

**CITY OF HOPE NATIONAL MEDICAL CENTER  
DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION**

**TITLE:** A PHASE II STUDY OF YTTRIUM-90-LABELED ANTI-CD20 MONOCLONAL ANTIBODY IN COMBINATION WITH HIGH-DOSE BEAM (BCNU, ETOPOSIDE, CYTARABINE AND MELPHALAN) FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH POOR RISK/RELAPSED B-CELL LYMPHOMA

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## TABLE OF CONTENTS

1.0	BACKGROUND AND RATIONALE	1
2.0	STUDY OBJECTIVES	6
3.0	STUDY DESIGN	7
4.0	DRUG FORMULATION	7
5.0	STAGING CRITERIA	11
6.0	INCLUSION CRITERIA	12
7.0	EXCLUSION CRITERIA	13
8.0	TREATMENT PLAN	13
9.0	STUDY CALENDAR - PREPARATIVE REGIMEN AND PBSCT	18
10.0	CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS	20
11.0	STATISTICAL CONSIDERATIONS	21
12.0	REGISTRATION GUIDELINES	23
13.0	RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE	23
14.0	DATA MANAGEMENT	23
15.0	ETHICAL AND REGULATORY CONSIDERATIONS	23
16.0	DATA SAFETY MONITORING PLAN: RISK LEVEL 3	24
17.0	REFERENCES	26

Appendix I Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Appendix II Modified Bearman Toxicity Scale

Appendix III Additional Assays to be Performed on Previously Collected Samples

## 1.0 BACKGROUND AND RATIONALE

Non-Hodgkin lymphomas are the sixth most common cause of cancer-related deaths in the United States. The incidence of NHL has increased by 50% over the past 15 years. The incidence of both indolent and aggressive lymphomas increases with age making these the most commonly diagnosed lymphoid malignancies in patients over 60 years of age.<sup>1</sup> Despite the use of aggressive combination chemotherapy regimens, approximately 30-40% of the patients with intermediate- and high-grade NHL do not achieve a complete remission (CR) or suffer a relapse after attaining a remission.<sup>2</sup> High-dose chemotherapy or chemo/radiotherapy followed by autologous bone marrow or stem cell transplantation (ASCT) has been shown to induce long-term disease control in about 10-50% of patients with relapsed and refractory intermediate- and high-grade lymphoma.<sup>3</sup> The benefit of high-dose therapy and ASCT has been proven to be superior to conventional salvage chemotherapy in a randomized study of 215 patients with chemotherapy-sensitive NHL in relapse reported by the Parma study group.<sup>4</sup> The 5-yr event-free survival (EFS) was 46% for ASCT group compared to 12% for the salvage therapy without transplantation ( $p=0.001$ ). Thus, high-dose therapy and ASCT has become a potential curative modality for patients with recurrent aggressive lymphoma. However, not all the patients derive long-term benefit from this treatment and recurrent disease remains the single most common cause of treatment failure after high-dose therapy and ASCT. Therefore, new therapeutic approaches within the ASCT setting are needed.

Patients with low-grade NHL have an indolent clinical course and are not cured by current treatment approaches. Although most patients can achieve a complete remission with standard treatment, the median duration of first CR ranges from 12 to 36 months. Although relapsed low-grade lymphoma may still respond to salvage therapy, the duration of subsequent remissions progressively decreases. High-dose therapy and ASCT has been shown to improve survival and increase the duration of remission in some patients with relapsed low-grade NHL.<sup>5</sup> However, because of the long natural history and the continued pattern of relapse post ASCT in some studies, the role of high-dose therapy and ASCT as a potential curative treatment for patients with relapsed low-grade lymphoma has not been clearly established.

Mantle cell lymphoma, one of the categories of low-grade lymphoma, remains one of the most difficult clinical challenges. Response rates with initial chemotherapy such as CHOP-Rituxan are over 90%, however, progression free survival remains short.<sup>6</sup> Therefore, new treatment strategies are needed to improve long-term survival. One of the explored strategies is the use of high dose therapy and autologous stem cell transplant as upfront consolidation. The optimal conditioning regimen for the consolidative phase remains a subject of study.

