium, potassium, chloride, and CO_2. Blood chemistries performed twice weekly until Day 28.

[4] Infectious disease titers include: CMV, Hepatitis panel (HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV1 antibody.

[5] Bone marrow aspirate and biopsy samples to pathology, aspirate for cytogenetic analysis. Only if bone marrow was involved with lymphoma.

[6] Neck CT only required if previous site of disease.

[7] Only in patients with known t(14;18) at any time since diagnosis.

[8] Two vials (20 cc) of nucleated cells from peripheral blood for future testing (see the Table C-1 in Appendix C for processing/shipping instructions).

[9] Immune reconstitution assays include: CD3, CD4, CD8, CD19, CD20, CD56 and quantitative immunoglobulin (IgM, IgG and IgA) levels.

[10] Only if clinically indicated.

[11] Height evaluation only required at baseline.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Overview

The study is a Phase II, single arm, multicenter trial. It is designed to confirm the efficacy in a multi-center BMT CTN study of a non-myeloablative allogeneic conditioning regimen of FCR. The study population is patients with relapsed follicular NHL receiving matched related or matched unrelated donor transplants. The sample size is 65 patients for this trial.

5.1.1. Primary Endpoint

The primary endpoint for the study is two-year progression-free survival. If any therapy not specified in the protocol is given to prevent relapse/progression or to induce a response, the patient will be considered to have experienced an event for the primary endpoint.

Patients who are lost to follow-up prior to two years will be censored at the time of the last observation, and the progression-free survival proportion will be estimated using the Kaplan-Meier method, where time-to-event is measured from enrollment to the minimum of the date of death, relapse/progression, last-follow-up or the two-year time point.

5.1.2. Accrual

It is estimated that two years of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age.

5.1.3. Study Duration

Patients will be followed for a minimum of two years post-transplant.

5.2. Sample Size and Power Considerations

The sample size is 65 patients for this trial. Ninety-five percent confidence intervals were calculated for varying probabilities based on the sample size. Table 5.2a provides confidence intervals for a variety of true underlying proportions. Of particular interest is where the PFS probability is 73%, which is the targeted 2-year PFS probability. For this setting, the confidence interval length is 22.9%. The percentages above and below 73% are meant to represent other plausible PFS percentages.

The precision of the estimates alternatively could be viewed as a lower bound on the rate of PFS. The probability to rule out PFS percentages of a certain size is known as "power." Table 5.2b provides the probability (or power) that the lower bound of a 95% two-sided confidence interval for the PFS probability will be greater than various PFS thresholds between 50% and 80%. In

particular, when the true PFS percentage is 73%, there is 80% power to rule out a PFS percentage of < 55%, which is the historical 2 year progression-free survival rate for this type of patient after autologous HSCT. This can equivalently be viewed as testing the following hypothesis: H_o: p = 0.55 versus H_1: p ≠ 0.55. Based on the table below, there is 80% power at α= .05 (two-sided) to reject the null hypothesis if the true PFS percentage is 73%.

TABLE 5.2a: CONFIDENCE INTERVAL LENGTHS AND POSSIBLE CONFIDENCE INTERVALS FOR VARIOUS UNDERLYING PROGRESSION-FREE SURVIVAL PROBABILITIES

N	Progression-free Survival %	Length of 95% Confidence Interval	Possible Confidence Intervals	
65	80	20.7	68.2	88.9
65	75	22.3	63.1	85.3
65	73	22.9	59.8	82.7
65	70	23.6	56.5	80.1
65	65	24.4	51.7	76.1
65	60	25.0	47.0	72.0
65	55	25.3	42.5	67.8

The PFS probability estimate will be based on the Kaplan-Meier product limit estimator using Greenwood's formula as the variance estimate. In the absence of censoring, the Kaplan-Meier estimate reduces to the simple binomial proportion.

TABLE 5.2b: PROBABILITY OF RULING OUT A THRESHOLD OF SIZE T OR LARGER FOR VARIOUS TRUE UNDERLYING PROGRESSION-FREE SURVIVAL PERCENTAGES, WITH N=65

	Probability of ruling out PFS Percentages of size T or smaller						
True PFS	T=0.75	0.73	0.7	0.65	0.6	0.55	0.5
0.75		0.04	0.08	0.31	0.65	0.89	0.99
0.73	0.05		0.04	0.20	0.50	0.80	0.97
0.70	0.14	0.05		0.09	0.30	0.61	0.91
0.65	0.42	0.24	0.11		0.08	0.28	0.68
0.60	0.73	0.55	0.35	0.13		0.08	0.35
0.55	0.93	0.82	0.67	0.38	0.10		0.12
0.50	0.99	0.96	0.89	0.69	0.31	0.11	

5.3. Interim Analysis and Stopping Guidelines

There will be no interim analyses for efficacy, since the primary endpoint is 2 year PFS. Monitoring of a key safety endpoint (treatment-related mortality [TRM]) will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

The rate of TRM will be monitored up to 100 days post-transplant. Monitoring will be performed monthly until enrollment is closed. Stopping rules will be defined separately for patients receiving related donor transplants and those receiving unrelated donor transplants, because of limited experience with this regimen in unrelated donor transplants in particular. Fewer than half of the patients in the study are anticipated to receive unrelated donor transplants; we base our stopping rules on anticipated accrual of 30 unrelated and 35 related donor transplant recipients.

A truncated Sequential Probability Ratio Test (SPRT) for a censored binomial outcomes will be used to monitor TRM as described below. This sequential testing procedure conserves type I error across all of the monitoring looks for TRM, but not across the two cohorts of patients being monitored separately. Thus the type I error for each cohort is approximately 5%, and across both cohorts, the study-wide type I error is < 10%.

The SPRT can be represented graphically. At each interim analysis, the total number of patients enrolled is plotted against the total number of patients who have experienced TRM. The continuation region of the SPRT is defined by two decision boundaries. Only the upper boundary will be used for monitoring the study to protect against high incidences of TRM. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that the TRM rate is higher than predicted by the observed number of patients enrolled on study. Otherwise, the SPRT continues until enrollment reaches the target goal.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_I)$. Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be slightly lower than the nominal level. The tests to be used in this protocol were developed from SPRT's described in more detail in the following subsections.

Related Donor Transplant Recipients

Treatment-related mortality in this trial is anticipated to be <=10% at 100 days for related donor transplant recipients. The stopping rule for treatment-related mortality in patients receiving related donor transplants will be triggered if there is significant evidence that the 100 day treatment-related mortality rate is more than 10% based on the truncated SPRT. This truncated SPRT is based on contrasting 10% versus 35% 100 day TRM, with nominal type I and II errors

of 7.5% and 10%, respectively. The common slope of the decision boundaries is 0.206 and the intercept for the upper boundary is 1.575. The stopping rule is summarized in Table 5.3a.

TABLE 5.3a: STOPPING BOUNDARIES FOR 100-DAY TRM AMONG PATIENTS RECEIVING RELATED DONOR TRANSPLANTS*

Number of Patients Enrolled, n	Stopping Boundary, x	Number of Patients Enrolled, n	Stopping Boundary, X
3-6	3	22-26	7
7-11	4	27-31	8
12-16	5	32-35	9
17-21	6		

* Stopping rule is triggered if >=x patients out of n enrolled experience TRM

The actual operating characteristics of the stopping guideline, shown in Table 5.3b, were determined in a simulation study that assumed uniform accrual of 35 individuals receiving related donor transplants over a three-year time period.

TABLE 5.3b: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR TRM AMONG PATIENTS RECEIVING RELATED DONOR TRANSPLANTS FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Treatment-Related Mortality				
True 100-Day Rate	10%	20%	25%	30%
Probability Reject Null	0.048	0.417	0.676	0.857
Mean Month Stopped	38.1	30.4	24.6	19.3
Mean # Endpoints in 100 Days	3.4	5.3	5.3	4.9
Mean # Patients with 100 Days Follow-up	33.9	26.6	21.1	16.1

The testing procedure for TRM among related donor transplant recipients rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day incidence is 10%, and 86% of the time when the rate is 30%. When the true 100-day TRM incidence is 30%, on average, the Data and Safety Monitoring Board will be consulted 19.3 months after opening, when 4.9 events have been observed in 16.1 patients undergoing related donor transplants with 100 days follow-up.

