

BMT CTN 0202

**Autologous vs. Non-Myeloablative Allogeneic
Hematopoietic Stem Cell Transplantation (HSCT)
for Patients with Chemosensitive Follicular Non-
Hodgkin's Lymphoma Beyond First Complete
Response or First Partial Response**

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BMT CTN PROTOCOL 0202 VERSION 4.0

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PROTOCOL SYNOPSIS - BMT CTN PROTOCOL #0202**Autologous vs. Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Chemosensitive Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response or First Partial Response**

Study Co-Chairpersons:	Ginna Laport, M.D. and Robert Negrin, M.D.
Accrual Objective:	A minimum of 80 patients with recurrent follicular non-Hodgkin's lymphoma (REAL classification follicle center lymphoma, follicular grades I and II or patients with histologically confirmed WHO classification follicular lymphoma grades 1, 2, 3a or 3b) and an HLA-matched sibling will be entered on the protocol. It is expected during the same period that an additional 187-320 patients without an HLA-matched sibling will be entered on the protocol.
Study Design:	This study is designed as a Phase II/III, multi-center trial, comparing two transplant strategies to determine whether non-myeloablative allogeneic HSCT will improve long-term progression-free survival compared to autologous HSCT. Recipients will be biologically assigned to the appropriate treatment arm depending on the availability of an HLA-matched sibling.
Accrual Period:	The estimated accrual period is three years.
Primary Objective:	The primary objective is to compare progression-free survival (PFS) at three years between the two treatment arms.
Secondary Objectives:	Secondary objectives for the comparison of non-myeloablative allogeneic HSCT vs. autologous HSCT are three-year overall survival, time to progression, time to complete response (CR) and partial response (PR), time to off-study therapy, incidence of infections, and incidence of NCI Common Terminology Criteria Adverse Events (CTCAE) Version 3.0 Grade ≥ 3 toxicities.
	Secondary objectives for the non-myeloablative allogeneic HSCT recipients include incidence and severity of acute and chronic GVHD, and incidence of primary and secondary graft failure.
	The efficacy of cyclophosphamide plus rituximab <i>in vivo</i> purging will also be evaluated as well as the prediction of disease relapse by measurement of t(14;18) by quantitative polymerase chain reaction (PCR).
	Quality of life as measured by the SF-36 and the FACT-BMT will be described in both patient populations.
Eligibility Criteria:	Eligible patients are ≤ 75 years of age with Karnofsky performance score $\geq 70\%$ who have histologically confirmed recurrent follicular lymphoma (REAL classification follicle center follicular grades I and II or patients with histologically confirmed WHO classification follicular lymphoma grades 1, 2, 3a or 3b). Patients must have received ≤ 3 prior treatment regimens. Monoclonal antibody therapy

and local radiation will not be counted as prior therapies. Patients must demonstrate chemosensitive disease by achieving reduction in lymph node axial diameter to < 3 cm or > 50% reduction in estimated lymph node volume AND \leq 20% BM involvement after their most recent salvage therapy. Patients do not have to express t(14;18).

Treatment Description:

Within 4 weeks of enrollment and after HLA typing and evaluation of potential sibling donors is complete, all patients will receive cyclophosphamide 4 gm/m² on Day 2 concomitantly with rituximab 375 mg/m² on Days 1 and 8. G-CSF 10 mcg/kg/day (autologous patients) or 5 mcg/kg/day (allogeneic patients) SQ or IV will be given starting 2 days after the initiation of cyclophosphamide. Patients assigned to the autologous HSCT arm will undergo leukapheresis upon blood count recovery. After the mobilization process is complete, autologous patients will then receive either fractionated total body irradiation (FTBI) 1200 cGy or BCNU 15 mg/kg. VP-16 60 mg/kg and cyclophosphamide 100 mg/kg will also be given followed by autologous HSCT. Patients must have an adequate autograft defined as $\geq 2.0 \times 10^6$ CD34⁺ cells/kg. Rituximab 375 mg/m² x 4 weekly doses, to begin on approximately Day +42, will be given as maintenance therapy. Patients with an HLA-matched sibling will receive a non-myeloablative conditioning regimen of fludarabine 30 mg/m²/day and cyclophosphamide 750 mg/m²/day from Day -6 to -4 followed by infusion of G-CSF mobilized donor hematopoietic stem cells. Rituximab 375 mg/m² will be administered on Day -13, -6, +1 and +8. GVHD prophylaxis will consist of tacrolimus (IV or PO) until Day +90 followed by a taper and methotrexate 5 mg/m² IV on Day +1, +3, and +6 post-HSCT. All patients will undergo PCR analysis for t(14:18) from the peripheral blood after blood count recovery from the cyclophosphamide/rituximab cytoreductive/mobilization regimen and on Day +28, +84, +180 and yearly post-HSCT if positive at any time from diagnosis to initial study evaluation.

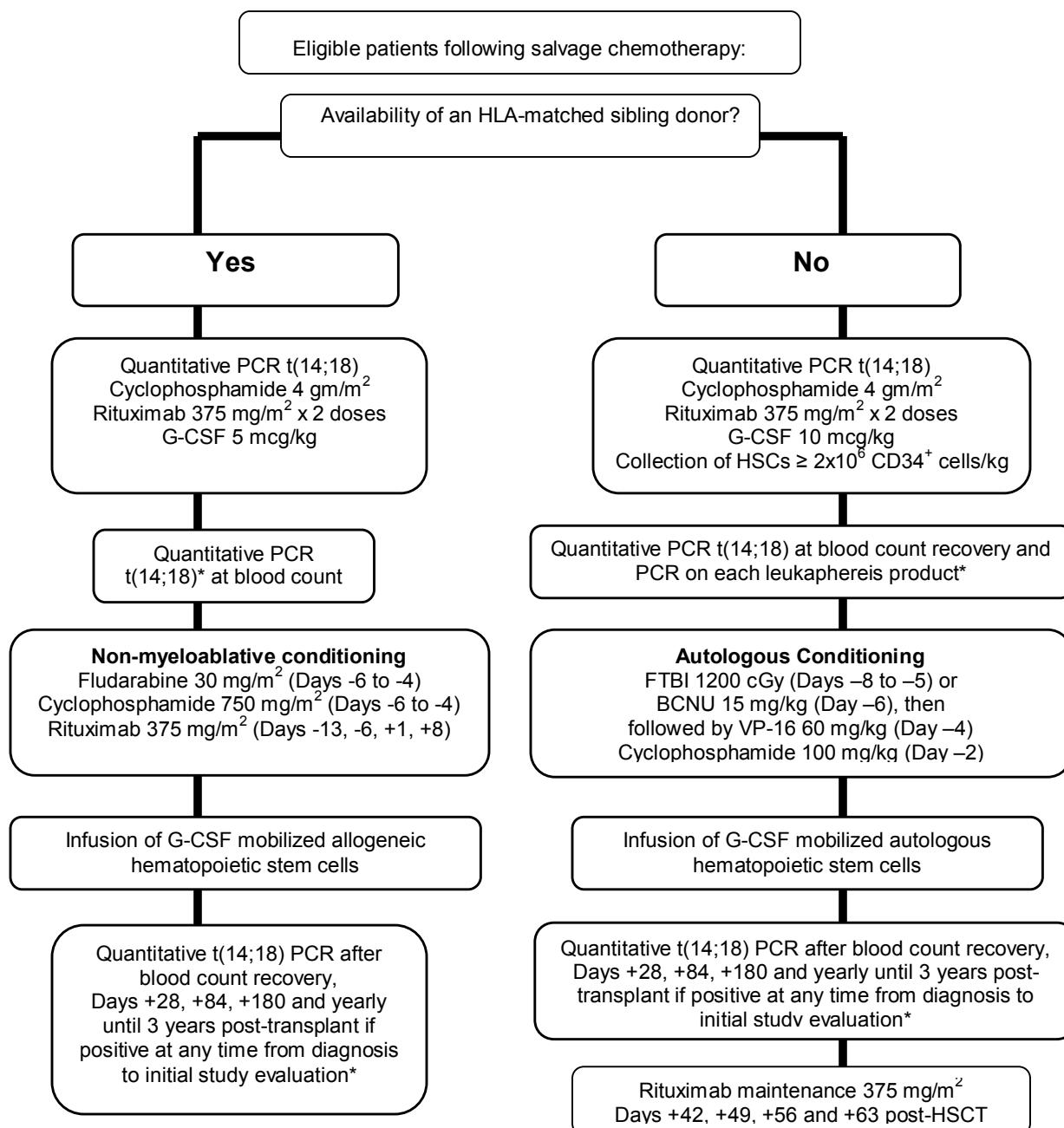
Quality of Life:

The FACT-BMT and MOS SF-36 instruments will be used to describe the health-related quality of life (HQL) of patients. A secondary analysis will compare the HQL between the two treatment arms. The self-report questionnaire will be performed prior to cytoreductive/mobilization therapy and at two years post-HSCT for English and Spanish speaking patients only.

Study Duration:

Patients will be followed for at least three years post-HSCT.

TREATMENT SCHEMA



* Only required for patients who had a positive PCR at any point prior to study entry or at the baseline screen on study.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Although patients with follicular non-Hodgkin's lymphoma (NHL) typically experience a relatively indolent course, the disease is rarely curable with conventional chemotherapy. Patients with follicular NHL are usually treated only when symptoms require palliation or if bulky disease exists since no survival advantage has been shown as compared to administering conventional treatment at initial diagnosis. While most patients achieve a remission with initial chemotherapy, a continuous pattern of relapse occurs resulting in progressively shorter remission durations. Additionally, the increased response rates conferred by anthracycline-containing regimens have not translated into improved survival and thus the median survival time of 6 to 10 years has not been significantly impacted over the last decade [1-3].

1.2. Autologous Hematopoietic Stem Cell Transplantation

In light of the discouraging results with conventional chemotherapy, high dose chemotherapy with autologous HSCT has been explored as an alternative approach in patients with follicular NHL. Several studies have shown improved disease-free survival (DFS) but one recently published study has also shown an advantage for overall survival [3-8]. The European Group for Blood and Marrow Transplantation (EBMT) conducted a randomized trial known as the CUP Trial in which 140 patients with relapsed follicular NHL were randomized to either chemotherapy alone, autologous HSCT with a purged autograft using monoclonal antibodies or autologous HSCT with an unpurged autograft. With a median follow-up of 69 months, the patients who received an autologous HSCT, purged or unpurged, show a significantly higher two-year progression-free and overall survival (OS). There was no difference between the two autologous HSCT arms in these endpoints. Overall survival at four years for the chemotherapy arm, unpurged autologous HSCT arm and purged autologous HSCT arm was 46%, 71% and 77%. The two-year progression-free survival (PFS) was 26%, 58% and 55% respectively. There was a significant reduction in hazard rates for both progression-free and overall survival when a comparison was made between the chemotherapy patients and the combined groups of autologous HSCT patients.

As with conventional chemotherapy, the outcome for patients who receive autologous HSCT is related to the number of prior chemotherapy regimens received. Patients transplanted in first remission benefit more than those receiving a transplant after numerous prior therapies. Two retrospective studies and one prospective study have shown that patients with follicular lymphoma undergoing autologous HSCT who had received > 3 prior chemotherapy regimens showed inferior survival compared to patients treated with < 3 prior regimens [3-6]. Bierman *et al* in one of the largest single institution retrospective analyses, reported on 100 patients with follicular NHL. That study demonstrated a 4-year estimated failure-free survival and overall survival of 44% and 65%, respectively [4]. Response rates (RR) were high with an 82% overall RR with 68% achieving a complete remission (CR). Treatment-related mortality was 8%.

However, despite these encouraging numbers, there was no definite evidence of a plateau in failure-free survival (See Figure 1). The retrospective study by Cao *et al* of 49 patients with follicular NHL showed similar results with a 4-year disease-free survival (DFS) and OS of 44% and 60%, respectively [5]. The prospective study of 64 follicular NHL patients reported by Rohatiner *et al* also concurred with these findings reporting a significant correlation between survival and the total number of previous regimens with patients who received < 3 regimens surviving longer compared to patients who received > 3 treatment cycles [6].

Another important factor influencing outcome is the previous sensitivity of the patients to chemotherapy. A recent EBMT analysis of 467 patients indicated that patients who had previously responded to chemotherapy have similar OS and PFS whether transplanted in 1st remission or after chemosensitive recurrence. The OS and PFS were considerably lower in patients with chemoresistant disease [7] (see Figure 2).

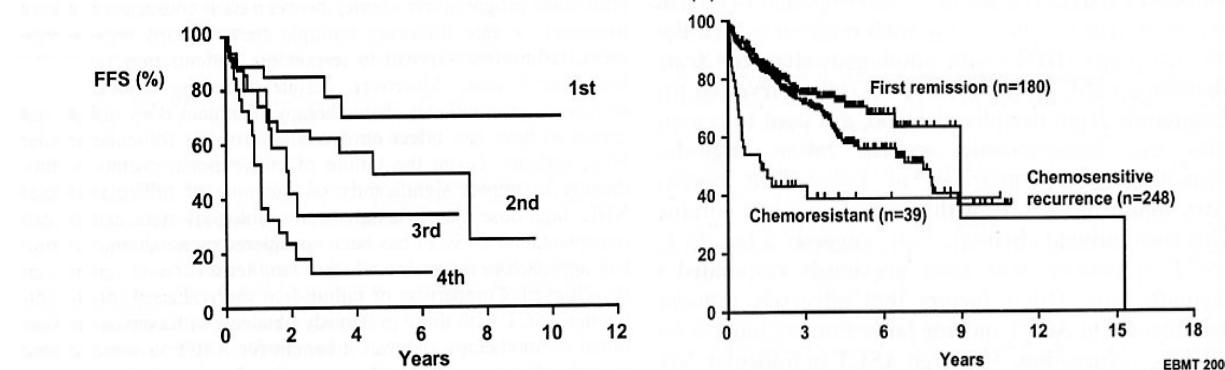


Fig. 1: Failure-free survival after autologous HSCT according to number of prior courses of chemotherapy

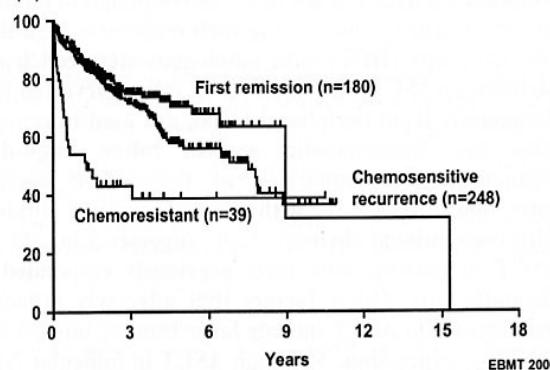


Fig. 2: EBMT registry data showing OS after autologous HSCT according to previous response to chemotherapy

1.3. Minimal Residual Disease

The characteristic t(14;18) gene translocation characteristic of 70-80% of patients with follicular NHL leads to overexpression of the *bcl-2* gene in the bone marrow even when there is no histologic evidence of bone marrow involvement [10]. The presence of the *bcl-2* rearrangement in the bone marrow of follicular NHL patients is another important prognostic indicator and there has been increasing evidence that the presence of the *bcl-2* rearrangement may be a useful surrogate endpoint to monitor treatment efficacy in indolent NHL [10,11]. In the t(14;18) translocation, the *bcl-2* gene is moved from chromosome 18 to the immunoglobulin heavy chain (IgH) locus on chromosome 14 [12]. The resultant *bcl-2* gene product is an inhibitor of apoptosis and it is believed that *bcl-2* overexpression may be an important factor in lymphomagenesis [13]. Cells bearing this translocation can be detected in the peripheral blood or bone marrow by the highly sensitive polymerase chain reaction (PCR) technique [14]. Thus PCR for t(14;18) provides a sensitive, quantitative and convenient measure of minimal residual disease and there is a clear association between the induction of molecular remission and PFS [11].

Freedman *et al* reported that the presence of minimal residual disease in the reinfused marrow was the most significant prognostic factor for relapse in the autologous HSCT setting [11]. In this particular study of 153 patients with follicular NHL, patients with *bcl-2* negative bone marrow after *ex vivo* purging with monoclonal antibodies had significantly longer relapse-free survival (RFS) compared to those who still had the detectable *bcl-2* rearrangement. The eight-year freedom from recurrence was 83% compared to 19% for patients who were PCR+ ($p=.0001$). Continued PCR negativity in follow-up bone marrow samples was also strongly predictive of continued CR and the 12-year OS from diagnosis was 69%. This data provided compelling evidence that autologous HSCT may prolong OS in patients with follicular NHL considering that historically the median OS from diagnosis has been 8 years.

1.4. *In Vivo* Purgung with Rituximab

Contamination of the hematopoietic stem cell graft by tumor cells is thought to be a major factor contributing to the high relapse rates seen with autologous HSCT. Reducing the rate of relapse may be achieved by pre-HSCT purging of the hematopoietic stem cell product followed by post-HSCT maintenance. Various *in vitro* methods have been utilized to decrease or eliminate residual tumor cells from the harvest product. Such techniques have included purging with B-cell monoclonal antibodies, chemotherapeutic agents such as mafosfamide and CD34⁺ positive selection [15-18]. While all of these methods have reduced the level of tumor cell contamination, most grafts have remained PCR positive and there have been no randomized trials to date strongly supporting the use of *in vitro* purging in this setting [8,19]. 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 [20]. For example, the above mentioned study by Freedman *et al* required the use of 3 monoclonal antibodies and rabbit complement to achieve successful marrow purging [11].

One of the most promising strategies to reduce relapse involves *in vivo* purging with rituximab. In contrast to *in vitro* purging methods aimed at removing contaminating tumor cells from the hematopoietic stem cell harvest, the administration of rituximab *in vivo* depletes the peripheral blood of all CD20⁺ cells preventing contamination of the graft by lymphoma cells [21]. Rituximab is a human/mouse monoclonal antibody recognizing CD20⁺, an antigen expressed on all cells of B cell lineage including B cell NHL [22]. Rituximab 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. The B cells in the peripheral blood of patients treated with rituximab are rapidly and effectively cleared for more than three months [21]. This strategy has been effectively used in patients with both aggressive and indolent lymphomas including untreated patients with follicular NHL and a low tumor burden [24-26].

Rituximab has been successfully incorporated into the hematopoietic stem cell mobilization regimen by several groups for the purpose of *in vivo* purging [27-32]. Rituximab purging has not demonstrated any negative effects with regards to hematopoietic stem cell yield or function with hematopoietic recovery being comparable following transplantation in purged versus unpurged patients [27]. Most importantly, the clearance of *bcl-2* positive cells in the graft has been unequivocally documented in B cell NHL patients including grafts from follicular lymphoma

patients. In a prospective study with 15 patients with mantle cell lymphoma or follicular lymphoma, Magni *et al* administered 2 cycles of intensive chemotherapy with 2 doses of rituximab [31]. Ninety-three percent of the patients who received rituximab had PCR-negative harvests compared to only 40% of 10 control patients who had received the identical therapeutic regimen without rituximab. Four other studies that incorporated rituximab into the mobilization regimen yielded PCR negative harvests ranging from 60%-100% of the products that were known to be PCR+ prior to collection [28-30, 33]. However, it should be noted that the largest sample size of these 5 studies consisted of only 13 patients. The optimal timing and dosing of rituximab administration during mobilization still remains to be clearly established but current reports have ranged from 1 to 4 doses. The effect of *in vivo* purging on clinical outcome is still not clear but should become more evident as the data mature.

1.5. Relapse Prevention with Rituximab

While *in vivo* purging addresses the problem of tumor contamination in the hematopoietic stem cell graft, the regrowth of persistent malignant cells in the recipient represents another obstacle to prolonged survival. Post-transplant or maintenance chemotherapy with rituximab in the follicular NHL setting is currently the subject of active investigation. Buckstein *et al* administered rituximab maintenance therapy to 17 patients with follicular NHL who had also received rituximab prior to the mobilization regimen. At a median of one year follow-up, all assessable patients remained in CR and all 7 patients evaluable for molecular monitoring remained *bcl-2* negative at 6 months. In this same study, four of 12 patients who received alpha-interferon instead of rituximab for maintenance relapsed at a median follow-up of 28 months [34]. Horwitz *et al* administered four weekly infusions of rituximab to 28 patients with NHL beginning 42 days after transplant with further infusions given at 6 months. All patients had rapid depletion of B cells with no increase in infection or significant adverse events except for an isolated neutropenia that occurred in 54% of patients. The neutropenic episodes did not result in significant adverse events and all episodes resolved spontaneously within seven days or responded to G-CSF administration. At a median follow-up of 30 months, the event-free survival and OS was 83% and 88% respectively [35]. In other published reports, Magni *et al* and Ladetto *et al* demonstrated the safety and feasibility of incorporating rituximab for the purposes of *in vivo* purging and post-HSCT maintenance in patients with B-cell NHL including follicular NHL [31, 33]. There are other ongoing studies evaluating rituximab maintenance therapy post-HSCT including a large comprehensive EBMT study that is evaluating both *in vivo* purging and maintenance with rituximab in a multi-center study with an accrual goal of 460 patients with follicular NHL in 2nd or 3rd remission.

