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Current version: 08/27/2019
Previous Version: 06/26/2019

Title of Protocol: A phase II trial of high-dose ^{90}Y-Ibritumomab tiuxetan (anti-CD20) followed by fludarabine and low-dose total body irradiation and HLA-matched allogeneic hematopoietic transplantation for patients with relapsed or refractory aggressive B-cell lymphoma

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1. Introduction

Nearly 60,000 cases of non-Hodgkin's lymphoma (NHL) are diagnosed each year in the USA and two-thirds of these die of this disease (SEER data). At the time of relapse, only a minority of affected patients with chemotherapy-responsive disease achieve long-term disease-free survival with high-dose therapy and autologous stem cell transplantation (ASCT)[1-4]. Relapses in the setting of ASCT likely occur due to the inability of the treatment regimen to eradicate lymphoma from the patient and/or the re-infusion of a tumor-contaminated stem cell product. In addition, high-dose therapy and ASCT is of limited utility in the setting of refractory disease, relapse following autologous transplantation or relapse in the setting of a poor stem cell reserve[5]. There are few potentially curative options for such patients. Likewise, the utility of standard allogeneic transplantation and non-ablative allogeneic transplantation is limited in these settings by their excessive toxicity and limited ability to eradicate rapidly progressive disease, respectively. This study will address this clinical challenge by evaluating a novel method to both limit toxicity and maximize direct anti-lymphoma effects in patients with relapsed B-cell NHL.

2. Background

Reduced intensity allogeneic conditioning regimens

One approach that has been studied in patients with relapsed B-cell NHL has been the use of high-dose therapy followed by allogeneic hematopoietic stem cell grafting, an approach which affords both an uncontaminated stem cell source and a potential graft versus lymphoma (GVL) effect. Allogeneic transplant trials for lymphoma have documented much lower relapse rates than comparable autologous transplantation studies[6]. Despite the potential advantages of allogeneic transplantation, this approach is infrequently employed in patients with relapsed lymphomas because of the high rate of treatment-related mortality (TRM) stemming from the toxicity of myeloablative conditioning regimens, and from graft versus host disease (GHVD) and infections.[6,7]

A strategy has recently been developed to mitigate the toxicity of high-dose therapy prior to allogeneic transplantation by employing reduced intensity conditioning regimens that provide sufficient immunosuppression to facilitate allogeneic engraftment while simultaneously limiting TRM [8,9-11]. This approach, relying on the immunologic GVL effect to eradicate disease, has proven to both reduce TRM and induce remissions in pilot studies[12]. Early observations, however, have suggested that patients with rapidly progressive or excessively bulky disease rarely benefit from this approach, presumably because the rate of the disease progression outpaces the GVL effect [11,13,14]. These findings support the need for identifying an approach to safely cytoreduce bulky tumors or control rapidly progressive disease in order to allow sufficient time for the allograft to mediate a GVL effect and maintain long-term remissions.

Radioimmunotherapy for NHL

Over the last 10 years radioimmunotherapy (RIT) has been developed as a novel, reduced-toxicity approach for the treatment of B-cell NHL. RIT, based on the exquisite radiosensitivity of NHL, involves delivering targeted therapy directly to tumor sites with the use of monoclonal antibodies. Studies have demonstrated that non-myeloablative doses of anti-CD20 RIT in patients with relapsed lymphomas can be safely delivered using either ^{131}I or ^{90}Y as the therapeutic radionuclide[15-18]. This "low-dose" RIT approach with agents such as Bexxar® (^{131}I-tositumomab) or Zevalin® (^{90}Y-ibritumomab tiuxetan) has resulted in response rates of 40-70% with moderate hematologic and minimal non-hematologic toxicity in patients with indolent NHL **(Figures 1 and 2)**. The highest complete response rates (>80%) and longest response durations in <u>all</u> histologic subtypes of B-cell NHL, however, were seen with escalated doses of radioisotope when

hematopoietic progenitor support is used to offset the hematopoietic toxicity [19]. Studies performed by our group demonstrated that targeted radiation doses of 27 Gy to normal organs when given alone and doses of 25 Gy to normal organs along with high doses of chemotherapy were well tolerated in these patients with relapsed lymphomas[19,20]. The same patients that received these optimal doses (27 Gy) of RIT had surprisingly low rates (<10%) of grade 3-4 non-hematological toxicity. Other groups using ^{90}Y-ibritumomab tiuxetan as a single agent have safely delivered doses up to 18.56 Gy to liver without non-hematologic toxicity [21](and Zevalin BLA/IND). Note that the median radiation exposure of red marrow with standard dose (32 mCi) ^{90}Y-ibritumomab tiuxetan is 1.5 Gy (range 0.8-2.1)[22]. Despite the tolerability, favorable response rates and remission durations, the majority of patients in these studies eventually experienced progression of their disease. Thus, though cytoreduction with minimal toxicity is possible for patients with B-cell NHL, additional measures are needed to maintain these remissions.

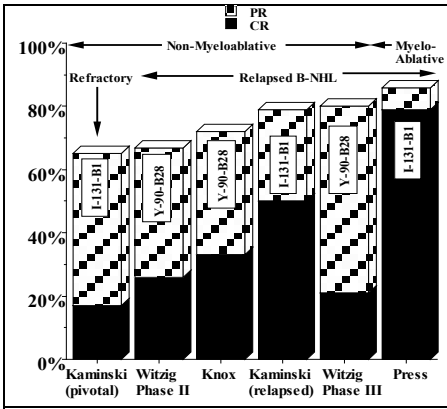

Fig 1: Response rates observed in selected clinical trials using radiolabeled anti-CD20 mAb to treat relapsed or refractory B-NHL (PR, hatched bars; CR, black).

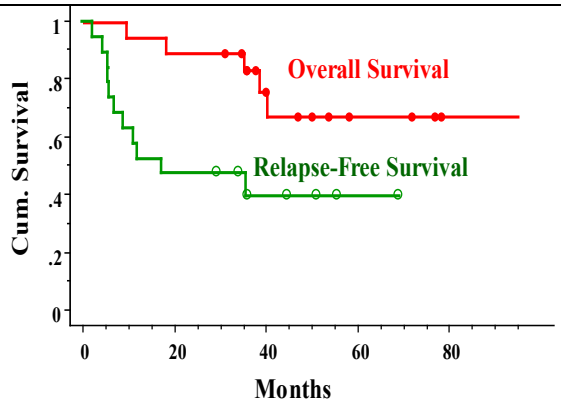

Fig. 2: Overall and Relapse-Free Survival of the first 37 Patients with Relapsed B cell Lymphomas treated in Seattle with Iodine-131-labeled anti-B cell mAb

High-dose radioimmunotherapy prior to autologous transplantation

Our group has pioneered the use of high-dose ^{131}I-labeled anti-B cell antibodies prior to autologous transplantation. These studies have indicated that up to 27Gy can be delivered to normal organs with ^{131}I as a single agent and up to 25Gy when combined with high dose chemotherapy[19,20]. Toxicity profiles are considerably lower than traditional high-dose conditioning when the single agent regimen is used, and comparable to TBI-based regimens when high-dose chemotherapy is added [20,23]. Notably, comparisons with non-randomized controls suggest that RIT improves both overall and progression-free survival [20,24]. Other groups have evaluated high-dose ^{90}Y-anti-CD20-containing regimens with similar results. Flinn et al have utilized high-dose ^{90}Y-Ibritumomab Tiuxetan with a dosimetry based strategy and reported that doses of up to 28 Gy to critical normal organs were tolerated[25]. Both Ferrucci and Devizzi and colleagues have treated patients with dose escalated ^{90}Y-Ibritumomab Tiuxetan prior to ASCT and were able to safely deliver doses up to 1.2-1.5 mCi/kg. [26,27] Devizzi, using 1.2 mCi/kg, demonstrated no TRM and complete remissions in 7 of 10 DLBCL patients. In the Ferucci study the normal organ with the greatest exposure (liver) received a median of 13 Gy (range 9.5-25.3 Gy) at the highest dose level of 1.5 mCi/kg, but only one of 5 patients experienced transient grade 3 hepatotoxicity. Importantly, these studies confirmed the feasibility, efficacy, and tolerability of using a high-dose mCi/kg dosing strategy of ^{90}Y-Ibritumomab Tiuxetan prior to autologous stem cell transplantation. Finally, other groups have combined high-dose ^{90}Y-Ibritumomab Tiuxetan with high-dose chemotherapy, demonstrating that an absorbed dose of 10 Gy can be combined with 100 mg/kg cyclophosphamide and 60 mg/kg etoposide or 15 Gy with BEAM conditioning was safe and

effective [28,29]. **Table 1** reviews many of the key trials using ^{90}Y-Ibritumomab Tiuxetan and ASCT. In summary, studies from a variety of centers conclude that high-dose ^{90}Y-Ibritumomab Tiuxetan prior to autologous transplantation is feasible, reproducible, and efficacious.