Unrelated Donor Transplant Recipients

Treatment-related mortality in this subgroup is anticipated to be <= 15% at 100 days. The stopping rule for treatment-related mortality in this subgroup will be triggered if there is significant evidence that the 100 day treatment-related mortality rate is more than 15% based on the truncated SPRT. This truncated SPRT is based on contrasting 15% versus 30% 100 day mortality, with nominal type I and II errors of 10% and 10%, respectively. The common slope of the decision boundaries is 0.219 and the intercept for the upper boundary is 2.476. The stopping rule is summarized in Table 5.3c. If this stopping rule is triggered, the DSMB will be notified to consider closure of accrual to patients receiving unrelated donor transplants.

TABLE 5.3c: STOPPING BOUNDARIES FOR 100-DAY TRM AMONG PATIENTS RECEIVING UNRELATED DONOR TRANSPLANTS*

Number of Patients Enrolled, n	Stopping Boundary, x	Number of Patients Enrolled, n	Stopping Boundary, x
4-6	4	17-20	7
7-11	5	21-25	8
12-16	6	26-29	9

* Stopping rule is triggered if >=x patients out of n enrolled experience TRM.

The actual operating characteristics of the stopping guideline, shown in Table 5.3d, were determined in a simulation study that assumed uniform accrual of 30 individuals undergoing unrelated donor transplants over a three-year time period.

TABLE 5.3d: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR TRM AMONG PATIENTS RECEIVING UNRELATED DONOR TRANSPLANTS, FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Treatment-Related Mortality				
True 100-Day Rate	15%	25%	30%	35%
Probability Reject Null	0.050	0.378	0.606	0.789
Mean Month Stopped	38.5	33.0	28.8	24.3
Mean # Endpoints in 100 Days	4.4	6.2	6.4	6.3
Mean # Patients with 100 Days Follow-up	29.3	25.0	21.4	17.9

The testing procedure for TRM among unrelated donor transplant recipients rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day incidence is 15%, and 79% of the time when the rate is 35%. When the true 100-day TRM incidence for this subgroup is 35%, on average, the Data and Safety Monitoring Board will be consulted 24.3

months after opening, when 6.3 events have been observed in 17.9 patients undergoing unrelated donor transplants with 100 days follow-up.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, HLA match, disease stage, number of prior regimens.

5.5. Analysis Plan

5.5.1. Analysis of Primary Endpoint

The primary analysis will consist of estimating the 2 year PFS probability based on the Kaplan-Meier product limit estimator. The 2 year PFS probability and confidence interval will be calculated. All patients receiving the first dose of Rituximab as part of the conditioning regimen on Day -13 will be included in this analysis, based on an intention to treat.

5.5.2. Analysis of Secondary Endpoints

- **Progression/ Relapse:** To assess the incidence of progression/relapse from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to progression/relapse will be considered as a competing risk.
- **Acute GVHD:** We will assess the incidence of grades II-IV and grades III-IV acute GVHD from day of transplant. The first day of acute GVHD onset at a certain grade will be used to calculate a cumulative incidence curve for that acute GVHD grade. An overall cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant with death considered as a competing risk.
- **First Clinical Onset of Chronic GVHD:** To assess the incidence and severity of chronic GVHD from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at two years post-transplant. Death prior to occurrence of chronic GVHD will be considered as a competing risk.
- **Treatment-Related Mortality (TRM):** TRM is death occurring in patients in continuous complete remission. A cumulative incidence curve will be computed along with a 95% confidence interval. Progression/relapse will be considered as a competing risk.
- **Overall Survival:** The survival distribution will be estimated by the Kaplan-Meier curve. All patients will be followed for a minimum of two years post-transplant for mortality.
- **Complete Response/Partial Response**: The frequencies and proportions of patients who have a CR/PR will be described with confidence intervals at each evaluation time.
- **Incidence of Off Study Therapy**: The cumulative incidence of use of off-study therapy will be calculated with 95% confidence intervals at each evaluation time. Death prior to use of off-study therapy will be considered the competing risk.

- **Quality of Life (SF-36):** Mean QOL scores and confidence intervals will be computed at each time point. A paired student t test will be used to look for differences in mean scores between baseline and 2 years after the HCT. To determine the magnitude of differences, standardized effect sizes (or z-scores) will be calculated. This will be done by taking the difference between the mean domain scores of the baseline score and the follow-up scores and dividing by the standard deviation of the baseline. Domain scores will also be compared between baseline and 2 years post-HSCT with a Bonferroni correction for multiple testing. In addition, mixed models for repeated measures data will be used to assess whether QOL is changing significantly over each time point among survivors.
- **Primary and Secondary Graft Failure:** The frequency and proportion of patients experiencing primary graft failure by Day 30, and the proportion of patients who have engrafted who subsequently experience secondary graft failure will be described with 95% confidence intervals.
- **Correlation of Rituximab levels with development of acute GVHD, chronic GVHD, relapse, and immune recovery:** Cox regression models will be fit to each outcome data, using time-dependent covariates to examine the effect of rituximab levels.
- **Infections:** Microbiologically documented infections will be reported by site of disease, date of onset, severity, and resolution, if any. This data will be captured via an event-driven case report form and will be collected from Day 0 until two years post-transplant. The incidence of definite and probably viral, fungal and bacterial infections will be tabulated for each patient according to the BMT CTN Manual of Procedures.
- **Toxicities:** Toxicities that occur over the course of time will be tabulated.

  Grade $\geq$ 3 toxicities will be tabulated for each patient at set intervals over the course of the study. The proportion of patients developing toxicity will be described.
- **Immunologic Reconstitution:** Immune reconstitution assays, which will include CD3, CD4, CD8, CD19, CD20, CD56, and quantitative immunoglobulins (IgM, IgG and IgA), will be performed at baseline, 3 months, 6 months, and 1 year post-transplant. This will also be assessed at 2 years post-transplant, if the 1 year assessment is abnormal. These will be summarized at each time point using descriptive statistics.

5.5.3. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. The type and severity of adverse events will be analyzed.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The Principal Investigator or another designated physician will conduct the conference. All potential risks associated with the use of rituximab, cyclophosphamide, and immunosuppressive drugs should be discussed as objectively as possible. It should be explained that patients offered this protocol have advanced FL with life expectancy of no more than several years with conventional treatments. Furthermore, if should be explained that the patient would be likely to benefit in terms of disease control and prolongation of survival from an autologous transplant alone, but would likely relapse from the disease. In addition, the risk of allogeneic transplant for FL should be described.

The consent document should be reviewed with the patient and family prior to proceeding to non-myeloablative HSCT.

Donor consent will be per institutional standards. At a minimum, the procedure for collecting hematopoietic stem cells and toxicities of G-CSF will be explained to the donor. The donor should be counseled as to the risks of treatment with G-CSF and be informed that leukapheresis at several time points may be necessary.

Informed consent from the patient will be obtained using a form approved by the Institutional Review Board of the institution enrolling the patient. Informed consent from the donor will be obtained using the standard NMDP donor informed consent form.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the BMT CTN Data and Coordinating Center upon enrollment.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of DLCL in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX B

INFORMED CONSENT FORM

Informed Consent to Participate in Research

DRAFT

Please read this form carefully. If there are words or part of this document that you do not understand, you should ask the research doctor or staff to explain any information that is not clear to you before making a decision whether to participate. Your participation is entirely voluntary. You may choose not to participate and you may withdraw at any time.

The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all or your questions. Please ask questions about anything that you do not understand.

If you are a parent or guardian of a patient younger than 18 years old and have been asked to read and sign this form, the "you" in this document refers to the patient.

This is a consent form for a research study. This form is to help you decide if you want to participate in this study.

The consent form describes a study for patients with follicular lymphoma who have entered remission from treatment with conventional chemotherapy but the lymphoma has now returned or started growing again. Follicular lymphoma is not curable with standard chemotherapy.

The purpose of this study is to see if this type of transplant called a non-myeloablative transplant can improve your chances of a long-term remission. Both your donor's immune system and the chemotherapy drugs that you receive as part of the transplant will be used against your lymphoma.

This study will give more information to doctors about future treatment choices. In addition:

- You will not be paid to be in this study.
- You or your insurance company will pay for all medical bills for your treatment.
- You will not be charged for research tests.
- You will also face the same risks and benefits as any other transplant patient.

Before you decide to join the study, please read the information below. Feel free to ask questions to understand your rights. It is your choice to take part in this study. You and your doctor will discuss other treatment options if you decide not to be in this study.