1.6. Allogeneic Hematopoietic Stem Cell Transplantation for Follicular Lymphoma

High dose chemoradiotherapy with allogeneic hematopoietic stem cell/bone marrow transplantation has also been considered for patients with recurrent follicular NHL with the goal of harnessing a graft-versus-lymphoma effect and to circumvent the tumor cell contamination associated with autologous hematopoietic stem cell harvests [36-38]. Considerable evidence has shown that an immune-mediated graft-versus-malignancy effect occurs after allogeneic HSCT and that it contributes to the achievement of durable remissions in patients with hematologic malignancies [39-41]. The most direct evidence of the graft-versus-malignancy effect is the re-

induction of CR by withdrawal of immunosuppression and/or the infusion of donor lymphocytes in patients who had relapsed after allogeneic HSCT [42, 43]. This treatment strategy has been widely described among patients with acute and chronic myelogenous leukemia with several responses seen in lymphoma and myeloma patients [44-46]. Von Besien *et al* described 4 patients with NHL who relapsed after allogeneic HSCT and then subsequently responded to withdrawal of immunosuppression [47].

Although no randomized trials have been performed, several studies have reported a lower risk of relapse compared to autologous HSCT. However, this benefit has been invariably offset by the treatment-related mortality associated with allogeneic HSCT. In 1997, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported the results of 113 patients with follicular NHL who underwent allogeneic HSCT with HLA-matched siblings [37]. The three-year probability of DFS and OS was 49% with only a 16% incidence of relapse. However, treatment-related mortality was 40% with pulmonary complications leading the causes of non-relapse deaths. A recently updated analysis from the CIBMTR compared the outcomes of 904 patients with follicular NHL who underwent either myeloablative allogeneic HSCT (n=176), purged autologous HSCT (n=131) or unpurged autologous HSCT (n=597). The risk for relapse was 54% lower in the allogeneic recipients ($p<.001$) and 26% lower in recipients of purged autotransplants ($p=.04$) than in recipients of unpurged autotransplants. However, in a multivariate analysis, the risk of treatment-related mortality was 4.4 times higher after allogeneic than after autologous transplantation ($p<.001$), which resulted in comparable 5-year probabilities of overall survival(52% after allogeneic, 62% after purged autologous, 55% after unpurged autologous)[48]. In a smaller retrospective study from the Netherlands, the results of 18 patients who underwent autologous HSCT was compared to 10 patients who received an allogeneic HSCT. The PFS rates after two years were 68% and 22% for the allogeneic and autologous patients, respectively. Three of the allogeneic patients died from treatment-related mortality as opposed to none of the autologous patients [36].

1.6.1. Non-myeloablative Allogeneic Hematopoietic Stem Cell Transplantation

Non-myeloablative allogeneic HSCT incorporates a less intensive preparative regimen and relies solely on the immunotherapeutic effects of the allograft to confer antileukemic activity rather than the cytoreductive effects of high dose chemotherapy. The therapeutic benefit of allogeneic HSCT is derived from donor immunocompetent T cells that mediate an important graft-versus-malignancy effect. Initial attempts to administer an allogeneic hematopoietic stem cell graft without a conditioning regimen resulted in high rates of graft failure [49]. Therefore, it became apparent that some degree of immunosuppression is required to achieve engraftment and sustained mixed chimerism. A mixed chimera patient has hematopoietic cells of donor and recipient origins for varying lengths of time following allogeneic hematopoietic stem cell transplantation as opposed to a complete chimeric patient where only cells of donor origin are detectable. A mixed chimeric state may be adequate to be clinically efficacious in patients with autoimmune diseases or inborn errors of metabolism. However, full donor chimerism or at least a high level of donor hematopoiesis may be a prerequisite to eliminate malignant cells and effect a cure [50, 51].

Non-myeloablative allogeneic HSCT also induces less immune compromise in the patient as the duration and depth of neutropenia is reduced and host-derived immunocompetent cells are not immediately eliminated. Furthermore, the less intense regimen has been shown to allow for faster recovery of a T cell repertoire that is more complex and robust compared to the T cell repertoire of patients who received a myeloablative regimen [52, 53]. The transfusion requirements of recipients of non-myeloablative allogeneic HSCT are also significantly reduced compared to recipients of myeloablative allogeneic HSCT [54].

Some of the most promising data employing non-myeloablative allogeneic HSCT in follicular NHL patients was recently reported by the M.D. Anderson Cancer Center [55]. Twenty patients with indolent NHL received a conditioning regimen of fludarabine and cyclophosphamide \pm rituximab. Tacrolimus and methotrexate were given for graft-versus-host disease (GVHD) prophylaxis. The median age was 51 years old (range 31-68 years old) and all patients had advanced recurrent disease or were previously treated. The median number of prior chemotherapy regimens ranged from 1-5 (median, 2). All had received salvage chemotherapy and had stable or responding disease. Twelve patients were in second or greater complete remission at the time of transplantation. All patients achieved a CR after transplantation with no recurrences at a median follow-up of 21 months. All patients achieved engraftment of donor cells with the median percentage of donor cells at 1 month being 80% (range, 10%-100%). The actuarial probability of being alive and in remission at 2 years was 84%. The incidence of grade II-IV acute GVHD was 20% and the cumulative incidence of chronic GVHD was 64%. Only one patient died from a treatment-related complication.

The EBMT recently described the use of reduced-intensity conditioning for 188 patients with low-grade lymphoma including 52 patients with follicular and small lymphocytic NHL. The median age of the low grade NHL patients was 46(range, 27-65). The median number of prior chemotherapy regimens was 3 (range, 1-5) and 29% had previously received an autologous HSCT. Forty-four (85%) demonstrated chemosensitive disease at the time of transplant. Most patients received a fludarabine-based preparative regimen with 10% of patients receiving BEAM (BCNU, etoposide, cytarabine, melphalan), a more intensive and ablative regimen. Of the low-grade NHL patients, the 2 year PFS and OS was 54% and 65% respectively with a 21% progression rate. Treatment-related mortality was 31%, which was considerably higher than the previously mentioned M.D. Anderson study. The use of a more intensive conditioning regimen most likely contributed to toxicity [56].

1.7. Study Approach and Treatment

Numerous studies have demonstrated that autologous HSCT has clearly improved the PFS for patients with follicular lymphoma yet disease relapse remains a major obstacle to eventual cure of the disease. This issue will be addressed by the addition of maintenance therapy with rituximab after autologous HSCT while the patient is in a state of minimal residual disease. For those patients with an HLA-matched sibling, initial results of non-myeloablative allogeneic HSCT hold promise and will rely primarily on the graft-versus-malignancy effect to generate an anti-tumor response with the incorporation of rituximab in the conditioning regimen to enhance tumor control early and allow time for the graft-versus-malignancy effect to establish. Adequate immunosuppression will be required to prevent both graft rejection and GVHD. In this study

these two treatment strategies will be compared in an effort to identify an optimal approach to the treatment of follicular NHL.

Patients with either follicular small cleaved or follicular mixed NHL who have received ≤ 3 prior regimens and who have demonstrated chemosensitive disease will receive initial cytoreductive therapy with cyclophosphamide and rituximab with G-CSF support. Patients will be biologically assigned to a treatment arm. Patients with an HLA-matched sibling will receive a non-myeloablative allogeneic HSCT using a conditioning regimen of fludarabine, rituximab and cyclophosphamide and an immunosuppressive regimen combined with tacrolimus and methotrexate for achieving donor engraftment and prevention of GVHD. Patients without an available HLA-matched sibling will undergo an autologous HSCT. The preparative regimen will consist of either total body irradiation or BCNU. VP-16 and cyclophosphamide will be given for both autologous preparative regimens. Rituximab will be administered to autologous patients post-HSCT to eradicate minimal residual disease. Quantitative PCR monitoring for the *bcl-2* fusion transcript will be performed at baseline, after blood count recovery from mobilization therapy, and on Days +28, +84, +180 and yearly until three years post-HSCT if positive at any time since diagnosis until the initial study evaluation. The primary objective will be to compare 3-year progression-free survival between the two groups.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

The overall study design is that of biologic assignment based on the availability of an HLA-matched sibling, to one of two strategies to improve the outcome for follicular lymphoma patients with chemosensitive disease. All patients will undergo cytoreduction with cyclophosphamide 4 gm/m² and rituximab 375 mg/m² x 2 doses. Rituximab will be given in two doses, approximately 1 week apart, with the cyclophosphamide administered the day after the first dose of rituximab. Patients assigned to the autologous arm will have their hematopoietic stem cells mobilized from this cytoreductive regimen. Patients with an HLA-matched sibling will undergo a non-myeloablative allogeneic HSCT. Pre-transplant conditioning will consist of fludarabine 30 mg/m²/day and cyclophosphamide 750 mg/m²/day x 3 days with rituximab 375 mg/m²/day on Days -13 and -6 pre-HSCT and on Days +1 and +8 post-HSCT. The immunosuppressive regimen will consist of tacrolimus and methotrexate (MTX) to control graft-versus-host and host-versus-graft reactions. Patients without an HLA-matched sibling who have collected an adequate autologous hematopoietic cell graft, defined as $\geq 2.0 \times 10^6$ CD34⁺ cells/kg, will receive a preparative regimen of total body irradiation (TBI) 1200 cGy or BCNU 15 mg/kg. In addition, VP-16 60 mg/kg and cyclophosphamide 100 mg/kg will be given for both autologous preparative regimens. Post-autologous HSCT therapy with rituximab 375 mg/m² weekly x 4 doses will commence between Days 42-75 post-HSCT.

A secondary analysis comparing the outcome of autologous HSCT patients will be made against contemporary/historical controls who underwent autologous HSCT but did not receive rituximab maintenance chemotherapy. These patients will be identified from the CIBMTR database.

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

Non-myeloablative allogeneic hematopoietic stem cell transplantation will reduce the rate of disease progression compared to autologous hematopoietic stem cell transplantation. For patients with a matched sibling donor, an allogeneic strategy may prove superior to an autografting strategy since the immunotherapeutic effects of an allograft is a potentially powerful therapy in eradicating minimal residual disease and conferring a lasting anti-tumor effect.

The addition of maintenance rituximab post-autologous HSCT will improve the PFS of patients compared to contemporary/historical controls undergoing autologous HSCT without maintenance rituximab.

2.2.2. Study Objectives

The primary objective is to compare 3-year progression-free survival between the two transplant arms. Secondary objectives will compare 3-year survival, time to progression, time to CR and PR, time to off-study therapy, incidence of infection and incidence of Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 Grade ≥ 3 toxicities. The efficacy of cyclophosphamide plus rituximab *in vivo* purging will also be evaluated as well as the prediction of relapse by measurement of t(14;18) by quantitative PCR. Other secondary outcomes in the allogeneic transplant arm include the incidence and severity of acute and chronic GVHD and primary and secondary graft failure. Health-related quality of life for English and Spanish speaking patients of both groups will be described and exploratory comparisons will be made between the two groups. The relative safety of the two arms will be assessed through the collection of toxicity data, routine laboratory monitoring and adverse event monitoring.

2.3. Patient Eligibility

Patients must meet specified eligibility criteria to enroll on the study. Additional criteria must also be met to continue to successive stages of the protocol. All questions regarding eligibility criteria should be directed to the Protocol Coordinator at 301-251-1161.

2.3.1. Initial Patient Inclusion Criteria

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

1. Patients with histologically confirmed recurrent REAL classification follicle center lymphoma, follicular grades I and II, OR patients with histologically confirmed WHO classification follicular lymphoma grades 1, 2, 3a or 3b. For either classification, the diffuse component or presence of large cleaved cells (if present) cannot be $> 50\%$ of high power field. Patients do not have to express t(14;18) to be eligible.
2. Patients who are ≤ 75 years old at time of first registration.
3. Patients who have received ≤ 3 prior regimens of chemotherapy. Monoclonal antibody therapy and involved field radiation therapy will not be counted as a prior therapy.
4. Patients who are beyond 1st CR or 1st PR AND who demonstrate chemosensitive disease are eligible for the study. Chemosensitive disease will be defined as < 20% bone marrow involvement in the aspirate or core biopsy with follicular lymphoma AND lymph node size in axial diameter of < 3 cm or a > 50% reduction in estimated lymph node volume to be measured as product of bi-dimensional measurements. PET scanning will not be used for staging or response purposes.
5. Patients with adequate organ function as measured by:
 - a) Cardiac: left ventricular ejection fraction at rest $\geq 45\%$
 - b) Hepatic: bilirubin $< 2x$ the upper limit of normal and ALT and AST $< 3x$ the upper limit of normal
 - c) Renal: creatinine clearance > 40 mL/min

- d) Pulmonary: DLCO, FEV1, FVC \geq 50% of predicted (corrected for hemoglobin)
- 6. If the patient is $<$ 18 years of age and they have reached the age of assent, then they must have completed the local IRB assent process.
- 7. Patients who have signed the informed consent.
- 8. Patients must be able to receive cyclophosphamide and rituximab mobilization chemotherapy no earlier than 3 weeks from the beginning of the most recent cycle of salvage chemotherapy and no later than 6 weeks from enrollment.

2.3.2. Initial Patient Exclusion Criteria

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

- 1. Karnofsky performance score $<$ 70%.
- 2. Patients with follicular lymphoma that show histologic evidence of transformation.
- 3. Patients with uncontrolled hypertension.
- 4. Patients with uncontrolled bacterial, viral or fungal infection (currently taking medication and progression without clinical improvement).
- 5. Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma *in situ*. Cancer treated with curative intent $>$ 5 years previous will be reviewed on a case-by-case basis by a Protocol Chair or Medical Monitor.
- 6. Female patients who are pregnant (positive β -HCG) or breastfeeding.
- 7. Patients seropositive for HIV.
- 8. Fertile men or women unwilling to use contraceptive techniques during treatment.
- 9. Prior autologous or allogeneic HSCT.
- 10. Known anaphylactic reaction to rituximab.

2.4. Patient Eligibility Criteria for Proceeding to HSCT

In order to continue on protocol and receive either an autologous or non-myeloablative HSCT, the following conditions must be achieved:

- 1. Collection of an autologous or allogeneic graft of $\geq 2.0 \times 10^6$ CD34 $^+$ cells/kg
- 2. Blood count recovery defined as ANC $>$ 1000/mm 3 and platelets $>$ 100 $\times 10^9$ /L

Patients must be able to proceed to either non-myeloablative allogeneic or autologous HSCT within six weeks of peripheral blood count recovery following the cytoreductive/mobilization regimen outlined in Section 2.7.3. Autologous patients will undergo leukapheresis upon blood count recovery.

If peripheral blood counts have not recovered within a standard time frame, the patient's treatment plan should be discussed with a Protocol Chair or Medical Monitor. A decision regarding the patient's future treatment will be made on a case-by-case basis.

2.5. Patient Eligibility Criteria for Maintenance Therapy for Recipients of Autologous HSCT

In order to be eligible to continue on protocol and receive maintenance therapy with rituximab, patients must have recovered sufficiently from their autologous transplant. Rituximab will be given to patients between Day 42 and Day 75 post-HSCT.

Recovery from autografting will be defined as achievement of the following clinical criteria:

1. Liver and renal function tests within the inclusion criteria for initial autograft.
2. Off intravenous antibiotics and off amphotericin B formulations for proven, probable or possible fungal infections.
3. No active CMV infections or for patients with CMV infection post-autograft, treated with ganciclovir, valganciclovir or foscarnet per institutional guidelines and CMV antigenemia negative.
4. Mucositis resolved and off hyperalimentation.

2.6. Allogeneic Hematopoietic Stem Cell Donor Criteria

2.6.1. Donor Inclusion Criteria

1. The donor must be a 6/6 HLA phenotypically matched sibling to the patient. The minimum level of typing is HLA -A, -B by serologic methodology and HLA DRB1 by DNA methodology.
2. If the donor is < 18 years of age and they have reached the age of assent, then they must have completed the local IRB assent process.
3. Donor must consent to G-CSF administration and to leukapheresis for HSC collection.
4. Donor must have adequate veins for leukapheresis or agree to placement of central venous catheter (femoral, subclavian).
5. Age \leq 75 years at the time patient is initially registered on study.

2.6.2. Donor Exclusion Criteria

1. Identical twin of patient.
2. Female patients who are pregnant (positive β -HCG) or breastfeeding.
3. Infection with HIV, viral hepatitis (B or C).
4. Known allergy to G-CSF.

5. Current serious systemic illness.
6. Uncontrolled bacterial, viral or fungal infection (currently taking medication and progression of clinical symptoms).
7. Donors receiving experimental therapy or investigational agents.
8. Donors with cancer other than treated basal cell or carcinoma *in situ* of cervix. Cancer treated with curative intent > 5 years previous will be reviewed on a case-by-case basis by a Protocol Chair or Medical Monitor.

2.7. Study Treatments

The immediate pre-HSCT 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 autologous and non-myeloablative allogeneic HSCT as defined by the treating institutions. All questions regarding study treatments should be directed to the Protocol Coordinator at 301-251-1161.

2.7.1. HLA-Typing of Potential Sibling Donors

All potential sibling donors must be HLA-typed. HLA-matched siblings must be evaluated for suitability for donation until either an HLA-matched sibling donor is identified or all HLA-matched siblings are excluded as donors. This testing and evaluation must be completed by the time of study enrollment.

2.7.2. Body Weight Formulas

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

1. Ideal Body Weight (IBW) Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 + 2.3 kg/inch over 5 feet

For patients less than 5 feet, subtract 2.3 kg/inch

2. Adjusted Ideal Body Weight (AIBW) Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.7.3. Cytoreductive Therapy/Mobilization Chemotherapy

2.7.3.1. Allopurinol

Patients may receive allopurinol 300 mg/day PO for 10 days starting one day prior to receiving the cyclophosphamide according to local institutional practice. (Dose adjusted according to renal function per standard recommendations.)

2.7.3.2. Cyclophosphamide and rituximab administration/mobilization

Prior to undergoing autologous or non-myeloablative allogeneic HSCT, all patients will receive cyclophosphamide 4 gm/m² with rituximab 375 mg/m² x 2 doses with G-CSF support. See Table 2.7.3.2 for the treatment schedule. **This regimen shall begin no earlier than 3 weeks from the beginning of the most recent cycle of salvage chemotherapy and no later than 6 weeks post-enrollment.** Rituximab may be administered in the office/hospital of the referring hematologist/oncologist. Cyclophosphamide must be administered at the transplant center.

Table 2.7.3.2: Cytoreductive/Mobilization Treatment Schedule

Day	1	2	3	4	5	6	7	8
Cyclophosphamide 4 g/m ²		X						
Rituximab 375 mg/m ²	X							X
G-CSF 10 mcg/kg or 5 mcg/kg *				X-----→				

1. **Cyclophosphamide:** 4 g/m² IV x 1 dose to be administered over 2 hours on Day 2 of the schedule. Hydration, if used per institutional guidelines, is to be started pre-cyclophosphamide and continued until 24 hours after the completion of the cyclophosphamide infusion. Alternatively, mesna may be used in doses per institutional guidelines (recommended usage is at least 20% of the cyclophosphamide dose prior to each dose of cyclophosphamide and repeated 4 hours and 8 hours after each cyclophosphamide dose).

Cyclophosphamide should be dosed based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). See Section 2.7.2 for body weight formulas.

2. **Rituximab:** 375 mg/m² IV x 2 doses total, with the first dose to be administered on Day 1 and the second dose administered on Day 8. Mix rituximab in either 0.9% NS or D5W according to institutional practice. Rituximab must be infused through an infusion pump and should not be mixed or diluted with any other solutions or drugs. Doses may be rounded to nearest vial size (e.g. if dose is \leq 750 mg, then round to 700 mg; if $>$ 750 mg, then round to 800 mg). Dosing is based on the body weight formulas in Section 2.7.2.

Premedication should be administered prior to rituximab per institutional guidelines (recommended: diphenhydramine 50 mg PO, 30 minutes prior to treatment and acetaminophen 650 mg PO, 30 minutes prior to treatment).

3. **G-CSF*:** 10 mcg/kg for the autologous patients administered at once, or fractionated to 5 mcg/kg SQ BID, or 5 mcg/kg for the allogeneic patients SQ or IV to start daily on Day 4 (2 days after cyclophosphamide administration). G-CSF dosing can be rounded based on patient's actual body weight (see Section 2.7.2 for body weight formulas) and available G-CSF vial sizes to best approximate of 10 mcg/kg or 5 mcg/kg (e.g. < 70 kg use 300 mcg vial, 70 to 90 kg use 480 mcg vial and > 90 kg use 2 x 300 mcg vials).