Table 1 Selected trials using high-dose ^{90}Y-Ibritumomab Tiuxetan as part of autologous stem cell transplant conditioning regimens for B-cell lymphomas

Author (Year)	**Maximum ^{90}Y dose/other therapy**	**n**	**Outcomes**
Nademanee (2005)[30]	10 Gy (105 mCi)/high dose CY/VP-16	31	2-year estimated RFS 78%
Winter (2009)[28]	17 Gy (104 mCi)/ high dose BEAM	33	3-year PFS 43%
Flinn (2006)[25]	28 Gy (143.1 mCi)/none	16	80%(62.5% CR)
Ferrucci (2007)[26]	1.5 mCi/kg (150 mCi)/none	13	NRM=7.6%
Divizzi (2008)[27]	1.2 mCi/kg (not reported)/none	30	69% EFS at 30 mo.

Impact of CD20 blocking on anti-CD20 tumor targeting.

Initial studies of anti-CD20 RIT indicated that the addition of unlabeled anti-CD20 MoAb was required to clear circulating B-cells, block sites of splenic sequestration, yield improved radiation delivery to nodal sites [15,31]. However, with the widespread use of rituximab, most B-NHL patients maintain persistent levels of anti-CD20 antibodies and few circulating B-cells. Preclinical data suggest that excess anti-CD20 antibody may impair CD20 directed tumor targeting [18,32]. Based on these observations, we will only use rituximab prior to the radiolabeled infusions in patients with serum rituximab levels potentially insufficient to optimize delivery isotope to nodal sites (<10µg/ml).

Synergy of radioimmunotherapy and nucleoside analogs

A potential method of optimizing anti-lymphoma RIT involves combining synergistic chemotherapeutic agents with RIT. Studies performed by our group evaluating co-incubation of various anti-lymphoma drugs and ^{131}I-anti-CD20 antibodies along with B-cell lymphoma lines *in vitro* showed maximal supra-additive levels of cell killing with nucleoside analogues cytarabine and fludarabine **(Table 2)**[33]. Though pilot studies looking at sequential fludarabine followed by low dose RIT have suggested feasibility [34], clinical data are limited regarding the concurrent or rapidly sequenced use of RIT followed by such drugs. A schema administering RIT in close proximity to drugs like fludarabine would more closely mirror the *in vitro* findings of synergy and may lead to improved outcomes.

Table 2 Dose modification factors (degree of synergy) of chemotherapeutic agents combined with a fixed low dose of ^{131}I-anti-CD20 antibody in human NHL cell lines

Drug	Dose Modification Factor (Degree of Synergy)	p value
Cytarabine	5.21+/- 0.47	<0.001
Fludarabine	4.00+/-0.25	<0.0001
Etoposide	2.35+/-0.07	0.0024
Doxorubicin	2.03+/-0.21	0.013
Cisplatin	1.10+/-0.07	0.12
4-HC	1.01+/-0.04	0.93

(A DMF of 1 represents additive effects, <1 represents antagonistic effects, and >1 represents synergistic/supra-additive effects.)

Safety of combining RIT, TBI, and chemotherapy

We and others have extensive experience combining RIT, high-dose TBI and high-dose chemotherapy in a single transplant conditioning regimen[35,36]. Selected studies are summarized in **Table 3**. Matthews et al reported that the delivery of 12.25 Gy to normal organs using radioimmunotherapy along with 12 Gy of TBI and 120 mg/kg of cyclophosphamide has acceptable toxicities and appeared to efficacious in preliminary analyses[35,37]. Similar studies were carried out by groups from Memorial Sloan Kettering combining high-dose anti-CD33 RIT with 12 Gy of TBI and 120 mg/kg of cyclophosphamide[38]. Based on the tolerability of studies combining high-dose RIT with high-dose TBI and high-dose chemotherapy, we anticipate that the proposed combination of RIT with low-dose TBI and low dose chemotherapy will be extremely well tolerated.

Table 3. Selected published trials that combine high-dose radioimmunotherapy with high-dose chemotherapy and ablative total body irradiation (TBI).

Author (Year)	Isotope	Dose	Target	Additional therapy	Leukemia type/ Setting	n
Appelbaum(1992)[36]	I-131	110-330 mCi	CD33	Cy/TBI	AML	4
Jurcic (1995)[39]	I-131	50-70 mCi/m^2	CD33	Bu/Cy	AML	19
Matthews (1999)[40]	I-131	3.5-12.25 Gy	CD45	Cy/TBI	AML/MDS/ALL	34
Bunjes (2001)[38]	Re-188	7.4 Gy	CD66	CY/TBI or Bu/Cy	AML/MDS	36
Burke (2003)[41]	I-131	122-437 mCi	CD33	Bu/Cy	AML/CML/MDS	31
Pagel (2005)[42]	I-131	12-24 Gy	CD45	Flu, TBI (2Gy)	AML/AML	33
Ringhoffer (2005)[43]	Re-188/ Y-90	9.7+/-5.3 Gy	CD66	Flu/ATG +/-Mel	AML/MDS	20
Pagel (2006)[44]	I-131	5.25 Gy	CD45	Bu/CY	AML- CR1	46

Use of low dose ^{90}Y-anti-CD20 RIT prior to reduced intensity allogeneic transplantation.

Despite the potential for long term remissions in B-NHL and CLL with the use of reduced intensity allogeneic transplantation, patients with adverse pre-transplant features are at high-risk of relapse. For example, MCL patients with ≥ 5 cm disease bulk pre transplant had a 47% chance of relapse as compared to 14% in those with < 5 cm disease [45]. Similar findings were seen in other histologies and in settings of chemoresistant disease and aggressive/transformed histology [11,13,14,46]. Presumably, relapse in this setting is based both on early disease control (as imparted by pretransplant salvage chemotherapy or the conditioning regimen) as well as long-term disease control via the graft-versus-lymphoma (GVL) effect. Data from the European Group for Blood and Marrow Transplantation (EBMT) support the importance of intensified conditioning to reduce relapse with patients receiving the least intensive regimen (Flu/TBI) experiencing a 2.7-fold higher relapse rate compared to those receiving other more intensive regimens[47]. Unfortunately, the non-targeted nature of more intensified regimens may increase toxicity and exclude patients with comorbidities.

