Phase III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-cell Non-Hodgkin's Lymphoma

BMT CTN PROTOCOL 0401
VERSION 8.0

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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
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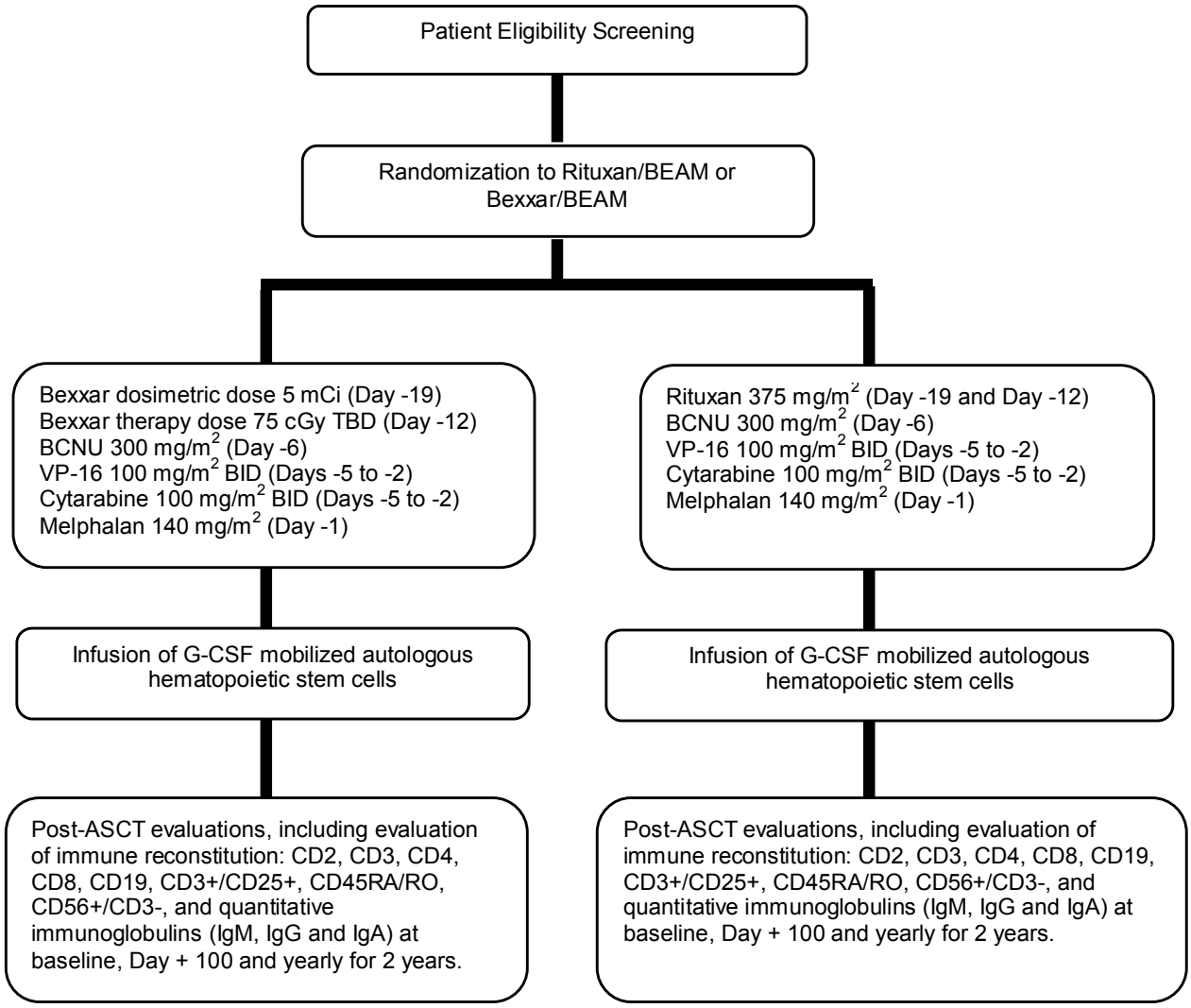
PROTOCOL SYNOPSIS - BMT CTN PROTOCOL #0401

Phase III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-Cell Non-Hodgkin's Lymphoma

Study Chairperson:	Julie M. Vose, M.D.
Primary Objective:	The primary objective of this study is to compare progression-free survival (PFS) after autologous hematopoietic stem cell transplantation (ASCT) for chemotherapy-sensitive diffuse large B-cell lymphoma using Rituxan/BEAM versus Bexxar/BEAM for pre-transplant conditioning.
Secondary Objectives:	Secondary objectives for the comparison are overall survival, time to progression, complete response (CR) and partial response (PR) proportion at Day 100, time to hematopoietic recovery, hematologic function, incidence of infection, maximum mucositis score by Day 21, immune reconstitution, treatment-related mortality, and development of myelodysplasia, secondary acute myelogenous leukemia, or abnormal cytogenetics.
Study Design:	This study is designed as a Phase III, multi-center trial, comparing PFS after autologous hematopoietic stem cell transplantation using a standard Rituxan plus BEAM transplant regimen versus a regimen adding Bexxar to BEAM.
Accrual Objective:	The trial will accrue 224 patients randomized equally between two treatment arms.
Accrual Period:	The estimated accrual period is two years.
Eligibility Criteria:	Eligible patients are 18-80 years of age with Karnofsky performance status $\geq$ 70% that have persistent or recurrent diffuse large B-cell lymphoma. Patients must have received 1-3 prior treatment regimens, including an induction chemotherapy and $\leq$ 2 salvage regimens. Monoclonal antibody therapy and local radiation will not be counted as prior therapies. Patients must have chemosensitive disease as demonstrated by at least a partial response (as defined by the criteria in Chapter 3) to induction or salvage chemotherapy. Patients must also have $\leq$ 20% BM involvement after their most recent salvage therapy. Patients cannot have transformed follicular lymphoma, evidence of MDS/AML, had prior autologous or allogeneic HSCT, or received prior radioimmunotherapy. Patients must also initiate conditioning therapy within 3 months of mobilization. Mobilization therapy may be employed per institutional guidelines, but all patients must receive one dose of Rituxan (375 mg/m^2) within 3 months prior to actual stem cell apheresis. Patients must have an adequate autograft (target $\geq$ 2.0 X

	10^6 CD34+ cells/kg; minimum $\geq$ 1.5 X 10^6 CD34+ cells/kg) to be eligible for the protocol.
Treatment Description:	Eligible patients will be randomized to receive either: 1.) Rituxan plus BEAM, with Rituxan 375 mg/m^2 IV Days -19 and -12, BCNU 300 mg/m^2 Day -6, Etoposide 100 mg/m^2 BID Days -5 to -2, Cytarabine 100 mg/m^2 BID Days -5 to -2, and Melphalan 140 mg/m^2 Day -1 followed by ASCT; or, 2.) Bexxar/BEAM with the dosimetric dose of 5 mCi Bexxar on Day -19 and the therapeutic dose calculated to administer 75 cGy total body dose (TBD) on Day -12. Patients will then receive BCNU 300 mg/m^2 Day -6, Etoposide 100 mg/m^2 BID Days -5 to -2, Cytarabine 100 mg/m^2 BID Days -5 to -2, and Melphalan 140 mg/m^2 Day -1 followed by ASCT.
Study Duration:	Patients will be followed for at least two years post-ASCT.

TREATMENT SCHEMA



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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background – Autologous Hematopoietic Stem Cell Transplantation for Diffuse Large Cell Lymphoma

Forty-fifty percent of patients with diffuse aggressive non-Hodgkin's lymphoma (NHL) are cured with standard anthracycline-based combination chemotherapy. However, among those who fail to achieve remission or relapse, standard salvage chemotherapy is effective in producing long-term disease-free survival in no more than 10% [1-4]. Based on the Phase III Parma trial and other Phase II trials, high-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) has become the standard of care for patients with chemotherapy-sensitive relapsed diffuse aggressive NHL [5-7]. In this setting, standard high-dose therapy and ASCT produce disease-free survival rates of 35-50% [8, 9]. Relapse is the major cause of failure after ASCT for lymphoma. It is unknown whether residual disease in the patient or the reinfusion of viable tumor cells is the major contributor to relapse – or both [10, 11]. Rituximab, a chimeric monoclonal antibody targeting CD20, is effective in treating recurrent follicular and diffuse large cell lymphoma [12, 13]. Recently, it has become common to include Rituxan during mobilization and as part of the therapeutic regimen in an attempt to decrease post-transplant relapse risk.

The addition of rituximab to salvage chemotherapy and/or during mobilization has been associated with improved progression-free survival [14-16]. In addition, some studies have used rituximab in the post-transplant setting [17]. Based on these Phase II studies, the addition of rituximab has become standard of care in the pre-transplant setting at many transplant centers.

Radioimmunotherapy is a novel immunotherapy approach recently approved for the therapy of recurrent NHL. This treatment combines monoclonal antibodies directed against the CD20 antigen with a radioconjugate through a stable conjugate linker. Consequently, it combines the mechanisms of action of the monoclonal antibody, such as complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and apoptosis, with radioisotope emissions which are capable of killing not only the cell bound by the antibody, but also adjacent cells that may not bind antibody. Iodine 131 (I-131) Tositumomab (Bexxar, Corixa Corp, Seattle, WA, and GlaxoSmithKline, Philadelphia, PA) is a radioimmunoconjugate with demonstrated anti-lymphoma effects. This molecule is a murine IgG2a antibody radiolabeled with I-131 [18]. Multiple single agent trials of Bexxar in patients with relapsed NHL demonstrate an overall response (OR) rate of 60-80% and a complete response (CR) rate of 20-40% [19-21]. These encouraging single agent results led to trials combining radioimmunoconjugates with standard chemotherapy. Press et al [22] studied sequential CHOP chemotherapy followed by consolidation with Bexxar therapy. Bexxar did not appear to add significant toxicity; however, the CR rate was increased from 39% to 66% [22].

1.2. Bexxar as Myeloablative Radioimmunotherapy in Transplantation

Bexxar has also been used in high-dose chemotherapy and ASCT. One approach is "high dose" or myeloablative radioimmunotherapy transplantation, pioneered by Press et al [23]. In this method, trace-labeled biodistribution studies first determine the maximum absorbed radiation doses to tumor and normal organs such as lung, liver, and kidney. Subsequent therapeutic infusions of Bexxar are given in doses calculated to deliver specific absorbed radiation doses to these organs, followed by autologous stem-cell rescue. Follow-up of 29 patients receiving this therapy demonstrated that 14 remained in remission from 27+ to 87+ months following ASCT [24]. A Phase I/II trial of Bexxar combined with etoposide, cyclophosphamide, and ASCT was subsequently reported [25]. In this trial, 52 patients with relapsed NHL received 1.7 mg/kg Tositumomab labeled with an amount of I-131 calculated to deliver target doses of 20-27 Gy to critical normal organs, followed by etoposide, cyclophosphamide and ASCT. The maximum tolerated doses of this regimen were the combination of 60 mg/kg etoposide and 100 mg/kg cyclophosphamide delivered with 25 Gy to critical normal organs. The estimated overall and progression-free survival (PFS) of all treated patients at two years were 83% and 68%, respectively [25].

1.3. Phase I/II and Phase II Trials of Bexxar + BEAM and ASCT for Lymphoma

An alternative to myeloablative Bexxar regimens is to add standard outpatient doses of Bexxar to a high-dose chemotherapy regimen. Using this type of dosing methodology, the patients received a dosimetric dose with 450 mg of unlabeled Tositumomab intravenously followed by a trace-labeled 5mCi (35 mg) dose of Iodine I 131 Tositumomab. Within one hour of the dosimetric dose of Iodine I 131 Tositumomab and before urination, a whole-body quantitative gamma camera image was obtained for baseline. Additional scans were performed on Days 2, 3, or 4 and 6 or 7 after the dosimetric dose. The methodology for determining the patient-specific millicurie activity was performed in accordance with the Medical Internal Radiation Dose Primer for Absorbed Dose Calculations. One week later, on Day –12 of the transplantation protocol, the therapy dose of Iodine I 131 Tositumomab was administered. The patients received 450 mg of unlabeled Tositumomab followed by the patient-specific dose calculated for administration based on the whole-body gamma camera images. Patients treated in the Phase I trial started at a dose of 30 cGy total body dose and escalated by 15 cGy every 3 patients to a maximum of 75 cGy total body dose of Iodine I 131 Tositumomab. Additional patients were added at the maximum tolerated dose of 75 cGy. This has been studied in patients with relapsed NHL using Bexxar with BEAM chemotherapy (BCNU, etoposide, cytarabine, and melphalan) and ASCT. A Phase I/II study was conducted in 23 patients with chemotherapy resistant relapsed aggressive NHL [26]. Their median age was 51 years (range 26 to 65 years). Patients had autologous stem cells collected prior to the initiation of therapy. They subsequently received a Bexxar dosimetric dose on Day -19 and a Bexxar therapeutic dose administered in a range of 30 to 75 cGy total body dose on Day -12 of the transplant. The patients had an average dose rate following the therapeutic Bexxar dose of 10 Mr/hr at 1 meter. The rates ranged from 7-14 Mr/hr. Patients then received a standard BEAM transplant regimen (BCNU 300 mg/m^2 Day -6, cytarabine 100 mg/m^2 BID Days -5 to -2, etoposide 100 mg/m^2 BID Days -5 to -2, and melphalan 140 mg/m^2 Day -1) followed by re-infusion of their unmodified autologous stem cells on Day 0. At 12 days after the

Bexxar infusion and prior to the autologous stem cells being infused they had an average dose rate of 0.60 Mr/hr (range 0.4 – 0.6 Mr/hr) at 1 meter. Hematopoietic recovery was similar to historical controls treated with BEAM alone with median times to an absolute neutrophil count of > 500/mm^3 of 10 days, to platelet independence of 12 days, and to red blood cell independence of 9 days. There were no treatment related deaths. Non-hematologic toxicities were similar to historical controls except for a slightly higher mucositis score in the patients receiving Bexxar plus BEAM. Six of the 23 patients received consolidative radiation therapy of 3600 – 4000 cGy to areas of bulky (> 3 cm) that was present at the time of relapse. The radiation was delivered after recovery of the cytopenias post-transplant and before Day +100. There were no unexpected toxicities from the involved field irradiation. The CR rate was 59% and the OR rate, 68%. With a median follow-up of 38 months (range, 27 to 60 months), 11 of 23 patients progressed. The 3-year event-free survival was 39% and overall survival, 55%. Two patients developed myelodysplastic syndrome (MDS) at 26 and 29 months post-transplant. A subsequent Phase II clinical trial using the maximum 75 cGy total body dose (TBD) Bexxar + BEAM and ASCT is currently finishing accrual and near completion. This Phase II trial is in the indicated patient population of chemotherapy sensitive diffuse large B-cell lymphoma. Thirty out of the planned 40 patients have been entered on that trial at the University of Nebraska Medical Center. The patients entered in the Phase II study range in age from 25-73 (median 54 years). Ten of the 39 patients have received post-transplant involved field irradiation to areas of prior bulky disease ($\geq$ 3 cm) at the time of relapse. At the time of the last interim analysis, the complete response rate for patients on this protocol was 74% and the estimated 1-year event-free survival was 79% and overall survival 82%. The engraftment in this trial so far is also within normal limits as expected for the BEAM transplant protocol No increase in unexpected toxicities has been seen in this trial, other than the slight increase in mucositis as was seen in the Phase I/II trial.