For the autologous HSCT patients, autologous hematopoietic stem cells will be collected after the cyclophosphamide + rituximab + G-CSF regimen. G-CSF will continue until leukapheresis is complete. Leukapheresis will commence per institutional guidelines and will continue until the target of $\geq 2.0 \times 10^6$ CD34⁺ cells/kg are collected. Cells will be cryopreserved per institutional guidelines. Patients who collect $\geq 1.0 \times 10^6$ CD34⁺ cell/kg but $< 2.0 \times 10^6$ CD34⁺ cells/kg will proceed to high dose chemotherapy.

Patients with $< 1.0 \times 10^6$ CD34⁺ cells/kg after three collections will continue to be followed for relapse, progression and survival. Patients may proceed to transplant off-study at the discretion of their attending physician and subsequent management of these patients is at the discretion of their attending physician.

For **autologous** HSCT patients, G-CSF will continue until leukapheresis is complete. For the non-myeloablative **allogeneic** HSCT patients, G-CSF will continue until ANC $> 500/\text{mm}^3 \times 3$ days.

2.7.4. High Dose Chemotherapy with Autologous HSCT

Patients without an available HLA-matched sibling will proceed to autologous HSCT. Patients must proceed to HSCT within six weeks of peripheral blood count recovery following the cytoreductive regimen outlined in Section 2.7.3. Blood count recovery will be defined as ANC $> 1000/\text{mm}^3$ and platelets $> 100 \times 10^9/\text{L}$. Two conditioning regimens are available: a chemotherapy only regimen or a TBI-based regimen. See Tables 2.7.3.2 and 2.7.4.1, respectively.

At the commencement of this trial, institutions must specify if they will be uniformly using the TBI-based or chemotherapy-based regimen. If for some reason in a center that has specified that the TBI regimen will be used (i.e. previous involved field radiation therapy precludes patient from TBI), a patient cannot receive TBI, the chemotherapy-based regimen specified below must be utilized and this must be noted at the time of patient registration.

Patients who are 60 years and older will be assigned to receive the chemotherapy-based conditioning regimen.

2.7.4.1. Conditioning regimen - chemotherapy-based regimen

Table 2.7.4.1: Autologous HSCT - Chemotherapy-Based Regimen

Day								
-6	-5	-4	-3	-2	-1	0	+5	
BCNU 15 mg/kg		VP-16 60 mg/kg		Cyclophosphamide 100 mg/kg		PBSCT	G-CSF 5 mcg/kg	

- BCNU:** 15 mg/kg based on the body weight formulas in Section 2.7.2 (maximum dose not to exceed 550 mg/m² based on actual body weight) IV x 1 dose to be administered over 2 hours on Day -6 pre-HSCT.
- VP-16:** 60 mg/kg IV x 1 dose to be administered over 4 hours on Day -4. VP-16 dosing should be based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). See Section 2.7.2 for body weight formulas. The concentrated etoposide solution (20 mg/mL) is to be drawn up into syringes and administered via a syringe pump or transferred to an empty non-DEPH bag for infusion. Administer the etoposide dose via a Y-site connection or an adjacent lumen running concomitantly with normal saline at 200 mL/hr.
- Cyclophosphamide:** 100 mg/kg IV x 1 dose to be administered over 2 hours on Day -2 pre-HSCT.
- Cyclophosphamide should be dosed based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). See Section 2.7.2 for body weight formulas.
- G-CSF:** 5 mcg/kg SQ or IV to start on Day +5 post-HSCT and continue until ANC > 500/mm³ x 3 days. G-CSF dosing should be based on actual body weight – see Section 2.7.2 for body weight formulas. G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5 mcg/kg (e.g., < 70 kg use 300 mcg vial, 70 to 90 kg use 480 mcg vial and > 90 kg use 2 x 300 mcg vials).

2.7.4.2. Conditioning regimen - total body irradiation-based regimen

Table 2.7.4.2: Autologous HSCT - TBI-Based Regimen

Day									
-8	-7	-6	-5	-4	-3	-2	-1	0	+5
FTBI	FTBI	FTBI	FTBI	VP-16 60 mg/kg		Cyclophosphamide 100 mg/kg		PBSCT	G-CSF 5 mcg/kg

1. Fractionated Total Body Irradiation: TBI may be administered according to either one of the following two schedules:

A) Hyperfractionated TBI: TBI is administered at a dose rate of < 20 cGy/minute. Doses of 120 cGy/fraction are administered at no less than 4-hour intervals three times/day or 2 times/day for a total of 10 doses (1200 cGy) over 4 days (Day -8, -7, -6 and -5). The exact number of treatments per day (one to three) can vary according to institutional practice but should include a total of 10 treatments over 4 days. Sequential doses are administered anterior→posterior with standard (5 half value) lung blocks shielding the lung parenchyma for the final 600 cGy. At the time of the last two TBI fractions, the blocked areas of anterior and posterior chest walls will be boosted with electrons to a cumulative chest wall dose of approximately 1200 cGy (300 cGy/fraction x 2 anteriorly and posteriorly). Alternatively, the TBI treatments may be administered with 50% transmission lung blocks anteriorly and posteriorly throughout, with the electron chest wall boosts to 1200 cGy (300 cGy x 2, anteriorly and posteriorly) administered during the course of the 10 TBI treatments. The energy of the electron beam will be chosen to deliver 90% of the dose to the chest wall. The dose will be calculated at the central axis in the midplane. Appropriate dosimetry will be confirmed prior to or during the 1st TBI treatment and compensators will be allowed to keep the dose inhomogeneity at $\leq 10\%$. Corrections for lung inhomogeneity are not required.

B) Fractionated TBI: This regimen calls for doses of 150 cGy/fraction administered at the same dose rate (< 20 cGy/min) twice daily for a total of 8 doses (1200 cGy) over 4 days (Day -8, -7, -6 and -5). Doses are separated by a minimum of 5 hours. The dose to the lungs will be reduced to 50% by partial transmission lung blocks used during all TBI treatments or full thickness (5 HVL) lung blocks during 5 TBI treatments. The chest wall should then be boosted to a cumulative total dose of 1200 cGy with electrons (300 cGy/fraction x 2 anteriorly and posteriorly). The dose will be calculated at the central axis in the midplane. Appropriate dosimetry will be confirmed prior to or during the 1st TBI treatment and compensators will be allowed to keep the dose inhomogeneity at $\leq 10\%$. Corrections for lung inhomogeneity are not required.

2. **VP-16:** 60 mg/kg IV x 1 dose to be administered over 4 hours on Day -4 pre-HSCT. VP-16 dosing should be based on the body weight formulas in Section 2.7.2. Infuse through an IV of normal saline at 250 cc/hr (see previous regimen comment).

3. **Cyclophosphamide:** 100 mg/kg IV x 1 dose to be administered over 2 hours on Day -2 pre-HSCT.

Cyclophosphamide should be dosed based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). See Section 2.7.2 for body weight formulas.

4. **G-CSF:** 5 mcg/kg SQ or IV to start on Day +5 post-HSCT and continue until ANC > 500/mm³ x 3 days. G-CSF dosing can be rounded based on patient's actual weight and available G-CSF vial sizes to best approximate 5 mcg/kg (e.g., < 70 kg use 300 μ g vial, 70 to 90 kg use 480 μ g vial and > 90 kg use 2 x 300 μ g vials).

2.7.4.3. Rituximab maintenance therapy

Patients must have sufficiently recovered from autologous HSCT as defined in Section 2.5 in order to receive rituximab maintenance therapy as specified below:

- Dose #1: Day +42 post-autologous HSCT
- Dose #2: Day +49 post-autologous HSCT
- Dose #3: Day +56 post-autologous HSCT
- Dose #4: Day +63 post-autologous HSCT

Rituximab should be given on or around Day +42 post-autologous HSCT but can be given up to Day +75 post-autologous HSCT if patients are not fully recovered by Day +42 post-autologous HSCT. If the patient has not fully recovered at Day +75 post-HSCT, a Protocol Chair or Medical Monitor should be contacted regarding future treatment plans. Rituximab will be administered weekly in doses of 375 mg/m^2 IV x 4. Mix rituximab in either 0.9% NS or D5W according to institutional practice. Rituximab must be infused through an infusion pump and should not be mixed or diluted with any other solutions or drugs. Premedication should be administered prior to rituximab per institutional guidelines (recommended: diphenhydramine 50 mg PO, 30 minutes prior to treatment and acetaminophen 650 mg PO, 30 minutes prior to treatment).

2.7.5. Non-myeloablative Allogeneic Stem Cell Transplantation for Patients with an HLA-matched Sibling

Within 6 weeks of peripheral blood count recovery following the cytoreductive regimen outlined in Section 2.7.3, patients with an available 6/6 HLA-matched sibling will proceed to a non-myeloablative allogeneic HSCT. Blood count recovery will be defined as ANC $> 1000/\text{mm}^3$ and platelets $> 100 \times 10^9/\text{L}$.

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

Table 2.7.5: Non-myeloablative Allogeneic HSCT Schedule*

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

* See Section 2.7.2 for body weight formulas.

2.7.5.1. Conditioning regimen

1. **Fludarabine:** 30 mg/m² IV x 3 doses total to be administered daily over 30 minutes on Days -6, -5 and -4 pre-HSCT. Dosing is based on the body weight formulas in Section 2.7.2.
2. **Cyclophosphamide:** 750 mg/m IV x 3 doses total to be administered daily over 1 hour on Days -6, -5 and -4 pre-HSCT. Administer cyclophosphamide approximately 4 hours after start of fludarabine infusion. Dosing is based on the body weight formulas in Section 2.7.2.
3. **Rituximab:** 375 mg/m² IV x 4 doses total to be administered on Days -13 and -6 pre-HSCT and Days +1 and +8 post-HSCT. Mix rituximab in either 0.9% NS or D5W according to institutional practice. Dosing is based on the body weight formulas in Section 2.7.2. Rituximab must be infused through an infusion pump and should not be mixed or diluted with any other solutions or drugs.

2.7.5.2. Graft-versus-host disease (GVHD) prophylaxis

Table 2.7.5.2: GVHD Prophylaxis Schedule

DAY	-2	-1	0	1	2	3	4	5	6
Tacrolimus 0.09 mg/kg PO or 0.03 mg/kg IV	X-----►								
Methotrexate 5 mg/m ² IV				X		X			X

1. **Tacrolimus:** 0.09 mg/kg/day PO, based on body weight formulas in Section 2.7.2, will start on Day -2 and continue until Day +90 post-HSCT. Tacrolimus (or cyclosporine, if applicable) will be given orally in a twice-daily divided dose. Tacrolimus dosing should be based on actual body weight – see Section 2.7.2 for body weight formulas. Doses should be adjusted to maintain whole blood “trough” levels at 5-15 ng/mL. Tapering of tacrolimus doses should commence starting at Day +90 post-HSCT to be completely discontinued by Day +180 post-HSCT unless GVHD Grade \geq III develops. An equivalent dose of IV tacrolimus may be used as per local institutional preference. Patients with severe intolerance to tacrolimus may be placed on cyclosporine.

Patients with severe intolerance to tacrolimus may be placed on cyclosporine at a starting dose of 5 mg/kg bid PO based on actual body weight. An equivalent dose of IV cyclosporine may be used as per institutional practice. Doses should be adjusted to maintain whole blood “trough” levels that target 500 ng/mL (upper end of therapeutic range) during the first month. Dose reductions should only be made if CSA toxicity is present or whole blood levels exceed 600 ng/mL in the absence of toxicity. Further CSA determinations should be performed weekly until CSA is stopped unless high levels are detected (i.e., > 600 ng/mL), or toxicity is suspected, in which case more frequent monitoring will be performed as clinically indicated. Dose reductions for high levels

without toxicity should be conservative (e.g., 25%) to avoid inadequate immunosuppression.

After Day 28, the CSA level is to be kept within 200-400 ng/mL, according to local institutional practice until the Day +90 taper is initiated.

2. **Methotrexate:** 5 mg/m² IVP will be administered on Days +1, +3 and +6 post-HSCT. In the event of renal/hepatic impairment, dose changes should be made according to the following guidelines:

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

2.7.6. Collection and Infusion of Allogeneic HSC

2.7.6.1. G-CSF administration to donors

All donors will receive **G-CSF 16 mcg/kg/day** for 5 consecutive days from Day -4 pre-HSCT to Day 0. G-CSF dosing should be based on actual body weight – see Section 2.7.2 for body weight formulas. G-CSF will be administered by daily subcutaneous injections. If necessary, based on volume, the G-CSF can be given in multiple injection sites. These doses will be administered before 10:00 AM each day. G-CSF dosing can be rounded based on donor weight and available G-CSF vial sizes to best approximate 16 mcg/kg.

2.7.6.2. HSC collection and evaluation

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

A minimum dose of **2.0 x 10⁶ CD34⁺ cells/kg** will be collected (according to institutional practices) and given. If **≥ 5.0 x 10⁶ CD34⁺ cells/kg** are collected on Day -1, a second collection will not be necessary. If **< 2.0 x 10⁶ CD34⁺ cells/kg** are collected after 2 aphereses, a 3rd collection must be performed on Day +1. All cells collected should be infused. Cryopreservation of donor hematopoietic stem cells may be acceptable, but this must be discussed in advance with a Protocol Chair or Medical Monitor.

If **< 1.0 x 10⁶ CD34⁺ cells/kg** are collected from the donor after three collections, patients may proceed to transplant off-study at the discretion of their attending physician and subsequent

management of these patients is at the discretion of their attending physician. However, such patients will continue to be followed for relapse, progression and survival.

Table 2.7.6.2: Treatment Schedule for Donor

Days	-4	-3	-2	-1	0	1
G-CSF 16 mcg/kg	X	X	X	X	X	
HSC Collection				X	X*	X**
HSC Administration					X	X**

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

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

2.7.6.3. Allogeneic hematopoietic stem cell infusion

All patients will receive unmodified (other than volume reduction) G-CSF mobilized hematopoietic stem cells from an HLA-matched sibling on Day 0 of the treatment regimen. The hematopoietic stem cells will be infused via a central venous catheter using standard blood infusion tubing.

2.8. Supportive Care

2.8.1. Post-autologous HSCT

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

2.8.1.1. Prophylaxis against infections

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

1. Anti-bacterial: In keeping with the BMT CTN MOP or local institutional standards.
2. Pneumocystis carinii: Prophylaxis will start at the time of engraftment or on Day +30 post-autologous transplant according to institutional preference. Prophylaxis should be continued until at least 6 months following the autologous HSCT.
3. Anti-fungal Therapy: Anti-fungal prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.
4. HSV/VZV: Antiviral prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.

5. IVIG: Replacement to be initiated according to institutional practice if IgG levels fall below 500 mg/dL.

2.8.1.2. 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.

2.8.1.3. Post-HSCT immunization schedule

Immunization may be given in keeping with the BMT CTN MOP (or local institutional practice).

2.8.2. Post Non-myeloablative Allogeneic HSCT

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

2.8.2.1. Prophylaxis against infections

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

Infectious prophylaxis will include prophylaxis for:

1. Anti-bacterial: In keeping with the BMT CTN MOP and local institutional standards.
2. Pneumocystis carinii: Prophylaxis will start at the time of engraftment or on Day +30 post non-myeloablative allogeneic HSCT transplant according to institutional preference. Prophylaxis should be continued for at least 1 month after the patient is off all immunosuppressive medications.
3. Anti-fungal Therapy: Anti-fungal prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.
4. HSV/VZV: Antiviral prophylaxis will be per local institutional practice and must be uniformly applied to all patients within each respective center.
5. CMV: Monitoring and preemptive treatment strategy will be in accordance with the BMT CTN Technical Committee (Infectious Diseases) MOP and local institutional practice. The duration of monitoring is recommended for at least 100 days post non-myeloblastic allogeneic HSCT and longer if the patient is on immunosuppressive medications.
6. IVIG: Replacement to be initiated according to institutional practice if IgG levels fall below 500 mg/dL. IgG levels to be drawn at 12 weeks, 6 months and 1 year post-HSCT (see Table 4.2.1 or 4.2.4.8b).

2.8.2.2. 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. Allogeneic transplant candidates who are CMV negative will receive CMV negative or filtered blood products from study entry.

2.8.2.3. Post-HSCT growth factors

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

2.8.2.4. Post-HSCT immunization schedule

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

2.8.2.5. Post-HSCT donor cellular infusions (DCI)

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

2.9. PCR Monitoring for t(14;18)

Quantitative PCR analysis for t(14;18) from peripheral blood will be performed on all patients at the time of registration. Samples will be collected and quantitative PCR will be performed by a centralized lab according to the following schedule. If patient was known to be t(14;18) negative prior to registration this test still must be performed once at the time of registration for documentation purposes. Patient's may have had a t(14;18) analysis that was positive prior to study entry (e.g. at diagnosis). Referring centers should be queried regarding prior patient testing for t(14;18). Patients with any positive test for t(14;18) since the time of diagnosis must have the subsequent t(14;18) PCR assessment samples collected. See Section 4.2 and Appendix C for schedule of samples and details on collection, processing, storage and shipment.

2.10. Participant Risks

Recipients of HSCTs incur risks from pre-HSCT conditioning and post-HSCT therapy, which must be weighed against the risk of the disease for which the HSCT is prescribed. Major risks following transplantation include: 1) Infection which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 2) GVHD, either acute or chronic in nature, may occur following allogeneic transplantation. The degree of GVHD varies from mild cutaneous reactions to extensive widespread and systemic involvement of skin, liver, and gastrointestinal tract. Probably due to a direct association, the incidence of fatal infection is

greater in patients developing GVHD; 3) Graft Failure can occur and is associated with a high risk of mortality; 4) End Organ Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., chemotherapy, antibiotics, anti-fungal medications, tacrolimus, cyclosporine, etc.), and as a result of destructive processes (e.g., infection, GVHD, etc.), and may have a fatal outcome; 5) Relapse or progression of lymphoma may occur, especially in patients with advanced disease status at time of treatment; 6) Unknown Toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain. Brain damage can result in severe loss of cognitive or neurologic function; and 7) Death.

2.11. 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.

2.11.1. Total Body Irradiation (TBI)

The radiation therapist performs the dosimetry calculations. TBI may cause nausea, vomiting, diarrhea, mucositis, myelosuppression, alopecia, and painful swelling of the salivary glands for a few days. Long-term effects include sterility, secondary malignancies and cataract formation.

2.11.2. Cyclophosphamide

Cyclophosphamide is an alkylating agent as well as an immunosuppressant. Toxicities include nausea, vomiting, myelosuppression, hemorrhagic cystitis, alopecia, sterility, mucositis, cardiomyopathy and jaundice. It is available as an IV and oral formulation.

2.11.3. Carmustine (BCNU)

Carmustine is an alkylating agent. Toxicities from carmustine include myelosuppression, nausea, vomiting, transient hypotension, dizziness, hyperpigmentation of the skin, hepatotoxicity and a delayed inflammatory lung response (pneumonitis). It is available as an IV formulation only.

2.11.4. VP-16 (Etoposide)

VP-16 is a semi-synthetic podophyllotoxin derivative. Toxicities include nausea, vomiting, myelosuppression, mucositis, hypotension, hand-foot syndrome (dermatitis), and occasionally fevers, peripheral neurotoxicity and hepatotoxicity. It is available as an IV and oral formulation.

2.11.5. Rituximab

Rituximab is a chimeric human/mouse monoclonal antibody directed against CD20⁺, an antigen expressed on all cells of the B cell lineage. It consists of a murine antigen binding region and a human Fc region. The majority of toxicities occur during infusion such as rigors, fevers, hypotension, dyspnea, and nausea/vomiting. Non-infusion toxicities include myelosuppression,

fatigue and tumor pain. It is available as an IV formulation only. Hepatitis B reactivation with fulminant hepatitis, hepatic failure and death is a risk in patients who have ever been infected with the hepatitis B virus and/or are carriers of hepatitis B. The risk of hepatitis B reactivation may continue for several months after rituximab administration.

2.11.6. Fludarabine

Fludarabine is a purine analog. Toxicities include myelosuppression, immunosuppression, edema, fever, chills, fatigue, rash, mild nausea/vomiting, paresthesias and myalgias. It is commercially available as an IV formulation only.

2.11.7. Methotrexate

Methotrexate is an antimetabolite that inhibits DNA synthesis and cell reproduction in malignant cells. Toxicities include mucositis, hyperuricemia, elevated liver functions tests, leukopenia, thrombocytopenia, nausea, vomiting, diarrhea, anorexia, malaise, fevers, chills, rash, nephrotoxicity and pneumonitis. It is available as an IV and oral formulation.