The incidence of lymphoma increases with age. Furthermore, the prognosis of lymphoma in older patients tends to be worse. This is due to a combination of factors; the biology of the disease, comorbidities that lead to increased toxicity with conventional chemotherapy or that require dose reduction of chemotherapy. The early transplant trials such as the PARMA study included younger patients (<60yrs). However, many of our patients are beyond this age range. For these patients with poor risk or relapsed lymphoma, new options are needed. Novel conditioning regimens that combine radioimmunotherapy with high dose chemotherapy are one such option.

### 1.1 Results of High-Dose Chemo/Radiotherapy and ASCT for NHL

Several high-dose therapy regimens have been used as preparative regimens for NHL and so far, none of these regimens have emerged to be the best regimen. However, since NHL is radiosensitive and based on the experience of acute leukemia, the combination of total body irradiation (TBI) and cyclophosphamide (Cy) has been widely used as a preparative regimen for patients with lymphoid malignancies. In an attempt to reduce relapse rates, etoposide has been added to the TBI and Cy regimen because of its known activity in lymphoma. The results of phase I and II studies of TBI 12.0 Gy, etoposide 60 mg/kg and Cy 100 mg/kg conducted at City of Hope<sup>7</sup>, Stanford University<sup>8</sup> and Fred Hutchinson Cancer Research Center (FHRC)<sup>9</sup> demonstrated the activity of this regimen in patients with lymphoid malignancies. The transplanted-related mortality within the first 100 days was 7-8% and the common causes of death were veno-occlusive disease (VOD), diffuse alveolar hemorrhage, and infection. The major transplant-related morbidities were mucositis and skin, toxicities which were fully reversible. Utilizing this regimen, Stanford reports 5-year event free survival (EFS) and overall survival (OS) probabilities of 52% (95% confidence interval (CI): 42-

62%) and 61% (95%CI: 50-73%) respectively for 134 NHL patients who underwent ASCT at their institution.

Between 2/87 and 8/98, 264 patients with intermediate or high grade non-Hodgkin lymphoma underwent ASCT at City of Hope Bone Marrow Transplant Program. Ninety-four patients underwent ASCT in first complete/partial remission, 40 in induction failure, and 130 in relapse or subsequent remission. Seventy-nine percent of patients received the combination of total body irradiation, high dose etoposide and cyclophosphamide as conditioning regimen. Carmustine was given instead of TBI for patients who were not able to receive TBI due to prior radiation, or if their age was greater than 60 years with borderline performance status. With a median follow-up of 4.4 years for the surviving patients (1-12.8 yrs.), the 5-year Kaplan-Meier estimates of probability of overall survival, progression-free survival, and relapse are 55% (95% CI: 49-61), 47% (95%CI: 40-53%) and 47% (95%CI: 40-54%) respectively. In univariate analysis, patients who received a total-body irradiation tended to have fewer relapses after transplant and improved survival but this was no longer significant at multivariable analysis. There were 27 deaths (10%) from non-relapse mortality, including 10 patients due to secondary malignancy. This result has been confirmed in the Southwestern Oncology Group cooperative trial. Despite its effectiveness, the relapse rates of 34-53% remain high. Thus, more effective preparative regimens are needed.

Options for new regimens include adding new agents or incorporating post transplant maintenance strategies. The limitation of adding new agents in the high dose setting is minimizing overlapping organ toxicity. Thus, targeted radioimmunotherapy against CD20 is an attractive option as it has relatively low toxicity to normal organs except the bone marrow.

## **1.2 Anti-CD20**

Anti-CD20 (anti-B1) is a murine monoclonal antibody of isotype IgG2a, raised against cryopreserved Burkitt lymphoma cells. The antibody reacts against the B1 antigen, an epitope of the CD20 developmental cell surface protein. CD20 is a 35 kD cell surface phosphoprotein found on 95% of normal mature B cells and more than 90% of B-cell non-Hodgkin lymphomas and B-cell chronic lymphocytic leukemias tested, but not on T cells, plasma cells, uncommitted hematopoietic-precursors stem cells, dendritic cells, granulocytes, monocytes, or erythrocytes, or on tumors of T cell, myeloid or erythroid origin. CD20 is not shed and does not modulate from the surface after binding of antibody.