To address this problem, we recently completed a phase II trial adding standard (0.4 mCi/kg) ^{90}Y-Ibritumomab Tiuxetan to a Flu/2 Gy TBI preparative regimen in B-NHL patients not in CR prior to matched related or matched unrelated allogeneic transplantation [48](and unpublished data). Forty patients were treated on this trial evaluating the primary endpoint of 100 day TRM. Despite over half of the patients carrying comorbidity indexes of ≥3 and a median tumor bulk of 4.2 cm, there was only one (3%) non-relapse death (MRSA sepsis) prior to day 100 with the RIT adding little apparent non-hematologic toxicity. Furthermore, responses were observed in half of patients at post transplant day 28 with 83% of patients experiencing some degree of tumor reduction (**Figure 3**). Poorer outcomes were associated with aggressive B-NHL and mantle cell lymphoma, whereas the best long-term disease-free survival was associated with early objective responses, even in patients with aggressive B-NHL or MCL (**Figures 4 and 5**). These data would suggest that improved early disease control could translate into prolonged disease-free survival mediated by the GVL effect, but improvements in early disease control and ultimately PFS are required for patients with aggressive and mantle cell histologies.

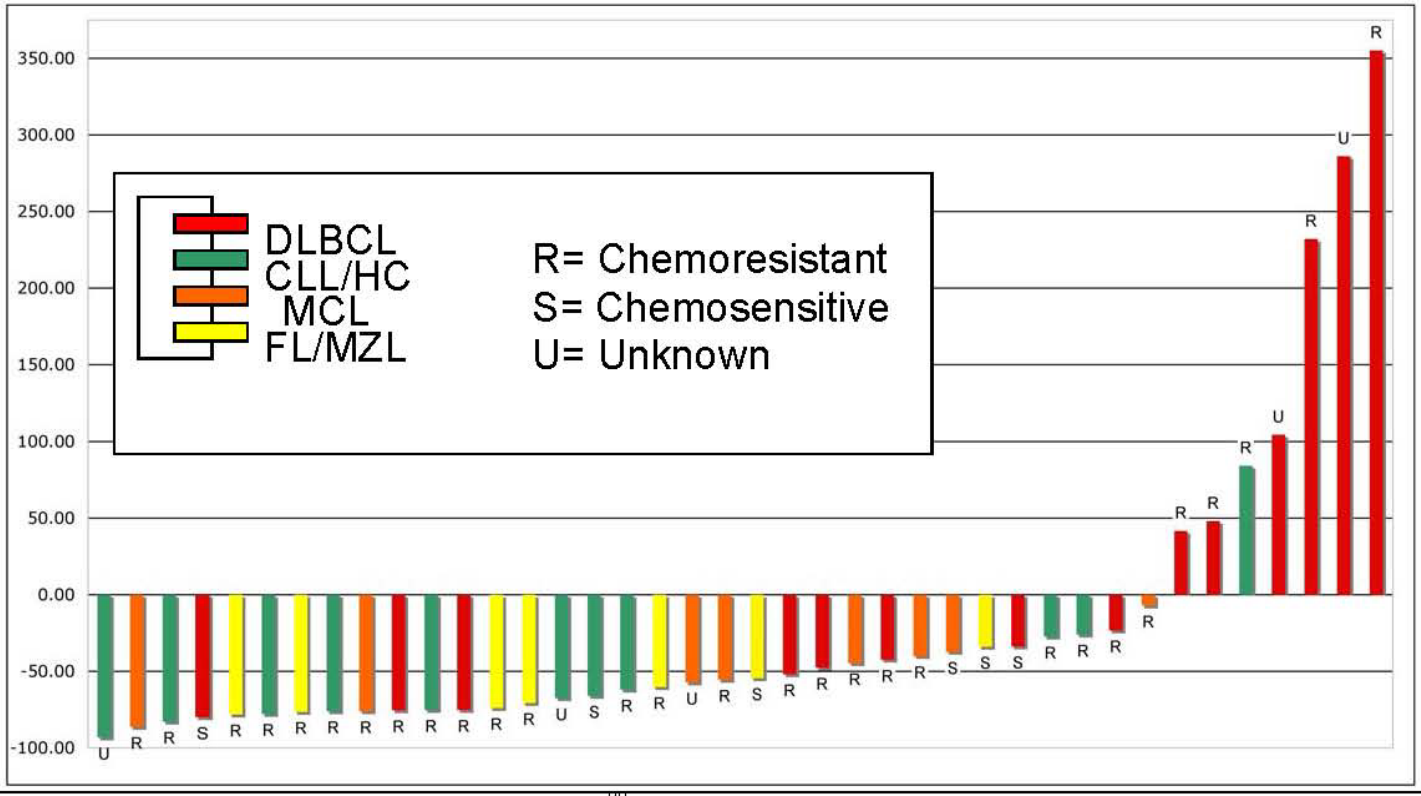

Figure 3: Waterfall plot of day 84 response following ^{90}Y-Ibritumomab Tiuxetan-based NMAT by histology and chemoresistance. DLBCL=diffuse large B-cell lymphoma, CLL=chronic lymphocytic leukemia, HCL=hairy cell leukemia, MCL=mantle cell lymphoma, FL=follicular lymphoma, MZL=marginal zone lymphoma. (For the 4 patients that died prior to day 84, the most recent response data prior to death was utilized)

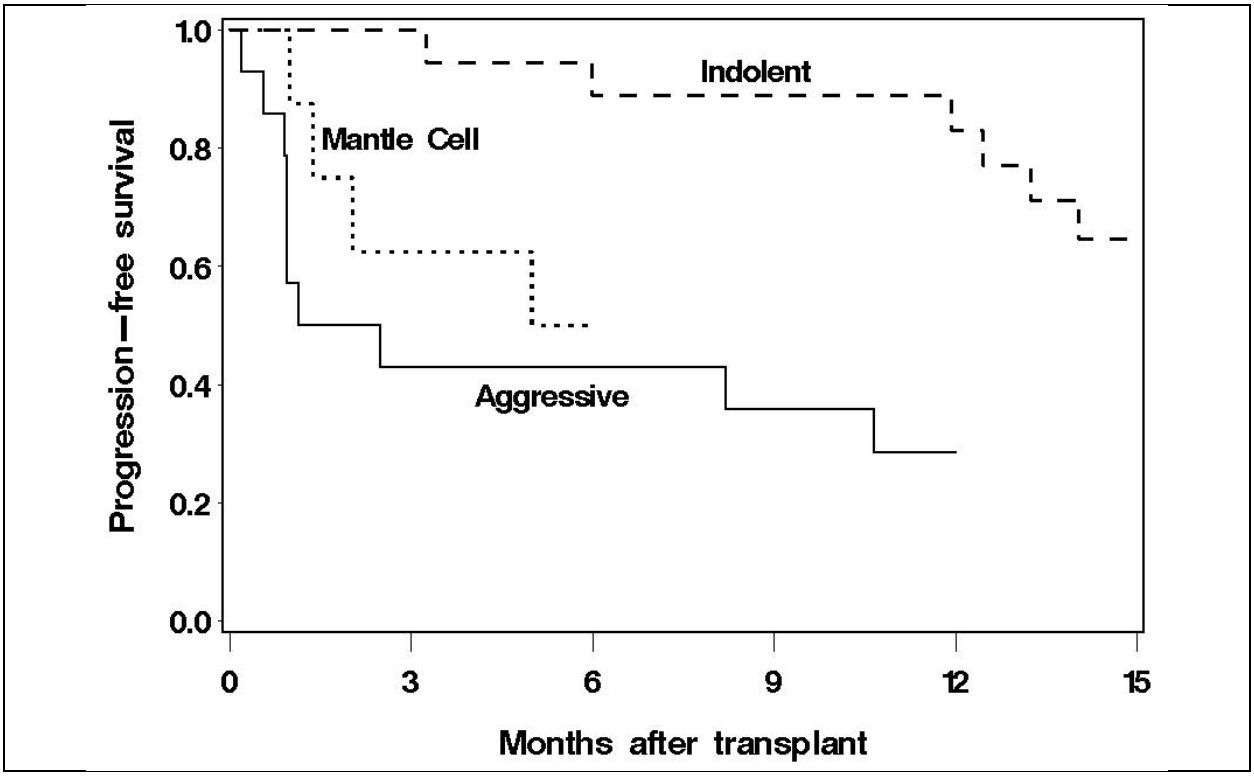

Figure 4: Progression free survival of B-NHL patients undergoing ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg) based transplantation, grouped by histology.