2.11.8. Tacrolimus

Tacrolimus is a macrolide antibiotic that is a potent immunosuppressant. Toxicities include hypertension, peripheral edema, headache, hyperkalemia, hypokalemia, hyperglycemia, hypomagnesemia, nausea, anorexia, vomiting, cramps, nephrotoxicity, elevated liver function tests, tremors, paresthesias, rash, pruritus, and increased susceptibility to infection. It is available as an IV and oral formulation.

2.11.9. G-CSF (filgrastim)

Filgrastim is a myeloid growth factor that stimulates the production, maturation and activation of neutrophils and activates neutrophils to increase their migration and cytotoxicity. Common toxicities include myalgias and medullary bone pain. The bone pain can be generally controlled with non-narcotic analgesia. Less common side effects include fluid retention, pericardial effusion, local inflammation at the injection site and rarely, cutaneous vasculitis. Transient laboratory abnormalities include mild elevations in uric acid, LDH, alkaline phosphatase, and leukocytosis. There have been reported cases of spleen swelling resulting in splenic rupture. It may be administered as an IV formulation or subcutaneously.

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-HSCT disease status. Once the patient has relapsed/progressed, these states are relative to the patient's best disease state. PET scanning, flow cytometric, cytogenetic and molecular studies will not be included in response definitions [57].

1. Complete Remission (CR):

- Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy.
- All lymph nodes and nodal masses must have regressed 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 - 1.5 cm before treatment must have decreased to ≤ 1 cm after treatment.
- The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical exam.
- If bone marrow was involved by lymphoma before treatment, this infiltrate must be cleared after treatment.
- Continued CR (CCR) will be applied to patients who were transplanted in CR.
- Complete Remission Undetermined (CRU) as above but a residual lymph node mass of > 1.5 cm must have regressed by $> 75\%$ in their sum of the products of the greatest diameters [56] (SPD) and individual nodes that were previously confluent must have regressed by $> 75\%$ in their SPD. Additionally, indeterminate bone marrow also applies here (increased number or size of aggregates without cytologic or architectural atypia).

2. Partial Remission (PR):

- $\geq 50\%$ reduction in SPD of the 6 largest dominant nodes or nodal masses.
- No increase in size of other nodes, liver or spleen.
- Splenic and hepatic nodules must regress by least 50% in the SPD.
- Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease.
- No new sites of disease.

3. Stable Disease (SD):

Less than a PR (see above) but is not progressive disease (see below).

4. Relapsed Disease (RD):

- Applies to patients previously classified as CR, CCR or CRU.
- Appearance of any new lesion or increase by $\geq 50\%$ in the size of previously involved sites.
- $\geq 50\%$ increase in greatest diameter of any previously identified node > 1 cm in its short axis or in the SPD of more than 1 node.

5. Progressive Disease (PD):

- Applies to patients previously classified as PR or SD.
- $> 50\%$ increase from nadir in the SPD of any previously identified abnormal node for PRs or SD.
- Appearance of new sites of disease.

3.2. Primary Endpoint to be Compared Between Autologous HSCT Recipients and Non-myeloablative Allogeneic HSCT Recipients**3.2.1. Three Year Progression-Free Survival**

The primary endpoint is three-year progression-free survival. Patients are considered a failure for this endpoint if they die or if they relapse/progress or receive anti-lymphoma therapy. The time to this event is the time from enrollment on study until death, relapse/progression, receipt of anti-lymphoma therapy, or last follow up, whichever comes first.

3.3. Secondary Endpoint to be Compared Between Autologous HSCT Recipients and Non-myeloablative Allogeneic HSCT Recipients**3.3.1. Three Year Overall Survival**

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

3.3.3. Time to CR and PR

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

3.3.4. Time to Off-study Therapy

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

3.3.5. Incidence of Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient. The proportion of patients in each treatment arm with these infections will be compared.

3.3.6. Incidence of CTCAE Version 3.0 Grade ≥ 3 toxicities

See the BMT CTN MOP for the CTCAE grading scales.

3.3.7. Treatment Related Mortality

Treatment related mortality (TRM) is defined as death occurring in a patient from causes other than relapse or progression.

3.4. Endpoints That Only Apply to Non-myeloablative Allogeneic Recipients

The following endpoints will be used to describe outcomes associated only for the recipients of the HLA-matched sibling allograft. They will not be compared between the two treatment arms.

3.4.1. Incidence of Primary and Secondary Graft Failure

Donor engraftment is defined as $> 5\%$ donor peripheral blood T cell chimerism by Day +56 post-HSCT. Primary graft failure is defined as a donor peripheral blood T cell chimerism $< 5\%$ at Day 56 post-HSCT. Methodological requirements for chimerism are outlined in the BMT CTN MOP.

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

3.4.2. Incidence and Severity of Graft-versus-Host Disease (GVHD)

See the BMT CTN MOP for definitions of acute and chronic GVHD.

3.5. Other Endpoints

3.5.1. Efficacy of Rituximab and Cyclophosphamide *in Vivo* Purging

In vivo purging will be measured as the proportion of patients whose peripheral blood converts from positive for t(14;18) by PCR prior to rituximab and cyclophosphamide to negative following this therapy.

For patients with known t(14;18) undergoing collection of autologous HSC, PCR for t(14;18) will be conducted on the collected products in addition to peripheral blood samples. Correlation between peripheral blood and apheresis product results for t(14;18) will also be determined.

3.5.2. Prognostic Value of t(14;18) by PCR in Predicting Relapse

A quantitative PCR for t(14;18) from peripheral blood will be carried out on patients with known t(14;18). Results of serial post-HSCT samples will be analyzed to determine if there is a threshold value that can reliably predict relapse.

3.5.3. Quality of Life

Health Related Quality of Life will be described pre-initiation of rituximab and cyclophosphamide cytoreductive/mobilization therapy for English and Spanish speaking patients of both groups utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. The questionnaires will be scored according to standard procedures. In addition, an exploratory comparison of the quality of life of the two groups will be made at two years post-autologous or non-myeloablative allogeneic HSCT.

3.6. Regimen-related Toxicities Safety Monitoring Endpoints

3.6.1. Allogeneic HSCT

There are two regimen-related toxicity monitoring plans for the non-myeloablative allogeneic HSCT arm. The rates of hepatic and renal toxicities will be monitored. Occurrence of these toxicities will be recorded as events.

1. Hepatic toxicity, defined as Grade 3 or higher toxicity from the CTCAE Version 3.0, under the adverse event type liver dysfunction/failure.
2. Renal toxicity is defined as serum creatinine > 3.0 mg/dL.

3.6.2. Autologous HSCT

There are two regimen-related toxicities that will be monitored in the autologous HSCT arm.

1. Neutropenia is defined as Grade 3 or higher toxicity from the CTCAE Version 3.0 under the adverse event type blood/bone marrow. This toxicity applies to the specific time period commencing with the first dose of rituximab post-HSCT and ending at one year post-HSCT.
2. Pulmonary toxicity/pneumonitis is defined as Grade 3 or higher toxicity from the CTCAE Version 3.0 under the adverse event type pulmonary/upper respiratory.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the Advantage EDCSM (internet data entry systems). Southwest Oncology Group (SWOG) centers should follow the instructions in Section 4.1.2 prior to following the instructions below. The following procedures should be followed:

1. Prior to initiation of rituximab and cyclophosphamide cytoreductive/mobilization therapy, an authorized user at the transplant center completes a screening form with demographic and eligibility questions. The Eligibility Form includes a question confirming that the patient signed the informed consent form.
2. If the patient is eligible, a study number is generated.
3. Potential sibling donors must be evaluated for suitability for donation until either an HLA-matched sibling donor is identified or all HLA-matched siblings are excluded as donors. The cytoreductive/mobilization therapy must begin no later than 6 weeks from enrollment. If an HLA-matched sibling is available, the donor and recipient HLA typing information is completed on the eligibility form. If an HLA-matched sibling is not available, the Sibling Information Form is required to obtain information pertaining to ineligibility of all siblings. This includes siblings not typed because of prior knowledge that they would not be eligible to donate for medical reasons, typed siblings that are not HLA matches and HLA-matched siblings who can not donate for medical reasons. Enrollment occurs at the time of biological assignment prior to the cytoreductive/mobilization therapy. Consent may be obtained in advance but the protocol assessments required prior to the cytoreductive/mobilization therapy should not be scheduled immediately after the consent is signed if the therapy is not imminent (within 4 weeks). Patients with a donor are then biologically assigned to the non-myeloablative allogeneic HSCT arm. Patients without an HLA-matched sibling donor are then biologically assigned to the autologous HSCT + rituximab maintenance therapy arm. If an HLA-matched sibling is identified but then declines to be a donor, the patient may proceed to the autologous HSCT. In accordance with the intention-to-treat principle for the primary analysis of three-year progression-free survival, this patient will be classified as an allogeneic HSCT patient since this was their original biologic assignment.
4. After recovery from cytoreductive/mobilization therapy, an authorized user at the clinical center completes the Pre-HSCT Checklist confirming that the patient has recovered and is eligible to receive either a non-myeloablative allogeneic HSCT or autologous HSCT.
5. If the patient is eligible, the treatment plan is continued and a visit schedule based on the transplant date is displayed for printing and is referred to as 'Segment A Follow-up.'
6. **For autologous HSCT patients only:** After recovery from autologous HSCT, an authorized user at the transplant center completes the Pre-Rituximab Checklist to confirm

the patient has recovered and is eligible to begin receiving rituximab maintenance therapy.

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. Affiliate institutions not approved to register patients directly with the Data Operations Center must register through their member institution. The Data Operations Center will request information from the SWOG Registration Form. The institution must have these documents completed entirely prior to registering the patient in the SWOG Web Registration System. In addition, the Data Operations Center will collect stratification information, will request the date that the 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 follow-up period for Segment A is 3 years.

Table 4.2.1: Follow-up Schedule - Segment A

Study Visit	Target Day (<u>+ 7 Days Prior to Day 100 Post-HSCT)</u> (<u>+ 28 Days After Day 100 Post-HSCT</u>)
1 week ^{1, 2, 3}	7 days
2 week ^{1, 2, 3}	14 days
3 week ^{1, 2, 3}	21 days
4 week ^{2, 3}	28 days
5 week ¹	35 days
6 week ¹	42 days
7 week ¹	49 days
8 week ⁴	56 days
9 week ¹	63 days
10 week ¹	70 days
11 week ¹	77 days
12 week ^{4, 5}	84 days
13 week ¹	91 days
14 week ¹	98 days
6 month ^{4, 5}	180 days
12 month ^{4, 5}	365 days
18 month	540 days
24 month ⁴	730 days
30 month	900 days
36 month ⁴	1,095 days

¹GVHD assessments for non-myeloablative allogeneic HSCT arm only²Chemistry panel required twice per week³Refer to Section 4.2.4.4 for frequency of follow-up for CBC⁴Chemistry panel required at this time point⁵IgG level required at this time point

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 the web-based data entry system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the web based data entry system and integrated into the DCC's 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 the web-based data entry system 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 the web based data entry system.

CIBMTR Data Reporting: All transplant centers will be required to **pre-register** patients with the CIBMTR for all transplant patients whether or not they enroll in a BMT CTN Protocol. In addition, the transplant center must complete the CIBMTR TED Day 100 Report Form (including the Core, Graft and Disease Inserts) and CIBMTR TED Follow-up Form (including the Core and Disease Inserts) yearly for all patients enrolled in BMT CTN protocols. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.2.2. Weekly GVHD Monitoring Post Non-myeloablative Allogeneic Transplant

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

4.2.3. Adverse Event Reporting

Unexpected, grade 3-5 Adverse Events (AE) will be reported through an expedited AE reporting system. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected adverse events will be reported using NCI's Common Terminology Criteria For Adverse Events Version 3.0 at regular intervals as defined on the Form Submission Schedule.

4.2.4. Patient Assessments

Tables 4.2.4.8a and 4.2.4.8b summarize patient clinical assessments over the course of the study. All assessments prior to and after the transplant are considered standard of care.

4.2.4.1. Evaluations prior to rituximab and cyclophosphamide

The following observations should be determined within the 4 weeks prior to initiating rituximab and cyclophosphamide mobilization chemotherapy. Observation 3 must be determined \leq 2 weeks before initiation of therapy. Observation 9c must be done after enrollment.

1. History, physical examination, height and weight.
2. Karnofsky performance score.
3. CBC with differential and platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT, AST, LDH, sodium, magnesium, potassium, chloride, and CO₂.

4. CMV titer, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex titre, syphilis, HIV and HTLV1 antibody).
5. EKG.
6. Left ventricular ejection fraction.
7. DLCO, FEV1, and FVC.
8. HLA typing of heparinized peripheral blood sample to determine availability of HLA-matched sibling. HLA -A, -B typing can be done by serologic or DNA methods. HLA DRB1 typing must be done by DNA methodology.
9. Baseline Disease Evaluation:
 - 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 to cytogenetics. Flow cytometry not required. Bone marrow core should be \geq 2 cm total for unilateral or bilateral samples.
 - c) 10 mL peripheral blood for quantitative PCR analysis of t(14;18).
- 10) Quality of life assessment.
- 11) ABO Rh blood typing.

4.2.4.2. Post initiation of rituximab and cyclophosphamide

Toxicity assessment upon blood count recovery post rituximab and cyclophosphamide mobilization chemotherapy and \leq 2 weeks prior to administration of the HSCT conditioning therapy.

4.2.4.3. Evaluations prior to the autologous or non-myeloablative allogeneic HSCT

The following observations will be done \leq 2 weeks prior to initiation of the HSCT conditioning therapy.

1. History, physical examination, height and weight.
2. Karnofsky performance score.
3. CBC with differential, platelet count, creatinine, bilirubin, LDH, alkaline phosphatase, AST, ALT, sodium, magnesium, potassium, chloride, and CO₂.
4. Creatinine clearance if clinically significant nephrotoxicity experienced with cyclophosphamide and rituximab.
5. Left ventricular ejection fraction if clinically indicated.
6. DLCO, FEV1 and FVC if clinically indicated.

7. Baseline Disease Evaluation:
 - a) Bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics only if bone marrow was involved with lymphoma at any time prior to the rituximab/cyclophosphamide therapy. Flow cytometry is not required. Bone marrow core should be \geq 2 cm total for unilateral or bilateral samples.
 - b) CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.
 - c) In patients with known t(14;18), 10 mL peripheral blood samples will be drawn for t(14;18) analysis by PCR. These samples will be processed and stored locally for later shipment to the BMT CTN Repository for batch analysis.
 - d) For autologous HSCT patients with known t(14;18), all leukapheresis products will be tested for t(14;18) analysis by PCR. These samples will be processed and stored locally for later shipment to the BMT CTN Repository for batch analysis.
8. Heparinized peripheral blood samples from all patients on the non-myeloablative allogeneic HSCT arm for chimerism assays.
9. Flow cytometry analysis of autologous or allogeneic graft per the Graft Characterization section of the BMT CTN MOP.
10. One vial (10 cc) of nucleated cells from patient's peripheral blood for future testing (see the table on pages C-4/5 for processing/shipping instructions).
11. Review consent document for non-myeloablative allogeneic or autologous HSCT with patient.

4.2.4.4. Post-HSCT evaluations

1. CBC at least twice a week from Day 0 until ANC > 500 for 2 days after nadir reached. Thereafter CBC twice per week until Day 28 (or 4 weeks), then at 8 weeks, 12 weeks, 6 months, one year and then yearly until three years post-HSCT.
2. Comprehensive chemistry panel defined as creatinine, LDH, bilirubin, alkaline phosphatase, AST, ALT, magnesium, sodium, potassium, chloride, CO₂ twice a week until Day 28 (or four weeks) and then at 8 weeks, 12 weeks, 6 months, one year and then yearly until three years post-HSCT.
3. Toxicity assessments at 4, 8, 12 weeks, 6 months, one year and every six months until three years post-HSCT.
4. Disease restaging at 12 weeks, 6 months, and 1 year and annually until three years post-HSCT.
 - a. Bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics. Flow cytometry is not required. Bone marrow core should be \geq 2 cm total for unilateral or bilateral samples.
 - b. CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.

- c. In patients with known t(14;18), 10 mL peripheral blood samples will be drawn for t(14;18) analysis by PCR. These samples will be processed and stored locally for later shipment to the BMT CTN Repository for batch analysis.
5. Measurement of IgG levels at 12 weeks, 6 months and 1 year post-HSCT.
6. Quality of life assessment at 2 years post-HSCT.

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

4.2.4.5. Prior to initiation of rituximab maintenance therapy in autologous HSCT recipients

The following observations will be done \leq 2 weeks prior to initiation of rituximab maintenance therapy. This assessment can coincide with the 4 week post-autologous HSCT assessment. If progressive disease is found during this assessment, the patient will be off-study but continued to be followed for survival. Subsequent therapy is at the discretion of their attending physician.

1. History, physical examination, height and weight.
2. Karnofsky performance score.
3. CBC with differential, platelet count, creatinine, LDH, bilirubin, alkaline phosphatase, AST, ALT, sodium, magnesium, potassium, chloride, and CO_2 .
4. Disease Evaluation:
 - a. Bone marrow biopsy and aspirate to pathology and aspirate to cytogenetics. Flow cytometry is not required. Bone marrow core should be \geq 2 cm total for unilateral or bilateral samples.
 - b. CT of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.
 - c. In patients with known t(14;18), a peripheral blood sample will be drawn for t(14;18) analysis by PCR. The Day +28 sample can be utilized for this particular time point. These samples will be processed and stored locally for later shipment to BMT CTN Repository for batch analysis.
5. Review consent document for rituximab maintenance therapy with patient.
6. HepB SAb, HepB SAg, HepB Core Ab.

4.2.4.6. Sampling schedule for quantitative PCR of t(14;18) from peripheral blood sample

1. At study entry.
2. For patients with positive PCR at any time since diagnosis. These samples will be processed and shipped quarterly to the BMT CTN Repository for batch analysis.
 - a. After blood count recovery from cyclophosphamide and rituximab cytoreductive/mobilization therapy.
 - b. Analysis of each leukapheresis product from autologous HSCT patients.
 - c. Post-HSCT:
 - Day +28 post-HSCT
 - Day +84 post-HSCT
 - 6 months post-HSCT
 - 12 months post-HSCT
 - Annually until 3 years post-HSCT

4.2.4.7. Sampling schedule for chimerism analysis of peripheral blood in non-myeloablative allogeneic transplant recipients

1. Pre non-myeloablative allogeneic HSCT
2. Day +28 post non-myeloablative allogeneic HSCT
3. Day +56 post non-myeloablative allogeneic HSCT
4. Day +84 post non-myeloablative allogeneic HSCT
5. 6 months post non-myeloablative allogeneic HSCT
6. 12 months post non-myeloablative allogeneic HSCT

4.2.4.8. Required observations for HLA-matched sibling donor

Routine allogeneic donor work-up will be in keeping with FACT guidelines, BMT CTN MOP and institution standard practice of care. Work-up to include the following:

1. History, physical examination, height and weight.
2. HLA typing of heparinized peripheral blood sample.
3. Laboratory tests:
 - a. CBC with differential and platelet count, creatinine, bilirubin, LDH, alkaline phosphatase, AST, ALT, magnesium, sodium, potassium, chloride, CO₂, hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), CMV, syphilis, herpes simplex, HIV and HTLV I serologies and ABO Rh blood typing.
 - b. If donor has antibodies against red cell antigens of the recipient, the titers will be determined.
 - c. CBC will be checked prior to and after each leukapheresis collection, thereafter if clinically indicated.
4. Heparinized peripheral blood samples (10 mL) for chimerism assays.

5. One vial (10 cc) of nucleated cells from donor's peripheral blood for future testing, collected prior to mobilization (see the table on pages C-4/5 for processing/shipping instructions).
6. Five vials, each containing $2-5 \times 10^6$ nucleated cells from the allograft stem cells (to be obtained for the central repository per the Graft Characterization section of the BMT CTN MOP).
7. Left ventricular ejection fraction if clinically indicated.
8. DLCO, FEV1 and FVC if clinically indicated.
9. Evaluation of toxicities experienced post initiation of G-CSF.

Donors must be contacted by phone approximately 30 days post initiation of G-CSF for a toxicity evaluation.