Anti-CD20 has been used extensively as a therapeutic agent for use in bone marrow purging. Clinical use of this antibody in marrow purging has shown it to be selective in eradicating B-cell lymphomas as well as normal B cells, while leaving other lymphocyte population intact. Some subpopulation of B cell precursors is left intact, as evidence by engraftment of the normal B cell compartment.

## **1.3 Yttrium-90**

Yttrium-90 (Y90, Zevalin<sup>®</sup>) is a chimeric antibody with a murine variable portion and a human IgG1 kappa constant portion that recognizes the CD20 antigens expressed on normal B cells and most malignant B-cell lymphomas. Yttrium 90 shows specificity for the CD20 antigen and binds with an apparent affinity of  $4.3 \times 10^{-9}$ M. Yttrium-90 has also been reported to induce apoptosis and to sensitize drug-resistant human B-cell lymphoma cell lines to cytotoxic chemotherapy.

## **1.4 Radionuclides for Radioimmunotherapy**

Yttrium-90 (<sup>90</sup>Y) (ZEVALIN<sup>®</sup>) may be an ideal radionuclide for radioimmunotherapy since it emits beta particles that are more potent than those delivered by <sup>131</sup>I. It is a pure beta emitter, making it a safer reagent for medical personnel to administer than <sup>131</sup>I. In addition, the short half-life also facilitates the use of <sup>90</sup>Y in combination with other agents; i.e. chemotherapy or total body radiation, as well as allows for high dose rates at localized sites. Unfortunately, <sup>90</sup>Y cannot be used for radioimmunoscintigraphy due to its absence of gamma emissions. Indium-111 has been substituted as an imaging reagent to show tumor localization in patients scheduled for <sup>90</sup>Y therapy, on assumption that its biodistribution closely mimics that of <sup>90</sup>Y. Using In-111 labeling, other murine monoclonal antibodies have been used successfully in clinical trials for cutaneous T-cell lymphoma and chronic lymphocytic leukemia, melanoma, and colon cancer.

Prior to the establishment of Yttrium-90 for clinical use, Iodine-131 had been the gold standard for

radioimmunotherapy due to its long track record in treating thyroid carcinoma. However, there are disadvantages to Iodine-131 which include its long half-life, the risks of radiation exposure to health care personnel and the nonspecific radiation to normal organs from the gamma components of Iodine-131.

### **1.5 Results of <sup>131</sup>I anti-B1 Monoclonal Antibody with Autologous Bone Marrow Support**

The use of radio-labeled monoclonal antibody (MAb) at myeloablative radiation dose followed by autologous stem cell rescue has been explored by investigators from The Fred Hutchinson Cancer Research Center. Press et al<sup>10</sup> conducted a trial utilizing a higher dose of <sup>131</sup>I labeled anti-CD20 antibody with autologous bone marrow rescue in 43 patients with B-cell lymphoma in relapse. In this study, sequential biodistribution studies were performed with escalating doses of antibody (0.5, 2.5, and 10 mg/kg) trace-labeled with 5 to 10 mCi of <sup>131</sup>I. Patients whose tumors were estimated to receive greater doses of radiation than liver, lungs, or kidneys (a favorable biodistribution) were eligible for the therapeutic infusion of <sup>131</sup>I labeled antibody. Of the 43 patients, 24 had a favorable biodistribution, and 19 received therapeutic infusion of 234-777 mCi of <sup>131</sup>I-labeled antibodies (58-1168 mg) followed by autologous marrow infusion. Sixteen patients achieved a CR, two had a partial response, and one had a minor response. Nine of the complete responders have remained in continuous CR for 3 to 53 months. Toxicities include myelosuppression, nausea, infection and two episodes of cardiopulmonary toxicity. In this study, cardiopulmonary toxicity was the dose limiting, non-hematopoietic toxicity of high-dose <sup>131</sup>I-labeled antibody.