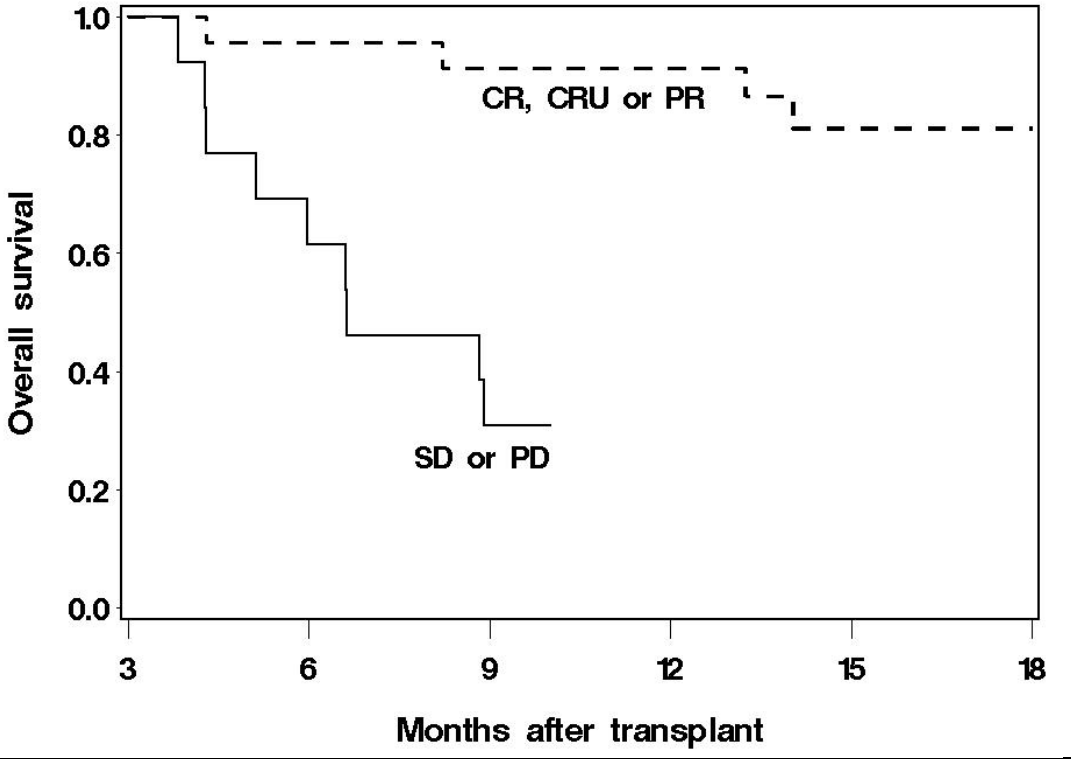

Figure 5: Landmark analysis of OS based on response at 3 months post transplant

Proposed use of escalated dose RIT and allografting

The goal of this protocol is to assess the safety and efficacy of delivering high-dose ^{90}Y-Ibritumomab tiuxetan (anti-CD20) prior to fludarabine (30 mg/m^2 x 3) and 2 Gy total body irradiation (TBI) followed by HLA matched allogeneic hematopoietic transplantation for patients with relapsed or refractory aggressive B-NHL. This work builds on prior data from our center and others, and complements data using I-131 anti-CD45 RIT in AML [70]. We posit that the high-dose targeted cytoreductive effect of RIT will confer prolonged remissions with minimal non-hematologic toxicity and that the immunologic GVL effect will prevent relapses. We anticipate that this novel strategy will reduce TRM as compared with standard ablative allogeneic transplantation regimens, while affording better cytoreduction and long-term disease control than current non-myeloablative conditioning regimens for patients with the highest-risk disease.

3. Objective

To assess the safety and efficacy of 1.5 mCi/kg (max 120 mCi) ^{90}Y-Ibritumomab tiuxetan (anti-CD20) combined with fludarabine (30 mg/m^2 x 3) and 2 Gy total body irradiation followed by HLA matched allogeneic hematopoietic transplantation for patients with relapsed or refractory aggressive B-cell lymphoma.

4. Endpoints

A. Primary Endpoint

1. 1-year progression-free survival

B. Secondary Endpoints

1. 100 day treatment-related mortality
2. Overall survival
3. Response rates at day 100
4. Engraftment and hematopoietic toxicity

5. Patient Selection

Results of tests and/or procedures conducted as per standard of care may be used for eligibility determination.

A. Inclusions

1. Patients must have a histologically confirmed diagnosis of aggressive B-cell lymphoma (DLBCL, BL, etc.) expressing the CD20 antigen and have failed at least one prior standard systemic therapy.

   Patients must have relapsed after high-dose therapy and autologous transplantation or be ineligible for high-dose therapy and autologous transplantation. Patients that have failed autologous transplantation are those with persistent disease >30 days after transplant. Those ineligible for autologous transplant include those with chemoresistant disease (i.e., patients who have not achieved a partial response or better with their most recent chemotherapy regimen), are expected to have a poor outcome from autologous transplant (e.g., DLBCL relapsing within one year of R-CHOP-like chemotherapy, double hit lymphoma, MYC+ lymphoma, persistent PET positivity after chemotherapy), are unable to collect sufficient or tumor-free autologous stem cells per Seattle Cancer Care Alliance (SCCA) standard practice, are unable to tolerate the high-dose autologous conditioning regimens, or who refuse a high-dose autologous transplant regimen.
2. Patients must have acceptable renal (Cr <2.0) and hepatic function (bilirubin <1.5mg/dL, and AST/ALT <3 x ULN), with the exception of patients thought to have Gilbert's syndrome, who may have a total bilirubin above 1.5mg/dL.
3. Patients must have an expected survival without treatment of >60 days and must be free of major infection including HIV.
4. Patients must have an HLA-identical related or HLA-matched unrelated donor.
5. Patients must be ≥ 18 years old.

B. **Exclusions**.

1. Receipt of systemic anti-lymphoma therapy within the following intervals prior to the therapeutic ^{90}Y-ibritumomab tiuxetan dose:
   a. < 30 days for intravenously-administered cytotoxic chemotherapy and/or monoclonal antibodies
   b. < 5 half-lives for all other anti-cancer agents (e.g., targeted therapies, corticosteroids, immunomodulatory agents, etc.)
2. Inability to understand or give an informed consent.
3. Active central nervous system lymphoma.
4. Pregnancy.
5. Fertile men or women unwilling to use contraceptive techniques during and for 12 months following treatment.

6. SWOG/ECOG performance score ≥2.
7. High-dose chemotherapy or external beam radiation therapy to lung, liver, or kidneys >20 Gy within the previous 100 days prior to therapeutic ^{90}Y-ibritumomab tiuxetan dose.
8. Medical condition that would contraindicate allogeneic transplantation as per standard practice guidelines (e.g., impaired cardiopulmonary function, hepatitis, etc).

6. Donor Selection

HLA-identical related donor or HLA-matched unrelated donor who meets standard Seattle Cancer Care Alliance (SCCA) and/or NMDP criteria for PBSC donation. Related donors should be matched by molecular methods at the intermediate resolution level at HLA-A, B, C, and DRB1 according to FHCRC Standard Practice Guidelines and to the allele level at DQB1. Unrelated donors should be identified using matching criteria that follows the FHCRC Standard Practice Guidelines limiting the study to eligible donors that are allele matched for HLA-A, B, C, DRB1, and DQB1 (Grade 1), and accepting up to one allele mismatch as per Standard Practice Grade 2.1 for HLA-A, B, or C. Participants with HLA-matched, related, non-sibling donors will be treated according to regimen for participants with HLA-matched unrelated donors. PBSC is the only permitted stem cell source.