Table 4.2.4.8a: Baseline, Pre-HSCT, Donor Evaluations

Required Studies/Testing	Prior to Rituximab and Cyclophosphamide	4 Weeks Post 1st Rituximab Dose (Pre-HSCT)	Pre-HSCT ¹	Pre-Rituximab Maintenance Therapy for Autologous HSCT Recipients ^{7, 16}	Donor
History, Physical Examination, Height and Weight	X		X	X	X
Karnofsky Performance Score	X		X	X	
CBC with differential, Platelet Count, Creatinine, Bilirubin, Alkaline Phosphatase, AST, ALT, LDH, Sodium, Magnesium, Potassium, Chloride and CO ₂	X ¹		X	X	X ^{2, 3}
ABO Rh Typing	X				X
Creatinine Clearance	X ¹		X ⁹		
CMV Titer, Hepatitis Panel (A,B,C) Herpes Simplex, Syphilis	X				X
HIV/HTLV1 Antibody	X				X
EKG	X				
LV Ejection Fraction	X		X ¹⁰		X ¹⁰
DLCO/FEV1/FVC	X		X ¹⁰		X ¹⁰
Toxicity Assessment		X			X ¹⁷
CT Neck, Chest, Abdomen and Pelvis	X ¹¹		X ¹¹	X ¹¹	
Bone Marrow Aspirate and Biopsy ⁸	X		X ¹⁸	X	
Peripheral Blood for t(14;18) PCR	X ¹²		X ^{13, 14}	X ^{15, 16}	
Peripheral Blood for HLA Typing	X				X
Blood Samples for Chimerism Assays			X ⁴		X
Nucleated Cells			X ⁶		X ^{5, 6}
Flow Cytometry Analysis of Graft			X		
Health Quality of Life	X				
Consent Review	X		X	X	

¹ To be performed within 2 weeks of starting conditioning therapy.² Including ABO Rh blood typing.³ CBC will be checked prior to and after leukapheresis collection. If donor has antibodies against red cell antigens of the recipient, the titers will be determined.⁴ For the allogeneic HSCT arm only.⁵ Five vials each containing 2-5 x 10⁶ nucleated cells from allogeneic donor HSC cryopreserved for central repository.⁶ One vial (10 cc) of nucleated cells from peripheral blood for future testing (see the table on pages C-4/5 for processing/shipping instructions).⁷ This assessment can be coincident with the 4 week post-HSCT assessment (see Table 4.2.4.8b).⁸ Bone marrow aspirate and biopsy samples to pathology, aspirate for cytogenetic analysis.⁹ Creatinine clearance must be done only if clinically significant nephrotoxicity experienced with cyclophosphamide and rituximab.¹⁰ If clinically indicated.¹¹ Neck CT only required if previous site of disease.¹² Even if the patient was known to be t(14;18) negative prior to registration, the test must still be performed at the time of registration for documentation purposes. This assessment is to be done after enrollment.¹³ Only in patients with known t(14;18) at any time since diagnosis.¹⁴ Additional samples for analysis of each leukapheresis product from autologous HSCT patients only.¹⁵ The Day +28 post-HSCT sample can be utilized for this time point.¹⁶ To be performed within 2 weeks of starting rituximab maintenance therapy.¹⁷ On Days 5 and 30 (via telephone) post initiation of G-CSF.¹⁸ Only if bone marrow was involved with lymphoma at time prior to the rituximab/cyclophosphamide.

Table 4.2.4.8b: Post-HSCT Evaluations

Study Assessments/ Testing	Weeks Post-HSCT														Months Post-HSCT						
	1	2	3	4 ⁶	5	6	7	8	9	10	11	12	13	14	6	12	18	24	30	36	
GVHD Assessments ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X
CBC ²								X				X			X	X		X		X	
Chemistry Panel								X				X			X	X		X		X	
Chimerism ⁵				X				X				X			X	X					
Bone Marrow Aspirate and Biopsy ^{3, 8}												X			X	X		X		X	
CT Neck, Chest, Abdomen and Pelvis ^{3, 7}												X			X	X		X		X	
Peripheral Blood for t(14;18) PCR ⁹				X								X			X	X		X		X	
IgG Levels												X			X	X					
Toxicity				X				X				X			X	X	X	X	X	X	
Health Quality of Life																	X				

¹ For allogeneic HSCT arm only.² Will be reported on case report form only on Day 28 to document engraftment for allogeneic HSCT arm only.³ Or at time of progression/relapse.⁴ Will not be reported on the case report form.⁵ Chimerism performed on CD3+ cells from peripheral blood.⁶ For the autologous HSCT arm: may coincide with the assessments required prior to initiation of rituximab maintenance therapy.⁷ Neck CT only required if previous site of disease.⁸ Bone marrow aspirate and biopsy samples to pathology. Bone marrow aspirate to cytogenetics.⁹ For patients with possible t(14;18) at any time from diagnosis to study entry.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Overview

The overall study design is a comparison of two treatment arms determined by biologic assignment, based on the availability of an HLA-matched sibling, in patients diagnosed with relapsed follicular non-Hodgkin's lymphoma. Patients without an HLA-matched sibling will receive an autologous HSCT. Patients with an HLA-matched sibling will receive a non-myeloablative allogeneic HSCT.

5.1.1. Primary Endpoint

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

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

The statistic for testing for differences in three-year progression-free survival between treatment arms is described in Appendix E. Basically, the statistic is a standardized weighted sum over strata formed by the clinical centers of differences in the Kaplan-Meier estimate of survival at the three-year time-point. If follow-up were complete (no censoring), the test statistic reduces to a Cochran Mantel Haenszel test of binomial proportions of progression-free survivors at the three- year time-point.

5.1.2. Accrual

Accrual will remain open until at a minimum, 80 patients are assigned to the allogeneic arm. It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Assuming that patients with HLA-matched sibling donors comprise 20-30% of eligible patients, approximately 187-320 patients will likely be accrued to the autologous arm during the time it takes to accrue the targeted number of patients on the allogeneic arm.

To adjust for differences in clinical care practices at participating institutions, the primary analysis of three-year progression-free survival will be stratified by transplant center. At least two individuals are required to estimate variability within a stratum so, at a minimum, each center must enroll two patients in each treatment arm. This requirement imposes some constraints on the selection of participating transplant centers.

In selecting transplant centers for participation, preference will be given to centers that perform both autologous and allogeneic transplants, and that anticipate enrollment of at least 12 patients. However, a pair of centers that collectively meet these criteria may be invited to participate (e.g. SWOG autologous program with its partner allogeneic program), one of the centers serving as the “center of record” for the purposes of monitoring and analyzing accrual or other study data.

5.1.3. Biologic Assignment

To prevent bias in determining whether donors are eligible or not for donation, and resultant bias in the biological assignment, all available siblings will be HLA-typed and all HLA-matched siblings will be assessed for donation whenever feasible. If a sibling is deemed unsuitable to be a donor, the reasoning will be reviewed with a Protocol Chair or the Medical Monitor. Patients with an HLA-matched sibling who is a suitable donor are biologically assigned to the allogeneic arm of the study. Patients without a suitable HLA-matched sibling donor are assigned to the autologous arm. The protocol requires that all potential donors be typed and evaluated prior to the initiation of cytoreductive/mobilization therapy, and within four weeks of enrollment.

5.1.4. Intention-to-Treat Principle

In accordance with the intention-to-treat principle for the primary analysis of three-year progression-free survival, patients will be classified according to their original biological assignment, regardless of the therapy actually received. Some secondary and tertiary analyses such as the assessment of Health Quality of Life or GVHD will be conducted on an as-treated rather than intention-to-treat basis.

5.2. Statistical Issues Related to Non-randomized Assignment

It is not feasible to randomly assign patients to autologous HSCT versus non-myeloablative allogeneic HSCT. A randomized study would entail enrolling only patients potentially eligible for the allogeneic transplant. Since patients with HLA-matched sibling donors comprise only 20-30% of the patient population, restricting enrollment to such patients would make it impossible to meet the accrual goals for the study in a timely fashion.

There are many possible sources of heterogeneity in a multi-center clinical trial. In a large randomized trial, chance ensures balance of both known and unknown risk factors across treatment arms. A non-randomized study is vulnerable to differential assignment of higher risk patients to one or the other treatment arm. Potential sources of heterogeneity include differences in: (1) selection of patients to screen for the study; (2) degree of compliance with biological allocation; (3) in clinical care practices at participating institutions; (4) baseline disease risk status; and, (5) in baseline factors such as recipient age and performance status. The data analytic plan to address each of these is discussed briefly.

5.2.1. Selection of Patients to Screen for the Study

Each transplant center is required to register consecutive transplant recipients with the Center for International Blood and Marrow Transplant Research (CIBMTR). Data are collected on all

transplanted patients, regardless of whether they are enrolled in a BMT CTN trial. These data will be used to determine if the proportion of allograft recipients, the demographic composition, the performance status and the disease risk of patients entered in the study are representative of the population of transplant patients treated at a center who were potentially eligible for entry in the study. Disease risk will be assessed using CIBMTR data on disease, disease stage and duration, age and performance status. Comparison of registered and enrolled patients will be performed separately within each treatment arm every four months.

5.2.2. Compliance with Biologic Assignment

The procedure for the biological assignment of patients is described in detail in Section 5.1 above. Centers will complete a BMT CTN Sibling Information Form that will capture information on whether each of the patient's siblings were typed and, if not, the reason why. This form will also capture information for HLA-matched siblings not identified as a suitable donor, and the reason(s) they are not donating. The DCC will query the transplant center for additional information as needed to validate the biological assignment, and to ensure that the patient is correctly classified in the final intention-to-treat analysis.

If an HLA-matched sibling is determined unsuitable by the center to be a donor, the reasoning will be reviewed with a Protocol Chair or the Medical Monitor. It is anticipated that the rates of donor refusal for the allograft transplant will be roughly comparable across institutions. Centers with rates of refusal significantly higher than the average will be reviewed by the DCC regarding their procedures for approaching and enrolling patients. As participation at the center level is by choice, it is expected that problems with violating the biologic assignment process will be limited.

Accrual of patients to the allogeneic arm will be monitored. Any center enrolling eight patients on the autologous arm without enrolling a patient on the allogeneic arm will be reviewed by the DCC to ensure protocol compliance. This will include a review of patients transplanted for follicular lymphoma off-study using data from the CIBMTR registration process described above. Corrective educational measures will be instituted for centers selectively enrolling patients or failing to follow the biologic assignment design of the protocol.

5.2.3. Effects of Transplant Center

To adjust for differences in clinical care practices at participating institutions, the primary analysis of three-year progression-free survival will be stratified by transplant center. At least two individuals are required to estimate variability within a stratum so, at a minimum, each center must enroll two patients in each treatment arm. Since a transplant center that fails to meet this goal will comprise a stratum that cannot contribute to the final test statistic, centers will continue enrollment until this requirement is met.

If patients with HLA-matched sibling donors comprise 25% of the patient population, centers that accrue at least 12 patients are likely to enroll at least two allograft patients by chance (probability > 80%). As noted previously, in selecting transplant centers for participation, preference will be given to centers that perform both autologous and allogeneic transplants, and

that anticipate enrollment of at least 12 patients. If necessary, centers doing only autologous transplants will be allowed to partner with a transplant center that performs allogeneic transplants to facilitate meeting this requirement and to broaden the range of centers able to participate.

5.2.4. Effects of Disease Risk Status

A post-hoc analysis will be performed assessing the comparability of patients allocated to each treatment arm with respect to disease risk status, as measured by number of prior regimens (0 or 1 versus 2 or more), and time from diagnosis to transplant. Number of prior regimens will be compared using a chi-squared test, and time from diagnosis to transplant will be compared using a Wilcoxon test. If statistically significant ($p < 0.10$) differences in the treatment arms are found in either of these disease risk prognostic factors, a secondary analysis of the primary endpoint will be performed adjusting for these covariates in a Cox proportional hazards model.

5.2.5. Effects of Baseline Factors

A post-hoc analysis will be performed assessing the comparability of patients allocated to each treatment arm with respect to baseline Karnofsky performance score and age. Performance status will be compared using a chi-square test; and age will be compared using a Wilcoxon test. If statistically significant ($p < 0.10$) differences in the treatment arms are found with respect to either of these baseline prognostic factors, a secondary analysis of the primary endpoint will be performed adjusting for these covariates in a Cox proportional hazards model.

Other baseline factors such as donor age and gender were considered, and rejected, as candidates for post-hoc adjustment. Donor age is highly correlated with recipient age when HLA-identical siblings are serving as donors. The range of ages in the study population is not anticipated to be wide enough to lead to imbalances in the treatment arms. Recipient-donor gender mismatch is not anticipated to be a strong predictor of outcome in the allograft transplant setting, and thus does not warrant adjustment.

5.3. Sample Size and Power Calculations

The study sample size is specified in terms of the targeted number of patients with an HLA-matched sibling donor. Accrual will remain open until at minimum, 80 patients are assigned to the non-myeloablative allogeneic HSCT arm. During the accrual period, enrollment will be open to all eligible patients, including those without HLA-matched sibling donors. The exact composition of the study population will depend on the series of eligible patients presenting at each clinic. During the accrual period we anticipate enrollment of 80 patients on the non-myeloablative allogeneic HSCT arm and 187-320 patients on the autologous HSCT arm.

Three-year progression-free survival after autologous HSCT is estimated to be 45% using data from the CIBMTR. A sample size of 80 non-myeloablative allogeneic HSCT recipients and 187 autologous HSCT recipients is sufficient to achieve $> 85\%$ power to detect a 20% difference between a three-year progression-free survival of 45% after autologous HSCT and three-year progression-free survival of 65% after non-myeloablative allogeneic HSCT, with a two-sided

level .05 test of proportions. Note that the final analysis will use a modified Mantel Haenszel test statistic stratified by clinical center, but the binomial test of proportions serves as a useful approximation and provides conservative estimates of power.

Table 5.3 shows the power under a variety of scenarios. The number of autologous HSCT patients is computed assuming that the number of patients with eligible HLA-matched sibling donors ranges from 20 to 30% of the total patient population.

Table 5.3: Power Under a Variety of Scenarios

Non-myeloablative Allogeneic HSCT Arm		Autologous HSCT Arm		Power
N	3-Year PFS	N	3-Year PFS	
70	.65	163	.45	.81
70	.65	210	.45	.83
70	.65	280	.45	.86
80	.65	187	.45	.86
80	.65	240	.45	.88
80	.65	320	.45	.90
90	.625	210	.45	.80
90	.625	270	.45	.83
90	.625	360	.45	.85

5.4. Interim Analysis and Stopping Guidelines

5.4.1. Guidelines for Accrual Monitoring

Each transplant center is required to enroll at least two patients in each treatment arm. If this requirement is not met after the first eight patients are enrolled, the DCC will contact the center, and will evaluate screening and referral practices. The investigation will not halt enrollment, which will continue until the goal of a minimum of two patients per arm is reached. During the final analysis, centers which do not have at least one death per treatment arm will be paired with the nearest geographically located center which fulfills the requirement to form a single strata.

In a simulation study, the proportion of subjects with HLA-matched sibling donors was assumed to be one-quarter of presenting eligible individuals. Once the target of 80 subjects with HLA-matched donors was reached, enrollment was continued only at those centers that had not yet enrolled 2 subjects per treatment group (the minimum required to compute the test statistic). This resulted in a slight excess in total enrollment. On average 81 subjects were allocated to the allograft arm, and 243 to the autograft arm.

5.4.2. Guidelines for Efficacy Monitoring

There are no planned interim analyses for efficacy in this study, because the anticipated accrual period is three years, and the primary endpoint is three-year progression-free survival. However,

if accrual is much slower than anticipated, the Data and Safety Monitoring Board will be consulted, and consideration will be given to interim analyses for efficacy in the fourth or fifth year, using either group sequential methods or stochastic curtailment to conserve type I error.

5.4.3. Guidelines for Safety Monitoring

There are several statistical guidelines employed in this study. These guidelines are designed to assist an independent Data and Safety Monitoring Board (DSMB) in overseeing the study. The DSMB may also request interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study.

The stopping guidelines monitor the incidence of transplant-related mortality and selected regimen-related toxicities. Transplant-related mortality (TRM) is defined as death in the absence of disease progression. TRM will be monitored separately in the autologous HSCT and non-myeloablative allogeneic HSCT arms. Tacrolimus or cyclosporine associated renal and hepatic toxicity will be monitored in the non-myeloablative allogeneic HSCT arm. Monitoring for TRM, renal and hepatic toxicity will commence with enrollment and will continue for six months post-HSCT.

The null hypotheses for sequential monitoring are that the true rate of TRM is less than 15% in the allogeneic arm and less than 8% in the autologous arm, and that the true incidence of each of the specified toxicities is less than 10%. If any of the observed incidence rates are substantially in excess of these targets, 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.

Transplant-related Mortality (TRM)

The rate of TRM up to six months post-HSCT will be monitored separately in each treatment arm. Monitoring will be performed monthly until enrollment to that treatment arm is closed. Each month, the null hypothesis that six month TRM is less than or equal to a threshold value will be tested against the alternative that it is greater than a threshold value. In the allogeneic arm, the threshold value will be 15%; in the autologous arm, the threshold value will be 8%. An extension of the Sequential Probability Ratio Test (SPRT) will be used. A description of this sequential testing procedure is provided below.

The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of observed deaths. The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring each treatment arm to protect against poor 180-day TRM. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more deaths than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment to the treatment arm reaches the target goal.

This procedure assumes an exponential distribution for the time until failure until six months post-HSCT, but censors follow-up time after six months. Only deaths without relapse or progression that occur on or before the patient has been followed for six months post-HSCT are counted. Total time on study is computed as time from enrollment to death, or to six months post-HSCT, whichever comes first, summed for all individuals on study.

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 a SPRT contrasting 15% versus 30% six-month TRM, in the non-myeloablative allogeneic HSCT arm, and 8% versus 14% in the autologous HSCT arm. The slope and intercept of the lower boundary are 2.00 and -6.48, respectively, for the non-myeloablative allogeneic HSCT arm, and 4.33 and -17.69, respectively, for the autologous HSCT arm.

The actual operating characteristics of the truncated tests, shown in Table 5.4.1a, were determined in a simulation study that assumed uniform accrual of either 80 non-myeloablative allogeneic HSCT recipients or 240 autologous HSCT recipients over a three year time period, and exponential time to failure after enrollment.

Table 5.4.1a: Operating Characteristics of Sequential Testing Procedure
Transplant-related Mortality
from a Simulation Study with 100,000 Replications

Operating Characteristics for Allogeneic Arm N = 80

True 6 Month Post-HSCT Mortality	15%	20%	25%	30%
Probability Reject Null	0.04	0.24	0.60	0.88
Mean Month Stopped	36.1	32.7	26.1	19.1
Mean # Deaths in 6 Mo.	11	13	13	11
Mean # Patients Enrolled	78	71	57	43

Operating Characteristics for Autologous Arm N = 240

True 6 Month Post-HSCT Mortality	8%	10%	12%	14%
Probability Reject Null	0.05	0.24	0.57	0.84
Mean Month Stopped	36.0	32.8	26.9	20.5
Mean # Deaths in 6 Mo.	18	20	19	17
Mean # Patients Enrolled	234	214	177	136

In the non-myeloablative allogeneic HSCT arm, the procedure rejects the null hypothesis in favor of the alternative 4% of the time when the true six-month TRM is 15%, and 88% of the time when the true rate is 30%. This corresponds to a type I error rate of $\alpha = 0.04$ and a type II error rate of $\beta = 0.12$. When the true six-month TRM is 30%, on average, the Data and Safety Monitoring Board will be consulted 19.1 months after opening, when 11 deaths have been observed in 43 patients.

In the autologous HSCT arm, the procedure rejects the null hypothesis in favor of the alternative 5% of the time when the true six-month TRM is 8%, and 84% of the time when the true rate is 14%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.16$. When the true six-month TRM is 14%, on average, the Data and Safety Monitoring Board will be consulted 20.5 months after opening, when 17 deaths have been observed in 136 patients.

Regimen-related Toxicities

The protocol specifies that the following toxicities are safety endpoints:

- 1) Grade ≥ 3 hepatic toxicity in the non-myeloablative allogeneic HSCT arm
- 2) Renal toxicity of serum creatinine > 3.0 mg/dL in the non-myeloablative allogeneic HSCT arm
- 3) Grade ≥ 3 neutropenia in the autologous HSCT arm after rituximab maintenance therapy
- 4) Grade ≥ 3 pulmonary toxicity/pneumonitis in the autologous HSCT arm

Hepatic and renal toxicities are considered sufficiently life-threatening to warrant use of statistical stopping guidelines to monitor these toxicities monthly. If cumulative incidence rates exceed the target threshold of 10%, the NHLBI will be notified and may require immediate DSMB review that could result in termination of enrollment to the non-myeloablative allogeneic HSCT arm.

Neutropenia and pneumonitis can often be successfully managed through early intervention, and statistical stopping guidelines will not be used to monitor these toxicities monthly. Instead, the cumulative incidence of these toxicities will be reported, along with other accumulated safety and efficacy data, to the DSMB at regularly scheduled meetings.