1.4. In Vivo Purging with Rituximab

Contamination of the hematopoietic stem cell graft by tumor cells is thought to be one factor contributing to the relapse after ASCT. Treatment aimed at removing lymphoma cells from the autologous graft has been used in an attempt to reduce the rate of relapse. Approaches include various *in vitro* techniques including purging with B-cell monoclonal antibodies, chemotherapeutic agents such as mafosfamide or use of CD34$^+$ positive selection [27-30]. While all of these methods reduce the level of tumor cell contamination, most grafts remain PCR positive for lymphoma cells and there are no randomized trials to date strongly supporting the use of *in vitro* purging in this setting [31]. Additionally, *in vitro* purging methods are typically expensive, labor intensive, require reagents that are not generally available and can be associated with substantial cell losses [32]. For example, the negative selection approach used by Freedman *et al* required the use of 3 monoclonal antibodies and rabbit complement to achieve successful marrow purging [33]. Consequently, most ASCTs for lymphoma currently use unpurged grafts.

A recent promising strategy for reducing relapse is *in vivo* purging with rituximab (RTX). In contrast to *in vitro* purging methods aimed at removing contaminating tumor cells from the hematopoietic stem cell harvest, administration of RTX *in vivo* prior to leukapheresis depletes the peripheral blood of all CD20+ cells preventing contamination of the graft by lymphoma cells [34]. RTX is a human/mouse monoclonal antibody recognizing CD20+, an antigen expressed on

all cells of B cell lineage including B cell NHL [12]. RTX eradicates B cells by complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. It can induce apoptosis in CD20+ cells and may be synergistic with chemotherapy. RTX rapidly and efficiently clears B cells in the peripheral blood for more than three months [12]. This strategy has been effectively used in patients with previously treated aggressive and indolent lymphomas [12, 13].

RTX has been successfully incorporated into the hematopoietic stem cell mobilization regimen by several groups for the purpose of *in vivo* purging [16, 34-35]. RTX administration does not demonstrate any negative effects on hematopoietic stem cell yield or function; hematopoietic recovery is comparable following transplantation in purged versus unpurged patients [16]. The optimal timing and dosing of RTX administration during mobilization still remains to be clearly established but current reports have used from 1 to 4 doses. Due to these reports, rituximab use with transplantation has now become the standard of care at many transplant centers.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

All patients will receive induction or salvage chemotherapy as indicated by their clinical circumstance to achieve at least a partial response (as defined by the criteria in Chapter 3) prior to conditioning. There must be $\leq$ 20% bone marrow involvement after their most recent salvage therapy. All patients will undergo stem cell mobilization per institutional standards, but must receive one dose of Rituxan (RTX) 375 mg/m^2 within 4 weeks prior to actual stem cell apheresis. Patients for whom an adequate graft is collected will be randomized to receive ASCT using either a standard RTX plus BEAM regimen versus a regimen adding Bexxar to BEAM.

2.1.1. Hypothesis

The study is designed to test the null hypothesis that adding the radioimmunoconjugate Bexxar to the pre-transplant conditioning will not affect toxicity or efficacy of high-dose therapy and ASCT for diffuse large B-cell lymphoma.

2.1.2. Study Objectives

The primary objective is to compare PFS between the two transplant arms. Secondary objectives are to compare overall survival, time to progression, CR and PR proportion at Day 100, time to hematopoietic recovery, hematologic function, incidence of infection, maximum mucositis score by Day +21, immune reconstitution, treatment-related mortality, incidence of myelodysplastic syndrome (MDS), secondary acute myelogenous leukemia (AML), or abnormal cytogenetics between the two arms.

2.2. Patient Eligibility

Patients must meet specified eligibility criteria for entry into the study.

2.2.1. Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Diagnosis of persistent or recurrent REAL classification diffuse large B-cell lymphoma, composite lymphoma with > 50% diffuse large B-cell lymphoma, mediastinal B-cell lymphoma.
2. Demonstration of CD20+ on at least one histologic specimen.
3. 18-80 years old at time of first registration.

4. Three or fewer prior regimens of chemotherapy over the entire course of their disease treatment (including one induction chemotherapy and no more than 2 salvage chemotherapies). Monoclonal antibody therapy and involved field radiation therapy will not be counted as prior therapies.
5. All patients must have chemosensitive disease as demonstrated by at least a partial response (as defined by the criteria in Chapter 3) to induction or salvage therapy.
6. $\leq$ 20% bone marrow involvement.
7. Patients with adequate organ function as measured by:
    a) Cardiac: American Heart Association Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Additionally, patients > 60 years of age must have a left ventricular ejection fraction at rest $\geq$ 40% demonstrated by MUGA.
    b) Hepatic: Bilirubin $\leq$ 2.0 mg/dL (except for isolated hyperbilirubinemia attributed to Gilbert syndrome) and ALT and AST $\leq$ 3x the upper limit of normal.
    c) Renal: Creatinine $\leq$ 2.0 mg/dL or creatinine clearance (calculated creatinine clearance is permitted) > 40 mL/min; no hydronephrosis on CT scan prior to mobilization.
    d) Pulmonary: DLCO, FEV1, FVC $\geq$ 45% of predicted (corrected for hemoglobin).
8. Patients must receive one dose of Rituxan (375 mg/m^2) within 3 months prior to actual stem cell apheresis.
9. Autologous graft with a minimum of $\geq$ 1.5 x 10^6 CD 34^+ cells/kg (target $\geq$ 2.0 x 10^6 CD 34^+ cells/kg). Peripheral blood stem cells (PBSC) are preferred; however, if PBSC mobilization fails, cells can be obtained by institutional practices (in cases where bone marrow will be used for transplantation, the required CD34+ dose does not apply and institutional practice for total nucleated cell dose should be used).
10. Initiate conditioning therapy within 3 months of mobilization.
11. Signed informed consent.

2.2.2. Patient Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. Karnofsky performance score < 70%.
2. Transformed follicular lymphoma.
3. Uncontrolled bacterial, viral or fungal infection (currently taking medication and with progression or no clinical improvement).
4. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma *in situ*. Cancer treated with curative intent < 5 years previously will not be allowed unless

approved by the Medical Monitor or Protocol Chair. Cancer treated with curative intent > 5 years previously will be allowed.

5. Pregnant (positive β-HCG) or breastfeeding. This patient population is excluded due to the lack of data on the use of Bexxar in patients who are pregnant or breastfeeding.
6. Seropositivity for HIV. This patient population is excluded due to the lack of data on the use of Bexxar in HIV positive patients and because the treatment regimens are too immunosuppressive for this patient population.
7. Fertile men or women unwilling to use contraceptive techniques from the time of initiation of mobilization until six-months post-transplant.
8. Prior autologous or allogeneic HSCT.
9. Patients with evidence of MDS/AML or abnormal cytogenetic analysis indicative of MDS on the pre-transplant bone marrow examination.
10. Patients with a prior severe reaction to Rituxan or G-CSF. Patients with severe reactions to G-CSF that receive pre-medication for control of the reaction are not excluded from study.
11. Patients who have received prior radioimmunotherapy.
12. Known hypersensitivity to murine proteins.

2.3. Study Treatments

The immediate pre-ASCT evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study. Similarly, special orders and procedures will be those defined by the BMT CTN Manual of Procedures (MOP). All patients enrolled on this protocol will be hospitalized in accordance with the procedures for recipients of ASCT as defined by the treating institutions.

2.3.1. Cytoreductive Therapy/Mobilization Regimen

2.3.1.1. Mobilization regimen and Rituxan administration

Mobilization therapy may be employed per institutional guidelines, but all patients must receive one dose of Rituxan (375 mg/m^2) within 3 months prior to actual stem cell apheresis

2.3.1.2. Conditioning regimen – Rituxan/BEAM

Table 2.3.1.2: Rituxan/BEAM + ASCT Regimen

Day								
-19	**-12**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
Rituxan 375 mg/m^2	Rituxan 375 mg/m^2	BCNU 300 mg/m^2	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Melphalan 140 mg/m^2	ASCT

1. **Rituxan:** 375 mg/m^2 IV to be administered on Days -19 and -12. Mix RTX in either 0.9% NS or D5W, for a final concentration between 1-4 mg/mL. RTX must be infused through an infusion pump and should not be mixed or diluted with any other solutions or drugs. The RTX package insert should be consulted for specific infusion guidelines.
2. **BCNU:** 300 mg/m^2 on Day –6, to be administered per institutional guidelines.
3. **Cytarabine (Ara-C):** 100 mg/m^2 BID on Days –5 through –2, for a total of 8 doses, to be administered per institutional guidelines.
4. **VP-16:** 100 mg/m^2 BID on Days –5 through –2, for a total of 8 doses, to be administered per institutional guidelines.
5. **Melphalan:** 140 mg/m^2 on Day -1, to be administered per institutional guidelines.
6. **Conditioning Regimen Administration Schedule:** The conditioning regimen administration schedule may be modified ± 1 day according to institutional practice. Day 0 will be the day of ASCT.

2.3.1.3. Conditioning regimen – Bexxar/BEAM

Table 2.3.1.3: Bexxar/BEAM + ASCT Regimen

Day								
-19	**-12**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
Bexxar Dosimetric Dose	Bexxar Therapy dose 75 cGy TBD	BCNU 300 mg/m^2	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Melphalan 140 mg/m^2	ASCT

1. **Thyroid Blockade:** Patients will be treated with Saturated Solution Potassium Iodide (SSKI) 4 drops PO TID, Lugol's solution 20 drops PO TID, or potassium iodide tablets 130 mg PO QD starting at least 24 hours prior to the dosimetric dose of the Iodine I 131 Tositumomab and continuing daily for 14 days following the therapeutic dose of Iodine I 131 Tositumomab. In addition, 60–120 minutes before the dosimetric and therapeutic dose of Iodine I 131 Tositumomab all patients will be given an additional dose of medication for thyroid blockade. The SSKI or Lugol's solution may be given with juice or cola to mask its taste.

   In no instance should a patient receive the dosimetric dose of Iodine I 131 Tositumomab if they have not yet received at least three doses of SSKI, three doses of Lugol's solution, or one 130 mg potassium iodide tablet (at least 24 hours prior to the dosimetric dose). Patient compliance will be ascertained and documented prior to administration of the dosimetric dose and therapeutic dose.
2. **Bexxar:** Patients will receive a 5 mCi Iodine I 131-Tositumomab dosimetric dose on Day -19, followed by 3 whole body gamma scan images over the ensuing week (day of administration – prior to urination, Day 2, 3, or 4 following urination, and Day 6 or 7 following urination). On Day -12 the patient will receive the amount of Iodine I 131 Tositumomab calculated to administer 75 cGy Total Body Dose (see Section 2.7). Prior to receiving the Iodine I 131 Tositumomab dosimetric and therapeutic doses, the patient will be given 450 mg of Tositumomab infused over 1 hour on Days -19 and -12.
3. **BCNU:** 300 mg/m^2 on Day –6, to be administered per institutional guidelines.
4. **Cytarabine (Ara-C):** 100 mg/m^2 BID on Days -5 through -2 for a total of 8 doses, to be administered per institutional guidelines.
5. **VP-16:** 100 mg/m^2 BID on Days –5 through –2, for a total of 8 doses, to be administered per institutional guidelines.
6. **Melphalan:** 140 mg/m^2 on Day -1, to be administered per institutional guidelines.
7. **Conditioning Regimen Administration Schedule:** The conditioning regimen administration schedule may be modified ± 1 day according to institutional practice. Day 0 will be the day of ASCT.

2.4. Supportive Care

2.4.1. Post-ASCT

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

2.4.1.1. Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the post-ASCT 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 carinii: Per local institutional guidelines and must be uniformly applied to all patients within each respective center.
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.

2.4.1.2. 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.