1. Name of the Subject ("Study Subject")

2. Title of Research Study

A Phase II Trial of Non-Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients with Relapsed Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response

3a. Principal Investigator Contact Information

Insert name, affiliation and contact information.

3b. Contact Information for Emergencies After Hours or on Weekends or Holidays

Call (xxx) xxx-xxxx, the in-patient Bone Marrow Transplant Unit. Ask to speak to the Charge Nurse.

4. Sponsors and Source of Funding or Other Material Support

The research in this study is paid for by the National Institutes of Health (NIH). The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) will direct the research study.

Rituximab was donated by Genentech. Genentech also gave some financial support to help pay the costs of this study. Genentech did not plan or design this study, nor will it have a part in analyzing the results of this study.

5. Study Purpose

A conventional allogeneic stem cell transplant is where the patient receives high doses of chemotherapy followed by an infusion of blood stem cells donated by a sibling (brother or sister) or unrelated donor who has the same tissue type (genetically matched). The blood stem cells would rescue your bone marrow from the toxic effects of chemotherapy. However, because the stem cells come from a healthy donor, these blood stem cells also replace your immune system with the donor's immune system. This new immune system also helps fight your lymphoma. This effect of an allogeneic stem cell transplant (SCT) is called a graft-versus-tumor effect. An allogeneic peripheral blood SCT is when a donor's stem cells are collected from his/her blood and then given to you after you receive chemotherapy, also known as conditioning therapy. In some cases the donor stem cells may be frozen before given to you. Unfortunately, the

traditional type of allogeneic SCT that uses high doses of chemotherapy and radiation can have many serious side effects and a high-risk of treatment-related death.

The inability of many lymphoma patients to tolerate a traditional allogeneic SCT may relate to combining the toxic effects of high-dose therapy and the immune effects of the allogeneic SCT. Recent studies have shown that a less toxic type of allogeneic SCT, called a non-myeloablative SCT (also sometimes called a mini transplant or reduced intensity transplant), can more safely be carried out. This lower intensity transplant appears to still control lymphoma. In this study, you will receive this type of transplant and receive lower doses of chemotherapy compared to the doses used in a conventional allogeneic SCT.

The purpose of this study is to determine how effective this non-myeloablative transplant will control and possibly cure your lymphoma. Non-myeloablative SCT has been shown to control your kind of lymphoma.

6. How many people will take part in the study?

As many as 65 patients will take part in this study at different hospitals in the United States.

7. Study Plan

Allogeneic stem cell transplant uses blood stem cells from a brother or sister donor or a matched unrelated donor for the transplant.

- Non-myeloablative SCT uses lower amounts of chemotherapy and radiation than what is used in standard allogeneic transplants.
- After the chemotherapy, the stem cells from your donor will be given to you.
- Your immune system will be replaced by the donor's immune system.
- A non-myeloablative SCT depends on the donor's immune system to destroy the lymphoma cells in your body.

<u>Rituximab Therapy</u>
You also will receive 4 doses of a drug called rituximab. Rituximab is a drug that is not considered chemotherapy but is called a monoclonal antibody. This drug works by attacking only the B cells in your body. B cells are a type of white blood cell in your blood; bone marrow and lymph nodes that normally help fight infection. However, in patients with follicular lymphoma, it is the B cells that become malignant (cancerous) and become lymphoma cells. Rituximab is already commonly used either alone or together with chemotherapy for patients with follicular lymphoma and other types of lymphoma.

You will have blood samples drawn to study the actions of Rituximab in your body. You will have 3-5 mL (about 1 teaspoon) of blood drawn on 5 different days (total of up to 25 mL). The first sample will be taken before the transplant. The remaining samples will be taken after the

transplant at 4 weeks, 3 months, 6 months and 1 year. This blood will be drawn from an existing central venous catheter or a temporary peripheral venous catheter.

8. Procedures and Tests

If you agree to participate in this study, your transplant process will include many steps to:

- Evaluate your health.
- Determine if you have a matched brother or sister donor.
- Prepare your body for a stem cell transplant.
- Receive your stem cell transplant.
- Help your body recover after transplant.
- Measure your health and well being over two years after your transplant.
- Measure your quality of life using surveys before your transplant and two years after your transplant.

If you have a matched brother or sister donor, they will also have a health evaluation, their cells collected for transplant and sign a consent for the study.

If your donor is an unrelated donor, that person will also have the same health evaluation as mentioned above with a sibling donor.

If you have a genetically (HLA) matched brother or sister or a matched unrelated donor, you will have a **non-myeloablative allogeneic SCT**. Your brother or sister or unrelated donor must be willing and able to donate blood stem cells for your transplant.

You will start the **conditioning regimen** also known as the **preparative regimen**. This is done to prepare your body for transplant. The schedule of the preparative regimen is provided in Table 1 if your donor is related to you or in Table 2 if your donor is unrelated to you.

Your doctor will use a combination of three drugs given through your veins:

- **Rituximab** – to lower the number of lymphoma cells, and
- **Cyclophosphamide** – also to lower the number of lymphoma cells and lower the chance of donor stem cell rejection, and
- **Fludarabine** – to lower the chance of donor stem cell rejection.

The purpose of using these drugs with chemotherapy is to weaken your immune system and lower the chance that your body will reject the donated stem cells and to reduce the amount of lymphoma in your body.

You will receive two more drugs during this process to lower the chance of rejecting the donor cells and to lower the chance of developing serious graft-versus-host disease:

- Tacrolimus

- Methotrexate

Graft-versus-host disease (GVHD) is a condition where the donated stem cells attack your skin, liver, intestines and other organs. There is about a 50-60% chance that GVHD will happen after a non-myeloablative allogeneic transplant, but in most cases it is a mild form of GVHD. GVHD can be both helpful and harmful. Mild GVHD may protect against the return of your lymphoma, by attacking the cancer cells. There is approximately a 10-15% chance that serious GVHD may cause organ damage or even death.

Tacrolimus can be taken as a pill or by injection into your vein. Your doctor will decide how you will take it. You will need to take the tacrolimus for at least 6 months. You may need to take it longer if you develop graft-versus-host disease. Methotrexate will be given through your vein for 3 doses on the first, third and sixth day after your transplant **if your donor is your brother or sister**.

If your donor is a matched unrelated donor, you will receive a 4th dose of methotrexate on the 11th day after transplant to decrease the risk of graft-versus-host disease.

TABLE 1: CONDITIONING SCHEDULE FOR NON-MYELOABLATIVE SCT FOR PATIENTS WITH A MATCHED BROTHER OR SISTER DONOR

	Days BEFORE Transplant							
	-13	-6	-5	-4	-3	-2	-1	0*
Fludarabine			✓	✓	✓			
Cyclophosphamide			✓	✓	✓			
Rituximab	✓	✓						
Tacrolimus						✓	✓	daily
Transplant								✓

* You will have your transplant on **"Day Zero (0)."**

	Days AFTER Transplant							
	1	2	3	4	5	6	7	8
Rituximab	✓							✓
Tacrolimus**	✓	✓	✓	✓	✓	✓	✓	✓
Methotrexate	✓		✓			✓		

** Tacrolimus will be given daily for at least 6 months or longer if GVHD occurs

TABLE 2: CONDITIONING SCHEDULE FOR NON-MYELOABLATIVE SCT FOR PATIENTS WITH A MATCHED UNRELATED DONOR

	Days BEFORE Transplant							
	-13	-6	-5	-4	-3	-2	-1	0*
Fludarabine			✓	✓	✓			
Cyclophosphamide			✓	✓	✓			
Rituximab	✓	✓						
Tacrolimus						✓	✓	daily
Transplant								✓

* You will have your transplant on **"Day Zero (0)."**

	Days AFTER Transplant								
	1	2	3	4	5	6	7	8	11
Rituximab	✓							✓	
Tacrolimus**	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methotrexate	✓		✓			✓			✓[1]

** Tacrolimus will be given daily for at least 6 months or longer if GVHD occurs
[1] This 4th dose of methotrexate is given if your donor is an unrelated donor.

9. How long will I be in the study?

You will be in the study for up to two years. Follow-up for transplant will last as long as you require care.

10. What are risks of this research study?

You will face risks from the transplant itself, and from treatments given before and after the transplant. Your doctor thinks these risks are less than the risk that you will die from your cancer if it is not treated.