The stopping guidelines for hepatic and renal toxicity were derived from an SPRT contrasting 10% versus 15% cumulative incidence rates, cumulated at six months post-HSCT. The slope and intercepts of the lower boundary are 3.74 and -12.97, respectively, for the non-myeloablative allogeneic HSCT arm. Refer to the description of the stopping guideline for TRM in Section 5.4.2 for a discussion of the statistical methodology used. The parameters of the SPRT were adjusted so that the probability of stopping would be approximately < 1%, 10% and > 85% at cumulative incidence of 5%, 10% and 20%, respectively.

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 actual operating characteristics of the truncated tests, shown in Table 5.4.1b, were determined in a simulation study that assumed uniform accrual of either 80 non-myeloablative allogeneic HSCT recipients or 240 autograft recipients over a three year time period, and exponential time to failure after enrollment.

**Table 5.4.1b: Operating Characteristics of Sequential Testing Procedure
Regimen-related Toxicities > 10%
from a Simulation Study with 100,000 Replications**

Operating Characteristics for Non-myeloablative Allogeneic HSCT Arm N = 80

True 6 Month Post-HSCT Incidence	5%	10%	15%	20%
Probability Reject Null	0.00	0.08	0.45	0.84
Mean Month Stopped		35.7	30.0	22.0
Mean # Events in 6 Mo.	3.8	7.3	9.1	8.6
Mean # Patients Enrolled	79.9	77.4	65.7	48.8

In the non-myeloablative allogeneic HSCT arm, the procedure rejects the null hypothesis in favor of the alternative 8% of the time when the true six-month incidence is 10%, and 84% of the time when the true rate is 20%. This corresponds to a type I error rate of $\alpha = 0.08$ and a type II error rate of $\beta = 0.16$. When the true six-month incidence is 20%, on average, the Data and Safety Monitoring Board will be consulted 22.0 months after opening, when 8.6 events have been observed in 48.8 patients.

5.5. Analysis Plan

All analyses are based on an intent-to-treat. In such an analysis, patients are in the non-myeloablative allogeneic HSCT arm if they have a suitable HLA-matched sibling donor whether or not the non-myeloablative allogeneic HSCT occurs.

5.5.1. Analysis of the Primary Endpoint

The primary outcome of the trial is lymphoma progression-free survival at three years post-HSCT. The primary null hypothesis of the study is that there is no difference in three-year progression-free survival between the autologous and non-myeloablative allogeneic HSCT arms. The alternative hypothesis is that progression-free survival differs between autologous and non-myeloablative allogeneic HSCT strategies. The primary outcome will be assessed in a final analysis to be performed after the last enrolled patient has been followed for three years post enrollment.

In the final analysis, the endpoint of 3-year progression-free survival will be estimated using the Kaplan-Meier product limit estimator, and compared between treatment arms using the modified Mantel-Haenszel test statistic stratified by clinical center. The test statistic is described in Appendix E. Additional secondary analyses utilizing this approach will: a) incorporate progression-free survival beyond the three-year time-point, and b) test for the effect of follicular lymphoma grade at entry on progression-free survival. Estimates of the differences between progression-free survival functions and confidence bands for these differences will be performed using the procedure of Zhang and Klein [58]. In the event that there are no significant differences between the arms, a *post-hoc* power analysis will be performed.

In a secondary analysis, outcomes in the autologous transplant arm at 1, 2, and 3 years post-HSCT will be compared to an external cohort registered with the CIBMTR. In a subset of autologous transplant patients registered with the CIBMTR who met the basic eligibility criteria for the study (age 18-70, chemosensitive disease, no more than 3 prior regimens, adequate graft and performance status), overall survival, disease-free survival, and relapse-free survival were .87, .64, and .32 at one year post-autologous HSCT, and .70, .45, and .48 at three years post-autologous HSCT, respectively. Using patient-level data from this trial and from the CIBMTR registry, the survival curves will be compared using the procedures of Zhang and Klein.

5.5.2. Analysis of Secondary Endpoints

A number of secondary outcomes will be examined to compare the patient's disease status over time between treatment arms.

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 enrollment. In a secondary analysis including only patients who received their HSCT, time-to-event will be measured from the date of HSCT. 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 enrollment. In a secondary analysis including only patients who received their HSCT, time-to-event will be measured from date of HSCT. Time to progression will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Time to CR and CR+PR:

The event is CR (CR or PR). The time to event is the time to CR (CR or PR). Patients who die in a state other than CR (CR or PR) are considered as failing from a competing risk. Patients alive and not in CR (CR or PR) at the time of last observation are censored at the time of last observation. In the primary analysis in all enrolled patients, time-to-event will be measured from enrollment. In a secondary analysis including only patients who received their HSCT, time-to-event will be measured from the date of HSCT. Time to CR (CR or PR) will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Time to Off-study Therapy:

The event is the initiation of any anti-lymphoma therapy other than that defined by the protocol treatment arms. Patients who die without initiation of an off-study therapy will be considered as experiencing a competing risk. Patients who do not receive an off-study therapy but are alive at the end of the study will be censored at the time of last observation. In the primary analysis in all enrolled patients, time-to-event will be measured from enrollment. In a secondary analysis including only patients who received their HSCT, time-to-event will be measured from date of HSCT. Time to off-study therapy will be compared between treatment arms using a log-rank test, and the cumulative incidence curves will be estimated.

Health Quality of Life:*Overview*

The goal of the Health Quality of Life (HQL) component of this trial is to describe the HQL of study participants. In addition, as possible, with the available sample size differences in quality of life among recipients of the two treatment strategies in this protocol will be examined. All

patients registered to the clinical trial are potentially eligible for the study, and consent for participation will be obtained as part of consent for the clinical trial. Patients who cannot communicate in English or Spanish, cannot complete HQL questionnaires due to cognitive, linguistic or emotional difficulties, will be excluded from the study. We anticipate that 90% of registered patients will be eligible, and that compliance will be roughly 80% among surviving patients, based on experiences with The Unrelated Donor Marrow Transplantation Trial (formerly the T Cell Depletion Trial) and other studies of HQL conducted for the NHLBI in bone marrow transplant recipients.

Instruments, Administration and Scoring Methods

In order to minimize response burden and increase the chance of complete response, the selection of instruments has been limited to the FACT-BMT [58] and the SF-36 [60, 61]. The FACT-BMT is comprised of a general core questionnaire, the FACT-G, evaluates the Quality of Life (QOL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The MOS SF-36 is a general assessment of health quality of life that has been widely applied in a variety of outcome studies and is being used in this trial as a generic measure of QOL.

HQL will be assessed through a self-administered questionnaire distributed to patients at clinic visits. The assessments will be conducted at baseline prior to the cytoreductive/mobilization therapy and at two years post-HSCT. The protocol permits administration within a two-week window before the target date for the first interview, and within a +/- two-week window centered on the target date for the subsequent yearly interviews. The HQL instruments will be scored according to standard methods for these tools. Specifically, the FACT-BMT will be scored using software provided in the FACIT Manual Version 4 [59], and the MOS SF-36 will be scored using software provided in the SF-36 Health Survey Manual and Interpretation Guide [60] and the SF-36 Physical and Mental Health Summary Scales: A User's Manual [61].

Analysis and Interpretation of Results

While descriptive analyses will consider all HQL outcomes, following the lead of David Celli in the analysis of ECOG Study 5592 [62], the primary HQL endpoint for hypothesis testing will be the Trial Outcome Index (TOI). The FACT-BMT TOI is derived by adding the scores on the Physical Well-Being and Functional Well-Being subscales of the FACT-BMT, to the BMT symptoms module score. At two years post-HSCT, it is anticipated that the TOI, which contains relevant questions about physical functioning and BMT symptoms, will be most sensitive to long term differences in HQL attributable to differences in treatment strategy.

The initial analysis of the questionnaire data will focus on describing and reporting the HQL of study participants, through tables, graphs, and summary statistics characterizing the HQL scores over time in each treatment arm. Differences in QOL between the autologous HSCT and non-myeloablative allogeneic HSCT arms will be assessed in several ways. First, the marginal QOL scores given that the patient is alive will be compared at the specific time points described above using simple T-tests. Second, the Integrated Quality Adjusted Survival [63] will be compared. This latter approach aggregates QOL over the entire period of observation, and accounts for potential differences in survival rates. If an examination of patterns of missing data indicates that there is substantial informative censoring due to causes other than death, techniques for joint

modeling of survival and longitudinal data developed by Schluchter [64], and extended by Ibrahim et. al [67], will be considered.

Statistical Power and Sample Size Considerations

The trial is not designed to be powered for a primary endpoint of detecting differences in QOL between the two treatment strategies. The HQL analysis in the study will be primarily descriptive. We can, however, estimate the power of the study to detect differences between the groups based on expected survival and prior HQL studies. The TCD Trial observed a baseline mean FACT-BMT TOI score of 67.2, with a standard deviation of 13.8 units, and a mean SF-36 Physical Component Score of 41.6, with a standard deviation of 10.2 units. These data are consistent with published norms for the FACT-BMT in HSCT recipients, and the SF-36 in cancer patients, respectively [59, 60, 61].

To illustrate the statistical power available, consider a comparison of the FACT-TOI at the two-year time point between the autologous HSCT and non-myeloablative allogeneic HSCT patients. Assuming 80 non-myeloablative allogeneic HSCT patients and 240 autologous HSCT patients, 90% of whom will be eligible for HQL study, a 80% survival rate at two years, and an 80% response rate, approximately 46 allograft patients and 138 autologous HSCT patients will complete the second year interview. The estimated sample size is sufficient to detect, with statistical power of 80%, a difference in the FACT-TOI score of 6.6 units, and a difference in the SF-36 PCS score of 4.9 units, using a two-sided level .05 T-test.

Incidence of Toxicities Grade ≥ 3 According to the CTCAE Version 3.0

For both arms, toxicities that occur over the course of time will be tabulated.

Grade ≥ 3 toxicities will be tabulated for each patient at set intervals over the course of the study. The proportion of patients developing toxicity will be compared between treatment arms.

Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient according to criteria in the BMT CTN Manual of Procedures. Infections will be classified by organism, site and severity. Infection burden will be compared between treatment arms.

Efficacy of Rituximab and Cyclophosphamide for *In Vivo* Purging

In vivo purging will be estimated by the proportion of patients whose peripheral blood converts from positive for the t(14;18) by PCR prior to cytoreductive/mobilization therapy to negative following this therapy. For patients in the autologous HSCT arm, the correlation between t(14;18) results for peripheral blood samples and for collected autologous HSC will also be estimated.

Prognostic Value of t(14;18) by PCR in Predicting Relapse

A quantitative PCR assay for t(14;18) will be done on peripheral blood in patients with known t(14;18). Results of serial post-HSCT samples will be analyzed to determine if there is a threshold value that can reliably predict relapse, using statistical methods for classification and regression trees. This analysis will be performed after the trial and the information will not be available to direct clinical care of patients.

5.5.3. Analyses of Patients on the Non-myeloablative Allogeneic HSCT Treatment Arm

Several outcomes in this study are specific to the non-myeloablative allogeneic HSCT arm. Between treatment arm comparisons will not be performed, but descriptive statistics will be computed.

Primary and Secondary Graft Failure

Engraftment is defined as having $\geq 5\%$ donor T cells in the peripheral blood (donor T cell chimerism). Median time to engraftment will be estimated from the cumulative incidence of engraftment, treating death as a competing risk. Time to engraftment will be measured from the date of receipt of the non-myeloablative allogeneic HSCT.

The rate of Primary Graft Failure will be estimated as the number of patients to engraft by Day 56 post-non-myeloablative allogeneic HSCT, divided by the total number of patients receiving a non-myeloablative allogeneic HSCT.

The rate of Secondary Graft Failure will be estimated as the number of patients who engraft (at any time prior to one year after receipt of the non-myeloablative allogeneic HSCT), and subsequently lose chimerism ($< 5\%$) in the first year post-engraftment, divided by the total number of patients who engraft in the first year after receipt of the non-myeloablative allogeneic HSCT.

Incidence and Severity of Graft-Versus-Host Disease

GVHD will be graded according to criteria in the BMT CTN MOP. The cumulative incidence curves for acute and chronic GVHD will be estimated treating death as a competing risk.

APPENDIX A

REFERENCES

APPENDIX A

REFERENCES

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APPENDIX B
CONSENT FORMS

PATIENT CONSENT**IRB #*****Informed Consent to Participate in Research***

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

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

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

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

The consent form describes a study for patients with follicular lymphoma who have entered remission from treatment with conventional chemotherapy but the lymphoma has now returned. Follicular lymphoma is not curable with standard chemotherapy. Standard stem cell transplants have been used to get patients into remission and improve survival, but the disease still returns.

This study will compare two types of transplants. The purpose is to see if one type of transplant has better results than the other. The study may also find that patients have similar results with either type of transplant.

The results that are important to the study include:

- ◆ Blood counts after transplant
- ◆ Possible occurrence of infection
- ◆ Graft-versus-host disease (GVHD)
- ◆ Return of lymphoma
- ◆ How long you live after transplant
- ◆ Your quality of life

PATIENT CONSENT**IRB #**

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

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

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

1. Name of the Subject (“Study Subject”)**2. Title of Research Study**

Autologous versus Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Chemosensitive Follicular Non-Hodgkin’s Lymphoma Beyond First Complete Response or First Partial Response

3a. Principal Investigator Contact Information

Insert name, affiliation and contact information.

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

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

4. Sponsor and Source of Funding or Other Material Support

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

PATIENT CONSENT **IRB #****5. Study Purpose**

This study will compare the results from two types of blood stem cell transplant along with the drug rituximab for patients who have follicular lymphoma. The two types of **stem cell transplant (SCT)** that are compared in this study are AUTOLOGOUS SCT and NON-MYELOABLATIVE ALLOGENEIC SCT. Both autologous SCT and non-myeloablative allogeneic SCT have successfully treated this kind of lymphoma.

6. Study Plan

Patients who are able to use matched, donated stem cells from a brother or sister will have an allogeneic non-myeloablative SCT. Patients without a matched brother or sister will have an autologous SCT.

An autologous SCT uses your own stem cells for the transplant:

- ◆ Before transplant, your stem cells are collected in a process called leukapheresis, then frozen (or cryopreserved).
- ◆ You will have high doses of chemotherapy, with or without radiation, to kill the lymphoma cells in your body.
- ◆ The high amounts of chemotherapy and radiation also damage your bone marrow and immune system.
- ◆ Your blood stem cells will be given back to you to undo the effects of the chemotherapy.

An allogeneic SCT uses blood stem cells from a brother or sister donor for the transplant. The type of allogeneic transplant used in this study is called a non-myeloablative allogeneic stem cell transplant .

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

Rituximab Therapy

Whether you receive the autologous or non-myeloablative allogeneic SCT, you also will receive several doses of a drug called rituximab. Rituximab is a drug that is not considered chemotherapy but is called a monoclonal antibody. This drug works by attacking only the B cells in your body. B cells are a type of white blood cell in your blood, bone marrow and lymph nodes that normally help fight infection. However, in patients with follicular lymphoma, it is the B cells that become malignant (cancerous) and become lymphoma cells. Rituximab is already commonly used either alone or together with chemotherapy for patients with follicular lymphoma and other types of lymphoma.

PATIENT CONSENT**IRB #****7. Procedures and Tests that are Being Done as Part of you Care**

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

- ◆ Evaluate your health.
- ◆ Determine if you have a matched brother or sister donor.
- ◆ Prepare your body for a stem cell transplant.
- ◆ Receive your stem cell transplant.
- ◆ Help your body recover after transplant.
- ◆ Measure your health and well-being over three years after your transplant.

If you have a matched brother or sister donor, in order for them to participate they will also have a health evaluation and if able to donate their cells collected for transplant and sign a consent for the study.

The treatment will start with **cytoreduction**. Cytoreduction is a process to kill as many lymphoma cells as possible in your body before transplant. All study participants will have cytoreduction before either type of stem cell transplant (autologous or allogeneic non-myeloablative). This process uses **chemotherapy** and rituximab to lower the number of lymphoma cells and another drug, filgrastim (G-CSF) to rebuild your white blood cells:

- ◆ **Rituximab** (also called Rituxan) – to lower the number of lymphoma cells,
- ◆ **Cyclophosphamide** – also to lower the number of lymphoma cells, and
- ◆ **Filgrastim (G-CSF)** – to increase production of healthy white blood cells.

Table 1: Cytoreduction Schedule

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Rituximab	✓							✓
Cyclophosphamide		✓						
Filgrastim				✓	✓	✓	✓	

If you will be receiving the autologous SCT, you will undergo a procedure called leukapheresis about 12-13 days after receiving the cyclophosphamide. This collects stem cells from your bloodstream as your blood counts recover from the treatment mentioned above. The stem cells are then frozen and stored (cryopreserved). The procedure is explained in more detail at the end of this form.

PATIENT CONSENT**IRB #****A) Non-myeloablative stem cell transplant**

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

Once your body recovers in about 4 to 6 weeks from the cytoreduction treatment, you will start the **conditioning regimen** also known as the **preparative regimen**. This is done to prepare your body for transplant.

Your doctor will use a combination of two drugs and rituximab given through your veins:

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

The purpose of this treatment is to weaken your immune system and lower the chance that your body will reject the donated stem cells.

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

- ◆ Tacrolimus
- ◆ Methotrexate

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

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

PATIENT CONSENT**IRB #****Table 2: Conditioning Schedule for Non-myeloablative SCT**

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

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

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

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

B) Autologous stem cell transplant

If you have an autologous stem cell transplant, you will have your own cells collected before the transplant.

Once your body recovers, about 4 to 6 weeks after the cytoreduction treatment, you will start the **conditioning regimen** which is also be called the **preparative regimen**. The conditioning regimen will be chemotherapy based and may include total body irradiation. Whether you receive irradiation in addition to chemotherapy will be determined by your physician and by what preparative regimen is routinely used at your particular hospital/institution. This depends on the doctors at your transplant center. Conditioning is done to prepare your body for transplant. All of the drugs listed below will be given through your veins except the filgrastim, which will be given subcutaneously (injection just under the skin). You will start daily subcutaneous injections of filgrastim starting 5 days after your transplant day to help your white blood cells recover faster.

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Your doctor will use:

- **Cyclophosphamide** – to lower the number of lymphoma cells
- **Rituximab** – also to lower the number of lymphoma cells
- **Carmustine or Fractionated Total Body Irradiation** – to lower the number of lymphoma cells
- **VP-16** – to lower the number of lymphoma cells
- **Filgrastim (G-CSF)** – to help your bone marrow make white blood cells after chemotherapy

Only one of the tables below will apply to you. It depends on if you receive total body irradiation plus chemotherapy, or chemotherapy alone. You will have your transplant on “**Day Zero (0)**.”

Table 3: Preparative Schedule Using Chemotherapy and Total Body Irradiation

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
	Radiation	Radiation	Radiation	Radiation	VP-16		Cyclophosphamide		Transplant

Table 4: Preparative Schedule Using Chemotherapy Only

Day	-6	-5	-4	-3	-2	-1	0
	Carmustine		VP-16		Cyclophosphamide		Transplant

Your rituximab maintenance therapy will start about six weeks after your transplant. You will receive 4 weekly doses of rituximab through your veins. The rituximab therapy is to remove any lymphoma cells that may have survived the high dose chemotherapy.

PATIENT CONSENT**IRB #****8. What are risks of this research study?**

Details of all potential side effects, including those that occur rarely, are discussed in the Appendix.

You will face risks from the transplant itself, and from treatments given before and after the transplant. Your doctor thinks these risks are less than the risk from your cancer. Your heart, lungs, liver, bladder, kidneys, brain or other organs may be damaged by the chemotherapy or irradiation, or by other drugs given to you after the transplant. Your risk of infection is also increased when undergoing a stem cell transplant. This is due to the chemotherapy that weakens your immune system. Potential infection can be caused by either a bacteria, virus or a fungal organism. Your doctors will monitor you closely for any sign of infection, especially fevers.

During the cytoreductive phase, the most common complications are fever, chills and shortness of breath during infusion of rituximab, nausea from the cyclophosphamide, and bone pain from the filgrastim. Patients will be at risk for infections and may need transfusions during the 7-14 days when the blood counts are low following this treatment. Those patients who will have stem cells collected may experience temporary numbness or tingling of the fingertips or around the mouth during the blood stem cell collection procedure.