2.4.1.3. Post-ASCT growth factors

All patients will receive G-CSF 5-10 mcg/kg beginning no later than Day +7 post-transplant until an ANC $\geq$ 500/mm^3 is obtained for 3 consecutive days. If patients fall below this level once the G-CSF has been stopped, it can be restarted. Patients that are known to experience severe reactions to G-CSF must be pre-medicated before administration.

2.4.1.4. Post-ASCT immunization schedule

Immunizations may be given in keeping with the BMT CTN MOP and local institutional practice.

2.4.1.5. Post-ASCT lymphoma therapy

Consolidative localized radiation therapy (maximum 3 sites) is allowed to areas of previous bulk disease (> 3 cm). Localized radiation should be completed by Day 100 post-transplant. No other anti-lymphoma therapy is allowed in the post-transplant setting or the patient will be considered to have progressed and will be off study. Specifically NO Rituxan maintenance therapy post-transplant is allowed.

2.4.1.6. Post-ASCT IVIg therapy

Administration of IVIg is not routinely used in autologous transplant patients.

2.5. Participant Risks

ASCT recipients incur risks from high-dose conditioning and post-ASCT therapy, which must be weighed against the risk of the disease for which the ASCT 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) 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), and as a result of destructive processes (e.g., infection), and may have a fatal outcome; brain damage can result in severe loss of cognitive or neurologic function; 3) Relapse or progression of lymphoma may occur, especially in patients with advanced disease status at time of treatment; 4) 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; and 5) Death.

2.6. 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.

2.6.1. Rituxan (Rituximab)

Rituxan (RTX) 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 myelosuppression, thrombocytopenia, fatigue and tumor pain. 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 RTX administration.

2.6.2. Bexxar (Tositumomab and Iodine I 131 Tositumomab)

The Bexxar therapeutic regimen is an anti-neoplastic radioimmunotherapeutic monoclonal antibody regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131 Tositumomab. The Bexxar therapeutic regimen consists of two discrete steps: the dosimetric and therapeutic steps. Each step consists of a sequential infusion of Tositumomab followed by Iodine I 131 Tositumomab. The likely side effects include myelosuppression and its sequelae (infections, hemorrhage). Less likely side effects include hypersensitivity reactions, and gastrointestinal toxicity including nausea, vomiting, abdominal pain and diarrhea. Uncommonly, a constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea has been reported during or within 48 hours of infusion. Also uncommonly, MDS, hypothyroidism, and the development of human anti-murine antibodies have been reported.

Bexxar will be supplied by GlaxoSmithKline free of charge. The administration and ordering instructions for Bexxar are outlined in Section 2.7 and Section 2.8, respectively.

2.6.3. Carmustine (BCNU)

Carmustine is an alkylating agent. Common side effects include myelosuppression, nausea, vomiting, headache, and jaw pain. Less common side effects include transient hypotension, dizziness, hyperpigmentation of the skin, hepatoxicity and a delayed inflammatory lung response (pneumonitis).

2.6.4. VP-16 (Etoposide)

VP-16 is a semi-synthetic podophyllotoxin derivative. Side effects that are likely to occur include nausea, vomiting and diarrhea, myelosuppression, mucositis, alopecia, and fatigue. Less likely side effects include a skin rash, peripheral neuropathy, and hepatotoxicity. Hypotension may occur if the drug is infused quickly. A rare but serious side effect is a small risk of developing a second cancer.

2.6.5. Cytarabine (Ara-C)

Cytarabine, commonly known as Ara-C, is a synthetic nucleoside. Likely side effects include myelosuppression, nausea, vomiting and diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash, and thrombophlebitis. Less likely side effects include conjunctivitis (when Ara-C is given at high doses, and preventable by the prophylactic use of corticosteroid eye drops), abdominal pain, alopecia, pruritis, headache, and the occurrence of a cytarabine syndrome characterized by fever, myalgias, arthralgias, chest pain, maculopapular rash, conjunctivitis and malaise - this syndrome occurs 6-12 hours following drug administration. Corticosteroids are beneficial in treating this syndrome. A rare but serious side effect is cerebral/cerebellar dysfunction (more common at very high doses and in older patients).

2.6.6. Melphalan

Melphalan, an alkylating agent, is a phenylalanine derivative of nitrogen mustard. At high doses, the likely toxicities include myelosuppression, gastrointestinal toxicity and alopecia. The duration of profound myelosuppression decreases with the use of stem cell transplantation and colony stimulating factors. Gastrointestinal toxicity, which includes potentially severe stomatitis, esophagitis and diarrhea, may require intravenous narcotics for mucositis related pain, intravenous hydration and alimentation, and antibiotics. Less likely is hepatotoxicity. Rare but serious toxicities reported include pulmonary fibrosis and interstitial pneumonitis, veno-occlusive disease of the liver, skin hypersensitivity, vasculitis, hemolytic anemia, allergic reactions, and a small risk of developing second cancers.

2.6.7. G-CSF (Filgrastim)

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. G-CSF stimulates the production, maturation and activation of neutrophils and activates neutrophils to increase their migration and cytotoxicity. Toxicities that are likely to occur include myalgias and medullary bone pain. The bone pain can be generally controlled with non-narcotic analgesia. Less likely side effects include fluid retention, pericardial effusion, local inflammation at the injection site and transient laboratory abnormalities including mild elevations in uric acid, lactic dehydrogenase (LDH), alkaline phosphatase, and leukocytosis. Rare but serious side effects include reported cases of spleen swelling resulting in splenic rupture, adult respiratory distress syndrome (ARDS) and allergic reactions.

2.7. Bexxar Administration

2.7.1. Dosing Schema

Patients will undergo two dosing phases. The first phase, termed "dosimetric dose," involves the IV administration of a low radioactive dose (5 mCi) of Iodine I 131 Tositumomab for the purpose of determining the rate of whole body clearance of radioactivity (residence time) so that the amount of radioactivity to deliver a 75 cGy total body radiation dose can be calculated (see Table 2.7.4.2). The calculated activity of Iodine-131 conjugated with Tositumomab will then be administered to deliver a 75 cGy total body radiation dose in the second phase of the study, termed "therapeutic dose." Patients who are obese will be dosed upon 137% of their lean body mass.

Both the dosimetric dose and the therapeutic dose will be immediately preceded by an IV infusion of 450 mg Tositumomab. Patients will be treated with a thyroid blockade medication starting at least 24 hours prior to the dosimetric dose of the Iodine I 131 Tositumomab and continuing daily for 14 days following the therapeutic dose of Iodine I 131 Tositumomab.

Administration of Iodine I 131 Tositumomab will be performed by personnel that have been trained and authorized to deliver such doses of radioisotope to patients. Special radiation precautions will be used during and after the administration of the radioimmunotherapy dose, as

required by the national and/or regional regulations for the radiopharmaceutical industry. Restrictions on patient contact with others will be set in accordance with these regulatory guidelines (NRC and state laws). The dosimetric and therapeutic doses may be given as either an outpatient or in-patient procedure depending on current NRC and state regulations.

Table 2.7.1
Iodine I 131 Tositumomab (Dosing Schema)

Time Relative to the Dosimetric Dose (Day 0)	Administration
Day –20	Initiate daily administration of oral iodine product for thyroid blockade at least 24 hours prior to dosimetric dose and continuing through 14 days post therapeutic dose
Day -19	Dosimetric dose[a] Thyroid blockade 60–120 minutes before Iodine I 131 Tositumomab infusion 450 mg of Tositumomab infused over 1 hour 5 mCi of Iodine I 131 Tositumomab infused over 20 minutes followed by a 10 minute saline flush
Day-12	Therapeutic dose[a] Thyroid blockade 60–120 minutes before Iodine I 131 Tositumomab infusion 450 mg of Tositumomab infused over 1 hour Individualized mCi dose of Iodine I 131 Tositumomab infused over 20 minutes followed by a 10 minute saline flush
Days -12 to +2	Oral iodine product discontinued 14 days following the therapeutic dose

[a] Premedication with acetaminophen and diphenhydramine 30–60 minutes prior to Tositumomab dose.

2.7.2. Dosage Preparation

Proper aseptic technique and precautions for handling radioactive materials should be employed. Appropriate shielding should be used during preparation and during administration to the patient.

2.7.2.1. Preparation of Tositumomab infusion

1) Withdraw 450 mg of Tositumomab by sterile technique.
2) Dilute with 0.9% sodium chloride, USP, to a total volume of 50 mL.
3) Gently invert the IV bag to mix the solution. Avoid foaming. Tositumomab solution may contain particles.

2.7.2.2. Preparation of dosimetric Iodine I 131 Tositumomab infusion

1) Allow approximately 60 minutes for thawing (at ambient temperature) the dosimetric Iodine I 131 Tositumomab. Thaw the frozen vial in a room temperature lead pot.
2) Place a 50-mL vial in a lead pot.
3) Determine the amount of each component needed according to the directions below (a Dose Preparation Worksheet is provided to assist in calculations):
   a. Calculate the volume of Iodine I 131 Tositumomab that is equal to 5.0 mCi, based on the activity concentration of the Iodine I 131 Tositumomab vial. Decay correction must be taken into account when determining the necessary volume.
   b. Calculate the volume of Tositumomab needed to bring the 5.0 mCi solution to a total protein mass of 35 mg.
   c. Calculate the volume of 0.9% sodium chloride needed to bring the solution to a final volume of 30 mL.
4) Transfer the 5.0 mCi volume of Iodine I 131 Tositumomab (Step 3a) into the shielded 50-mL vial.
5) Add the calculated volume of Tositumomab from Step 3b. This additional amount of antibody is to be drawn from the 3-mL Tositumomab vial.
6) Dilute the preparation with 0.9% sodium chloride, USP, to a final volume of 30 mL (Step 3c).
7) Calibrate the prepared solution to confirm the activity dose.

2.7.2.3. Preparation of therapeutic Iodine I 131 Tositumomab infusion

1) Allow approximately 60 minutes for thawing (at ambient temperature) the therapeutic Iodine I 131 Tositumomab. Thaw the frozen vial in a room temperature lead pot.
2) Place a 50-mL vial in a lead pot.
3) Determine the amount of each component needed according to the directions below (a Dose Preparation Worksheet is provided to assist in calculations):
   a. Calculate the volume of Iodine I 131 Tositumomab that is equal to the specified activity determined by dosimetry, based on the activity concentration of the Iodine I 131 Tositumomab vial. Decay correction must be taken into account when determining the necessary volume.
   b. Calculate the volume of Tositumomab needed to bring the solution to a total protein mass of 35 mg. If the amount of Tositumomab in the dose preparation is already ≥ 35 mg, no additional Tositumomab will be added.
   c. Calculate the volume of 0.9% sodium chloride needed to bring the solution to a final volume of 30 mL.

4) Transfer the calculated volume of Iodine I 131 Tositumomab (Step 3a) for a Total Body Dose of 75 cGy into the shielded 50-mL vial.
5) Add the calculated volume of Tositumomab from Step 3b, if needed. This additional amount of antibody is to be drawn from the 3-mL Tositumomab vial.
6) Dilute the preparation with 0.9% sodium chloride, USP, to a final volume of 30 mL (Step 3c).
7) Calibrate the prepared solution to confirm the activity dose.

2.7.3. Administration of Iodine I 131 Tositumomab

2.7.3.1. Thyroid blockade

Patients will be treated with Saturated Solution Potassium Iodide (SSKI) 4 drops PO TID, Lugol's solution 20 drops PO TID, or potassium iodide tablets 130 mg PO QD starting at least 24 hours prior to the dosimetric dose of the Iodine I 131 Tositumomab and continuing daily for 14 days following the therapeutic dose of Iodine I 131 Tositumomab. In addition, 60-120 minutes before the dosimetric and therapeutic dose of Iodine I 131 Tositumomab all patients will be given an additional dose of medication for thyroid blockade. The SSKI or Lugol's solution may be given with juice or cola to mask its taste.

In no instance should a patient receive the dosimetric dose of Iodine I 131 Tositumomab if they have not yet received at least three doses of SSKI, three doses of Lugol's solution, or one 130 mg potassium iodide tablet (at least 24 hours prior to the dosimetric dose). Patient compliance will be ascertained and documented prior to administration of the dosimetric dose and therapeutic dose.

2.7.3.2. Dosimetric dose administration

On Study Day -19 of the Iodine I 131 Tositumomab calendar, patients will receive an IV administration of 450 mg Tositumomab followed by an IV administration of the dosimetric dose (refer to Section 2.7.2 for dose preparations).

Prior to administration, verify the patient's compliance with thyroid blockade supplements. Sixty to 120 minutes before the Iodine I 131 Tositumomab infusion, patients will be given an additional dose of thyroid blockade. Thirty to 60 minutes before the Tositumomab infusion, patients will be premedicated with acetaminophen 650 mg PO and diphenhydramine 50 mg PO (unless the patient is hypersensitive to acetaminophen or diphenhydramine).

Vital signs must be taken approximately every 15 minutes during each of the Tositumomab infusions.

Tositumomab will be given as an IV infusion, through an in-line filter, over one hour or longer, depending on the occurrence of infusion-related AEs. Following the administration of

Tositumomab, infuse the dosimetric dose (35 mg of Tositumomab containing 5mCi of Iodine I 131 Tositumomab) over 20 minutes.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Iodine-131.

At the end of the infusion of the dosimetric dose, the syringe or IV bag must be refilled with 0.9% Sodium Chloride for Injection, USP, and the contents infused over a period of 10 minutes.