Your heart, lungs, liver, bladder, kidneys, brain or other organs may be damaged by the chemotherapy or by other drugs given to you after the transplant. Rarely, the damage to your organs may be permanent.

Your risk of infection is also increased when undergoing a stem cell transplant. This is due to the chemotherapy that weakens your immune system. Potential infection can be caused by either a bacteria, virus or a fungal organism. Your doctors will monitor you closely for any sign of infection, especially fevers.

There is a risk that your donor's stem cells may not grow after being given to you. This is called graft failure. If graft failure occurs, this may result in low blood counts for a long period of time.

Graft failure can be fatal unless you have a second transplant.

Refer to the Appendix for additional risks and toxicities.

11. What other choices are there if I do not take part in this study?

Participation in this study is entirely voluntary. You are free to refuse to be in the study, and your refusal will not affect current or future health care you receive at this institution. You and your doctor will discuss any other treatment options available to you including:

- Treatment with other drugs or combination of drugs.
- A standard stem cell transplant.
- No therapy directed against your lymphoma at this time, with care to help you feel more comfortable.

12. Are there benefits to taking part in this research study?

You may receive no direct benefits from this study. You may or may not benefit from the scheduled medical assessments required for this study, and extra support from personnel working for this study.

You may be helping other patients get better treatment in the future. A total of 65 patients nationwide will be enrolled on this study. If any new information regarding unexpected side effects are seen in any of the other patients enrolled, you will be informed as soon as possible.

13. What will be done with my blood sample?

A sample (4 teaspoons) of your blood will be collected pre-transplant and stored and used only for research purposes. Usually this blood sample can be collected from you at the time of routine blood collections. If this is not possible, then it would be drawn directly from your central venous catheter.

Your confidentiality will be maintained because no identifying markers (name, etc.) will remain with the sample.

If you agree to allow your blood to be kept for research, you are free to change your mind at any time. We ask that you contact {Principal Investigator} in writing and let him know you are withdrawing your permission for your blood to be used for research. His mailing address is on the first page of this form. Any unused blood will be destroyed.

We will do our best to make sure that your personal information will be kept private and secure. The chance that this information will be given to someone else is very small.

DNA from your stored blood and tissue samples and your health information might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH).

Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease.

If your coded genetic and clinical information is used in such a study, the researcher is required to add the DNA test results and non-identifying information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

You are free <u>not</u> to take part in this additional future research. There will be absolutely no change in your care as a result of your refusal to give these additional samples. Please indicate your choice(s) below:

❑ No, I do not agree to have a blood sample drawn for future research.

❑ Yes, I agree to have blood drawn for future research.

_____ _____

Signature Date

14. What are the costs?

You and/or your insurance company will pay all medical expenses relating to, or arising from stem cell transplantation. Research tests will not be charged to you.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

15. Will I be paid to take part in this research study?

No.

16. What will happen if I am sick or hurt because of this study?

If you are injured or become ill while taking part in this study, medical care will be provided at this center. No funds have been set aside to pay you if you are injured. You or your insurance company will be charged for ongoing medical care and/or hospitalization.

Contact your doctor or one of the people listed at the start of this form if you are concerned about a research-related injury.

17. Can I change my mind about taking part in this research study?

You may decide to quit this study at any time, for any reason, without notice. However, if you quit after you have had some or all of the treatment but before your transplant, then your blood counts may not return and you could die.

If you decide to quit, we ask that you tell [the Principal Investigator] in writing (his/her address is on the front page of this form). If you do take back your consent, there will be no penalty and you will not lose anything you are entitled to and will continue to receive medical care.

If you have any questions about your rights as a study subject, you may phone the Institutional Review Board (IRB) office at /number/.

18. Can my information still be collected and used if I leave the research study?

If you quit the study, we ask that you let us continue using all information that was already collected. We also ask that you let your doctor continue to tell us about your progress until 5 years after your transplant. You may say no at any time.

19. Can the Principal Investigator remove me from this research study?

You can be taken off the study (with or without your consent) for any of these reasons:

- Staying in the study would be harmful to you.
- You need treatment not allowed in this study.

- You do not follow directions.
- The FDA or study sponsors cancel the study.

20. How will my information be kept private?

The centers and doctors in charge of this study will keep your personal information as private as possible. They will do their best to see that it is shared only when required by state or federal law or the terms of this consent. It is impossible to promise total privacy.

In addition to following state and federal law, the organizations listed below may read or copy your records to make sure the study information is correct. Your research and medical records will have your name on them. They will include things such as your medical history, results of your blood tests and exams, as well as reports about your treatment and office visits. We will do all we can to keep your medical records private. Your name will not be used in any report of study results.

In order to understand the results of the study, people from the /Center Name/ and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center (DCC) will need to see medical records with your name on them. These people include:

- Doctors in the study,
- Transplant center committees,
- People (who are not doctors) who check the safety and progress of studies,
- Members of the Institutional Review Board (this committee safe-guards the rights of persons taking part in research), and
- People from the government (the National Institutes of Health and the Food and Drug Administration) might also need to see medical records with your name on them.

Your research and medical records may be shown to these organizations:

- /Institution/
- The National Institutes of Health (NIH)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Board (IRB)
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center (DCC), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

- The NCI-sponsored Cooperative Groups that enroll patients on this trial through the CTSU

For questions about access to your medical records, please contact /name / at/number/.

21. How long do you keep my information?

Study records will be kept indefinitely by the transplant center for re-analysis and follow-up.

If you have questions about the keeping of your research records or access to your files, please call /name/at /number/.

22. How will the researcher(s) benefit from your being in this study?

The researchers have no money invested in this study. But, in general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in the scientific press. In addition, the Principal Investigator is being paid a small amount to cover the cost of performing the study at their Center.

23. HIPAA[1] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *Phase II Trial of Non-Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients with Relapsed Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response*.

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., CT scan, blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(*list hospitals, clinics or providers from which health care information can be requested)*

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

_____

_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. Ginna Laport Study Chairperson, and staff/laboratories at Stanford Hospitals and Clinics
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., TBD for quantitative PCR testing and Covance Laboratories, Inc. for measurement of rituximab blood levels.
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data and coordinating center, including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

24. Further Information

If you have further questions concerning this study at any time, you are free to ask your physician whose contact information is available on the cover page of this consent form.

If you have questions regarding your rights as a research participant, you may also contact a representative of the IRB at (XXX) XXX-XXXX.

Dr./Ms./Mr. _____ has explained the above matters to you and you understand that explanation. She/he has offered to answer your questions concerning the procedures involved in this study. You understand the purpose of this treatment as well as the potential benefits and risks that are involved. You have decided to volunteer after reading and understanding all the information on this form. You hereby give your informed and free consent to be a participant in this research investigation. Upon signing this form you will receive a copy.

25. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how privacy will be protected:

_____ _____
Signature of person obtaining consent Date

Consenting Adults

The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask the questions I have, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will receive a signed copy of this consent form.

Adult Consenting for Self. By signing this form, you voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

Signature of Adult Consenting for Self	Date

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to participate in this study. You are not waiving any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

Signature of Parent/Legal Representative	Date
Print Name of Legal Representative	Relationship to Participant

Participants Who Cannot Consent But Can Read and/or Understand about the Study

Although legally you cannot "consent" to be in this study, we need to know if you want to take part. If you decide to take part in this study, and your parent or the person legally responsible for you gives permission, you both need to sign. Signing below means that you agree to take part (assent). The signature of your parent/legal representative above means that he or she gives permission (consent) for you to take part.

Assent Signature of Participant	Date

APPENDIX TO PARTICIPANT CONSENT

RISKS AND TOXICITIES RELATED TO A HEMATOPOIETIC CELL TRANSPLANT

There are certain risks related to a blood stem cell transplant. There are risks from the medications and therapy you will receive as part of the conditioning for the transplant and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. In general, the majority of these side effects are temporary. In rare instances, permanent toxicity may occur.

Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
What it means: This type of side effect may occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.	What it means: This type of side effect may occur in 20% of patients or less. This means that 20 patients or less out of 100 might get this side effect.	What it means: This type of side effect does not occur very often, but can occur in less than 2% of patients. This means that 1 or 2 patients out of 100 might get this side effect.

Risks Related to the Transplant Conditioning Regimen

Fludarabine: This medication is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells.