In an attempt to reduce toxicity to normal tissues and to directly deliver higher dose of radiation to tumor sites, <sup>131</sup>I-labeled-anti-CD20 MAb has been incorporated into high-dose therapy regimen instead of TBI. Press et al<sup>11</sup> reported results of a phase I/II study to define the MTD of an <sup>131</sup>I-labeled anti-B1 monoclonal antibody which can be given with high-dose etoposide and cyclophosphamide in conjunction with ASCT in 38 (26 low-grade; 12 aggressive) NHL patients. Patients were treated in cohorts of 4 patients each with <sup>131</sup>I-anti-B1 antibody doses (2.5 mg/kg, 318-840 mCi) calculated to deliver 20-27 Gy of radiation to dose-limiting, critical normal organs, followed by etoposide (0 or 60 mg/kg), cyclophosphamide (100 mg/kg), and ABMT (15 patients) or ASCT (22 patients). Of the 37 evaluable patients, 33 (89%) were currently alive and 29 (78%) were progression-free after a median follow-up of 1.5 yr. Toxicities included grade 4 myelosuppression in all patients, grade 2-3 nausea in 26 (70%), pulmonary infiltrate in 4 and grade 3 VOD in 2 patients. There were four deaths; 3 from progressive NHL and 1 from disseminated varicella. These results suggest that <sup>131</sup>I- anti-B1 antibody can be given at doses delivering up to 25 Gy to critical normal organs, with pulmonary and gastrointestinal toxicities being dose-limiting.

### **1.6 Results of Bexxar (<sup>131</sup>I Anti-CD20 Monoclonal Antibody) in combination with High Dose Chemotherapy followed by Autologous Stem Cell Rescue**

In a phase I trial, Vose and colleagues from Nebraska Medical Center evaluated the addition of standard dose Bexxar (<sup>131</sup>I-Anti-CD 20) given sequentially with BEAM (BCNU, etoposide, Ara-C and melphalan) followed by ASCT in patients with primary induction failure or chemo-refractory recurrent non-Hodgkin lymphoma.<sup>17</sup> Twenty-three patients were included in this pilot study. There were no treatment-related deaths. The overall response rate was 66% with complete response rate of 57% and partial remission rate of 9%. With a median follow-up of 38 months, the overall survival was 55% and event free survival was 39% respectively. Short and long term toxicities were similar to BEAM alone. This suggests that the combination of Bexxar with high dose chemotherapy can be administered without increased toxicity.

While the superiority of this approach over conventional radiation based regimens has not been proven, retrospective studies comparing high dose radioimmunotherapy (RIT) versus total body irradiation based (TBI) regimens suggest a benefit. Gopal et al performed a multivariate comparison of 125 patients with follicular lymphoma treated with high dose RIT with <sup>131</sup>I. The RIT regimen had a lower 100 day transplant related mortality and improved OS compared to TBI based regimens.<sup>28</sup> This suggests that further study of these RIT based conditioning regimens is warranted.

### **1.7 Therapeutic Use of Anti-CD20 Antibody and Yttrium90 Anti-CD20 Antibody**

A Phase I dose escalation pharmacokinetic trial of anti-CD 20 given as a single intravenous infusion using doses ranging from 10 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> in patients with relapsed or refractory low-grade lymphoma was reported by Maloney et al.<sup>14</sup> The median half-life of the free antibody at doses ranging from 100 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> was 4.4 days (range 1.6-10.5 days). In Phase II clinical studies, anti-tumor activity has been

observed in patients with relapsed or refractory low-grade or follicular B-cell NHL. The majority of adverse events was mild to moderate and included fever, fatigue, chills and nausea, which were primarily associated with the initial infusions. No quantifiable human anti-mouse antibodies (HAMA) or human anti-chimeric antibodies (HACA) were observed. Depletion of peripheral B-cells occurred rapidly following the first infusion with recovery beginning 6 months post-treatment. Despite this depletion of B-cells, there was minimal change in serum IgG, IgM, and IgA levels and no increase in the frequency or severity of infectious complications. Anti-tumor activity was observed at various disease sites, including peripheral blood, bone marrow, lymph nodes, spleen and abdominal masses.