Upon completion of the infusion, all pieces of the administration apparatus (syringe or vial, tubing, in-line filters, etc.) must be packaged and placed in a dose calibrator to measure the residual activity. The actual activity administered (net to patient) will be calculated as original vial/syringe calibrated activity minus residual activity. Discard vials, needles, and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

2.7.3.3. Whole body dosimetry

Gamma camera images will be used for whole body dosimetry. Whole body dosimetry for the purpose of determining the appropriate activity in mCi for the therapeutic dose will be performed for each patient. Three whole body anterior and posterior gamma camera scans will be obtained. The first scan will occur within 1 hour after the completion of the administration of the dosimetric dose (before urination). The remaining two scans will occur on two of the following days: Day -17, Day -16, or Day -15, and Day –14, -13 or Day -12.

These scans will be obtained by using a gamma camera with an appropriate high-energy collimator at a scan speed of 10-30 cm/min. The images from these three days will be used to perform organ and tumor dosimetry and for a visual assessment of biodistribution.

The counts from Day -19; Day -17, -16, or -15; and Day –12, -13 or -14 will be used to calculate the appropriate activity to deliver a total body dose of 75 cGy for the therapeutic dose (when calculating whole body dosimetry, the order of preference for the second scan is Day -15, -16, -17). On each of these three days, whole body counts, background counts, and counts of a calibrated standard will be obtained and recorded. Patients who are obese will be dosed upon 137% of their lean body mass (refer to Table 2.7.4.1 for definition of obese). The mCi dose will be calculated according to instructions provided with this protocol. Details of the dose calculations are provided in Table 2.7.4.2.

The biodistribution of Iodine I 131 Tositumomab should be assessed by determination of total body residence time and by visual examination of whole body camera images from the first image taken at the time of Count 1 (within an hour of the end of the infusion) and from the second image taken at the time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities, an evaluation of the third image at the time of Count 3 (6 to 7 days after

administration) may be necessary. If either of these methods indicates that the biodistribution is altered, the Iodine I 131 Tositumomab therapeutic dose should not be administered.

Expected biodistribution:

- On the first imaging timepoint: Most of the activity is in the blood pool (heart and major blood vessels) and the uptake in normal liver and spleen is less than in the heart.
- On the second and third imaging timepoints: The activity in the blood pool decreases significantly and there is decreased accumulation of activity in normal liver and spleen. Images may show uptake by thyroid, kidney, and urinary bladder and minimal uptake in the lungs. Tumor uptake in soft tissues and in normal organs is seen as areas of increased intensity.

Results indicating altered biodistribution:

- On the first imaging timepoint: If the blood pool is not visualized or if there is diffuse, intense tracer uptake in the liver and/or spleen or uptake suggestive of urinary obstruction the biodistribution is altered. Diffuse lung uptake greater than that of blood pool on the first day represents altered biodistribution.
- On the second and third imaging timepoints: uptake suggestive of urinary obstruction and diffuse lung uptake greater than that of the blood pool represent altered biodistribution.
- Total body residence times of less than 50 hours and more than 150 hours.

2.7.3.4. Calculations of therapeutic dose

Calculation of Iodine-131 Activity
The following equation is used to calculate the activity of Iodine-131 to administer to the patient as Iodine I 131 Tositumomab to achieve the desired total body dose of radiation (75 cGy):

$$\textbf{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi h)}}{\text{Residence Time (h)}}$$

The methods for determining the activity hours (mCi h) and residence time (h) are described below.

Activity Hours (mCi h)
In order to determine the activity hours (mCi h), look up the patient's maximum effective mass based on the patient's gender and height in Table 2.7.4.1. Then, using either the patient's weight or maximum effective mass, *whichever is less*, look up the value for activity hours (mCi h) in Table 2.7.4.2.

Residence Time (h)
The first step in calculating the percent-injected activity is to determine the background-corrected total body count, as described above, at Day -19; Day -17, -16, or -15, and Day -13 or -12. The order of preference for the three scans to be used in dose calculations is Days -19, -15, -12; Days -19, -16, -12; and Days -19, -17, -12. Thus if the Day -15 image was obtained, it should be used for dose calculations. Next, determine the time (in hours) from the start of the

Iodine I 131 Tositumomab dosimetric dose infusion to the acquisition of each whole body count. The percent injected activity remaining at each time point is then calculated by dividing the background-corrected whole body count for that time point by the background-corrected whole body count from the first time point (Day -19) and multiplying by 100.

Plot the times from the start of the infusion and the percent injected activity values for the last 2 time points in the Figure in Section 2.7.4 in order to determine the residence time. The last 2 time points would correspond to Day -17, -16, or -15 (the order of preference is Day -15, -16, then -17) and Day -12. Draw a best-fit line from 100% (the pre-plotted Day 0 value) through the 2 plotted points (if the line does not intersect the two plotted points, one point must lie above the best-fit line and one point must lie below the best-fit line). Determine the x-axis value of the graph at the point where the best-fit line intersects the horizontal 37% injected activity line; this is the total body residence time (h).

2.7.3.5. Therapeutic dose administration

The therapeutic dose will be administered on Day -12 or one week following the dosimetric dose. Those patients who experienced an anaphylactic response following the dosimetric dose will not continue into this phase of the study.

The patient's compliance with thyroid blockade should be verified. Sixty to 120 minutes before the Iodine I 131 Tositumomab infusion, patients will be given a dose of thyroid blockade. Thirty to 60 minutes before the Tositumomab infusion, patients will be pre-medicated with acetaminophen 650 mg PO and diphenhydramine 50 mg PO (unless the patient is hypersensitive to acetaminophen or diphenhydramine).

Tositumomab will be given as an IV infusion, through an in-line filter, over 1 hour or longer, depending on the occurrence of infusion-related AEs.

Vital signs must be taken approximately every 15 minutes during each of the Tositumomab infusions.

Following the administration of Tositumomab, infuse the therapeutic dose (35 mg of Tositumomab containing the patient-specific amount of tellurium-derived Iodine I 131 Tositumomab) over 20 minutes.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Iodine-131.

At the end of the infusion of the therapeutic dose, the syringe or IV bag must be refilled with 0.9% Sodium Chloride for Injection, USP, and the contents infused over a period of 10 minutes.

Upon completion of the infusion, all pieces of the administration apparatus (syringe or vial, tubing, in-line filters, etc.) must be packaged and placed in a dose calibrator to measure the

residual activity. The actual activity administered (net to patient) will be calculated as original vial/syringe calibrated activity minus residual activity. Discard vials, needles, and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

2.7.4. Dose Modifications/Discontinuations

For excessively obese patients (patients weighing more than 137% of their lean body mass), the calculations to determine the Iodine I 131 Tositumomab activity to administer will use 137% of the patients' lean body weight rather than their actual body weight (refer to Table 2.7.4.1).

All patients who are discontinued due to an infusion related adverse events should be followed until the resolution or stabilization of the event. Any randomized patient who receives study drug then discontinues, regardless of reason, will not be allowed to re-enroll in this study.

Table 2.7.4.1
Maximum Effective Mass

Men			Women		
Height (ft–inches)	**Height (cm)**	**Maximum Effective Mass (kg)**	**Height (ft–inches)**	**Height (cm)**	**Maximum Effective Mass (kg)**
4'–5"	134.5	**40.5**	4'–5"	134.5	**40.7**
4'–6"	137.0	**44.2**	4'–6"	137.0	**43.8**
4'–7"	140.0	**47.9**	4'–7"	140.0	**47.0**
4'–8"	142.0	**51.6**	4'–8"	142.0	**50.2**
4'–9"	145.0	**55.3**	4'–9"	145.0	**53.3**
4'–10"	147.5	**59.0**	4'–10"	147.5	**56.5**
4'–11"	150.0	**62.7**	4'–11"	150.0	**59.7**
5'–0"	152.5	**66.3**	5'–0"	152.5	**62.8**
5'–1"	155.0	**70.0**	5'–1"	155.0	**66.0**
5'–2"	157.5	**73.7**	5'–2"	157.5	**69.2**
5'–3"	160.0	**77.4**	5'–3"	160.0	**72.3**
5'–4"	162.5	**81.1**	5'–4"	162.5	**75.5**
5'–5"	165.0	**84.8**	5'–5"	165.0	**78.7**
5'–6"	167.5	**88.5**	5'–6"	167.5	**81.8**
5'–7"	170.0	**92.2**	5'–7"	170.0	**85.0**
5'–8"	172.5	**95.8**	5'–8"	172.5	**88.2**
5'–9"	175.5	**99.5**	5'–9"	175.5	**91.3**
5'–10"	178.0	**103.2**	5'–10"	178.0	**94.5**
5'–11"	180.5	**106.9**	5'–11"	180.5	**97.7**
6'–0"	183.0	**110.6**	6'–0"	183.0	**100.8**
6'–1"	185.5	**114.3**	6'–1"	185.5	**104.0**
6'–2"	188.0	**118.0**	6'–2"	188.0	**107.2**
6'–3"	190.5	**121.7**	6'–3"	190.5	**110.3**
6'–4"	193.0	**125.4**	6'–4"	193.0	**113.5**
6'–5"	195.5	**129.0**	6'–5"	195.5	**116.7**
6'–6"	198.0	**132.7**	6'–6"	198.0	**119.8**
6'–7"	200.5	**136.4**	6'–7"	200.5	**123.0**
6'–8"	203.0	**140.0**	6'–8"	203.0	**126.2**
6'–9"	205.5	**143.8**	6'–9"	205.5	**129.3**
6'–10"	208.5	**147.5**	6'–10"	208.5	**132.5**
6'–11"	211.0	**151.2**	6'–11"	211.0	**135.7**
7'–0"	213.5	**154.9**	7'–0"	213.5	**138.8**

Multiply pounds by 0.454 to obtain kilograms. Multiply inches by 2.54 to obtain centimeters. To calculate the maximum effective mass for patient heights not included in above table, use the following formulas:

Males: **Maximum Effective Mass (kg)=65.76 + 1.452 (Ht. in cm – 152)**
Females: **Maximum Effective Mass (kg)=62.34 + 1.247 (Ht. in cm – 152)**

Adapted from (K. Zasadny, R. Wahl, *et al.*, J Nuc Med 1995; 36(5):214. "Total Body Mass Lean").

Table 2.7.4.2 -- Activity Hours

Mass[1] (kg)	Activity Hours (mCi h)	Mass[1] (kg)	Activity Hours (mCi h)	Mass[1] (kg)	Activity Hours (mCi h)	Mass[1] (kg)	Activity Hours (mCi h)	Mass[1] (kg)	Activity Hours (mCi h)
40.0	**4638**	60.0	**6686**	80.0	**8670**	100.0	**10595**	120.0	**12463**
40.5	**4690**	60.5	**6737**	80.5	**8718**	100.5	**10643**	120.5	**12509**
41.0	**4743**	61.0	**6787**	81.0	**8767**	101.0	**10690**	121.0	**12556**
41.5	**4796**	61.5	**6838**	81.5	**8816**	101.5	**10738**	121.5	**12602**
42.0	**4848**	62.0	**6888**	82.0	**8864**	102.0	**10785**	122.0	**12648**
42.5	**4901**	62.5	**6938**	82.5	**8913**	102.5	**10833**	122.5	**12694**
43.0	**4953**	63.0	**6989**	83.0	**8961**	103.0	**10880**	123.0	**12741**
43.5	**5005**	63.5	**7039**	83.5	**9010**	103.5	**10927**	123.5	**12787**
44.0	**5057**	64.0	**7089**	84.0	**9058**	104.0	**10975**	124.0	**12833**
44.5	**5109**	64.5	**7139**	84.5	**9106**	104.5	**11022**	124.5	**12879**
45.0	**5160**	65.0	**7189**	85.0	**9154**	105.0	**11069**	125.0	**12925**
45.5	**5212**	65.5	**7238**	85.5	**9202**	105.5	**11116**	125.5	**12971**
46.0	**5264**	66.0	**7288**	86.0	**9251**	106.0	**11163**	126.0	**13017**
46.5	**5315**	66.5	**7338**	86.5	**9299**	106.5	**11210**	126.5	**13063**
47.0	**5366**	67.0	**7387**	87.0	**9347**	107.0	**11257**	127.0	**13109**
47.5	**5418**	67.5	**7437**	87.5	**9394**	107.5	**11304**	127.5	**13155**
48.0	**5469**	68.0	**7486**	88.0	**9442**	108.0	**11351**	128.0	**13200**
48.5	**5520**	68.5	**7536**	88.5	**9490**	108.5	**11398**	128.5	**13246**
49.0	**5571**	69.0	**7585**	89.0	**9538**	109.0	**11445**	129.0	**13292**
49.5	**5621**	69.5	**7634**	89.5	**9585**	109.5	**11492**	129.5	**13337**
50.0	**5672**	70.0	**7683**	90.0	**9633**	110.0	**11538**	130.0	**13383**
50.5	**5724**	70.5	**7733**	90.5	**9682**	110.5	**11585**	130.5	**13429**
51.0	**5775**	71.0	**7783**	91.0	**9730**	111.0	**11632**	131.0	**13474**
51.5	**5826**	71.5	**7833**	91.5	**9779**	111.5	**11678**	131.5	**13520**
52.0	**5878**	72.0	**7883**	92.0	**9827**	112.0	**11725**	132.0	**13565**
52.5	**5929**	72.5	**7932**	92.5	**9875**	112.5	**11771**	132.5	**13611**
53.0	**5980**	73.0	**7982**	93.0	**9924**	113.0	**11818**	133.0	**13656**
53.5	**6031**	73.5	**8031**	93.5	**9972**	113.5	**11864**	133.5	**13701**
54.0	**6082**	74.0	**8081**	94.0	**10020**	114.0	**11910**	134.0	**13747**
54.5	**6133**	74.5	**8130**	94.5	**10068**	114.5	**11957**	134.5	**13792**
55.0	**6184**	75.0	**8180**	95.0	**10117**	115.0	**12003**	135.0	**13837**
55.5	**6234**	75.5	**8229**	95.5	**10165**	115.5	**12049**	135.5	**13882**
56.0	**6285**	76.0	**8278**	96.0	**10213**	116.0	**12095**	136.0	**13928**
56.5	**6335**	76.5	**8327**	96.5	**10261**	116.5	**12141**	136.5	**13973**
57.0	**6386**	77.0	**8376**	97.0	**10309**	117.0	**12187**	137.0	**14018**
57.5	**6436**	77.5	**8425**	97.5	**10357**	117.5	**12233**	137.5	**14063**
58.0	**6486**	78.0	**8474**	98.0	**10404**	118.0	**12279**	138.0	**14108**
58.5	**6536**	78.5	**8523**	98.5	**10452**	118.5	**12325**	138.5	**14153**
59.0	**6586**	79.0	**8572**	99.0	**10500**	119.0	**12371**	139.0	**14198**
59.5	**6636**	79.5	**8621**	99.5	**10548**	119.5	**12417**	139.5	**14242**