Autologous transplant patients commonly experience some nausea when receiving the chemotherapy or irradiation. Infusion of the stem cells may be accompanied by an unusual taste for a few hours, transient nausea, and occasionally shortness of breath. Nausea, diarrhea and sore throat usually occur about a week after transplantation and lasts for several days. The blood counts are very low for about 2 weeks after transplantation, and during this time, the patient is at high risk for infection and bleeding. Most patients require transfusions of red blood cells and platelets during this time. While the risk of early death following autologous transplant is low, death could occur. The patient may also fail transplant treatment due to relapse of lymphoma.

Allogeneic transplant patients may experience any of the side effects from chemotherapy, drug therapy or cell therapy as listed in the appendix. The patient's blood counts are expected to be low for about 1 week after transplant and this increases the risk of serious and even life-threatening infection. Transfusions of blood and/or platelets and/or intravenous antibiotics may be necessary. There is a possibility that the donor cells will not "take", in other words, not engraft. The period of low blood counts could then be longer but the patient's own marrow function and cell count recovery would be expected to recover. If engraftment occurs, there is about a 50% chance that graft versus host disease (GVHD) will occur. GVHD occurs when the donor's immune system attacks the patient's organs. The most common organs affected are: 1.) the skin which would result in rash, peeling, and/or deeper injury, 2.) the gut which would cause diarrhea, cramping and possible blood loss, and 3.) the liver which would cause inflammation and/or dysfunction or failure. Medications, including tacrolimus and methotrexate will be given to reduce the risk of acute GVHD. However, if GVHD occurs, additional therapy would be required to treat it. The GVHD might be stopped or it could progress and result in life-threatening medical problems, including late chronic GVHD or possibly death. It is possible that the patient could experience injury to any organ or system as a result of required medications,

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transfusions, transplant, and/or other therapies. While the risk of early death following non-myeloablative transplant is low, death could occur. The patient may also fail transplant treatment due to relapse of lymphoma.

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

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

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

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

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

You may be helping other patients get better treatment in the future.

11. What will be done with my blood and tissue samples?**Research Blood Samples**

Genetic material is any sample of tissue, blood, fluid, etc. obtained from you during the study. With your permission, 10 mL of your blood will be collected prior to the transplant and stored to be used solely for research purposes. The samples will be stored for future studies that will look at responses to treatment based on factors not yet known. These factors may relate to characteristics of your follicular NHL or to how your body tolerated the study treatments. Usually these blood samples can be drawn from you at the time of routine blood collections. Your confidentiality will be maintained because no identifying markers (name, etc.) will remain with the sample.

All BMT CTN research samples will be paired with the respective donor or recipient sample and 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 #0202 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator's request for these samples is approved by the committee, 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

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completion of the main protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

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

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

- I agree to have 10 mL of blood collected for future research.
- No, I do not agree to have 10 mL of blood collected for future research.

Signature

Date

12. What if not enough cells are collected to use for transplant?

Your doctor will decide if it is safe to proceed to the planned transplant procedure, depending on how many stem cells are actually collected. The risk of being transplanted with a low number of stem cells is that your blood counts may return to normal levels very slowly or they may stay low permanently. If this occurs, you may need many blood and/or platelet transfusions and/or your risk of infection may increase. If you do not proceed to transplant, your doctor can offer other alternatives such as chemotherapy and/or radiation if he/she feels this is appropriate.

13. What are the costs?

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

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

PATIENT CONSENT **IRB #****14. Will I be paid to take part in this research study?**

No.

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

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

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

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

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

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

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

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

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

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

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

- Staying in the study would be harmful to you.
- You need treatment not allowed in this study.
- You do not follow directions.
- The study is cancelled.

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19. How will my information be kept private?

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

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

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

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

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

- /Institution/
- The National Institutes of Health (NIH)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Board (IRB)
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data Coordinating Center (DCC)
- Southwest Oncology Group (SWOG)

Information related to or resulting from your stem cell transplant will be reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary organization of basic and clinical scientists working together in an effort to gather information on results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

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

PATIENT CONSENT**IRB #****20. How long do you keep my information?**

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

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

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

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

22. HIPAA¹ 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 *Autologous vs. Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Patients With Chemosensitive Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response or First Partial Response*.
- b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., CT scan, blood tests, biopsy results).
- c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:
(list hospitals, clinics or providers from which health care information can be requested)

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

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

- Principal Investigator and the researcher's staff
- Dr. Ginna Laport and Dr. Robert Negrin, Study Chairpersons, and staff/laboratories at Stanford Hospitals and Clinics
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., TBD for quantitative PCR testing.
- National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
- 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)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

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

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

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

h. This authorization does not have an expiration date.

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23. Further Information

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

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

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

PATIENT CONSENT**IRB #****24. Signatures**

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

Signature of person obtaining consent

Date**Consenting Adults**

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

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

Signature of Adult Consenting for Self

Date

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

Signature of Parent/Legal Representative

Date

Print Name of Legal Representative

Relationship to
Participant

PATIENT CONSENT

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

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

Assent Signature of Participant

Date

PATIENT CONSENT**IRB #****APPENDIX TO PARTICIPANT CONSENT****RISKS AND TOXICITIES RELATED TO A STEM CELL TRANSPLANT**

There are certain risks related to a blood stem cell transplant. There are risks from the medications and irradiation (if given) therapy you will receive as part of the conditioning for the transplant and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person.

Risks Related to the Transplant Conditioning Regimen**SECTION A****FOR ALL PATIENTS (AUTOLOGOUS AND ALLOGENEIC PATIENTS):**

Rituximab (Rituxan): This medication is used to reduce cancer cells. Common side effects associated with rituximab include a reaction such as fevers chills or shortness of breath during the actual infusion of the drug. This typically can happen with your very first infusion of this drug. Your doctor or nurse may need to temporarily slow down or stop the drug infusion until your symptoms lessen. A much less common side effect can be a severe allergic reaction called anaphylaxis, which could cause severe shortness of breath, low blood pressure or tightness in your throat. Rituximab can also temporarily cause a low white blood cell count and/or weaken your immune system for up to several months after your last dose of rituximab, which may increase your risk of infection during that time period. 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.

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

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(heart failure). If this occurs you may have shortness of breath and have fluids build-up in your body. Cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced but you would still be able to have intercourse. Women who are still menstruating may have irregular periods or may no longer have any periods. Whether you are a man or woman, this medication will likely greatly decrease your chances of being able to have a child.

Filgrastim (also called G-CSF for Granulocyte Colony Stimulating Factor) : Less than $\frac{1}{2}$ teaspoon (2 mL) filgrastim will be injected under your skin each day and this could cause some minor pain at the injection site. Most people experience varying levels of pain in their bones when treated with this drug which usually feels like muscle aches, bone pain and/or headaches. The pain is usually relieved with acetaminophen (Tylenol™). Aspirin or aspirin-containing drugs must not be taken during filgrastim administration and during leukapheresis without physician approval. A less common side effect is a skin rash. These symptoms go away within a few days after stopping the drug. Other rare potential side effects include signs of allergy such as a rapid heart rate, dizziness, shortness of breath, itching or rash. Temporary changes in laboratory values that monitor liver and bone changes can also occur as well as a temporary increase in your white blood cell count. These return to normal after stopping the drug.

Rarely, people receiving filgrastim have experienced swelling of their spleen and on occasion, internal bleeding from rupture of the spleen. Rupture of the spleen can present as general fatigue and weakness, flank or abdominal pain or loss of consciousness from low blood pressure. Rupture of the spleen can be very serious and is potentially life threatening. Management of this problem could require blood transfusions or surgery. There is less than a 1% chance of this occurring. If you have any unusual symptoms, you should report them immediately.

Risks and Procedures Related to the Transplant Procedure

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

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

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

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lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

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

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy, radiation therapy, or both. Veno-occlusive causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve but can potentially cause death.

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

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

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

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

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

Risk to the Unborn

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

Sterility and Future Childbearing Potential for Men and Women

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

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells

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

SECTION B**For AUTOLOGOUS STEM CELL TRANSPLANT PATIENTS:**

VP-16 (etoposide): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. VP-16 may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss and skin peeling, especially in the areas of your hands, feet and underarms. VP-16 slows the making of new blood cells. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. VP-16 also lowers your immune (defense) system and as a result you may have more infections. VP-16 can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced but you would still be able to have intercourse. Women who are still menstruating may

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

Total Body Irradiation (applicable to certain patients receiving the autologous SCT): Total body irradiation may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), mouth sores, and painful swelling of the saliva glands for a few days. You may also experience short-term hair loss. Total body irradiation kills both sick and normal marrow, leading to a lack of red blood cells, white blood cells, and platelets. The short-term loss of these blood cells could cause you to become anemic, develop an infection, and/or bleeding. This will continue until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. There is a risk that cataracts (cloudiness) may develop in your eyes. This may mean partial loss of vision, and you may need contact lenses or surgery to remove the cataracts. The total body irradiation dose used will probably result in sterility (not being able to have children) as noted in the cyclophosphamide paragraph on the previous page. It is not known whether the use of total body irradiation will cause more side effects or problems with your health in the future.

Carmustine (also called BCNU) and Etoposide (also called VP-16) (applicable to certain patients receiving the autologous SCT): Side effects from these drugs include nausea (feeling sick to your stomach), vomiting (throwing up), low blood counts, skin rash, diarrhea (loose stools), mouth sores, fevers, and fatigue. Rarely, liver and/or kidney damage can occur. Because of your weakened immune system, a less common side effect is an infection that can be caused either by a bacteria, virus or fungus for which you will be immediately treated with antibiotics. A delayed but less common side effect of the BCNU that can occur about 1-2 months after transplant is pneumonitis or inflammation of your lungs. This can present as a persistent cough, shortness of breath, fevers, persistent fatigue, chest discomfort when taking a deep breath or a sudden decrease in stamina. This would be treated with prednisone. Lung injury from BCNU usually gets better with treatment but some patients have permanent lung damage and some patients die from this side effect.

Leukapheresis: During this procedure, your central venous catheter will be connected to the leukapheresis machine. This machine draws blood out of part of your catheter continuously and filters the stem cells out of your blood stream. The rest of your blood is then returned to your body via another part of your line. Your blood will be thinned with an anticoagulant during the collection procedure to keep your blood from clotting (clogging and thickening) in the tubing and in the machine. This anticoagulant sometimes causes low calcium levels in your blood, which you would feel as temporary numbness or tingling of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine so that oral or intravenous calcium can be given to you. If not corrected, this complication could progress to severe muscle cramps. Other possible unpleasant effects of the collection procedure include lightheadedness, nausea or more rarely, fainting due to temporary lowering of the blood pressure, as well as becoming chilled during the procedure. This procedure takes about 3-4 hours per daily session. Depending on the number of stem cells in your blood, it usually takes 1-3 daily sessions to collect enough stem cells.

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SECTION C

For **ALLOGENEIC STEM CELL TRANSPLANT** PATIENTS:

Fludarabine (applicable to patients receiving the allogeneic SCT): This medication is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells. Likely side effects you may experience are low white blood cell count with increased risk of infection, low platelet count with increased risk of bleeding, and anemia (low red blood cell count) with tiredness or low energy.

Risk Related Specifically to the ALLOGENEIC Transplant Procedure:

Graft-versus-Host Disease (GVHD)

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

Risks Related to the Medications Used to Help Prevent Graft-versus-Host Disease (GVHD)

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

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

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

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. It may

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also cause nausea (feeling sick to your stomach) and vomiting (throwing up). Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidney is already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

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

DONOR CONSENT**IRB #*****Informed Consent to Participate in Research***

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

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

This is a consent form for a research study. This clinical trial is a research study to determine better treatment for patients with follicular lymphoma.

We invite you to join this study because:

- Your brother or sister has follicular lymphoma
- Your blood stem cells are a match for your brother or sister
- Your brother's or sister's disease may be treated by a blood stem cell transplant, and
- Your brother or sister want to join the follicular lymphoma research study

It is very important for you to know your choices before you decide to join a research study.

Your brother or sister who has low grade follicular lymphoma may be helped by a blood stem cell transplant (SCT). Stem cells are cells found in the bone marrow and blood stream that rebuild your blood, bone marrow and the immune system.

This study uses two sources of blood stem cells for transplant: autologous and allogeneic.

- An **autologous transplant** uses blood stem cells collected from the **patient**.
- An **allogeneic transplant** uses blood stem cells collected from a **brother or sister** who are a tissue match with the patient.

Doctors currently use both sources of blood stem cells for transplants. The doctors do not know which type of transplant, autologous or allogeneic, is the better treatment for patients with

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follicular lymphoma. Information from this study will help doctors understand the best treatment choices for follicular lymphoma.

We determined that you are a tissue-match to your brother or sister by testing your blood. We tested to see if your antigens matched your brother or sister's antigens. Since all of these antigens matched, your brother or sister is a tissue-match with you. Therefore, your brother or sister has been assigned to receive an allogeneic stem cell transplant.

This consent describes the collection of stem cells from your blood to transplant into your brother or sister. The donation process for stem cells is not experimental. The treatment for your brother or sister is part of a research clinical trial.

This consent form outlines the process, potential risks and benefits of donating your stem cells for transplantation into your brother or sister.

1. Name of the Donor**2. Title of the Research Study**

Autologous vs. Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) For Patients With Chemosensitive Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response or First Partial Response

3a. Principal Investigator Contact Information

Insert name, affiliation, and contact information.

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

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

4. Sponsor and Source of Funding and Other Material Support

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

DONOR CONSENT**IRB #****5. Study Purpose**

You are being invited to participate in this research study because current therapy does not help everyone with follicular lymphoma.

The goal of this clinical research study is to determine whether autologous or allogeneic stem cell transplantation is the better therapy for patients with low grade follicular lymphoma who require a transplant to treat their disease.

You are being asked to donate blood stem cells to your brother or sister because you are a tissue match with them. Donating blood stem cells is not experimental.

6. What will be done if you take part in this research study?

You will undergo a brief medical evaluation and a series of blood tests to prepare for the possible stem cell donation. The following tests and procedures will be done:

- Medical history, physical examination
- Blood tests
- Urine tests
- If you are a woman able to have children, a blood test to check for pregnancy will be done. If you are pregnant, you cannot take part in this study.
- Other tests, such as a chest x-ray or electrocardiogram (ECG or EKG, a picture of the electrical action of the heart) will be done if your physician feels it is necessary.

If your medical evaluation shows any problems or concerns, you will be told about them. This will be kept private and not shared with your brother or sister unless you agree.

Procedures:

Only a small quantity of stem cells is normally present in the blood. A drug called filgrastim, also called G-CSF (granulocyte-colony stimulating factor), can increase the number of these stem cells in the blood. This drug allows enough stem cells to be collected from you for transplantation into your brother or sister.

If the medical exam and blood tests confirm that you are a suitable donor, you will receive injections of filgrastim into the skin (like an insulin injection) once a day for 5 days to help the release of your stem cells into your blood. You must come to the donor center or clinic each day for the filgrastim injections unless these can be arranged at home.

On the fourth and fifth day of filgrastim injections (and possibly the sixth day) you will go to the donor center to have stem cells collected by a machine called a blood cell separator. The procedure of collecting stem cells is called apheresis. Each apheresis procedure takes about 4 to

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6 hours. The procedure of collecting stem cells involves removing blood from a vein in one arm, passing the blood through the machine where stem cells are collected, and the rest of your blood cells and plasma (the liquid portion of your blood) are returned to you through a vein in your other arm. This procedure will involve placing a needle in each of your arms, collecting the cells over approximately four to six hours during which time you will be required to lie relatively still. If the veins in your arms are not large enough for the needles, you will need to have a temporary central venous catheter placed to collect your stem cells. A central venous catheter is a sterile flexible tube that will be placed into a large vein under local anesthesia. Your physician will explain this procedure to you in more detail and you will be required to sign a separate consent form for this procedure.

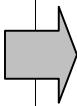
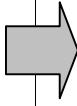
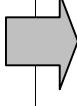
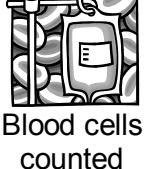
Sometimes, not enough stem cells are obtained with two aphereses. If this occurs, you will need to undergo a third apheresis procedure to try to collect enough stem cells.

This process will not remove all of your blood and bone marrow of stem cells. Healthy people have enough stem cells after the collection (aphereses) to make a normal amount of blood cells and the body will replace the lost stem cells with new ones.

You will be weighed and have blood tests (1-2 teaspoons) including a complete blood count before each collection. We repeat the complete blood count after each apheresis procedure.

The following table summarizes the schedule and procedures you undergo when donating stem cells.

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DONATION SCHEDULE					
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
 Filgrastim (16 mcg/kg/SQ) injection					You may need to do another day
			 More blood tests done		You may need to do another day
			 (Apheresis) Blood stem cell collection		You may need to do another day
			 Blood cells counted		You may need to do another day

7. How long will I be in the study?

You will be in the study for up to a few months from the time you sign the consent until approximately one month after stem cell collection. The actual process of taking filgrastim and then collecting your stem cells though takes less than a week. You will be contacted by phone approximately 30 days after initiation of G-CSF. You will be asked to answer questions about your health since your stem cells were collected.

Your doctor may decide to take your brother or sister off this study if their condition becomes worse, side effects of their treatment are severe or life threatening, or the treatment is no longer in their best interest. If your brother or sister leaves the study there will be no need for you to donate stem cells.

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Your doctor may also decide to take you off this study if the filgrastim or if the leukapheresis procedure causes severe, unmanageable or life threatening side effects to you.

You may stop participating at any time. However, if you decide to leave the study, we encourage you to talk to the study doctor first. Leaving the study early may affect your brother or sister's treatment.

8. Will you provide blood samples for research?**Research Blood Samples**

Genetic material is any sample of tissue, blood, fluid, etc. obtained from you during the study. With your permission, 3-5 teaspoons from your stem cell collection and 3-5 teaspoons of your blood (taken from your vein) will be collected prior to the recipient's transplant and stored to be used solely for research purposes. The samples will be stored for future studies that will look at responses to treatment based on factors not yet known. Your confidentiality will be maintained because no identifying markers (name, etc.) will remain with the sample.

All BMT CTN research samples will be paired with the respective donor or recipient sample and 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 #0202 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator's request for these samples is approved by the committee, 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.

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

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You are free not to take part in this additional future research. There will be absolutely no change in your care as a result of your refusal to give these additional samples. Refusal to participate does not affect your brother or sister's care. Please indicate your choice(s) below:

- I agree to have blood and stem cells collected prior to the recipient's transplant for future research.
- No, I do not agree to have blood and stem cells collected prior to the recipient's transplant for future research.

Signature

Date**9. What will happen if not enough stem cells are collected from me?**

The doctor will decide if it is safe to proceed to the planned transplant procedure, depending on how many stem cells are actually collected. The risk of being transplanted with a low number of stem cells is that your sibling's blood counts will return to normal levels very slowly or they may stay low permanently. If this occurs, he/she may need many blood and/or platelet transfusions and/or the risk of infection may increase. If he/she does not proceed to transplant, the doctor can offer other alternatives such as chemotherapy and/or radiation if he/she feels this is necessary.

10. What are the possible discomforts and risks?

There may be side effects from taking filgrastim and donating stem cells. The filgrastim and leukapheresis may cause some, all or none of the side effects listed below. You should discuss these with your doctor. In addition, there is always the chance of new, unexpected or previously unknown side effects. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the filgrastim and leukapheresis is stopped.

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Risks and side effects include:

Filgrastim (G-CSF): Less than $\frac{1}{2}$ teaspoon (2 mL) filgrastim will be injected under your skin each day and this could cause some minor pain at the injection site. Most people experience varying levels of pain in their bones when treated with this drug which usually feels like muscle aches, bone pain and/or headaches. The pain is usually relieved with acetaminophen (TylenolTM). Aspirin or aspirin-containing drugs must not be taken during filgrastim administration and during leukapheresis without physician approval. A less common side effect is a skin rash. These symptoms go away within a few days after stopping the drug. Other rare possible side effects include signs of allergy such as a rapid heart rate, dizziness, shortness of breath, itching or rash. Temporary changes in laboratory values that monitor liver and bone changes can also occur as well as a temporary increase in your white blood cell count. These return to normal after stopping the drug.

Rarely, normal donors receiving filgrastim have experienced swelling of their spleen and on occasion, internal bleeding from rupture of the spleen. Rupture of the spleen can present as general fatigue and weakness, flank or abdominal pain or loss of consciousness from low blood pressure. Rupture of the spleen can be very serious and is potentially life threatening. Management of this problem could require blood transfusions or surgery. There is less than a 1% chance of this occurring. Other, unpredictable side effects may, occur which have not been reported. If you have any unusual symptoms, you should report them immediately.

Possible interactions of filgrastim with other drugs have not been fully evaluated; therefore, it is important that you report all drugs, both prescription and non-prescription to your physician. Long-term (beyond one year) safety data on filgrastim administered to normal, healthy people is limited but so far has not identified any late problems for donors.