A phase III trial to assess the safety and efficacy of anti-CD20 antibody, 375 mg/m<sup>2</sup>, given once weekly for four doses in 166 patients with relapsed or refractory low-grade or follicular NHL was reported by McLaughlin et al.<sup>15</sup> The overall response rate in 151 evaluable patients was 50% (9CR; 67 PR). The median duration of response has not been reached after a median follow-up of 9+ months. Conversion to negative bcl-2 status occurred in 57% of patients who were positive at baseline and subsequently reevaluated after the fourth infusion. No positive HAMA responses were observed in 67 patients evaluated and the incidence of HACA was less than 1%. Severe neutropenia and thrombocytopenia were observed in less than 2% of patients. Anti-CD20 has also been studied in 44 patients with relapsed diffuse large B-cell and mantle cell lymphoma. The overall response rate was 31%, with a 10% CR rate. Thus anti-CD20 monoclonal antibody has become a very effective salvage therapy for CD20+ B-cell low- and intermediate-grade NHL and this treatment has become an important addition to our armamentarium.

Anti-CD20 has also been studied in combination with chemotherapy. Czuczman et al conducted a Phase II multi-center study evaluating the safety and anti-tumor activity of anti CD20 375 mg/m<sup>2</sup> for six doses in combination with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy in 40 patients with low-grade NHL.<sup>16</sup> Combination therapy appeared safe and toxicity profile observed was consistent with that seen with CHOP alone. No HAMA or HACA responses were observed. The overall response rate in 35 patients who completed treatment was 100% (21 CR; 14 PR). The median time to disease progression has not been reached with follow-up time of 9-27+ months. Seven of eight patients who were bcl-2 positive at baseline by polymerase chain reaction (PCR) became negative in both peripheral blood and bone marrow following treatment.

Several randomized trials have now confirmed the superiority of combining chemotherapy with immunotherapy. The GELA trial and the MINT trial confirmed the superiority of CHOP rituximab over CHOP alone in both event free survival and overall survival in elderly patients and in younger patients with diffuse large cell lymphoma.<sup>17,18</sup>

#### *Yttrium-90 Clinical Studies*

A Phase I/II dose escalation study of <sup>90</sup>Y-murine anti-CD20 monoclonal antibody (MAb) in patients with recurrent B-cell lymphoma was performed by Knox et al.<sup>19</sup> The primary objectives of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-CD20 MAb on the biodistribution of <sup>111</sup>In-anti-CD20 MAb; (b) to determine the maximal tolerated dose of <sup>90</sup>Y-anti-CD20 MAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of <sup>90</sup>Y-anti-CD20 MAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin lymphoma were treated. Biodistribution studies with <sup>111</sup>In-anti-CD20 MAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of approx 13.5, 20, 30, 40, and 50 mCi <sup>90</sup>Y-anti-CD20 MAb. Three patients were retreated at the 40 mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of <sup>90</sup>Y-anti-CD20 MAb therapy was 72%, with six complete responses and seven partial responses, and freedom from progression of 3-29+ mo following treatment. Radioimmunotherapy with less than or equal to 50 mCi <sup>90</sup>Y-anti-CD20 MAb resulted in minimal non-hematologic toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of less than or equal to 40 mCi <sup>90</sup>Y-anti-CD20 MAb were not myeloablative.

A phase II study by Witzig et al established the activity of Yttrium-90 in patients with rituximab refractory follicular lymphomas. Fifty-seven patients were treated. The patients first received a dose of rituximab, 375mg/m<sup>2</sup>, day 1 and day 8 to deplete peripheral blood B cells. The first 28 patients had indium-111 imaging performed on day 1 (see below).<sup>20</sup> The estimated radiation doses were acceptable allowing for

Yttrium 90 treatment in all the patients. The overall response rate was 74% (15% CR 59% PR). The time to progression for responders was 8.7 months. The therapy was well tolerated. The adverse events were primarily hematologic and transient. No patient discontinued therapy because of an adverse event. The incidence of grade 4 neutropenia was 35% though only 7% of patients required hospitalization for fever.