[1] The minimum of the patient's actual weight (kg) or maximum effective mass (kg) from Table 2.7.4.1. For values between 140 kg and 160 kg, use the following formula: **Activity Hours (mCi h)=14287 + (88.74) (Wt in kg – 140)**

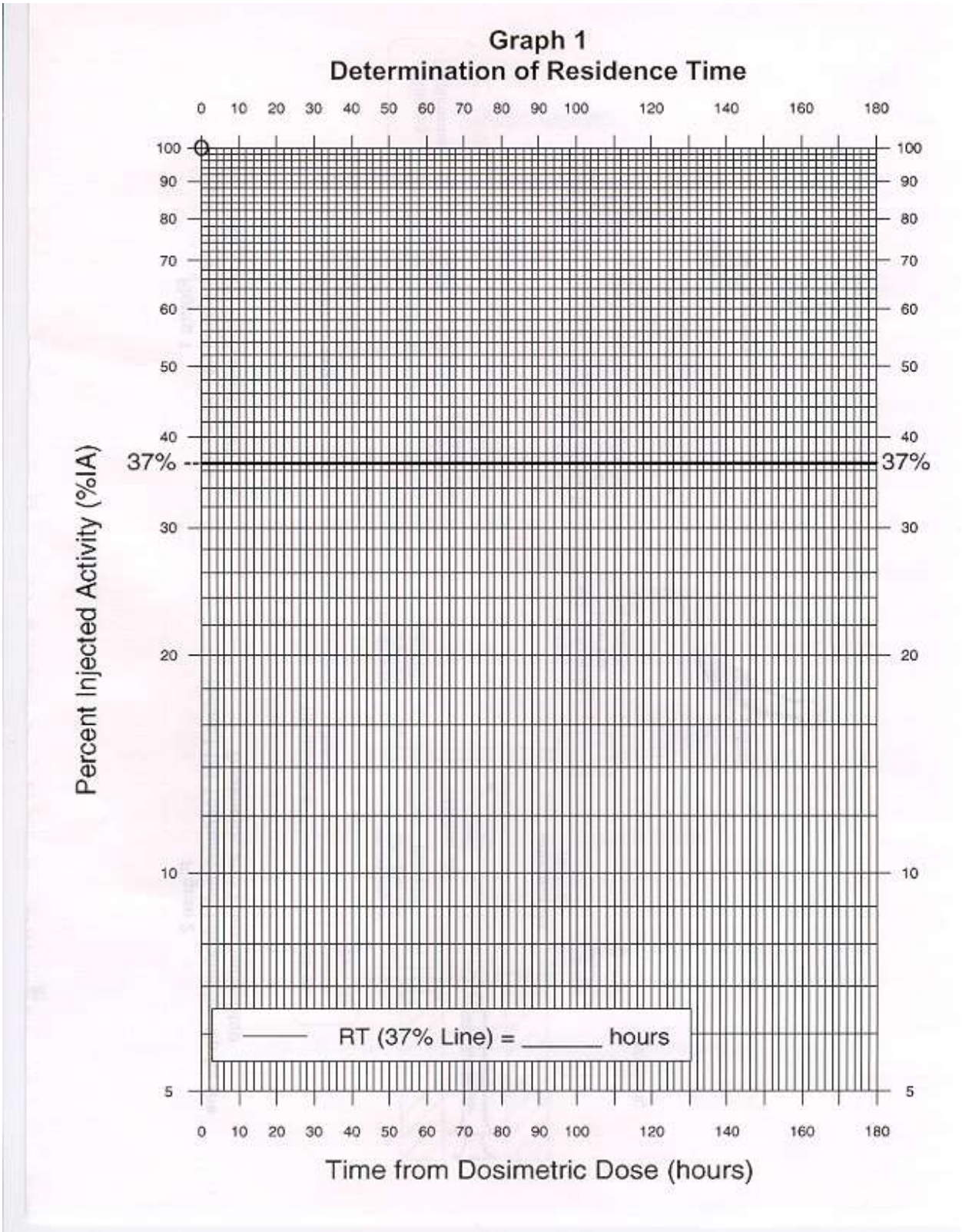
Graph 1
Determination of Residence Time
0 10 20 30 40 50 60 70 80 90 100 120 140 160 180
100 90 80 70 60 50 40 30 20 10 5
37%
37%
Percent Injected Activity (%IA)
RT (37% Line) = _____ hours
Time from Dosimetric Dose (hours)

Figure 2.7.4.3

2.8. Bexxar Ordering Instructions

As soon as a patient is randomized to the Bexxar arm, it is recommended that the clinic coordinator alert the Nuclear Medicine Department staff so that coordination for patient scheduling can begin.

Please note that Bexxar can be ordered as early as 4 weeks, but no less than 1 week, prior to the planned date of dosimetric dose administration (Day -19). Please refer to the "Study Drug Order Form" located in Appendix E.

The clinic coordinator should fill out the top portion of the form (i.e. patient ID#, PI, Site information, etc.), and submit it to the Nuclear Medicine Department for further completion of the form. The Nuclear Medicine Department will initially be responsible for completing the section titled the "Nuclear Medicine/ Radiation Oncology Information," (i.e. Prescribing Physician Name, Main Contact Person name and information). The Prescribing Physician is also responsible for completing the information regarding the expected administration dates and times (including possible alternate dates) of the dosimetric and therapeutic doses of Bexxar.

To complete the drug order placement, fax the completed form to the radiopharmacy. The radiopharmacy will then further complete the Study Drug Order Form and fax it to the BEXXAR Service Center.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Definition of Disease Status

Patients at each data collection period are classified into one of the following states. Until relapse/progression, all disease classifications are relative to the patient's pre-ASCT 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 would be physical examination, laboratory testing, bone marrow biopsy and aspirate, PET scans, and CT scans of 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." [36]

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 or mantle-cell 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 ≤ 1.0 x ≤ 1.0cm 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 ≥ 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 (e.g. a trial in patients with MALT lymphoma), 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 to be Compared Between Rituxan/BEAM and Bexxar/BEAM + Autologous HSCT

The primary endpoint is progression-free survival (PFS). Patients are considered a failure for this endpoint if they die or if they relapse/progress or receive anti-lymphoma therapy, other than post-transplant consolidative localized radiation (maximum 3 sites) to sites of prior bulk disease pre-transplant (> 3cm). The time to this event is the time from randomization until death, relapse/progression, receipt of anti-lymphoma therapy, or last follow up, whichever comes first.

3.3. Secondary Endpoints to be Compared Between Rituxan/BEAM and Bexxar/BEAM + Autologous HSCT

3.3.1. Overall Survival

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

3.3.2. Time to Progression

The event is relapse/progression. The time to this event is measured from randomization. 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. CR and CR+PR Proportion at Day 100

The event is whether or not the patient has CR (or PR) at Day 100. The time to event is measured from the time of randomization to the time to CR (or PR).

3.3.4. Time to Hematopoietic Recovery

Time to neutrophil recovery will be the first of two consecutive days of $\geq$ 500 neutrophils/μL following the expected nadir. Time to platelet engraftment will be the date platelet count is $\geq$ 20,000/μL for the first of two consecutive labs with no platelet transfusions 7 days prior.

3.3.5. Hematologic Function

Hematologic function will be defined as ANC > 1,500 neutrophils/μL, hemoglobin > 10 g/dL without transfusion support, and platelet count > 100,000/μL without transfusion support and will be measured at Day 100 and 1 year.

3.3.6. Incidence of Infection

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.

3.3.7. Maximum Mucositis Score by Day + 21

Mucositis severity will be recorded twice weekly as per the modified oral mucositis assessment scale (OMAS). Mucositis scores will be recorded for the first three weeks post-transplant. Both peak and mean mucositis scores will be analyzed.

3.3.8. Treatment-related Mortality

Treatment-related mortality (TRM) is defined as death occurring in a patient from causes other than relapse or progression and will be measured at 1 year.

3.3.9. Incidence of MDS/ AML and New, Abnormal Cytogenetics

MDS or AML is defined as the existence of a bone marrow biopsy report with the diagnosis of MDS or AML.

3.3.10. Immunologic Reconstitution

This will be measured in all patients prior to the initiation of the Day –19 Bexxar or Rituxan (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 CD2, CD3, CD4, CD8, CD19, CD3+/CD25+, CD45 RA/RO, CD56+/CD3-, and quantitative immunoglobulins (IgM, IgG and IgA).

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). Southwest Oncology Group (SWOG) centers should follow instructions in Section 4.1.2 **prior** to following the instructions below. The following procedures should be followed:

1. Within 4 weeks to 1 week prior to initiation of conditioning therapy, an authorized user at the transplant center completes initial screening by entering patient demographics and Segment A of the Enrollment Form in AdvantageEDC. The eligibility screening includes questions that will verify eligibility, capture the proposed start date of conditioning, date of most recent dose of Rituxan, start date of leukapheresis, and a question confirming that the patient signed the informed consent form.
2. If the patient is eligible, a study number is generated.
3. Immediately after completing Segment A of the Enrollment Form, an authorized user at the clinical center completes the enrollment process by entering Segment B of the Enrollment Form in AdvantageEDC confirming that the patient is eligible to receive conditioning and transplant. Segment B of the Enrollment Form will capture the total number of cells that was collected. At this time, randomization to a standard RTX plus BEAM conditioning regimen or a Bexxar plus BEAM regimen will occur.
4. Once randomization occurs, the treatment plan is continued and a visit schedule based on the treatment start date is displayed for printing and is referred to as 'Segment B Follow-up Schedule.'

4.1.2. SWOG Patient Registration Procedures

Patients from Southwest Oncology Group (SWOG) Member, CCOP and approved Affiliate institutions must be registered through the SWOG Data Operations Center in Seattle using the SWOG Web Registration System. The Web Registration System will request the date informed consent and HIPAA authorization were obtained, and will obtain the date of IRB approval for each entry.

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.

Follow-up Visits: Follow-up visits will begin as soon as patients are randomized onto the study. The follow-up period for Segment B is 2 years.

Table 4.2.1: Follow-up Schedule

Study Visit	Target Day (± 2 Days Prior to Day 100 Post-ASCT) (± 28 Days After Day 100 Post-ASCT)
1 week	7 days
2 week	14 days
3 week	21 days
4 week	28 days
5 week	35 days
6 week	42 days
8 week	56 days
100 day	100 days
6 month	180 days
12 month	365 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 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.

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 #0403 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. Unexpected, grade 3-5 AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 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.

4.2.3. Patient Assessments

Tables 4.2.3.3a and 4.2.3.3b summarize patient clinical assessments over the course of the study.

4.2.3.1. Evaluations prior to the ASCT conditioning therapy

The following observations need to be performed within 4 weeks of enrollment.

1. History, physical examination, height and weight.
2. Karnofsky performance status.
3. CBC with differential, platelet count, creatinine, bilirubin, LDH, alkaline phosphatase, ALT, AST, sodium, magnesium, potassium, chloride, and CO_2.
4. CMV titer, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex titer, syphilis, HIV and HTLV1 antibody.
5. EKG.
6. Thyroid function test.
7. β-HCG serum pregnancy test for females of childbearing potential.
8. One vial (10cc) of nucleated cells from patient's peripheral blood for future testing.

9. Signed informed consent form.
10. Blood samples for evaluation of immune reconstitution by flow cytometry (CD2, CD3, CD4, CD8, CD19, CD3+/CD25+, CD45RA/RO, and CD56+/CD3-) and quantitative immunoglobulins (IgM, IgG, and IgA).

The following observations need to be performed within 4 months of enrollment:

1. Creatinine clearance (calculated creatinine clearance is permitted).
2. Chest X-ray if clinically indicated.
3. Left ventricular ejection fraction, if the patient is > 60 years of age.
4. DLCO, FEV1 and FVC.
5. Toxicity assessment to assess mobilization-related toxicities.
6. Baseline disease evaluations:
    a. CT scans of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.
    b. Bone marrow biopsy and aspirates to pathology and aspirate for cytogenetics. Flow cytometry is not required. Target bone marrow core should be ≥ 2 cm total for a unilateral or bilateral sample. If the bone marrow core is ≤ 2 cm, a second biopsy is required only if the results of the first biopsy are suboptimal.

The following observations may be determined any time since diagnosis of DLBCL:

1. Demonstration of CD20+ on at least one histologic specimen.

4.2.3.2. Evaluations prior to administration of BEAM

A toxicity assessment will be performed on Day –7 or – 6, prior to the patient receiving BEAM, in order to assess Bexxar and Rituxan-related toxicities.