Likely Side Effects	**Rare Side Effects**
• Lower white blood cell count with increased risk of infection • Lower platelet count with increased risk of bleeding • Anemia (low red blood cell count) • Feeling tired and sleepy	• Nausea (feeling sick to stomach) • Vomiting (throwing up) • Diarrhea (loose stools) • Feeling short of breath • Pneumonia • Numbness and tingling of the fingertips and toes • Difficulty thinking clearly • Trouble seeing or problems with your eyes • Coma

Rituximab (Rituxan): This medication is used to reduce cancer cells. Most side effects occur during the actual infusion of the drug. This typically can happen with your very first infusion of this drug. Your doctor or nurse may need to temporarily slow down or stop the drug infusion until your symptoms lessen.

Likely Side Effects	Less Likely Side Effects	Rare Side Effects
• Shaking chills • Fever • Itching	• Low blood pressure • Shortness of breath • Rash • Nausea/Vomiting • Diarrhea • Headache • Throat irritation • Night sweats • High blood sugar level	• Low blood counts • Tiredness • Pain from areas of lymphoma • Cardiac arrhythmia (abnormal heart rhythm) • Chest pain • Kidney failure • Angioedema (swelling) • Angina (chest pain) • Progressive Multifocal Leukoencephalopathy (PML) (fatal viral infection of the brain)

Common side effects associated with rituximab include a reaction such as fevers chills or shortness of breath during the actual infusion of the drug. A much less common side effect can be a severe allergic reaction called anaphylaxis, which could cause severe shortness of breath, low blood pressure or tightness in your throat. Rituximab can also temporarily cause a low white blood cell count and/or weaken your immune system for up to several months after your last dose of rituximab, which may increase your risk of infection during that time period.

Cyclophosphamide (Cytoxan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder (blood in your urine). A few patients may have bladder damage and bleeding for a longer time. You may be given large amounts of intravenous fluids through your central line to protect your bladder. The central line is placed just prior to receiving the cyclophosphamide (within a few days of the first dose). A bladder catheter (thin plastic tube) may be inserted into your bladder, if your physician thinks that it can help you. Cyclophosphamide slows the making of new blood cells. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. Cyclophosphamide also lowers your immune (defense) system and as a result you may have more infections. In a small number of patients, cyclophosphamide can damage the heart muscle causing the heart not to pump as well (heart failure). If this occurs you may have shortness of breath and have fluids build-up in your body. Cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced. Women who are still menstruating may

have irregular periods or may no longer have any periods. Whether you are a man or woman, this medication may greatly decrease your chances of being able to have a child.

Graft-versus-Host Disease (GVHD)

After the graft begins to function, there is a further risk of a reaction of the graft against your tissues. This reaction is called GVHD and may cause a skin rash, or abnormalities of the liver, or stomach. GVHD may cause nausea (feeling sick to your stomach), vomiting (throwing up), lack of appetite, stomach cramps, diarrhea (loose stools), and bleeding of the gut. Chronic GVHD may occur later after transplantation and may involve problems with the eyes, mouth, lips, throat and liver. Early (acute) or late (chronic) GVHD may become severe enough to result in death. GVHD is treated with drugs that weaken the immune system, and therefore make you more susceptible to infections.

Risks Related to the Medications Used to Help Prevent GVHD

NOTE: These drugs also decrease the risk of rejection of the donor cells.

Tacrolimus: This medication is used to try to prevent GVHD. The immediate side effects you may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. In rare cases, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. It may also cause nausea (feeling sick to your stomach) and vomiting (throwing up). Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidney is already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the mediation may not be given at all.

Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause you to have more infections (especially viral infections and pneumonia) for several months after transplant.

Risks and Procedures Related to the Transplant Procedure

The following risks are not specifically related to any one drug or the transplanted donor cells, but they are risks that are a part of the transplant procedure. The following applies to **ALL** patients.

Venipuncture: Although you may require a central venous catheter to donate cells, there may be an occasional need to have an intravenous catheter placed in your arm(s) or you may need to have blood withdrawn from the veins of your arm(s). Drawing blood from the arm may be associated with bleeding into the skin and may very rarely result in an infection.

Central Venous Catheter: A central venous catheter is a flexible sterile tube that can be placed into a large vein either under the collar bone or in your groin area so that blood can be withdrawn. This tube is placed under local anesthesia and will be placed just prior to receiving the cyclophosphamide/rituximab that is given during the cytoreduction process. Complications include blood clots and infection. Clotting may necessitate removal of the catheter or treatment of the clot by injecting a medicine that dissolves blood clots. If you develop an infection, you will require treatment with antibiotics. If the catheter is placed under the collarbone, other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs, brain and other organs can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Mouth Sores and Diarrhea: The chemotherapy causes irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea and you may need medication to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and radiation therapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: Although your major organs function well, it is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that cannot always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage can be life threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. It is rare, but your kidneys could be affected, causing anemia or high blood pressure. There is also a risk you may develop a second cancer including leukemia as a result of the chemotherapy, and/or your lymphoma. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant but can occur sometimes within five years after transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a drug that is often given to help eliminate this excess fluid. This drug may cause hearing loss and loss of body chemicals such as potassium and sodium.

Risk to the Unborn

The treatment that you are undertaking has not been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some form of effective birth control.

Sterility and Future Childbearing Potential for Men and Women

Chemotherapy may cause lasting effects on the reproductive potential of both men and women treated in this manner. It should be emphasized that your cancer treatment/therapy may cause your menstrual periods to become irregular or cease altogether. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use birth control. It is important that both men and women use birth control while on this study.

Risks Related to the Infusion of Peripheral Blood Stem Cells

The stem cell infusion is given similar to a blood transfusion. The infusion of stem cells usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. You will be given pre-medications just prior to the infusion to decrease the risk of a reaction. Common, less serious reactions for patients include mild wheezing, mild shortness of breath, back or chest pain or lightheadedness. In rare instances, a severe allergic reaction can occur called anaphylaxis, which could cause a drop in blood pressure or extreme difficulty in breathing. You will be monitored very closely.

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. HLA TYPING

HLA typing will be performed for all patients and donors in American Society of Histocompatibility and Immunogenetics (ASHI)-approved laboratories designated by the transplant centers. Minimum HLA typing for related donors must be performed by DNA methods for HLA-A and -B at intermediate resolution and DRB1 at high resolution. Minimum HLA typing for unrelated donors must be performed by DNA methods for HLA-A, -B, -C, and -DRB1 at high resolution consistent with NMDP standard procedures.

The donor must be either:

a. 6/6 HLA –A, B, and DRB1 matched sibling or
b. 8/8 HLA-A, B, C and DRB1 matched unrelated donor.

2. CHIMERISM

A 10 mL peripheral blood sample must also be obtained from the patient at weeks 4, 8, and 12, then at 6 and 12 months post-transplant.

3. MORPHOLOGY/CYTOGENETICS STUDIES

Unilateral bone marrow biopsies are required for pathology analysis and bone marrow aspirates are required for cytogenetic analysis prior to the conditioning regimen. Other bone marrow assessments as summarized in the schedule of evaluations (Chapter 4) do not require the inclusion of bone marrow morphology/cytogenetics unless the original diagnostic marrow or the baseline marrow documented abnormal morphology/cytogenetics.

Pathology and cytogenetic studies will be conducted per institutional guidelines.

4. GRAFT CHARACTERIZATION

Flow Cytometry and Immunoglobulin Monitoring: The hematopoietic stem cell content of the product (graft) should be determined using CD45-FITC and CD34-PE staining to identify stem cells within the WBC component of the product.

Assays: Blood for flow cytometry will be taken at the following time points: prior to HSCT, at 3 months, 6 months, and 1 year post-transplant. The following tests will be performed:CD3, CD4, CD8, CD19, CD20 and CD56; and quantitative immunoglobulins (IgM, IgG and IgA). These tests will be performed per institutional guidelines and in keeping with the BMT CTN MOP.

5. QUANTITATIVE POLYMERASE CHAIN REACTION (PCR)

Peripheral blood (10 mL) will be collected for determination of the presence of t(14;18) by quantitative PCR. PCR will be performed at the local transplant center according to institutional standards.

All other PCR t(14;18) assessments (i.e., all post-baseline samples at 3 months, 6 months, 1 year, and 2 years post-transplant) as summarized in the schedule of evaluations (Chapter 4) are not required to be obtained unless the patient had a positive test at any time from initial diagnosis.