7. Informed Consent

Subjects will be referred to SCCA/UW for consideration of a PBSC transplant. Both subject and donor will be completely evaluated. The protocol will be discussed thoroughly with subject, donor and other significant individuals by the attending physician and/or investigators. All known risks to the subject and donor will be described. The study procedures and available alternative forms of therapy will be reviewed as objectively as possible, and the risks and hazards of the procedures explained. Consent will be obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. A summary of the conference will be dictated for the medical record detailing what was covered.

Related donors will be counseled and consented in accordance with standard SCCA procedures and using the standard donor consent form. Unrelated donors will be counseled and consented according to the guidelines of the NMDP and other donor centers.

8. Protocol Registration

Patients will be assigned to the protocol by the Clinical Coordinator, who will register the patient with the Registration Office, (206) 667-4728, between 8:30 a.m. and 4:00 p.m., Monday through Friday. After hours, the Registration Office can be reached by paging (206) 995-7437. Eligibility criteria will be verified by the research coordinator and the investigator before any patient is registered on study.

9. Plan of Treatment

Treatment will be initiated in the outpatient department and patients will be admitted only as medically necessary for control of transplant complications.

A. Outline of treatment plan (Table 4). The day of treatment is listed in order to give a loose time-frame. An individual study calendar is created for each patient, with modifications permitted in consideration of clinical and logistical needs.

Time Point	Event
<4 weeks pre therapy	Staging studies (CT, bone marrow, flow, PCR) and organ function assessment as detailed under Section 10.A.
24 to 48 hours prior to therapy infusion	Administer 250 mg/m^2 of rituximab per product labeling and institutional guidelines.
Day -14 (± 2 days relative to transplant)	*Therapy infusion:* ^{90}Y-ibritumomab tiuxetan infusion (1.5 mCi/kg ^{90}Y-ibritumomab tiuxetan mCi/kg actual body weight, maximum of 120 mCi)
Day -4 to -2	Fludarabine 30 mg/m^2 IV QD x 3
Day -3	Cyclosporine (CSP) initiated
Day 0	2 Gy total body irradiation (TBI) Allogeneic Stem Cell Infusion Mycophenolate mofetil (MMF) initiated
Post therapy	*Assessments:* Staging studies/disease assessment: ~1 and 3 months after transplant per protocol. Six months and 12 months after transplant patient will be followed for disease progression and survival. Thereafter, patients will be followed for survival for up to 2 years after transplant. *Immunosuppression:* **CSP: Related Donors**- to day +56, then taper off by day +180 **Unrelated Donors**- +100, then taper off by day +180. **MMF: Related Donors-**to +27 and then discontinue **Unrelated Donors**- to +40, taper off by + 96

TBI=total body irradiation, CSP= cyclosporine, MMF= mycophenolate mofetil.

B. Treatment regimen overview

1. 24 – 48 hours prior to therapy dose:
   250 mg/m^2 of rituximab administered IV per product labeling and institutional guidelines.
2. Day -14 (± 2 days), therapy dose:
   ^{90}Y-ibritumomab tiuxetan administered IV. Dose: 1.5 mCi/kg actual body weight (maximum of 120 mCi). See statistical section.
3. Days –4 to –2: Fludarabine 30 mg/m^2/day i.v. (3 doses total)
4. Day -3: Begin immunosuppression with CSP 4 mg/kg p.o. b.i.d.
5. Day 0: TBI 2.0 Gy at 6-7 cGy/min from a linear accelerator.

6. Day 0: Hematopoietic cell infusion from HLA-identical donor per standard practice guidelines.
7. Day 0: Begin immunosuppression with MMF (15 mg/kg p.o. b.i.d. [patients with *related donors*] or t.i.d. [patients with *unrelated donors*]) 5-10 hours following PBSC infusion.

C. Rituximab

Dose: Rituximab is given 24 – 48 hours prior to therapy infusion at a dose of 250 mg/m^2. Premedications include: Dexamethasone 10mg po/IV, Diphenhydramine 50 mg po/iv and acetaminophen 650 mg po.

Infusion rate: In general, initiate infusion at a rate of approximately 50 milligrams/hour (mg/hr). If no infusion reactions occur, the rate will be escalated by 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If infusion reactions occurred during the infusion, follow guidelines as per product labeling and institutional guidelines (e.g., the infusion may be slowed, temporarily interrupted and re-started at one-half the previous rate, or discontinued depending on severity of symptoms).

D. ^{90}Y-ibritumomab tiuxetan

Dose: The target ^{90}Y dose will be 1.5 mCi/kg actual body weight (maximum of 120 mCi). The antibody dose (ibritumomab tiuxetan) will be determined based on the volume required for radiolabeling with the desired number of millicuries ^{90}Y, per radiolabeling processes used with standard Zevalin. This is expected to require up to approximately 8 mg of antibody. ^{90}Y-ibritumomab tiuxetan will be provided by the manufacturer (Acrotech Biopharma, LLC) and radiolabeling pharmacy (Cardinal Health). The product will be provided in a volume and packaging format agreed upon by Cardinal Health and SCCA. Premedications for the therapeutic infusion include Dexamethasone 10mg po/IV, Diphenhydramine 25-50 mg po/iv, and acetaminophen 650 mg po.

Infusion rate: ^{90}Y-ibritumomab tiuxetan should be infused over 30 minutes via a central line within 24 - 48 hours of the completion of rituximab dose. Patients will receive one liter of normal saline over 2-4 hours following the therapy infusion. Following this, patient will be encouraged to increase oral fluid intake. Additional IVF will be given at the discretion of the treating physician.

E. Fludarabine

Fludarabine will be administered on days –4 to –2. Dose: 30 mg/m^2 IV administered per routine pharmacy guidelines.

F. Total Body Irradiation (TBI)

Day 0: TBI 2.0 Gy administered per SCCA standard practice. TBI to be administered prior to peripheral blood stem cell (PBSC) infusion, in general between 10:00 a.m. and 1:00 p.m. if possible to avoid proximity to CSP/MMF administration.

G. Collection of donor stem cells

Donor PBSC will be collected as per institutional or NMDP standard practice.

H. Hematopoietic stem cell transplant

Patients will receive unmodified G-CSF mobilized PBSC from an HLA-identical related or unrelated donor on day 0 of the treatment regimen, infused per standard practice guidelines.

Cryopreservation of DLI will not be covered in this protocol.

I. Immunosuppression

Day –3: Related Donors: Commence CSP at 4.0 mg/kg p.o. b.i.d. from day -3 to day +56, then if no GVHD taper off by day +180. Unrelated Donors: For patients with matched unrelated donors, CSP at 4.0 mg/kg p.o. b.i.d. is given from day –3 to day +100, then is tapered to day 180. If GVHD is present immunosuppression will follow standard practice guidelines and/or the direction of the primary treating physician. CSP whole blood "trough" levels (i.e., just prior to the next dose) will be evaluated starting on day 0 post-transplant. Routine patient monitoring and dose adjustments will in general follow the guidelines of the standard practice manual. In general, CSP trough levels will be targeted to 400 ng/mL through day +28, then 120-360 ng/mL thereafter, but these goals can be adjusted at the discretion of the attending physician. Equivalent i.v. doses of CSP may be utilized at the discretion of the attending physician.

Day 0: Related Donors: MMF will be given at 15 mg/kg p.o. b.i.d. (30 mg/kg/day), with the first dose administered 5-10 hours after the PBSC infusion is complete. MMF will continue at full dose through day +27 and then be discontinued without a taper. Unrelated Donors: MMF will be given at 15 mg/kg p.o. t.i.d. (45 mg/kb/day), with the first dose administered 5-10 hours after the PBSC infusion is complete. MMF will continue at full dose through day +40, at which point it will be tapered to be stopped by day +96. Equivalent i.v doses of MMF may be utilized at the discretion of the attending physician. MMF dose adjustment may occur at the discretion of the attending physician or PI (for reasons such as toxicity, impending graft rejection, etc.).