4.2.3.3. Post-ASCT evaluations

1. CBC at least twice a week from Day 0 until ANC > 500/mm^3 for 2 days after nadir reached. Thereafter CBC twice per week until Day 28 (or 4 weeks), then at 8 weeks, Day 100, 6 months, one year and two years post-ASCT.
2. Toxicity assessments at 4 weeks, 8 weeks, Day 100, 6 months, one year and two years post-ASCT.
3. Mucositis assessment twice a week until Day 21 using the modified oral mucositis assessment scale (OMAS).
4. Disease restaging at Day + 100, 6 months, one year and two years post-ASCT.
    a. If patient had known bone marrow involvement with lymphoma prior to conditioning therapy, bone marrow biopsy and aspirate to pathology and aspirate for cytogenetics.

Flow cytometry is not required. Target bone marrow core should be ≥ 2 cm total for a unilateral or bilateral sample. If the bone marrow core is ≤ 2 cm, a second biopsy is required only if the results of the first biopsy are suboptimal. If the patient demonstrates unexplained cytopenias, regardless of prior marrow involvement, at any time point following hematologic recovery, a bone marrow for morphology and cytogenetics to rule out MDS/AML should be performed.

b. CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.

5. Thyroid function test at one and two years post-ASCT.
6. Evaluation of immune reconstitution by flow cytometry (CD2, CD3, CD4, CD8, CD19, CD3+/CD25+, CD45 RA/RO, and CD56+/CD3-) and quantitative immunoglobulins (IgM, IgG and IgA) at Day 100 and one year post-ASCT. Evaluation of immune reconstitution is also required at two years post-ASCT if results are abnormal at one year post-ASCT.

The following observations are recommended, but not required, post-ASCT:

1. Comprehensive chemistry panel defined as creatinine, LDH, bilirubin, alkaline phosphatase, ALT, AST, magnesium, sodium, potassium, chloride, CO_2 twice a week until Day 28 (or four weeks) and then at 8 weeks, Day 100, 6 months, one year and two years post-ASCT.
2. DLCO, FEV1 and FVC at one and two years post-ASCT.

Table 4.2.3.3a: Pre-ASCT Evaluations

Required Studies/Testing	Prior to Conditioning for ASCT[1]	Prior to Administration of BEAM
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	
Creatinine Clearance	X[2, 3]	
CMV Titer, Hepatitis Panel, Herpes Simplex Titer, Syphilis, HIV and HTLV antibody	X[4]	
Chest X-ray, if clinically indicated	X[2, 5]	
EKG	X	
Left Ventricular Ejection Fraction, if > 60 years of age	X[2]	
DLCO, FEV1, FVC	X[2]	
Thyroid Function Test	X	
β -HCG Serum Pregnancy Test for Females of Childbearing Potential	X	
Toxicity Assessment	X[2]	X
CT Neck, Chest, Abdomen and Pelvis	X[2, 6]	
Bone Marrow Aspirate and Biopsy	X[2, 7]	
Immune Reconstitution Assays	X[8]	
Nucleated Cells	X[9]	
Informed Consent	X	

[1] To be performed within 4 weeks of enrollment, unless otherwise indicated.
[2] To be performed within 4 months of enrollment.
[3] Calculated creatinine clearance is permitted.
[4] Hepatitis panel includes HepA Ab, Hep B SAb, Hep B SAg, Hep B Core Ab, and HepC Ab.
[5] To be performed if clinically indicated.
[6] Neck CT only required if previous site of disease.
[7] Bone marrow biopsy and aspirates to pathology and aspirate for cytogenetics. Flow cytometry not required. Bone marrow core should be ≥ 2 cm total for a unilateral or bilateral sample.
[8] Immune reconstitution assays to include CD2, CD3, CD4, CD8, CD19, CD3/CD25, CD45RA/RO, CD56+/CD3-, and quantitative immunoglobulin (IgM, IgG and IgA) levels.
[9] One vial (10cc) of nucleated cells from peripheral blood for future testing.

Table 4.2.3.3b: Post-ASCT Evaluations

Study Assessments/ Testing	Weeks Post-ASCT						Months Post-ASCT		
	1	2	3	4	8	Day 100	6	12	24
CBC	X[1]				X	X	X	X	X
Chemistry Panel[2, 3]	X[4]				X	X	X	X	X
Toxicity Assessment				X	X	X	X	X	X
Mucositis Assessment[5]	X	X	X						
Bone Marrow Aspirate and Biopsy[6]						X	X	X	X
CT Neck, Chest, Abdomen and Pelvis[7]						X	X	X	X
DLCO, FEV1, FVC[3]								X	X
Thyroid Function Test								X	X
Immune Reconstitution Assays[8]						X		X	X[9]

[1] To be performed at least twice weekly from Day 0 until ANC > 500/mm^3 for 2 days after nadir reached. Thereafter, twice weekly until Day 28 (or 4 weeks).
[2] Chemistry panel to include creatinine, LDH, bilirubin, alkaline phosphatase, ALT, AST, magnesium, sodium, potassium, chloride, CO_2. The chemistry panel is recommended, but not required post-ASCT.
[3] The chemistry panel and pulmonary function tests are recommended, but not required post-ASCT.
[4] To be performed twice weekly until Day 28 (or 4 weeks).
[5] To be performed twice weekly until Day 21.
[6] If previously known bone marrow involvement with lymphoma prior to conditioning therapy, bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics. Flow cytometry is not required. Bone marrow core should be ≥ 2 cm total for a unilateral or bilateral sample.
[7] Neck CT only required if previous site of disease.
[8] Immune reconstitution assays include CD2, CD3, CD4, CD8, CD19, CD3/CD25, CD45RA/RO, CD56+/CD3-, and quantitative immunoglobulin levels (IgM, IgG and IgA).
[9] Immune reconstitution assays are not required at two years post-ASCT, unless results from the one year post-ASCT assays are abnormal.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Overview

This study is designed as a Phase III, multi-center trial, comparing progression-free survival (PFS) after autologous hematopoietic stem cell transplantation (ASCT) using a standard Rituxan/BEAM transplant regimen versus a regimen adding Bexxar to BEAM. The target enrollment is 224 patients. The study design consists of randomization in a 1:1 ratio of standard Rituxan/BEAM transplant regimen versus a regimen adding Bexxar to BEAM. Randomization will be stratified by transplant center.

5.1.1. Accrual

Accrual will remain open until 224 patients are enrolled. It is estimated that two years of accrual will be necessary to enroll the targeted sample size.

5.1.2. Primary Endpoint

The primary endpoint for the study is progression-free survival (PFS). If any therapy not specified in the protocol is given to prevent relapse/progression or to induce a response, the patient will be considered an event for this endpoint. Time-to-event is measured from randomization to the minimum of the date of death, relapse/progression, or last-follow-up. If any patients are lost to follow-up, they will be censored at the time of the last observation. The study will remain open until the last patient enrolled has been followed for two years.

5.2. Sample Size and Power Calculations

PFS will be compared by treatment arm using a log rank test. Data from the IBMTR/ABMTR registry suggest that the hazard for PFS is negligible after two years post-transplant, so power calculations are based on two years of follow up. The sample size of 112 patients per group is sufficient to maintain type I error of 5% across all planned interim analyses (see below) while providing > 80% statistical power for a two-sided test to detect an increase in the PFS at two years from 0.5 in the standard arm to 0.7 in the experimental arm. It is assumed that there is a 5% dropout rate.

5.3. Interim Analysis and Stopping Guidelines

Interim analyses for efficacy will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately six-month intervals. Monitoring of primary graft failure as a key safety endpoint 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.

5.3.1. Interim Analysis for Efficacy

Analyses will be performed as described below for the primary endpoint. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis. Toxicities and adverse events will be captured on case report forms. A core set of toxicities, which include gastrointestinal, renal, hemorrhagic, cardiovascular, neurologic, coagulation, vascular, pulmonary, and hepatic toxicities, will be collected in accordance with the guidelines outlined the BMT CTN Manual of Operating Procedures. At each interim analysis time point, a log-rank test will be performed to detect a difference in PFS between treatment arms. In order to preserve the over-all type I error rate at 5%, the critical value for the test statistic will be inflated above 1.96, the value that would be used if no repeated testing were used. Equivalently, the nominal p-value at which an observed difference is declared significant will be reduced below 0.05. The actual critical values and nominal p-values will be computed using statistical methods for group sequential testing with O'Brien Fleming boundaries.

As an example, Table 5.3.1a shows the critical values and nominal p-values for tests conducted at 0.5, 1.0, 1.5, 2.0 and 4.0 years after the study opens to enrollment. The column labeled "Number of Events" shows the average number of individuals who have died post-transplant assuming uniform accrual over a two-year period. The fraction of patients who died, as compared to a denominator comprised of the total sample of 224, quantifies the "statistical information" from which the critical values, nominal p-values and cumulative type I error are computed.

Table 5.3.1a Critical Values and Nominal P-Values

Calendar Time	Number of Events	Statistical Information	Critical Value	Nominal P-value	Cumulative Type I Error
0.5	3.5	0.0404	8.000	0.00000	0.00000
1.0	13.2	0.1535	8.000	0.00000	0.00000
1.5	28.1	0.3285	3.7401	0.00018	0.00018
2.0	47.6	0.5555	2.7939	0.00509	0.00527
4.0	85.7	1.0000	1.9747	0.04473	0.05000

In practice, the rate of accrual or timing of DSMB meetings may not be as anticipated. To permit necessary flexibility in scheduling interim analyses, the critical values will be recomputed to correspond to the actual available statistical information using the "use-function" approach of Lan and DeMets.

5.4. Statistical Stopping Guidelines

A statistical stopping guideline for primary graft failure will be employed in this study. This guideline is designed to assist an independent Data and Safety Monitoring Board (DSMB) in overseeing the study. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study.

The null hypothesis for sequential monitoring is that the true rate of primary graft failure is less than 10%. Primary graft failure is defined as failure to reach an ANC of 500/dL. If the observed incidence rate is substantially in excess of this target, the null hypothesis will be rejected, and the NHLBI will be notified. These guidelines are provided as an "early warning" system. Suspension of enrollment is not automatic, but at the discretion of the NHLBI upon recommendation of the DSMB, which will have the opportunity to request and review additional analyses.

Primary graft failure at Day 21 will be monitored separately in each treatment arm for all transplanted patients. Patients will be analyzed according to their randomized treatment assignment. Monitoring will be performed monthly until enrollment to that treatment arm is closed. Each month, the null hypothesis that the primary graft failure at Day 21 is less than or equal to 10% will be tested against the alternative that it is greater than 10%.

A Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions for primary graft failure at Day 21 between each treatment arm will be used. This sequential testing procedure conserves type I error across all of the monthly examinations. The SPRT can be represented graphically. At each monthly interim analysis, the number of endpoints (e.g., subjects with primary graft failure at Day 21), is plotted against the total number of subjects observed to Day 21. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring each treatment arm to protect against excessive primary graft failure at Day 21. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more primary graft failures at Day 21 than predicted by the number of patients at risk on Day 21. Otherwise, the SPRT continues until enrollment to the treatment arm 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 $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRTs:

- Slope of the parallel lines for monitoring primary graft failure at Day 21 is 0.366 and the intercepts are –1.066 and 0.74.
- An SPRT contrasting 10% versus 20% primary graft failure at Day 21, with nominal type I and II errors of 9% and 20%, respectively.

The actual operating characteristics of the truncated test, shown in Table 5.4.1, were determined in a simulation study. The simulation assumed uniform accrual of 224 patients, 112 assigned to each treatment arm, over a two-year time period.

Table 5.4.1
Operating Characteristics of Sequential Testing Procedure for
Primary Graft Failure at Day 21 from a Simulation Study with 100,000 Replications

True Rate of Primary Graft Failure at Day 21	10%	15%	20%
Probability Reject Null	0.06	0.44	0.87
Mean Month Stopped	23.1	18.4	11.6
Mean # Events in 21 days.	10.6	12.7	10.6
Mean # Patients Enrolled	107.9	86.0	54.5

Primary graft failure at Day 21 is monitored in all subjects (N = 112) separately in each treatment arm. The SPRT rejects the null hypothesis in favor of the alternative 6% of the time when the true 21 day non-engraftment is 10%, and 87% of the time when the true primary graft failure at Day 21 is 20%. This corresponds to a type I error rate of α=0.06 and a type II error rate of β=0.13. When the true rate of primary graft failure at Day 21 is 20%, on average, the DSMB will be consulted 11.6 months after opening, when 10.6 events have been observed in 54.5 patients**.** Note that the SPRT procedure is adequately powered to distinguish between a rate of primary graft failure at Day 21 of 10% and 20% in each of the arms.

5.5. Analysis Plan

5.5.1. Analysis of the Primary Endpoint

The primary outcome of the trial is lymphoma progression-free survival. The primary null hypothesis of the study is that there is no difference in progression-free survival between the treatment arms. In the primary analysis, the intention-to-treat principle that is based on all patients as randomized will be used and progression-free survival will be estimated using the Kaplan-Meier product limit estimator, and compared between treatment arms using a log-rank test.

5.5.2. Analysis of Secondary Endpoints

Overall Survival

The event is death from any cause. Patients alive at the time of the last observation are censored at the time of the last observation. In the primary analysis in all enrolled patients, time-to-event will be measured from randomization. In a secondary analysis including only patients who received their ASCT, time-to-event will be measured from the date of ASCT. Overall survival will be compared between treatment arms using a log-rank test, and the survival curves will be estimated using the Kaplan Meier Estimator.

