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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7 Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin
8 National Cancer Institute
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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
Roswell Park Cancer Institute
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University of Wisconsin Hospital and Clinics
Vanderbilt University Medical Center
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

Cathy Gurgol, Data Manager/Protocol Monitor
BMT CTN Data and Coordinating Center (DCC)
The EMMES Corporation
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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
1-888-651-CTSU (2878)
CTSU General Information Line 1-888-823-5923 OR
ctsucontact@westat.com

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.

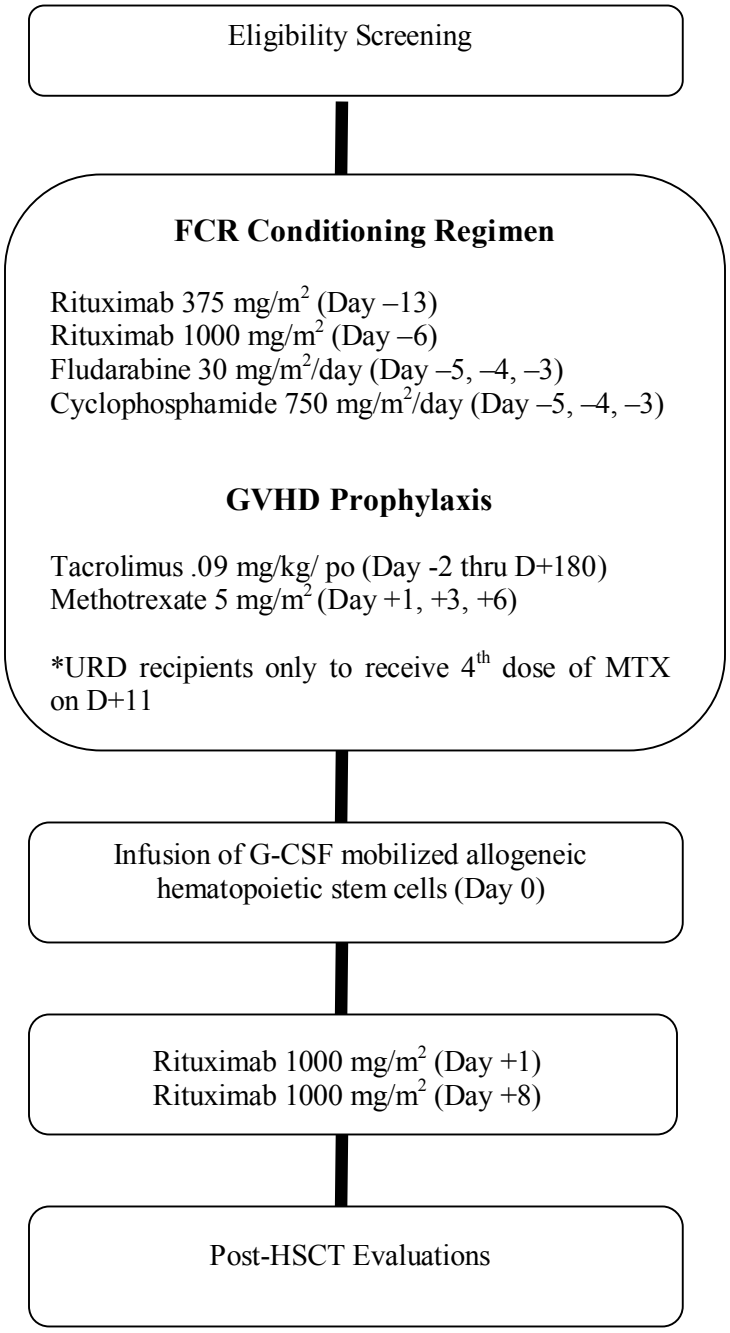
Eligibility Criteria: Eligible patients are ≤ 75 years of age with Karnofsky performance status ≥ 70% who have histologically confirmed recurrent follicular lymphoma (REAL classification follicle center follicular grades I and II or patients with histologically confirmed WHO classification follicular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

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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

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.

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.