J. ABO incompatibility

All patients with ABO incompatibility should be evaluated and treated according to standard practice.

K. Post-transplant growth factors

Given the theoretical risk of driving myeloid cell production during exposure to an antimetabolite, patients should not receive post-transplant growth factors while receiving MMF. Growth factors should not be given unless severe persistent neutropenia develops or persists past day +27 post-transplant (ANC ≤ 100/ul for > 5 days). As MMF may cause myelosuppression, consideration should be given to reducing the dose of MMF prior to the start of growth factor.

L. Infection prophylaxis

Patients will receive prophylaxis for PCP, fungus, VZV, and HSV as per standard practice. The start of the conditioning regimen will in general be considered the date of treatment dose.

M. Post-transplant Donor Lymphocyte Infusion (DLI)

DLI will not be a component of this trial. Patients requiring DLI for chimerism or disease progression will be treated on alternate protocols or as standard practice. Complete responses may require 6 months or more to evolve in NHL patients treated

with RIT. Thus, patients on this protocol will not be considered a treatment failure/DLI candidate for stable disease alone. Patients will require objective evidence of disease progression to be considered treatment failures.

N. Criteria for removal of individual patients

Individual patients may be removed from the trial for the following reasons:

- patient request,
- patient no longer meets eligibility criteria at the time of therapy dose,
- serious infusion reaction or other toxicity preventing further administration of treatment regimen.

Patients removed from the study due to toxicities will be monitored for continuing toxicities until resolution.

10. Patient and Donor Evaluations

A. Patient Pretransplant Baseline Evaluation

Pre transplant work up will occur as per standard practice for patients undergoing myeloablative allogeneic transplantation, including standard clinical staging assessments for lymphoma (e.g., CT scans of chest, abdomen, and pelvis, and neck at the discretion of treating MD or investigator; bone marrow biopsy if indicated; etc.), PET-CT scan within 21 days prior to ^{90}Y-ibritumomab tiuxetan dose is strongly recommended but not required and standard clinical workup for transplant including pulmonary function testing. In addition, the following assessments will be performed:

1. Echocardiogram or MUGA scan in all patients to assess cardiac ejection fraction (common in clinical workup per standard practice, but not required in all instances).

B. Patient Post-transplant Evaluations

The primary endpoint of this study is 1-year progression-free survival, with secondary endpoints including 100-day response and mortality rates, and overall survival. Timing of all post-transplant evaluations, including those identified as protocol-specific, may vary based on each patient's individual course of clinical care. Patients typically remain under the care of the SCCA Outpatient Service for approximately 100 days post-transplant, but the actual time frame will vary for individual patients. Similarly, certain response evaluations that may be described as occurring at "day +28 and day +84," "four and twelve weeks," or "one and three months" post- transplant are expected to be conducted within these general time frames.

Appropriate post-transplant evaluations are consistent with standard practice for patients undergoing myeloablative allogeneic transplantation. Common follow-up guidelines used when patients are followed on an outpatient basis are summarized in Table 5 below. All hospitalized patients have daily clinical assessments.

Table 5: General Post-Transplant Outpatient Monitoring Guidelines

Assessment	*Interval*	
	When ANC<500 or PLT<20K	When ANC≥500 and PLT≥20K
CBC	Daily	Weekly
Electrolytes	Weekly	Weekly
Liver Function Tests	Weekly	Weekly
Clinical assessment	Weekly	Weekly

In addition, the following protocol-specific assessments will be performed at the approximate timepoints indicated:

1. CT scan of chest abdomen and pelvis with bi-dimensional measurement of disease for staging of lymphoma at day +~28 and +~84. Neck CT will be requested for patients with neck involvement. PET-CT is required at day ~+84 (or sooner to confirm CR). Note that patients who are in complete remission (CR) pre-transplant do not need a follow up PET-CT.
2. On or near day +84 post-transplant, patients with baseline marrow involvement will have bone marrow done to confirm CR as per standard criteria.[71] Patients with a negative marrow at an earlier post-transplant time point do not need to have the marrow repeated. Additional bone marrow studies will be at the discretion of the attending physician.
3. GVHD evaluations will be performed as per standard of care.

Following day +100 or discharge from the SCCA, patients will typically return to their primary care physicians under the guidance of the FHCRC/SCCA Long-Term Follow-Up After Hematopoietic Stem Cell Transplant General Guidelines for Referring Physicians. Patient follow-up will be performed according to institutional standards by the FHCRC Long-Term Follow-Up (LTFU) Department under the FHCRC/SCCA Master Protocol for Collection of Clinical Data and Storage of Leftover Specimens from Patients Treated According to FHCRC Protocols (Protocol #0999.209). We will monitor survival and progression reported under the standard long-term follow-up protocol, and will record this data at 6 and 12 months, and annually thereafter for 2 years for long-term analysis and reporting, until 2 years after transplant or patient request to withdraw from study follow-up. If there is not sufficient LTFU data available at 12 months after transplant to assess both survival and disease status (e.g., radiologic imaging reports; blood and bone marrow assessments as needed), we will request records from the patient's primary care physician.

C. GVHD Evaluation

GVHD evaluations should in general follow standard practice guidelines and a full evaluation should be performed before departure from the center.

D. Donor Evaluations

Donor evaluations will follow the standard practice guidelines.

11. Definitions

A. Disease and Response Criteria: Response will be interpreted by investigator review of radiographic findings along with MD assessed physical findings and bone marrow or blood reports and will follow the revised response criteria.[71]

B. Graft rejection is defined as < 1% peripheral blood donor T cells on day +28 and/or later.

C. Treatment Failure: Disease progression as **defined by the** revised response criteria [71] at any time after Day 0 will be considered a treatment failure. Because complete responses may require 6 months or more to evolve in NHL patients treated with RIT, stable disease alone will not be considered a treatment failure for patients on this

protocol. Patients will require objective evidence of disease progression to be considered treatment failures.

12. Toxicities and Complications

A. Rituximab

Rituximab can cause severe, including fatal, infusion reactions associated with hypersensitivity and anaphylaxis. All patients receiving rituximab will be given premedications as described under section 9.C. Some patients treated with rituximab have experienced tumor lysis syndrome, severe (including fatal) mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML) resulting in death. Other significant toxicities may include Hepatitis B virus reactivation with fulminant hepatitis, increased risk of infection, cardiac arrhythmia, renal toxicity, and bowel obstruction or perforation. The most common adverse reactions associated with rituximab infusion include infusion reactions, fever, chills/rigors, infection, asthenia, lymphopenia, nausea, vomiting, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, myalgia, dizziness, and hypertension.

B. ^{90}Y-ibritumomab tiuxetan

The most serious toxicities observed following radiolabeled ibritumomab tiuxetan are prolonged and severe cytopenias, and secondary malignancies including myelodysplastic syndrome and/or acute myeloid leukemia. Severe cutaneous and mucocutaneous reactions, some fatal, have been reported following a therapeutic regimen using rituximab and ^{90}Y-ibritumomab tiuxetan. The most common adverse reactions include cytopenias, fatigue, abdominal pain, nausea, nasopharyngitis, asthenia, diarrhea, cough, and pyrexia.

C. Fludarabine

Clinical toxicities of fludarabine include: myelosuppression, primarily lymphopenia and granulocytopenia, alopecia, rash, dermatitis, nausea, vomiting, anorexia, stomatitis, diarrhea, somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness, hepatocellular toxicity with elevation in serum transaminases, and interstitial pneumonitis. These effects are reversible when the drug is discontinued. Immunosuppression observed with the use of fludarabine increases the risk of infection which can be life-threatening.

D. Total body irradiation (TBI)

See Standard Practice Manual for information on associated toxicities.