Time to Progression

The event is relapse/progression. Death without relapse/progression is considered a competing risk. Patients alive with no history of relapse/progression are censored at the time of the last observation. In the primary analysis in all enrolled patients, time-to-event will be measured from randomization. In a secondary analysis including only patients who received their ASCT, time-to-event will be measured from date of ASCT. Time to progression will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

CR and CR+PR Proportion at Day 100

The event is whether or not the patient has CR (CR or PR). In the primary analysis in all randomized patients, time-to-event will be measured from randomization. In a secondary analysis including only patients who received their ASCT, time-to-event will be measured from the date of ASCT. The proportion of CR (CR or PR) will be compared between treatment arms using a Fisher's exact test.

Time to Hematopoietic Recovery

Time to neutrophil recovery will be the first of two consecutive days of $\geq$ 500 neutrophils/μL following the expected nadir. Time to platelet engraftment will be the first day of one week without a platelet transfusion when the platelet count is $\geq$ 20,000/μL. Time to neutrophil recovery and platelet engraftment will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Hematologic Function at Day 100

Hematologic function will be ANC > 1,500 neutrophils/μL, hemoglobin > 10 g/dL without transfusion support, and platelet count > 100,000/μL without transfusion support. Hematologic function at Day 100 and 1 year will be compared between treatment arms.

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. 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. The proportion of patients developing infections will be compared between treatment arms.

Maximum Mucositis Score by Day +21

Mucositis score will be computed using the modified oral mucositis assessment scale (OMAS), a continuous measurement between certain ranges. This score can then be used to compare the treatment arms and analyzed with the t-test or multiple regressions, adjusting for other important variables.

Transplant-related Mortality

Transplant related mortality (TRM) is defined as death occurring in a patient from causes other than relapse or progression. Time to TRM will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Incidence of MDS/ AML and New, Abnormal Cytogenetics

The rate of MDS/AML and new, abnormal cytogenetics will be compared between the treatment arms using test of proportions or logistic regression, adjusting for other variables.

Immunologic Reconstitution

Immune reconstitution assays, which will include CD2, CD3, CD4, CD8, CD19, CD3+/CD25+, CD45RA/RO, CD56+/CD3-, and quantitative immunoglobulins (IgM, IgG and IgA), will be performed at baseline, Day +100, and 1 year post-transplant and will be compared between the treatment arms. This will also be assessed at 2 years post-transplant, if the 1 year assessment is abnormal.

APPENDIX A

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APPENDIX A

REFERENCES

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APPENDIX B

CONSENT FORM

Informed Consent to Participate in Research

Principal Investigator Contact Information
(Insert contact information for PI at your site)

Study Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Additional support is provided by GlaxoSmithKline Corporation, which makes one of the drugs (Bexxar) used in this study. GlaxoSmithKline will provide this drug free of charge. However, this company did not plan or design this clinical trial and will not have a part in analyzing the results of this study.

Introduction
This is a clinical trial, which is a research study to answer specific medical questions. The information from this study will help future patients. The Study doctor (the person in charge of the research) will explain the clinical trial to you. Clinical trials include only people who choose to join the study.

Please take your time to decide if you want to join this study. Some people find it helpful to talk about the study with their family and friends before they make a decision. It may also be useful to talk with your doctor and other people on your health care team about the study. If you have questions or want to know more about the study, you can ask them for more information.

You are being asked to take part in this study because you have Non-Hodgkin's Lymphoma (NHL) which has either not fully responded to treatment or has returned after an initial response. In this situation, many patients with NHL are treated with autologous peripheral blood stem cell transplantation. An autologous peripheral blood stem cell transplant is when your own stem cells are collected from your blood, frozen, and then given back to you after you receive chemotherapy, also referred to as conditioning therapy. There are a number of ways that an autologous stem cell transplant can be done.

Why is this study being done?
An important part of the transplant procedure is the high dose chemotherapy (called the conditioning regimen) given to try to get rid of all lymphoma cells. Although many people are cured of their NHL with this therapy, the lymphoma comes back in a large minority. This study compares two different conditioning regimens, one using the drugs Rituxan and BEAM (a mixture of the chemotherapy drugs BCNU, Etoposide, Ara-C, and Melphalan) and the other using the drugs Bexxar and BEAM, to find out which is better at curing lymphoma or if they are the same. In this study, you will get either the Rituxan/BEAM conditioning regimen or the Bexxar/BEAM conditioning regimen. You will not get both. Results of this trial will help doctors make better treatment decisions for future patients.

How many people will take part in the study?
Two hundred twenty-four patients will take part in this study. Half of the patients (112 patients) will receive the Rituxan/ BEAM pre-transplant conditioning and half (112 patients) will receive the Bexxar/ BEAM pre-transplant conditioning.

What will happen if I take part in this research study?
Before you begin the study **–** You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. The tests include:

- Medical history
- Physical examination, including height and weight
- Blood and urine tests
- EKG
- Heart function tests
- Pulmonary (lung) function tests
- Thyroid function test
- Tests to evaluate your lymphoma including scans and a bone marrow biopsy
- A blood pregnancy test if you are a woman able to have children; if you are pregnant, you will not be able to take part in this study.

During the study *(you can refer to the Study Chart later in this consent as you read this)* **–**

Randomization

All the exams, tests, and procedures described to this point are part of regular cancer care and may be done even if you do not join the study. However, if you were receiving regular cancer care, your doctor would choose the next treatment for you. As part of this study, we want to compare regular cancer care to an experimental treatment. To do this, you will be **randomized**

into one of the two conditioning regimen study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. You have a 50/50 chance of receiving each therapy. Neither you nor your doctor can choose the group you will be in.

Conditioning Regimen

The conditioning regimen is used to kill the lymphoma cells in your body.

- If you are in Group 1, you will receive the Rituxan/BEAM pre-transplant conditioning regimen. You will receive Rituxan on the 19th and 12th days before your transplant by intravenous infusion (through your vein). You will receive BEAM chemotherapy starting 6 days before your transplant. You will then receive the autologous cells that were collected and frozen during mobilization (this day that you receive your cells is referred to as Day 0). BEAM is a very common combination of chemotherapy drugs that has been widely used in transplants for NHL. Rituxan is an antibody against lymphoma cells that is commonly used both to treat lymphoma without a transplant and as part of transplant care.
- If you are in Group 2, you will receive the Bexxar/BEAM pre-transplant conditioning regimen. You will receive Bexxar on the 19th and 12th days before your transplant by intravenous infusion**.** You will receive BEAM chemotherapy starting 6 days before your transplant. On Day 0, you will receive the autologous cells that were collected and frozen after during mobilization. Bexxar is a new drug that was FDA approved for treatment of certain types of lymphoma but has not been used extensively in treatment of diffuse large B cell lymphoma or in transplants for NHL. The use of Bexxar is the investigational part of this study.

Reinfusion of Stem Cells (Transplantation)

After the conditioning regimen, the stem cells that were previously collected and frozen will be thawed and reinfused into you through your catheter. The cells will travel to your bone marrow where they'll begin making healthy, new blood cells. This step is necessary because the high dosages of chemotherapy given to you during the conditioning regimen will not only destroy lymphoma cells, but healthy cells in your bone marrow as well. Until the new stem cells begin producing healthy blood cells, you will be at an increased risk of excessive bleeding or developing an infection.

Description of Study Drugs

Rituxan (Rituximab) - Rituxan is a drug that can recognize lymphoma cells and either kill them and/or cause other immune cells in the body to kill them.

Bexxar - Bexxar is also a drug that recognizes lymphoma cells but, in addition, has a radioactive compound attached to it. When Bexxar attaches to lymphoma cells, the cells are killed by the radiation released by the radioactive compound. Bexxar is given to patients by physicians and

staff with experience in handling radioactive compounds, usually in the Nuclear Medicine Department of a hospital. Most patients receive this treatment as an outpatient. However, because the radioactivity of Bexxar lasts for several days, you will have to follow some precautions for several days to avoid exposing others to radiation. You will receive instruction on these precautions before treatment but they include sleeping in a separate bed and avoiding close, prolonged contact with children and pregnant women. The risk to others is very low.

BEAM- BEAM is a mixture of several chemotherapy drugs that interfere with the growth of cancer cells and are widely used to treat NHL:

BCNU (also called carmustine)

Etoposide (also called VP-16)

Ara-C (also called cytarabine)

Melphalan

When you are finished taking these drugs and have received your transplant, you will be watched closely. For this study, you will have the following tests at least twice per week for the first 4 weeks and then again at 8 weeks, 100 days, six months, one year and two years after transplantation:

- Medical history
- Physical examination
- Blood and urine tests

In addition to these tests, you will have blood drawn to test how well your immune system is working at 100 days, six months, one year, and two years after your transplant. Tests of your thyroid gland and your lung function will be done at one year and two years after your transplant. Your doctor may also require you to have tests of your thyroid gland for more than two years after your transplant.

Tests and exams to look at the status of your lymphoma will be done 100 days, 6 months, 1 year and 2 years after your transplant. These will include scans and bone marrow biopsies.

All of these exams, tests or procedures are part of regular medical care after a transplant and may be done even if you do not join the study. The schedule for testing is only for tests required for the study. Some of these tests will be done more frequently than described here if your doctor thinks it is necessary for your medical care.

How long will I be on this study?

After your transplant, the study doctor will ask you to visit the office for follow-up exams for two years to receive the study tests and procedures described above. Your doctor will also collect information on how you are doing for up to five years after your transplant.

Follow up for your transplant will last as long as you require care. However, we would like to keep track of your medical condition for the rest of your life by contacting you and the doctor

providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study and transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care. It is not necessary for you to agree to follow-up for longer than 5 years to participate in this study.

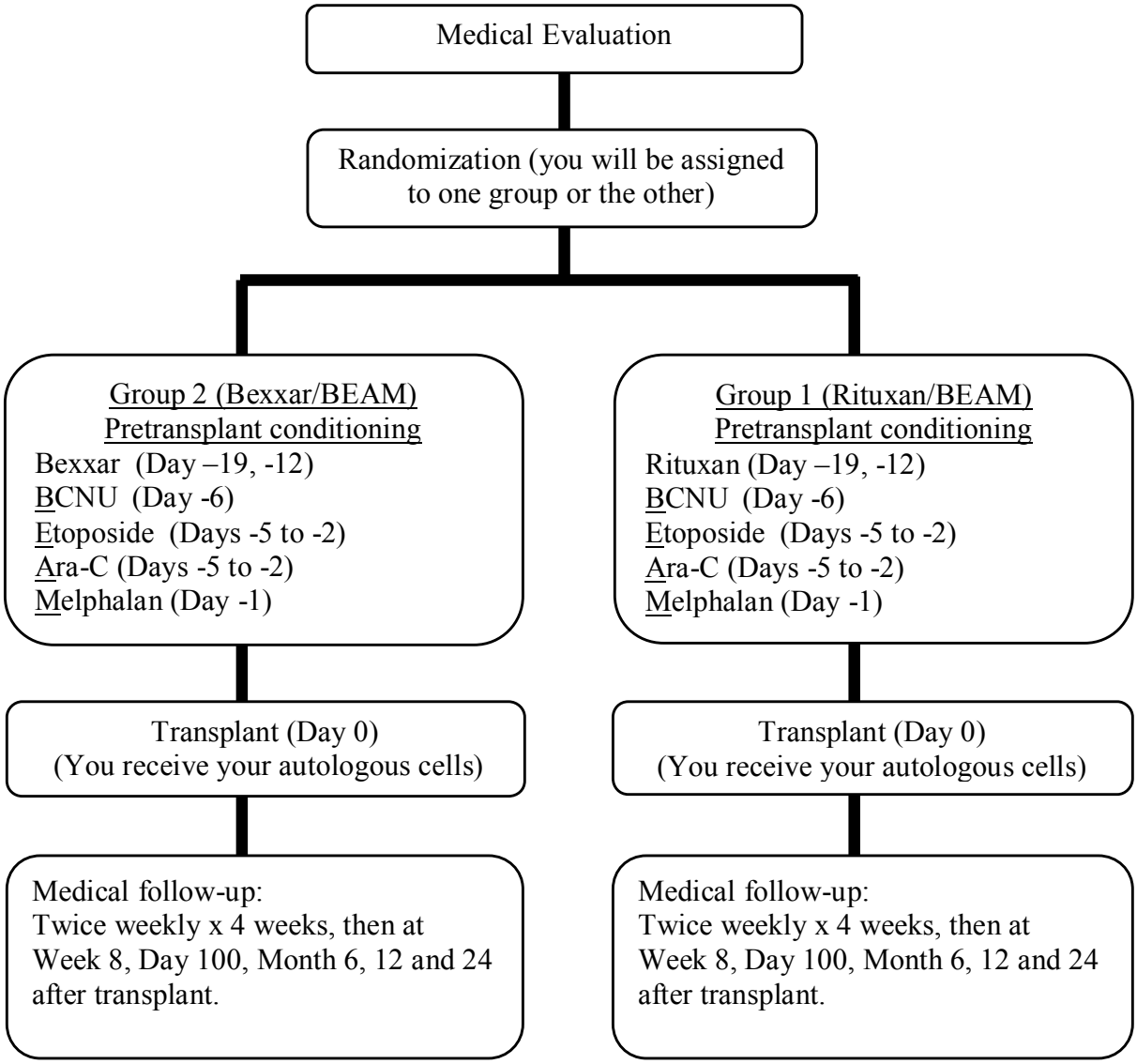
Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the medications can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Can the Study Doctor withdraw me from the study?
You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The study doctor decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking is found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