Qualitative PCR assessment is acceptable if quantitative measurement is not possible.

6. RESEARCH SPECIMENS

BMT CTN research samples will be given unique bar code designations that cannot be linked back to the recipient.

Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the main protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

For Patients:
A 20 mL peripheral blood sample will be collected prior to transplant for future research testing and will be shipped to the BMT CTN Repository in compliance with the shipment procedures specified in the BMT CTN MOP and the 0701 Laboratory Sample Guide.

7. SERUM RITUXIMAB SAMPLES

Blood samples to test for serum rituximab levels will be collected from all patients. The first sample will be taken pre-transplant within 4 weeks prior to the initiation of conditioning therapy, then at 4 weeks, 3 months, 6 months and 1 year post-transplant.

At each time point, 3-5 ml of blood should be collected into a red/gray top vacutainer tube. It is strongly recommended that standard venipuncture techniques be used to collect these samples. In cases where venipuncture is not indicated, a central line is acceptable. Blood samples should be allowed to clot upright at room temperature for 30 minutes. (If using plain red top vacutainer with no clot activator, allow the blood to clot at room temperature for 60 minutes). Samples should be promptly centrifuged to isolate the serum (supernatant) from the red blood ccells at 1000 x g (approximately 2000 rpm) for at least 10 minutes. The serum should be placed into 1 mL aliquots, labeled and promptly frozen at -20º C or below.

Specimen Management
C/O Gualberto Flores
Immnochemistry Services
Covance Laboratories Inc.
3635 Concorde Parkway, Suite 100
Chantilly, VA 20151
Phone: (703) 245-2200 Ext. 5440
Fax: (703) 245-2291
Gualberto.flores@covance.com

TABLE C-1: SCHEDULE OF LABORATORY EVALUATIONS

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
HLA Typing	5 mL peripheral blood or according to institutional practice	Store according to institutional practice	Prior to conditioning therapy.	N/A	Transplant Center
Chimerism	10 mL peripheral blood or according to institutional practice	Store according to institutional practice	Four weeks, 8 weeks, 3 months, 6 months and 1 year post- transplant for patient.	N/A	Transplant Center
Pathology/ Cytogenetic Studies	Volume of bone marrow biopsy and aspirate determined according to institutional practice	Store according to institutional practice	Within 4 weeks prior to conditioning therapy. Bone marrow biopsies and aspirates must be done prior to the transplant, and at 3 months, 6 months, and yearly until 2 years post-HSCT only if previously documented bone marrow involvement prior to cytoreductive therapy or at time of clinical suspicion for progression.	N/A	Transplant Center
Flow Cytometry CD3, CD4, CD8, CD19, CD 20, CD56	Volume of graft determined according to institutional practice	Store according to institutional practice	Prior to infusion of allogeneic stem cell product and at 3 months, 6 months and 1 year post-HSCT.	N/A	Transplant Center
IgM, IgG, IgA Levels	Volume of blood determined according to institutional practice	Store according to institutional practice	Prior to infusion of allogeneic stem cell product and at 3 months, 6 months and 1 year post-HSCT.	N/A	Transplant Center
PCR for Presence of t(14;18)	10 mL peripheral blood (5 mL in each vacutainer)	For baseline sample: 2 x 6 mL lavender top EDTA vacutainers.	Any positive test from the time of diagnosis then required at study entry, then 3 months, 6 months, 1 year, and 2 years post-HSCT.	N/A	Transplant Center

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
Patient Research Specimen Nucleated Cells from Peripheral Blood	20 mL peripheral blood	No additional processing	Within 4 weeks prior to conditioning therapy. .	Peripheral blood tubes will be shipped on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of isolated of isolated viable PBMCs. Guidelines for specimen handling and shipment to the Repository is detailed in the BMT CTN MOP and 0701 Laboratory Sample Guide.	N/A
Serum Rituximab Samples	3-5 mL peripheral blood	Allow to clot for 30 minutes at room temperature, then obtain serum and freeze samples upright at or below -20°C	Within 4 weeks prior to conditioning therapy, then at 4 weeks, 3 months, 6 months, and 1 year post-HSCT	Ship on dry ice to Covance Laboratories Inc. in compliance with shipping procedures specified in the BMT CTN MOP and Laboratory Sample Guide	Covance Laboratories, Inc.

APPENDIX D

SUGGESTED GUIDELINES FOR RITUXIMAB ADMINSTRATION

APPENDIX D

SUGGESTED GUIDELINES FOR RITUXIMAB ADMINSTRATION

Protocol Consent Signed: ____ Yes

Patient Name:_____ Diagnosis:_____

Height:_____cm Weight: _____kg BSA: _____m^2

Allergies:_____

Premedications:

1. Acetaminophen 650 mg po
2. Diphenhydramine 25-50 mg po or IVPB

DOSE #1:

RITUXIMAB (375 mg/m^2) _____mg in NS (at a final concentration of 1 mg/mL) on Day -13_____.

DOSES # 2, 3 and 4:

RITUXIMAB (1000 mg/m^2) _____mg in NS (at a final concentration of 1 mg/mL) IVPB on Day -6_____, Day +1_____ and Day +8_____.

Rituximab is stable 12 hours after removal from the refrigerator and has a combined stability (refrigerator plus room temperature) of 36 hours.

Infuse at increasing rates only if:

- SBP within 20 mmHg of baseline
- Pulse > 60 or < 120
- Temp < 38 C

If any of the following occurs: Fever (temp > 38.5 C), rigors, hypotension, and/or mucosal congestion/edema, **HOLD** infusion until improvement of symptoms.
When symptoms improve, resume infusion at HALF the previous rate.

Standard Rate for 1st Dose:

- 50 mL/hr for 1 hr, THEN
- 100 mL/hr for 30 min (if VS as noted above), THEN
- 150 mL/hr for 30 min (if VS as noted above), THEN
- 200 mL/hr for 30 min (if VS as noted above), THEN
- 250 mL/hr for 30 min (if VS as noted above), THEN
- 300 mL/hr for 30 min (if VS as noted above), THEN
- 400 mL/hr (MAX RATE) for remainder (if VS as noted above)

Rates for Doses # 2, #3 and #4:
Infuse at INCREASING rates:

- 100 mL/hr for 30 min (if VS as noted above), THEN
- 200 mL/hr for 30 min (if VS as noted above), THEN
- 300 mL/hr for 30 min (if VS as noted above), THEN
- 400 mL/hr for (MAX RATE) for remainder (if VS as noted above)

If patient is unable to tolerate faster rates, continue rituximab at the best tolerated rate until the infusion is complete.

Medication as Needed (PRN)

1. **Acetaminophen** 650 mg po every 4 hours prn for temp > 38 C for 48 hrs only after each RTX infusion. (Note: max dose of acetaminophen = 4 gm/24 hrs)
2. **Meperidine** 25 mg IV every 2 hrs prn chills (if chills persist, call MD).
3. **Diphenhydramine** 25 mg in NS 50 mL IVPB every ____ hrs prn rigors and/or allergic reaction.

Vitals Signs
Per institutional guidelines.

Suggested Anaphylactic Precautions/Medications
Prior to administering rituximab have the following medications IMMEDIATELY available and give if anaphylaxis occurs:

1. Hydrocortisone 100 mg IV
2. Diphenhydramine 25 mg IV
3. Epinephrine (1:1000) 0.5 mL IV

Attending Physician Signature:_____

Pager:_____ Date:_____ Time:_____

APPENDIX E

ADVERSE EVENT REPORTING GUIDELINES

APPENDIX E

ADVERSE EVENT REPORTING GUIDELINES

An adverse event (AE) is an unplanned, unwanted event which occurs to a study participant and which is possibly related to the use of protocol therapy. While some events may not initially appear to be associated with the use of the study treatment, a relationship may not emerge until sufficient numbers of reports accumulate from various Transplant Centers.

It is BMT CTN policy that adverse events must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment.

ADVERSE EVENT DEFINITIONS

Adverse Event - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of definite, probable, possible, unlikely, or unrelated).

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

Serious Adverse Event (SAE) - Any adverse event that results in any of the following outcomes: death, a life threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected Adverse Event - Any adverse event, the specificity or severity of which is NOT listed in the study protocol, product inserts or informed consent document.

Attribution - The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

Definite — The adverse event is ***clearly related*** to the study drug/device/procedure/ treatment(s).