E. Stem cell transplant

See Standard Practice Manual for information on associated toxicities.

F. Cyclosporine (CSP)

See Standard Practice Manual for information on associated toxicities.

G. Mycophenolate mofetil (MMF)

See Standard Practice Manual for information on associated toxicities.

13. Guidelines for Serious Adverse Event Reporting

A. DEFINITIONS

Adverse Event (AE) – Any side effect or untoward medical occurrence in a subject enrolled in a clinical trial, which does not necessarily have to have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with study participation.

Serious Adverse Event (SAE) – An adverse event that results in any of the following outcomes:

- Death.
- Life-threatening AE (placing the patient, in view of the investigator, at immediate risk of death from the reaction).
- Inpatient hospitalization or prolongation of hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly or birth defect.
- An important medical event that requires intervention to prevent one of the above outcomes.

Unexpected Adverse Event – An AE that is not consistent in nature or severity with the product information documented in the protocol, consent form, and/or prior reports.

B. MONITORING AND RECORDING AES

B.1 Responsibility for AE monitoring

As noted under section 14, the PI meets regularly with the study coordinator, during which time any adverse events that have not already been reported to the PI are discussed.

B.2 Time frame for monitoring AEs

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of first exposure to a study intervention (i.e., the start of the rituximab infusion associated with the therapy dose) through day +100 post-transplant or through discharge prior to that date from the SCCA system to care of the patient's primary physician. AEs with an onset date prior to the first exposure to an investigational product will not be recorded, except in the event of clinically significant worsening of the AE during the specified monitoring time frame.

B.3 AE grading

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 (**http://evs.nci.nih.gov/ftp1/CTCAE/About.html**).

All patients undergoing allogeneic transplantation using any investigational or standard myeloablative approach are expected to experience multiple grade 1-3 adverse events. These events will be reviewed and captured in the source documentation. Through day 100 (or through discharge prior to that date from the SCCA system), non-hematologic adverse events of ≥ grade 3, possibly related events of grade 2 that have not previously been observed with components of the study regimen, and all serious adverse events will be captured in protocol-specific case report forms. Grade ≤4 hematologic toxicity is expected and will only be recorded as time to engraftment. After day 100 patients will be tracked only for progression and survival.

The following events are ***not*** identified as AEs in this study:

- Disease progression or relapse. However, clinical events associated with progression/relapse may be reportable as AEs.
- Hospitalization for the purpose of facilitating stem cell transplant is not considered an AE. Any AE requiring prolongation of this hospitalization will be recorded and subject to applicable SAE reporting.
- Medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs. However, an event or condition requiring such procedures may be an AE.
- All patients undergoing hematopoietic stem cell transplant are expected to have ≤ Grade 4 pancytopenia as an intended therapeutic effect. These hematologic AEs will therefore be tracked and recorded only as time to recovery of blood counts/engraftment.
- Abnormal laboratory values will be identified and recorded as AEs only if clinical intervention is required as a result.

B.4 AE attribution

Association or relatedness to the study agent will be assessed by the investigator as follows:

- *Definite*: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- *Probable*: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- *Possible:* The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- *Unlikely:* Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- *Unrelated:* The event is clearly related to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.

An AE is considered *related* if it is assessed as definitely, probably, or possibly related; *unrelated* if it is assessed as unlikely related or unrelated.

C. REPORTING AES

Adverse event reporting to the Institutional Review Board will occur in accordance with FHCRC IRB policies. All unexpected and serious adverse events that may be due to study treatment or intervention, and other unanticipated problems that involve risk to research

participants or others, will be reported to the FHCRC Institutional Review Office as soon as possible and within the IRB's required time frame from the investigator learning of the event. The FHCRC Adverse Event Reporting Form, Unanticipated Problem Reporting Form, or appropriate equivalent will be completed for this reporting. If necessary due to limited information available, an incomplete report form will be faxed at the initial report, followed by a completed report within the time frame dictated by IRB policy. SAEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

All deaths except those from relapse of malignancy, but otherwise regardless of attribution, that occur within the first 100 days following transplant will undergo expedited reporting to the FHCRC IRB. If the patient has returned to the care of the referring physician prior to day 100 post-transplant, the death will be subject to expedited reporting based on the time we learn of the death. Deaths occurring after 100 days will not undergo expedited reporting although they will be included in annual reports and publications of the study.

In the event of study closure due to toxicities, or activation of any other stopping/suspension rule, the FHCRC IRB would be notified promptly within 7 days of the determination.

D. SAES ASSOCIATED WITH HEMATOPOIETIC STEM CELL TRANSPLANT

Certain events that are commonly observed as SAEs following stem cell transplant are described here in order to facilitate assessments of attribution. SAEs that are identified as routinely experienced in the allogeneic transplant setting would typically be assessed as unrelated to elements of the RIT regimen used in this protocol. The following list represents some of the most frequent SAEs expected in this setting and is not intended to be comprehensive. Symptoms associated with graft versus host disease are described under Appendices C and D.

CTCAE Category	Toxicity
Blood and lymphatic system disorders	*As noted above, all patients undergoing stem cell transplant are expected to have ≤ Grade 4 pancytopenia as an intended therapeutic effect. These hematologic adverse events will be tracked and recorded only as time to recovery of blood counts/engraftment.* Febrile neutropenia
General disorders and administration site conditions	Fatigue Fever Rigors, chills
Gastrointestinal	Diarrhea Dysphagia Esophagitis Mucositis/Stomatitis Nausea Vomiting
Hemorrhage/Bleeding	Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia
Infections and infestations	*Infections may be associated with neutropenia following HCT*

CTCAE Category	Toxicity
Metabolism and nutrition disorders	Anorexia Dehydration Hypokalemia (e.g., potassium < 2.5 can result from wasting induced by transplant-related medications)
Reproductive system and breast disorders	Reproductive system and breast disorders – Other: Sterility/infertility

14. Data and Safety Monitoring Plan

Ongoing trial oversight is carried out by the principal investigator, Dr. Gopal, and the study coordinator. These individuals will meet at least monthly to review recently acquired data, stopping rules, and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above. All investigators on the protocol have received formal training in the ethical conduct of human research.

Institutional support of trial monitoring is provided in accordance with the FHCRC Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, the FHCRC Research Trials Office coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits. In addition, protocols are reviewed at least annually by the Protocol and Data Monitoring Committee (PDMC) and the Institutional Review Board (IRB). The PDMC reviews accrual, adverse events, stopping rules, and adherence to the data and safety monitoring plan. The FHCRC IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of both committees is necessary to continue the study.

This protocol is a single institution phase II trial that does not employ gene therapy and, thus, does not require a separate data safety monitoring board. The trial will comply with the standard guidelines set forth by the regulatory committees of the FHCRC (Scientific Review Committee, IRB, PDMC) and other state and federal guidelines.

15. Records

Research staff under the supervision of the investigators will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Radiologic data from scanning will be stored in the Division of Nuclear Medicine. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

16. Statistical considerations

A Primary endpoint: The primary objective of this protocol is to examine the efficacy of this approach in patients with aggressive B-NHL. Prior data from FHCRC1726 using standard dose Zevalin prior to NMAT indicated that approximately 30% of patients were estimated to be alive and progression-free at 1 year. This study will be deemed successful if the 1 year PFS of this highest-risk group of patients is 54% or greater. If the true rate of 1 year PFS using the proposed approach is 54%, then **24 patients** will

provide 80% power to detect a statistically significantly increased rate of PFS from the fixed rate of 30%, based on a one-sample chi-square test with one-sided significance level of five percent.