STUDY CHART


Medical Evaluation
Randomization (you will be assigned to one group or the other)
Group 2 (Bexxar/BEAM)
Pretransplant conditioning
Bexxar (Day –19, -12)
BCNU (Day -6)
Etoposide (Days -5 to -2)
Ara-C (Days -5 to -2)
Melphalan (Day -1)
Group 1 (Rituxan/BEAM)
Pretransplant conditioning
Rituxan (Day –19, -12)
BCNU (Day -6)
Etoposide (Days -5 to -2)
Ara-C (Days -5 to -2)
Melphalan (Day -1)
Transplant (Day 0)
(You receive your autologous cells)
Transplant (Day 0)
(You receive your autologous cells)
Medical follow-up:
Twice weekly x 4 weeks, then at Week 8, Day 100, Month 6, 12 and 24 after transplant.
Medical follow-up:
Twice weekly x 4 weeks, then at Week 8, Day 100, Month 6, 12 and 24 after transplant.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. Many of these side effects are possible regardless of the type of autologous transplant you receive. It is possible that some of these side effects are increased by the drugs used in this study or that these drugs will have new side effects that we don't know about now.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Potential Side Effects

Rituxan		
Likely	**Less Likely**	**Rare but Serious**
• 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 • Chest pain • Renal failure • Angioedema • Angina • Progressive Multifocal Leukoencephalopathy (PML)
GCSF (Filgrastim)		
Likely	**Less Likely**	**Rare but Serious**
• Muscle pain • Bone pain	• Fluid retention • Fluid around the heart • Pain and swelling at the injection site	• Allergic reactions • Spleen swelling • Spleen rupture • Difficulty breathing

Bexxar		
Likely	**Less Likely**	**Rare but Serious**
• Low blood counts	• Allergic reaction • Nausea/vomiting • Abdominal pain • Diarrhea • Low thyroid hormone • Constipation • Anorexia • High blood pressure • Headache • Itching • Sweating • Skin rash • Cough	• Fever, shaking chills • Low blood pressure • Difficulty breathing • Abnormal bone marrow • Second cancers, including MDS and leukemia • Human Anti-Mouse Antibodies
BEAM		
Likely	**Less Likely**	**Rare but Serious**
• Low blood counts • Nausea/vomiting • Mouth sores • Sores in esophagus • Abdominal pain/diarrhea • Difficulty eating • Hair loss • Fatigue	• Liver problems • Lung problems • Low blood pressure • High levels of uric acid • Skin rash • Chills	• Liver failure • Severe lung problems • Severe allergic reactions • Second cancers, including MDS and leukemia • Life-threatening infection • Disease of the peripheral nervous system • Sterility

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

Hepatitis B Reactivation: In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as Rituxan. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop taking Rituxan. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking Rituxan or after stopping treatment, you should tell your study doctor immediately. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Progressive Multifocal Leukoencephalopathy (PML): In the past, the FDA has reported a very rare case of two deaths that were reported after patients had been treated with Rituxan for systemic lupus erythematosus (SLE). These deaths have been caused by a viral infection of the brain called progressive multifocal leukoencephalopathy (PML). In rare cases, you may encounter problems with speech or movement, or in very rare cases death. Please notify your doctor immediately if you have any new or worsening memory loss, trouble thinking, difficulty walking, or changes in vision.

Potential Allergic Reactions to Murine Proteins: Bexxar is a mouse (murine) protein antibody. You should notify your physician if you know that you have received a product containing mouse antibodies. Some patients that have previously been exposed to products containing mouse antibodies may develop their own antibodies against mouse proteins. This may happen to you after you receive Bexxar. These are called human anti-mouse antibodies or HAMA. The presence of HAMA may possibly make a person more likely to develop an allergic reaction to mouse proteins, but this is not proven. Unfortunately, there is no well-accepted test for measuring HAMA and it is not known whether the presence of HAMA would let us know if you would have an allergic reaction to mouse proteins. Therefore, we will not be testing for HAMA in this study. In the event that you do have an allergic reaction, epinephrine (a drug used for cardiac arrest) and antihistamines (drugs used for allergic reactions) will be available at your bedside during the administration of Bexxar.

This study is designed to help persons who are suffering from Non-Hodgkin's Lymphoma (NHL). A risk remains, however, that neither treatment arm will be successful in curing or improving your illness.

After you have recovered from your stem cell transplantation, your doctor may consider additional radiation to areas where you have had lymphoma. If so, your doctor will review with you the rationale and potential side effects at that time.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. This research study is comparing two pre-transplant conditioning regimens. At this time doctors do not know if one conditioning regimen has better results than the other, or if they both have the same results. We do know that the information from this study will help doctors learn more about transplantation for NHL. This information could help future patients with NHL.

What other choices do I have if I do not take part in the study?
Your other choices may include:

- Treatment with other drugs or a combination of drugs without a transplant.
- An autologous stem cell transplant that is not part of the study or another type of transplant.
- No therapy directed against your lymphoma at this time.

Talk to your doctor about your treatment choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The company that manufactures Bexxar will provide this drug at no cost. All other costs of your care including the chemotherapy drugs and costs associated with administration of them will need to be paid by you and/or your health plan/insurance company. All of the medical tests, evaluations and procedures in this study are considered part of standard medical care.

The companies that make the drugs used in this study did not plan or design this clinical trial. They will also not have a part in analyzing the results of this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- Members of the Blood and Marrow Transplant Clinical Trials Network, which is conducting this study
- The National Heart Lung and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Southwest Oncology group (SWOG), clinical trials cooperative group

Information about the results of this study will also be provided to the GlaxoSmithKline Company (which makes Bexxar) but without any identifying information.

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 III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-cell Non-Hodgkin's Lymphoma*.

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., 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)

_____

_____

_____

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:

- Members of the BMT CTN Data and Coordinating Center and 0401 Protocol Team
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Southwest Oncology group (SWOG), clinical trials cooperative group
- 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)

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

- 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
- Other:

_____

_____

_____

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.

****

About Using Blood for Research

Please note: This section of the informed consent form is about future research studies that will be done using blood samples from people who are taking part in the main study described above. You may give blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to giving blood samples for future research studies. You can say "yes" or "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

We would like to have a blood sample for future research. If you agree, 1 tablespoon (10 mL) of blood will be obtained at the time other blood samples are drawn at the beginning of the study and will be kept and may be used in research to learn more about cancer and other diseases. When the sample is given to investigators for research, no information about name, address, phone number of other information that will let the researcher know who you are will be provided.

The sample collected for research purposes will be sent to the National Heart, Lung, and Blood Institute (NHLBI) sample repository in Maryland. The sample will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the repository where your sample is being stored does not have a link to this code. Your sample will be stored at this repository until the entire sample has been used for the research tests or until the end of the study. Any research performed on this sample must first be approved by an advisory panel at the NHLBI.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About: The choice to let us have a blood sample for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits: The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks: The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice: Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

- ❑ Yes, I agree to have blood drawn for future research.
- ❑ No, I do not agree to have blood drawn for future research.

_____ _____
Signature *Date*

****

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____*[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Witness _____

Date_____

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____
Signature of person conducting informed consent

_____
Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. PATHOLOGY/CYTOGENETICS STUDIES

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

Pathology and cytogenetic studies will be conducted per institutional guidelines.

2. MEASUREMENTS OF POST-TRANSPLANT IMMUNE RECONSTITUTION

Background and Rationale: Following peripheral blood stem cell transplantation, total B-cells (CD19+) are reconstituted to normal levels within 2-4 months [1-3]. T-cell recovery typically demonstrates relatively normal to elevated numbers of CD8+ cells, with CD4+ numbers remaining low for a year or longer, resulting in a persistently inverted CD4+/CD8+ ratio. CD45+RO+ memory cell numbers usually exceed CD45+RA+ naïve T-cell numbers during the first year, suggesting that T-cell recovery represents the expansion of mature T cells and a limited T-cell repertoire. NK cells recover early post transplant, and may reach normal values within one month.

The effect of post-autologous peripheral blood stem cell transplant adjuvant rituximab on immune reconstitution, as measured by lymphocyte subsets and quantitative immunoglobulins, has been reported by Horwitz et al [4]. In a prospective study of weekly rituximab for 4 to 8 doses beginning post-transplant Day 42, B-cell recovery was delayed in all patients and suppressed immunoglobulin G (IgG) levels and pneumococcus antibody titers in a subset. B-cell counts, measured by CD20+ and CD19+ cells, were low in absolute number in the majority of patients at study entry, and declined to zero in all patients receiving rituximab. Recovery occurred from 18-24 months after transplant. Mean CD3+ numbers were only mildly depressed during the 24 months post transplant; whereas, mean CD4+ cell numbers were decreased throughout the first year but recovered by 24 months. Natural killer cells were present in normal quantities throughout the study period.

A depletion of or a substantial drop in CD20-positive peripheral blood cells was observed in 47 of 59 patients shortly after treatment with ^{131}I tositumomab (Bexxar) for relapsed or refractory B-cell non-Hodgkin's lymphoma [5]. The median time to B-cell recovery (defined as a return to the normal range of the absolute number of CD20-expressing cells) was 3.6 months (95% CI: 3.2-6.6). No significant effect on T-cell counts was observed.

Assays: Blood for flow cytometry will be taken at the following time points: prior to the initiation of the Day -19 Bexxar or Rituxan (baseline), at Day + 100, and yearly for 2 years. The two year post-ASCT assay is not required unless the results from the one year post-ASCT assay were abnormal. The following tests will be performed: CD2, CD3, CD4, CD8, CD19, CD3/CD25, CD45 RA/RO, CD56+/CD3-, and quantitative immunoglobulins (IgM, IgG and IgA). These tests will be performed per institutional guidelines.

3. RESEARCH SPECIMENS

BMT CTN research samples will be given unique bar code designations that cannot be linked back to the donor or the recipient. All research samples will become property of the NHLBI after conclusion of the BMT CTN Protocol #0401 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If the committee approves an Investigator's request for these samples, the NHLBI may provide a panel of the specimens requested using unique code numbers. 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 All Patients: Peripheral blood (10mL nucleated cell sample) will be collected for future testing at the time of disease staging and shipped quarterly to the Repository in compliance with the shipping procedures specified in the BMT CTN MOP.

SCHEDULE OF LABORATORY EVALUATIONS

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
Flow Cytometry for analysis of CD2, CD3, CD4, CD8, CD19, CD3/CD25, CD45 RA/RO, and CD56+/CD3-	Per institutional guidelines	Store according to institutional practice	At baseline and at Day 100, 1year, and 2 years post-transplant[1]	N/A	Transplant Center
Quantitative Immunoglobulins (IgM, IgG and IgA)	Per institutional guidelines	Store according to institutional practice	At baseline and at Day 100, 1year, and 2 years post-transplant[1]	N/A	Transplant Center
Patient Research Specimen Nucleated Cells from Peripheral Blood	10 mL peripheral blood	Obtain white blood cell pellet (by ficoll) and freeze in cryovial at -70°	Prior to initiation of the ASCT conditioning therapy	Frozen shipment quarterly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD

[1] Immune reconstitution assays are not required at two years post-ASCT, unless results from the one year post-ASCT assays are abnormal.

REFERENCES IN APPENDIX C

1. Ashihara E, Shimazaki C, Yamagata N, Hirata T, Okawa K, Oku N, Goto H, Inaba T, Fujita N, Nakagawa M. Reconstitution of lymphocyte subsets after peripheral blood stem cell transplantation: two-color flow cytometric analysis. Bone Marrow Transplant 1994;13:377-381.
2. Steingrimsdottir H, Gruber A, Bjokholm M, Svensson A, Hansson M. Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications. Haematologica 2000;85:832-838.
3. Schlenke P, Sheikhzadeh S, Weber K, Wagner T, Kirchner H. Immune reconstitution and production of intracellular cytokines in T lymphocyte populations following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2001;28:251-257.
4. Horwitz SM, Negrin RS, Blume KG, Breslin S, Stuart MJ, Stockeri-Goldstein KE, Johnston LJ, Wong RM, Shizuru JA, Horning SJ. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. Blood 2004;103:777-783.
5. Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M, Regan D, Fisher S, Gutierrez J, Kroll S, Stagg R, Tidmarsh G, Wahl R. Radioimmunotherapy with iodine 131I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000;96:1259-1266.

APPENDIX D

HUMAN SUBJECTS

APPENDIX D

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, chemotherapy agents, BEAM or Bexxar should be discussed as objectively as possible.

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

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

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 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 IBMTR 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 E

STUDY DRUG (BEXXAR) ORDER FORM

GSK Protocol #105918

Study Drug Order Form

Phase III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-cell Non-Hodgkin's Lymphoma
(BMT CTN Protocol 0401)

Patient Identification Number: _____

Investigator: _____

Site Name: _____ **Date:** _____

Study/Site Coordinator: _____
Street Address: _____
City, State, Zip Code: _____
Phone #: _____ Fax #: _____

Radiopharmacy Contact Information

Contact Person: _____
Street Address: _____
City, State, Zip Code: _____
Phone #: _____ Fax #: _____

Nuclear Medicine/Radiation Oncology Contact Information

Prescribing Physician Name (Authorized User): _____

Prescribing Physician Signature: _____

Contact Person: _____
Street Address: _____
City, State, Zip Code: _____
Phone #: _____ Fax #: _____

Dosimetric: Date: Time: Therapeutic: Date: Time:

Dx Alternate: Date(s): Tx Alternate: Date(s):

Site Name Where the Tositumomab will be administered: _____

Contact Person: _____
Street Address: _____
City, State, Zip Code: _____
Phone #: _____ Fax #: _____

To complete Drug order placement:

1. **Fax completed form to your radiopharmacy.**
2. **Have your radiopharmacy place order by faxing form to (877) 279-1512. Your Radiopharmacy can call the BEXXAR Service Center (877) 423-9927 if additional scheduling requirements are needed.**
3. **If you have any questions regarding the order process please contact the Bexxar Service Center at (877) 423-9927.**