Probable — The adverse event is ***likely related*** to the study drug/device/procedure/ treatment.

For BMT CTN studies: the adverse event is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship.

Possible — The adverse event ***may be related*** to the study drug/device/procedure/ treatment(s).

For BMT CTN studies: the adverse event could be attributed to the subject's underlying medical condition or other concomitant therapy, but the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/treatment administration lead the investigator to believe that there could be a causal relationship.

Unlikely — The adverse event is ***doubtfully related*** to the study drug/device/ procedure/treatment(s).

Unrelated — The adverse event is ***clearly NOT related*** to the study drug/device/procedure/ treatment(s).

For BMT CTN studies: the adverse event is most plausibly explained by the subject's underlying medical condition or other concomitant therapy, or the adverse event has no plausible biological relationship to study drug/device /treatment.

Common Terminology Criteria Adverse Events (CTCAE) – a descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term. An appendix for grading BMT-related complex/ multi-component events is included. A copy of the CTCAE guidelines is located at http://ctep.cancer.gov/reporting/.

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Unexpected Adverse Events

Exhibit E-1 provides unexpected adverse event reporting requirements for study centers participating in a Phase II or III BMT CTN study. Adverse events should be reported using CTCAE terminology and severity scales. Unexpected adverse events that occur within 2 years post-transplant should be reported.

Reporting requirements are calibrated to the severity of the event and the perceived relationship of the event to the study drug/device/treatment. All Grade 3-5 unexpected adverse events must be reported to the BMT CTN DCC in an expedited manner irrespective of the attribution of the event to the study drug/device/procedure/treatment.

In general, investigators should report adverse events as diseases or syndromes whenever possible, instead of reporting individual component symptoms, signs, laboratory abnormalities, and sequelae.

Expected Adverse Events

Exhibit E-2 provides expected adverse event reporting requirements for study centers participating in a Phase II or III BMT CTN study. Adverse events should be reported using CTCAE terminology and severity scales.

All fatal (Grade 5) expected adverse events will be reported in an expedited manner to the DCC. Most protocol-specific life-threatening or disabling (Grade 4) and other non-fatal expected adverse events will be reported on study forms submitted on a defined forms submission schedule. Grade 4 adverse events not collected on study forms should be reported in an expedited manner.

In addition, each protocol team must develop an interim analysis plan using the CTCAE grading scale (or Bearman scale if appropriate) to monitor protocol-specific expected adverse events. The plan will be included in the study protocol.

The Protocol Coordinator and Medical Monitor will review the adverse events monitored for stopping guidelines on a regular basis to be specified in the protocol, but at least monthly.

Additionally, the Protocol Coordinator and Medical Monitor will review events reported on the protocol-specific toxicity form (see below) and the GVHD forms on a regular basis to assess whether there are safety concerns that should be referred to the DSMB. The Medical Monitor may seek additional guidance from one of the MD DCC Principal Investigators (PI) in these assessments as long as the DCC PI‘s institution is not participating in the protocol under consideration.

Monitoring Adverse Events

Unexpected Adverse Events
Unexpected adverse events will be reported via a web-based AE system. Protocol Coordinators will review daily all submitted unexpected adverse events and forward the information to the Medical Monitor for review.

All unexpected adverse events will be reviewed by the Medical Monitor at, or associated with the DCC, within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, transplant centers will have 4 business days to respond to the request for additional information.

The Medical Monitor has medical expertise relevant to the study protocol and may request the participant's treatment assignment when reviewing the adverse event. The Medical Monitor or

DCC representative is responsible for notifying the NHBLI Project Officer immediately of all Grade 3-5 unexpected adverse events and of any concerns regarding the frequency or type of adverse event(s) on a study or study treatment arm. The NHLBI Project Officer (or designee) is responsible for reviewing the adverse event materials to determine if the materials are complete. If there are any concerns regarding the type or frequency of the event, the NHLBI Project Officer will request that the DSMB Executive Secretary notify the DSMB Chair. The DSMB Chair will review the adverse event materials, determine if the information is complete, determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study. Full documentation of the procedures will be available at the DCC.

The DCC will prepare semi-annual summary reports of all unexpected adverse events for the NHLBI Project Officer and DSMB Chair. Semi-annual reports will be made available on a secure website and the NHLBI Project Officer and DSMB Chair will be notified by e-mail when the materials are posted.

Expected Adverse Events

The DCC will prepare semi-annual summary reports of all Grade 5 expected adverse events for the NHLBI Project Officer and the DSMB Chair. Semi-annual reports will be made available on a secure website and the NHLBI Project Officer and DSMB Chair will be notified by e-mail when the materials are posted. Grade 3-5 expected adverse events defined in the interim analysis plan will be reported as defined in the protocol.

Any concern regarding the type or frequency of a Grade 3-5 expected adverse event will be reported to the NHLBI Project Officer who will determine if referral to the DSMB is warranted. If required, data materials will be provided by the DCC. The DSMB Executive Secretary will arrange for review by the DSMB Chair. The Chair will determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study.

The DCC will ensure that any additional reporting requirements defined by the NHLBI Project Officer, DSMB Chair and other oversight groups are identified and implemented.

The DCC in collaboration with the NHLBI Project Officer will determine the exact content of these summary reports and the reporting schedule.

EXHIBIT E-1

REPORTING UNEXPECTED ADVERSE EVENTS ON A BMT CTN PHASE II OR III STUDY

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENTS
5 - Fatal 4 - Life-threatening or Disabling	All attributions	Submit unexpected adverse event form to the DCC within 24 hours of the event. For Grade 5, also submit study death form to the DCC. Submit a summary of the adverse event to the DCC within 4 working days. For Grade 5, the summary should include potential contributing causes of death. Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/treatment, resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse event.
3 – Severe	All attributions	Submit unexpected adverse event form to the DCC within 3 working days of the adverse event. Submit a summary of the adverse event to DCC within 4 working days
	Definite Probable Possible	Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/treatment, resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse event. Multiple recurrences of the same adverse event should be reported separately.
	Unlikely Unrelated	Information reported for the adverse event must include: name of adverse event, date of first onset, peak severity, and relationship to the study drug/device/treatment. Multiple recurrences of the same adverse event should be reported together. *Note: Any adverse event prompting a change in the administration of study drug/device/treatment must include resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse event.*

EXHIBIT E-2

REPORTING EXPECTED ADVERSE EVENTS ON BMT CTN PHASE II OR III STUDIES

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENT
5 – Fatal	All attributions	Submit study death form to the DCC within 24 hours of death. Submit death summaries and/or autopsy reports of the expected adverse event to DCC quarterly or as requested. The summaries should include potential contributing causes of death.
4 – Life-threatening or disabling	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date. If the event is not captured on a study from, report using the AE system in an expedited manner. *Note: Selected Grade 3-5 events will be tracked and regularly monitored by the DCC and DSMB as specified in protocol-specific monitoring plans.*
3 – Severe	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date.

ADVERSE EVENT REPORTING AND MANAGEMENT

Because all or most study participants in BMT CTN trials will be receiving potentially toxic preparative therapy, significant regimen-related toxicity is anticipated. Study CRFs are designed to capture information on these adverse events. Likewise, substantial mortality is anticipated and will be captured via filing of appropriate CRFs. All unexpected adverse events must be reported for the duration of the studies.

The Protocol Coordinator will review both expected and unexpected toxicities with the Medical Monitor on a regular basis. The Medical Monitor may seek guidance from one of the MD DCC Principal Investigators (PI) in these assessments as long as the DCC PI 's institution is not participating in the protocol under consideration.

Monitoring Toxicity

The Protocol Team for each study develops a protocol-specific Toxicity Form. The items on the Toxicity Form are a subset of the CTCAE Version 3.0 relevant to the particular study. The Toxicity Form is submitted at regular time intervals defined by the Protocol Team.

GENENTECH REPORTING

Unexpected grade 3-5 adverse events (AE) will be reported by the Data and Coordinating Center, password-protected e-mail attachments, to Genentech Drug Safety twice per year (Tel: 888-835-2555; Fax: 650-225-4682 or 650-225-4683). Annual reports listing expected toxicities will be reported by password-protected e-mail attachments.

APPENDIX F

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

Important

This protocol does not follow the standard CTSU participation procedures for regulatory collection or patient enrollment. The flow chart on the next page illustrates the 0701 site activation and patient enrollment process.