Leukapheresis; A needle will be placed in each arm. Pain and bruising could occur in both arms, but severe bleeding in the arm is rare. Your blood will be thinned with an anticoagulant during the collection procedure to keep your blood from clotting (clogging and thickening) in the tubing and in the machine. This anticoagulant sometimes causes low calcium levels in your blood, which you would feel as temporary numbness or tingling of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine so that oral or intravenous calcium can be given to you. If not corrected, this complication could lead to severe muscle cramps. Other possible unpleasant effects of the collection procedure include lightheadedness, nausea or more rarely, fainting due to temporary lowering of the blood pressure, as well as becoming chilled during the procedure.

You will lose some blood cells called platelets with the stem cells. These cells help stop bleeding. If your platelet count falls enough to place you in danger of bleeding, (less than 30,000 mL) any further collections will be delayed until your platelet count increases.

Central Venous Catheter; If your arm veins are inadequate (too small) to allow leukapheresis, you will need a central venous catheter to donate cells. A central venous catheter is a flexible sterile tube that can be placed into a large vein either under the collar bone or in your groin area

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so that blood can be withdrawn. This tube is placed under local anesthesia. Complications include blood clots and infection. Clotting may require removal of the catheter or treatment of the clot by injecting a medicine that dissolves blood clots. If you develop an infection, you will require treatment with antibiotics. If the catheter is placed under the collarbone, other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

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

Risks to the Unborn: Since the filgrastim used in this study can affect an unborn baby, you should not become pregnant or father a baby while on filgrastim.

11a. What are the possible benefits to you for taking part in this study?

If you agree to take part in this study, there is no direct medical benefit to you.

11b. What are the possible benefits to others?

The possible benefit to your brother or sister may be improvement in the control of their lymphoma and possibly prolonged survival. We hope the information learned from this study will benefit other patients with lymphoma in the future.

12. If you choose to take part in this study, will it cost you anything?

There is no financial benefit to you by participating in this treatment protocol. Usually, the insurance policy of the stem cell recipient will cover the cost of the donor evaluation and stem cell collection. The transplant coordinator will help you identify insurance coverage before you incur charges for your evaluation and donation. If you have concerns or questions regarding coverage or potential charges, you should contact (contact person's name) at (xxx) xxx- xxxx to review the situation.

13. Will you receive compensation for taking part in this research study?

No.

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14. What if you are injured because of the study?

You agree to take the risks listed above. If you experience an injury that is directly caused by this study, only the professional medical care you receive at the [participating clinical facility] will be provided without charge. Hospital expenses will be paid by you or your insurance provider. No other compensation is offered. By signing this form, you have not waived any of your legal rights.

15. What other options or treatments are available if you do not want to be in this study?

Participation in this study is entirely voluntary. You are free to refuse to be in the study and your refusal will not influence current or future health care you receive at this institution.

Instead of being in this study, your brother or sister may have these options:

- Treatment with other drugs or combination of drugs.
- A standard autologous stem cell transplant.
- A traditional allogeneic or non-myeloablative stem cell transplant.
- No therapy at this time, with care to help them feel more comfortable.

Your brother or sister may receive these treatments at this or other centers even if you or they choose not to take part in this study.

16a. How can you withdraw from this research study?

If you agree to be in this study, you are free to change your mind. At any time you may withdraw your consent to be in this study. If you do withdraw your consent, there will be no penalty and you will not lose any benefits to which you are otherwise entitled. If you decide to withdraw, we ask that you notify [Principal Investigator] in writing; his/her mailing address is on the first page of this form.

You must be aware, however, that a decision not to participate once treatment of your brother or sister begins, could have serious harmful consequences for the health of your brother/sister. Not donating stem cells after your brother or sister has received their pre-transplant chemotherapy and/or irradiation may result in his or her death.

If you have any questions regarding your rights as a donor, you may phone the Institutional Review Board (IRB) office at (xxx) xxx-xxxx.

16b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we will ask your permission to continue using all information about you that has already been collected as part of the study prior to your withdrawal.

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16c. Can the Principal Investigator withdraw you from this research study?

Your participation can be withdrawn (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.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant
- Other protocol-specific reasons; for example, if the dose of treatment and/or drugs you have been given has been found to be unsafe.
- The study is cancelled by the National Institutes of Health (NIH) for other administrative reasons.

17. How will your privacy and the confidentiality of your research records be protected?

Study records that identify you will be kept confidential as required by law. You will not be identified by name in the study records. Your records will be assigned a unique code number. The key to the code will be kept in a locked file in the Data Coordinating Center. Authorized persons from [Clinical Center Name], the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect the confidentiality of them to the extent permitted by law. This research study is sponsored and conducted under the authority of the National Institute of Health; therefore, the sponsor and the sponsor's agent also have the legal right to review your research records. Otherwise, your research records will not be released without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

18. Expiration Date for Retention of Records

The study results will be retained in your research record for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

DONOR CONSENT**IRB #****19. How will the researcher(s) benefit from your being in this study?**

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals. In addition, the sponsor is paying the Principal Investigator to conduct this study.

20. HIPAA¹ 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 *Autologous vs. Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Patients With Chemosensitive Follicular Non-Hodgkin's Lymphoma Beyond First Complete Response or First Partial Response*.
- b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., CT scan, blood tests, biopsy results).
- c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:
(list hospitals, clinics or providers from which health care information can be requested)

- d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:
 - Principal Investigator and the researcher's staff
 - Dr. Ginna Laport and Dr. Robert Negrin, Study Chairpersons, and staff/laboratories at Stanford Hospitals and Clinics

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

DONOR CONSENT**IRB #**

- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., TBD for quantitative PCR testing.
- National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
- 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)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

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

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

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

h. This Authorization does not have an expiration date.

21. Further Information

If you have further questions concerning this project at any time, you are free to ask them of Dr. _____, who will be available to answer them. His/her telephone number is located on the first page of this consent.

If you have further questions about your disease you are also free to contact The Cancer Information Service of the National Cancer Institute (NCI) using their toll-free number 1-800-422-6237.

DONOR CONSENT**IRB #****22. Signatures**

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

Signature of person obtaining consent

Date**Consenting Adults**

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

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

Signature of Adult Consenting for Self

Date

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

Signature of Parent/Legal Representative

Date

Print Name of Legal Representative

Relationship to Participant

DONOR CONSENT

IRB #

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

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

Assent Signature of Donor

Date

APPENDIX C
LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. HLA TYPING

HLA testing and evaluation must be completed within four weeks of study enrollment and prior to the initiation of the cytoreductive/mobilization therapy. The cytoreductive/mobilization therapy must begin no later than four weeks from enrollment.

HLA typing of heparinized peripheral blood can be done by either serologic or DNA methods for HLA-A, -B. DNA methods must be utilized for DRB1.

The specimens for HLA typing will be:

- a) Donor - 5 mL peripheral blood sample(s) from sibling member, and
- b) Patient - 5 mL peripheral blood sample from the recipient.

2. CHIMERISM - Non-myeloablative Allogeneic HSCT Patients and Donor

A heparinized peripheral blood sample from patient and donor is required for chimerism studies 2 weeks pre-allogeneic HSCT to subsequently determine the host or donor origin of ANC recovery. All pre-HSCT samples will be stored for future evaluation of post-HSCT chimerism.

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

3. PATHOLOGY/CYTOGENETICS STUDIES

Unilateral bone marrow biopsies aspirates are required for pathology analysis and bone marrow aspirates are required for cytogenetic analysis prior to the cytoreductive/mobilization 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.

4. FLOW CYTOMETRY

According to the BMT CTN Graft Evaluation MOP, the hematopoietic stem cell content of the product (graft) should be determined using CD45-FITC and CD34-PE staining to identify stem cells within the WBC component of the product.

Allogeneic donor products will also be analyzed to determine the B, T and NK cell content using CD3, CD4, CD8, CD19 and CD56 expression as detected by flow cytometry. Autologous grafts require CD34 enumeration at a minimum.

Flow cytometry will be done in keeping with the BMT CTN MOP and local institutional practice, and will be performed prior to infusion of the graft.

5. IMMUNOGLOBULIN MONITORING

IgG levels will be monitored in non-myeloablative allogeneic and autologous HSCT patients. IgG levels should be determined at 12 weeks, 6 months and 1 year post-HSCT. Testing will be done in keeping with the BMT CTN MOP and local institutional practice.

6. POLYMERASE CHAIN REACTION (PCR)

Peripheral blood (10 mL) will be collected for determination of the presence of t(14;18) by PCR. The initial evaluation (i.e., baseline sample) will be shipped directly to the BMT CTN Reference Laboratory, The Methodist Hospital (TMH), and results will be obtained real-time directly from TMH to the appropriate Transplant Center. The baseline sample will be labeled with labels provided by the NHLBI Repository. Baseline samples will be collected using two, 6.0 mL lavender top EDTA vacutainers (BD #367863) with 5 mL of peripheral blood in each vacutainer. Baseline samples will be shipped cool, using frozen gel packs, via Federal Express priority overnight Monday through Friday prior to the initiation of the cytoreductive/mobilization therapy. The BMT CTN DCC will provide all shipping costs for these samples.

It is the responsibility of the CRA, or designated individual, at the Transplant Center to inform TMH of an upcoming shipment via fax or email. The communication should contain the date of shipment, the patient(s) transplant center-specific identifier and Federal Express tracking number. The Protocol Coordinator at EMMES should be copied on e-mail communications and/or receive a copy of the faxed documents via fax at 301-251-1355.

All other PCR t(14;18) assessments (i.e., all post-baseline samples) as summarized in the schedule of evaluation (Chapter 4) are not required to be obtained unless patient had a positive test at any time from initial diagnosis. Other PCR samples will be collected using two 6.0 mL lavender top vacutainers (5.0 mL of peripheral blood in each vacutainer) with an ACD additive (BD #364816), processed by ficoll to obtain a white blood cell pellet and shipped quarterly to the NHLBI Repository, SeraCare BioServices, in compliance with the shipping procedures specified in the BMT CTN MOP.

Misti Dowell
NHLBI Repository
SeraCare BioServices
217 Perry Parkway
Gaithersburg, MD 20877
Phone: (301) 208-8100; Fax: (301) 208-8829

7. RESEARCH SPECIMENS

BMT CTN research samples will be paired with the respective donor or recipient sample and 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 #0202 study. An NHLBI Biologic Specimen Repository Utilization Committee will advise NHLBI on requests for samples to perform research with these anonymous samples. If an Investigator's request for these samples is approved by the committee, 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 Donors:

Five vials, each containing $2-5 \times 10^6$ nucleated cells (~1ml per cryovial) from the donor stem cells must be obtained prior to the allogeneic transplant. Transplant Centers should follow controlled-rate freezing SOPs for cryopreserving research samples as for product storage. Samples will be shipped annually to the NHLBI Repository in compliance with the shipping procedures specified in the BMT CTN MOP.

In addition, peripheral blood (10 mL nucleated cell sample) will be collected prior to mobilization and shipped quarterly to the Repository in compliance with the shipping procedures specified in the BMT CTN MOP.

For Patients:

Peripheral blood (10mL nucleated cell sample) will be collected for future testing prior to the non-myeloablative allogeneic or autologous transplant and shipped quarterly to the Repository in compliance with the shipping procedures specified in the BMT CTN MOP.

SCHEDULE OF LABORATORY EVALUATION

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
HLA Typing	5 mL peripheral blood or according to institutional practice	Store according to institutional practice	Prior to cytoreductive/mobilization therapy.	N/A	Transplant Center
Chimerism	10 mL heparinized peripheral blood or according to institutional practice	Store according to institutional practice	2 weeks prior to the initiation of allogeneic HSCT conditioning therapy for patient and donor. Weeks 4, 8 and 12, 6 months and one year post-allogeneic transplant for patient.	N/A	Transplant Center
Pathology/ Cytogenetic Studies	Volume of bone marrow biopsy and aspirate determined according to institutional practice	Store according to institutional practice	Prior to cytoreductive/mobilization therapy. Bone marrow biopsies and aspirates must be done prior to the transplant, prior to initiation of rituximab maintenance therapy (if applicable) and at 12 weeks, 6 months, and yearly until 3 years post-HSCT only if previously documented bone marrow involvement prior to cytoreductive/mobilization therapy or at time of clinical suspicion for progression.	N/A	Transplant Center
Flow Cytometry	Volume of graft determined according to institutional practice	Store according to institutional practice	Prior to infusion of autologous or allogeneic stem cell product.	N/A	Transplant Center
IgG Levels	Volume of blood determined according to institutional practice	Store according to institutional practice	12 weeks, 6 months and 1 year post-HSCT.	N/A	Transplant Center
Donor Research Specimen Nucleated Cells From Allograft	5 vials each containing 2 - 5 x 10 ⁶ nucleated cells from <u>allograft</u> (~1 mL for each vial)	Follow controlled-rate freezing SOPs for cryopreservation of samples as for product storage at -150°	Prior to allogeneic transplant at time of donation.	Liquid nitrogen shipment yearly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD

	Type of Sample	Type of Storage	Dates Samples Obtained	Shipping Specifications	Test Location
Donor Research Specimen Nucleated Cells from Peripheral Blood	10 mL peripheral blood	Obtain white blood cell pellet (by ficoll) and freeze in cryovial at -150°	Prior to donor mobilization.	Frozen shipment quarterly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD
Patient Research Specimen Nucleated Cells from Peripheral Blood	10 mL peripheral blood	Obtain white blood cell pellet (by ficoll) and freeze in cryovial at -150°	≤ 2 weeks prior to initiation of HSCT conditioning non-myeloablative allogeneic or autologous transplant.	Frozen shipment quarterly to Repository in compliance with shipping procedures specified in the BMT CTN MOP	TBD
PCR for Presence of t(14;18)	10 mL peripheral blood (5 mL in each vacutainer)	For baseline sample: 2 x 6 mL lavender top EDTA vacutainers. For all other samples: obtain white blood cell pellet (by ficoll) and freeze in cryovial at -150°.	Any positive test from the time of diagnosis then required prior to transplant and post-HSCT maintenance therapy (if applicable); 4 and 12 weeks, 6 months, 12 months and annually until 3 years post-HSCT. <u>For autologous patients who were positive at study entry or prior:</u> Each time leukapheresis product obtained.	Baseline sample shipped real-time on frozen gel packs, via Federal Express priority overnight to Baylor College of Medicine, The Methodist Hospital. All other samples frozen shipment quarterly to NHLBI Repository in compliance with shipping procedures specified in the BMT CTN MOP.	Baseline sample: The Methodist Hospital; Post-baseline samples: TBD

APPENDIX D
HUMAN SUBJECTS

APPENDIX D**HUMAN SUBJECTS****1. Subject Consent**

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

The consent document should be reviewed with the patient and family prior to proceeding to either non-myeloablative or autologous HSCT and rituximab maintenance therapy (for autologous HSCT patients).

The procedure for collecting hematopoietic stem cells and toxicities of G-CSF will be explained to the donor. The donor should be counseled as to the risks of treatment with G-CSF and be informed that leukapheresis at several time points may be necessary.

Informed consent from the donor and patient will be obtained using a form approved 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 CIBMTR and from published data on incidence of FL in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX E

THE STATISTIC FOR TESTING THREE-YEAR PROGRESSION-FREE SURVIVAL

APPENDIX E

THE STATISTIC FOR TESTING THREE-YEAR PROGRESSION-FREE SURVIVAL

The test statistic for this protocol is motivated by two requirements:

- 1) The test statistic must consider only long-term differences in PFS.

Differences in engraftment, graft-versus-host disease, and infectious complications may cause crossing hazards of mortality early in the study, and it is not desirable for these early survival differences to affect the final study outcome.

- 2) The test statistic must be robust and maintain its size and power in the face of sparse strata.

The study is not randomized, clinical center effects are problematic and a stratified test will be employed. Many clinical centers, each potentially enrolling a small number of patients, will be required to meet the study's accrual goals.

The study focuses on a primary endpoint of three-year progression-free survival, as this endpoint will be unaffected by crossing hazards of mortality early in the study, and reflects the primary interest in long term cure. Information past the three-year time-point is not considered in the primary analysis, as it complicates the interpretation and description of the endpoint, e.g. "three years and longer progression-free survival."

If the data were not subject to censoring, the ideal test statistic would be the stratified Cochran Mantel Haenszel test comparing the proportion of subjects who are alive without progression at three years post-transplant. However, it is more realistic to assume that some individuals will be censored prior to the three-year time-point. We propose to use a modified stratified CMH test, where the Kaplan-Meier actuarial estimates of survival replace the binomial proportions of survivors.

This test statistic is based on the paper "A Partially Grouped Logrank Test" by Sposto, Stablein and Carter-Campbell, *Statistics in Medicine*, Vol. 16, 695-704 (1997). The authors argue that in the setting where early differences in survival are irrelevant to the ultimate outcome, a grouped log-rank test which groups all information prior to a specified time point (t_c) is preferable to a weighted log-rank test that de-emphasizes early differences in survival but does not ignore them. The authors derive the mean and variance of the contribution of the grouped data table to the Mantel-Haenszel version of the logrank statistic, using a hypergeometric argument.

Grouped Data Table

	Failure	Non-Failure	At Risk
Group 1	x	$N_1 - x$	N_1
Group 0	y	$N_0 - y$	N_0
Total	$z = x + y$	$N - z$	N

Sposto et. al. estimate the quantities in the grouped table as follows: $x' = N_1(1 - \hat{S}_1(t_c))$, and $y' = N_0(1 - \hat{S}_0(t_c))$, where N_1 and N_0 are the numbers initially at risk, and $\hat{S}_1(t_c)$, $\hat{S}_0(t_c)$ are the product limit estimates of the survival functions at time t_c .

Under the assumption that $S_1(t) = S_0(t) = S(t)$ for all $t < t_c$, and using the asymptotic normal approximation to the distribution of the product limit estimate, Sposto et. al. show that the conditional distribution of x' given $z' = x' + y'$ is normal with mean $E(x' | z') = \frac{z'N_1}{N}$ and variance $V(x' | z') = N_1N_0V[\hat{S}(t_c)]$, where $\hat{S}(t_c)$ is the product limit estimate in both samples combined, and $V[\hat{S}(t_c)]$ is its asymptotic variance, which in practice, is estimated using Greenwood's formula.

Sposto et. al. propose the following product limit based log rank test statistic:

$$LR_{PL} = \frac{\left[(x' - E(x' | z')) + \sum_{t_i > t_c} S_i \right]^2}{\hat{V}(x' | z') + \sum_{t_i > t_c} V_i}$$

where S_i and V_i are the usual logrank numerator and denominator contributions for ordered failure times $t_i > t_c$.

We re-express the test statistic in a simpler form as follows:

$$LR_{PL} = \frac{\left[N_0(\hat{S}(t_c) - \hat{S}_0(t_c)) + \sum_{t_i > t_c} S_i \right]^2}{N_1N_0\hat{V}[\hat{S}(t_c)] + \sum_{t_i > t_c} V_i}$$

In the primary analysis of the endpoint of three-year progression-free survival, we set $t_c = 3$ years, and do not collect information past this time point. The square root of the LR_{PL} test statistic is then summed over clinical strata to obtain a stratified test, and a continuity correction is introduced. Using notation specific to our application, the test statistic is now written:

$$Z_{PL} = \frac{\left| \sum_{strata} N_{Auto} (\hat{S}_{Pooled}(3) - \hat{S}_{Auto}(3)) \right| - 1/2}{\sqrt{\sum_{strata} N_{Auto} N_{Allo} \hat{V}(\hat{S}_{Pooled}(3))}}$$

It should be noted that in the absence of censoring, this test statistic reduces to the Mantel-Haenszel test for comparing binomial proportions in stratified data.

In the secondary analysis of the endpoint of three-year progression-free survival, we again set $t_c = 3$ years, but use the original Sparto et. al. test statistic, LR_{PL} , which includes the terms for the contributions of the log-rank test statistic after the three-year time-point. It is not anticipated that LR_{PL} will lead to qualitatively different results from Z_{PL} , but the extra information may improve the power of the test substantively if accrual is much slower than anticipated.

The Mantel-Haenszel formulation of the log rank test maintains its large sample properties in modest sample sizes, even though it is comprised of sparse strata corresponding to individual death times. Similarly, the test statistic Z_{PL} has been shown in simulation studies to control type I error at nominal target levels even in the presence of moderate censoring and sparse strata.

When follow-up is complete (no censoring) the power of test statistic Z_{PL} is that of a stratified CMH test of binomial proportions. The power calculations given in Chapter 5, Statistical Considerations, are based on large sample results for the unstratified chi-squared test in the absence of center-to-center heterogeneity, but have been confirmed by simulations using stratified test statistic Z_{PL} in the presence of center-to-center heterogeneity.