B Stopping rule for safety: This trial will be paused prematurely due to toxicity if there is sufficient evidence suggesting that the true incidence of TRM within 100 days of transplant exceeds 20%. TRM will be defined for this purpose as death in the absence of progressive lymphoma that can be possibly, probably, or definitely attributed to the radioimmunotherapy. Sufficient evidence will be taken to be an observed rate of TRM within 100 days of transplant that corresponds to a one-sided 80% confidence interval with a lower limit greater than 20%. For this rule, patients will be stratified into 2 arms and evaluated separately, (1) those that have received >20 Gy prior radiation therapy and (2) all others. These limits will be examined after every 5th enrolled patient within each arm becomes eligible for evaluation. Operationally, the given arm will be suspended if we observe the following numbers of events out of sequentially treated patients in a given arm within the first 100 days of transplant: 3/5, 4/10, 5/15, 6/20, or 8/25. If an arm of the study is halted, we will assemble an independent data safety monitoring committee to advise us as to how to proceed. Table 6 summarizes the operating characteristics of this stopping rule, where the probability of stopping the trial is estimated from 10,000 Monte Carlo simulations.

Table 6. Probability of stopping the trial for excess treatment-related deaths.

Number of patients	True rate of TRM	Probability of stopping
10	10%	0.02
15	10%	0.02
20	10%	0.03
10	30%	0.38
15	30%	0.53
20	30%	0.64
10	40%	0.64
15	40%	0.81
20	40%	0.91

17. Termination of the Study

Study enrollment will be terminated upon complete accrual of patients or when stopping rules described above have been met. The study will remain open throughout patient survival in order to continue data collection from long-term evaluations.

18. Ethnic and Gender Distribution Chart (based on prior accrual)

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	9	13	22
Ethnic Category Total of All Subjects*	10	14	24
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	9	13	22
Racial Categories: Total of All Subjects*	10	14	24

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APPENDIX A

SWOG/ECOG Performance Status

PERFORMANCE STATUS SCALE

STATUS[1,2] (Karnofsky)	SCALE		"WHO" - STATUS[3,4] (Zubrod-ECOG)
Normal, no complaints	100	0	Normal activity
Able to carry on normal activity Minor signs or symptoms of disease	90	1	Symptoms, but ambulatory
Normal activities for effort	80		
Cares for self, unable to carry on normal activity or to do active work	70	2	Some bed time, but in bed less than 50% of normal daytime
Requires occasional assistance, but able to care for most of own needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed more than 50% of normal daytime
Disabled, requires special care and assistance	40		
Severely disabled, hospitalization indicated though death not imminent	30	4	Unable to get out of bed
Very sick, hospitalization necessary, active supportive treatment necessary	20		
Moribund	10		
Dead	0		

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APPENDIX B:
ACUTE GVHD ASSESSMENT

Staging by Individual Organ Involvement

SKIN: measured by rash first appearing generally between 10 and 70 days after transplant. (excludes rashes of known viral or other origin)

Stage	Description
1	Maculopapular rash <25% BSA
2	Maculopapular rash 25 – 50% BSA
3	Generalized erythroderma
4	Generalized erythroderma with bullous formation and desquamation

LIVER*: measured by total serum bilirubin

Stage	Description
1	2.0 – 2.9 mg/dL
2	3.0 – 5.9 mg/dL
3	6.0 – 14.9 mg/dL
4	≥ 15.0 mg/dL

GUT:** includes only diarrhea occurring after Day +21

Score	Adult	Pediatric***
1	upper GI (anorexia, nausea, vomiting) with diarrhea of <1000 mL/day	upper GI (anorexia, nausea, vomiting) with diarrhea of <555 mL/m^2/day
2	1000 – 1499 mL/day diarrhea	556-833 mL/m^2/day diarrhea
3	≥ 1500 mL/day diarrhea	>833 mL/m^2/day diarrhea
4	severe abdominal cramping, bleeding or ileus caused by GVHD	

* In cases where another cause of hyperbilirubinemia antedated the onset of rash, the liver score should be decreased by one stage.

** In cases where peak GI symptoms are exacerbated by a cause other than GVHD, the gut score should be decreased by one stage.

*** Pediatric patients <17 years of age

Overall Grade

The determination of an overall GVHD grade should be based on the organ stage, response to treatment and whether GVHD was a major cause of death.

Overall Grade	Organ Stage	Qualifying Conditions	Additional Qualifying Conditions
I	Stage 1 -2 skin	No liver or gut	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD.
II	Stage 3 skin or Stage 1 liver or Stage 1 gut	N/A	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD, but glucocorticoid treatment after the onset of GVHD was generally sufficient to control the disease.
III	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**without** GVHD as a major contributing cause of death	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD and that additional treatment after the onset of GVHD did not readily control the disease.
IV	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**with** GVHD as a major contributing cause of death	GVHD was resistant to both the prophylactic immunosuppressive regimen and any additional treatment after the onset of the disease.

APPENDIX C:

CHRONIC GVHD GRADING*

In all cases, concomitant processes (i.e. infections or drug reactions) must be ruled out. Karnofsky or Lansky Clinical Performance scores, 60%, > 15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chronic GVHD are categorized by organ systems as listed below.

Skin	Erythema, dryness, pruritus, pigmentary changes (i.e. hyperpigmentation, vitiligo), mottling, papulosquamous plaques, nodules, exfoliation, macular-papular or urticarial rash, scleroderma, morphea (one or several circumscribed, indurated and shiny lesions)
Nails	Ridging, onychodystrophy, onycholysis
Hair	Premature graying, (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia, decreased body hair
Mouth	Dryness, burning, gingivitis, mucositis, striae, atrophy, erythema, lichenoid changes, ulcers, labial atrophy or pigmentary changes, tooth decay, tightness around the mouth
Eyes	Dryness, burning, blurring, gritty eyes, photophobia, pain
Vagina/vulva	Dryness, dyspareunia, stricture or stenosis, erythema, atrophy or lichenoid changes not included
Liver	Elevated liver function tests not due to other causes (alkaline phosphatase $\geq$ 3x upper limit of normal, AST or ALT $\geq$4x upper limit of normal or total serum bilirubin $\geq$ 2.5; in the absence of chronic GVHD involving other organs, liver biopsy is required to confirm diagnosis)
Lung	Bronchiolitis obliterans (see diagnostic indicators), cough, wheezing, dyspnea on exertion, history of recurrent bronchitis or sinusitis
GI	Anorexia, nausea, vomiting, weight loss, dysphasia, odynophagia, malabsorption
Fasciitis	Stiffness and tightness with restriction of movement, occasionally with swelling pain, cramping, erythema and induration, most commonly affecting forearms, wrists and hands, ankles, legs, and feet, inability to extend wrists without flexing the fingers or the elbows, contractures
Serositis	Chest pain or cardiopulmonary comprise due to pericarditis or pleuritis
Muscle	Proximal muscle weakness, cramping
Skeletal	Arthralgia of large proximal girdle joints and sometimes smaller joints

Laboratory testing and diagnostic indicators of chronic GVHD*

Eye	Schirmer's test with a mean value ≤ 5mm at 5 minutes, or symptomatic with values of 6-10mm or keratitis detected by slit lamp examination
Liver	Elevated liver function tests not due to other causes (see definition of clinical limited and extensive chronic GVHD)
Lung	New obstructive lung defect defined as FEV1 < 80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV1/FVC by > 12% within a period of less than 1 year. A diagnosis of bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar lavage and evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scans o the chest. A thoracoscopic lung biopsy may be necessary in order to confirm the diagnosis of bronchiolitis obliterans in patients who have obstructive lung disease without air trapping when chronic GVHD involving other organs is absent
Esophagus	Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry
Muscle	Elevated CPK or aldolase, EMG findings consistent with myositis
Blood	Thrombocytopenia (usually 20,000-100,000/μl), eosinophilia, hypogamma-globulinemia, hypergammaglobulinemia, and autoantibodies occur in some cases

* From Standard Practice Guidelines for "Chronic Graft-versus-Host Disease Classification at the time of presentation" developed by Long Term Follow-Up at the FHCRC