SITE ACTIVATION FLOW CHART

Document Access

1. Download protocol and regulatory documents (including BMT CTN 0701 Affiliate Center Application Form) from the members' section of the CTSU website at www.ctsu.org

↓

Pre-Approval

1. Fax the Affiliate Center Application Form to BMT CTN Data and Coordinating Center (DCC)/EMMES at 240-306-0963

2. Receive pre-approval authorization email from BMT CTN DCC/EMMES

3. Fax the draft consent form to BMT CTN DCC/EMMES at 240-306-0964

4. Submit the protocol to local IRB then complete the following steps:

↓

Regulatory Document Submission

(Steps 1 and 2 may be done in parallel)

1. Complete the regulatory documents as specified in Table 1: Regulatory Documents Collected by CTSU, and submit these documents to the CTSU

2. Complete the study-specific documents/procedures as specified in Table 2: Study-Specific Document/Procedures Collected by the DCC/EMMES

3. Receive activation notification from EMMES upon completion of documents in Tables 1 and 2

↓

Patient Enrollment

1. Enroll patient via AdvantageEDC system
   (DCC/EMMES will forward information needed for enrollment funding and audit to the CTSU for further transmission to the Cooperative Group credited with the enrollment.)

REGISTRATION

Investigator / Research Associate Registration

1) Obtaining a CTEP-IAM account

All participating investigators and research staff must be registered members of the CTSU. Access to the members' section of the CTSU web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system. To register:

- Go to the CTSU web page at www.ctsu.org and click on the Register tab on the upper right of your screen and follow links to the CTEP-IAM application, OR, go directly to https://eapps-ctep.nci.nih.gov/iam/ and click on the "New Registration" link on the left hand side of your screen and click on "Request New Account".
- Complete CTEP-IAM application instructions
- You will receive an email from the CTSU providing the status of your application within 2 to 3 business days. Once you receive your email from the CTSU, you may use your new CTEP-IAM username and password to access the members' section of the CTSU web site.

2) (Investigators Only) Obtaining an NCI Investigator number

Before the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV [signed and dated], Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU web site (logon to www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Site Pre-Approval by BMT CTN

(Note: Sites are strongly advised to consider whether they are capable of enrolling, at minimum, two patients per year to this trial, before proceeding with IRB approval.)

Before submitting this study to your local IRB, your site must first be pre-approved for participation by the BMT CTN:

1) Download the BMT CTN Protocol #0701 Affiliate Center Application form from the site registration forms section of the 0701 web page on the members' section of the CTSU web site at www.ctsu.org.

2) Complete the Affiliate Center Application and fax, as indicated on the form, to the BMT CTN Data and Coordinating Center (DCC)/EMMES.

3) Once you receive notification from the DCC/EMMES that your center has been pre-approved, fax or email the draft informed consent form to the BMT CTN 0701 protocol coordinator at EMMES. The BMT CTN DCC will also notify the CTSU Regulatory Office when your site is pre-approved.

4) The BMT CTN DCC will notify you when you are able to proceed with Site Registration.

Site Registration

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit the CTSU IRB Certification Form to the CTSU Regulatory Office in Philadelphia before patient enrollments may commence.

Tables 1 and 2 at the end of this appendix outline the documents to be collected by the CTSU Regulatory Office and the documents/procedures required by the BMT CTN Data and Coordinating Center (DCC), respectively. It is recommended that the site fulfill CTSU and BMT CTN DCC requirements in parallel. The CTSU Regulatory Office and BMT CTN DCC will share documentation and information regarding the status of all registering sites.

Fulfilling CTSU Requirements for Site Registration (Table 1)

1) Download site registration forms from the 0701 Web page located on the members' section of the CTSU web site:
   - Go to www.ctsu.org
   - Enter user name and password under "Members Login" section on the left portion of the screen
   - Click on the Protocols tab in the upper left of your screen
   - The protocol browser uses a "tree-based navigation" structure that allows users to browse through the available protocols within the CTSU by using the drill-down capability of the tree.
   - Drill down By Lead Organization (BMT CTN) or By Cancer Type (Lymphoma) or By Study Type (Cancer Treatment or Phase II) and select trial #0701
   - Click on the Site Registration Documents link
   - Download and complete the following forms:
     - CTSU IRB/Regulatory Transmittal
     - CTSU IRB Certification Form
     - BMT CTN 0701 Financial Disclosure Form

- Mail or FAX completed forms **along with the other required items listed in Table 1** to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone - 1-866-651-2878
FAX – 215-569-0206

2) Checking Your Site's Status for Table 1 Requirements

Check the status of your registration packets by querying the RSS site registration status page of the CTSU web site.
- Go to www.ctsu.org
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

3) Notifying the BMT CTN

CTSU Operations will send an email notification to the BMT CTN Data and Coordinating Center (DCC) upon approval of your site's regulatory documentation.

Fulfilling BMT CTN Requirements for Site Registration (Table 2)

1) Complete the documents and procedural requirements as specified in Table 2. Contact the BMT CTN 0701 protocol coordinator if questions arise.

Notification of Site Approval

1) The BMT CTN DCC will notify your site and the CTSU once all registration requirements have been met and enrollments may commence.

Patient Registration

The BMT CTN DCC will grant user rights to the AdvantageEDC^{SM} system for performing patient enrollments. (Note: users must be certified by the DCC prior to assignment of rights. Refer to the AdvantageEDC webcast and practicum information in Table 2 for certification requirements). Follow the BMT CTN guidelines in Section 4.1 of the protocol for patient enrollment procedures.

DATA SUBMISSION AND QUALITY ASSURANCE

The study protocol and supporting materials are posted on the 0701 Web page located on the members' section of the CTSU web site (www.ctsu.org). All study data must be entered using the BMT CTN AdvantageEDC system. Hard copies of study data forms will not be accepted by

the BMT CTN DCC. Data validation and quality assurance will also be managed via AdvantageEDC.

ADVERSE EVENT REPORTING

Sites will assess adverse events in accordance with the guidelines outlined in the protocol. Adverse event reporting will be conducted through an expedited AE reporting system within AdvantageEDC.

Sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Table 1: Regulatory Documents Collected by CTSU Regulatory Office

1. Evidence of approved allogeneic transplant center status	One of the following is required: -FACT credentialed allogeneic transplant center -NMDP-approved allogeneic transplant center -Cooperative Group-approved allogeneic transplant center
2. BMT CTN Financial Disclosure Form	Signed Financial Disclosure for Principal Investigator for protocol 0701
3. Lab Normals	High and low normal lab values valid at the time of initial center approval.
4. CLIA and/or CAP certification	Valid at the time of initial center approval
5. CTSU IRB/Regulatory Approval Transmittal Form	Standard CTSU cover sheet
6. CTSU IRB Certification Form	Standard form to document local IRB approval
7. Final Approved Consent Form, stamped	A copy of the stamped IRB-approved Informed Consent Form for protocol 0701

Table 2: Study-Specific Documents/Procedures Collected by the Data and Coordinating Center (DCC)/EMMES

1. Affiliate Application	**For Site Pre-Approval:** Application for participation as an Affiliate Center in the BMT CTN. The Affiliate Application may be downloaded from the site registration documents section of the 0701 page of the members' section of the CTSU website. The Affiliate Application must be approved prior to centers submitting any other documentation for protocol 0701
2. Preview of consent form	A copy of the consent form for review/approval prior to IRB submission
3. Study Roster	A listing of names, phone numbers and email addresses of staff participating on protocol 0701, including PI, Clinic Coordinator, Data Coordinator, Lab Coordinator and Pharmacist
4. EMINENT Clinical Site Contact Form	A copy of the EMINENT Services Clinical Site Contact Information Form
5. AdvantageEDC Webcast Training	Mandatory attendance at one AdvantageEDC (electronic data capture system) webcast training by each staff member responsible for enrolling patients and completing supplementary follow-up forms
6. AdvantageEDC Practicum	Mandatory completion of one AdvantageEDC Practicum by each staff member that attended webcast training
7. GlobalTrace Webcast Training	Mandatory attendance at one GlobalTrace (specimen shipping system) webcast training by each staff member responsible for shipping samples
8. Pre-Study Site Initiation Conference Call/Visit	Mandatory pre-study site initiation call/visit to discuss protocol 0701

APPENDIX G

REFERENCES

APPENDIX G

REFERENCES

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