The dosimetry from the Witzig trial as well as other single agent studies of Yttrium-90 was reported by Wiseman et al.<sup>21</sup> Forty-two patients with low- and intermediate-grade NHL received Yttrium-90 following injection of unlabeled rituximab (cold antibodies) followed by 2 mg of mouse anti-CD20 antibody labeled with 5 mCi <sup>111</sup>In (IDEC-In2B8). <sup>90</sup>Y 0.2, 0.3, or 0.4 mCi/kg was given 7 days following <sup>111</sup>In. The patients had <sup>111</sup>In dosimetry performed by serial whole body gamma camera imaging, urine collection and blood sampling at 0, 2, 6, 24, 48, 72, 96 and 144 hours. The highest mean calculated <sup>90</sup>Y radiation dose to a normal organ was spleen with 24.16 rads/mCi (0.6-67.0), followed by liver with 17.2 rad/mCi (9.4-39.2) and lungs with 12.9 rads/mCi (4.2-67.7). <sup>90</sup>Y dose of 0.4 mCi/kg was the MTD for bone marrow toxicity (thrombocytopenia and neutropenia). These results suggest that: 1) no organ was irradiated beyond safety levels; 2) <sup>111</sup>I can serve as a predictor of <sup>90</sup>Y; 3) rituximab dose of 250 mg/m<sup>2</sup> has been established as the “cold” antibody with added benefits of its therapeutic effect; and 4) bone marrow toxicity was the dose-limiting effect with full and predictable recovery.

The use of Yttrium-90 as a single agent in older patients with refractory NHL has been studied. Schilder et al reported on an integrated analysis of four clinical trials comprising 211 patients. They were in three cohorts; <60 yrs, 60-69 yrs, >70 yrs. Complete remission rates and hematologic toxicities were similar across the cohorts. This suggested that Yttrium-90 is effective and well tolerated in older patients.<sup>22</sup>

### **1.8 Yttrium-90 and High Dose Chemotherapy**

The use of dose escalated IDECY2B8 combined with high dose chemotherapy is an ongoing study at Northwestern University.<sup>23</sup> To date, 33 patients have been treated. Because of the dose increase of the Yttrium, dosimetry monitoring is required to deliver patient specific defined radiation doses to critical organs. A report of the 33 patients treated with Yttrium-90 and high dose BEAM (BCNU, Etoposide, Cytarabine, Melphalan) was presented at the American Society of Clinical Oncology meeting by Jane Winter. The investigators noted that the most common grade 3-4 toxicities were infection, fever, and stomatitis. Engraftment times were similar to BEAM alone. This suggests that the combination of this isotope with high dose chemotherapy is well tolerated. However, the need for dosimetry makes the Winter protocol a more difficult regimen to utilize. Furthermore, it is unclear that increasing the Yttrium-90 dose provides any clinical benefit.

### **1.9 Study Proposal**

Therefore, our pilot trial at the City of Hope utilized standard dose Yttrium-90 in combination with high dose BEAM. The protocol treated 38 patients with a combination of standard dose Yttrium-90 (0.4 mCi/kg) and high dose BEAM (BCNU, Etoposide, Cytarabine, Melphalan) chemotherapy. Data on 24 patients with adequate follow-up was presented at the American Society of Clinical Oncology meetings.<sup>24</sup> The patient population was older than our standard transplant population (median age 60 yrs). The toxicity profile of this regimen was similar to high dose BEAM alone. The major toxicity was pulmonary (grade 3) in three patients. This included interstitial pneumonitis and sepsis associated respiratory distress. Engraftment times were similar to high dose BEAM alone. At the time of reporting, with a median follow-up of 13.0 months, progression free survival was 74%.

We propose to expand upon this initial experience in a larger series of patients. Our pilot study established the safety of this regimen and suggested short-term efficacy. However, given the small numbers of patients spread among diverse histologies, the long-term efficacy of this regimen is still unproven. For example, we conducted a retrospective analysis of patients > 50 years of age who were treated with high dose BEAM versus those treated with Zevalin plus high dose BEAM. This analysis was presented at the American Society of Hematology Meeting in 2006. Analysis of patients with diffuse large cell lymphoma showed a significant difference in ZBEAM vs. BEAM, with the two year OS/PFS in the ZBEAM group of 88%/62% versus 65%/67% in the BEAM group. In contrast, no significant difference was seen between the conditioning regimens for patients with mantle cell lymphoma. The number of patients with follicular lymphoma or transformed lymphoma was too small in both groups to make a comparison. We therefore wish to further study the effects of ZBEAM conditioning in a larger number of patients with different

histologies. This new study will enroll patients with poor risk or relapsed follicular lymphoma (grade1-3), mantle cell lymphoma, diffuse large B-cell lymphoma and transformed low-grade lymphoma. There will be no upper age limit but organ function criteria must be met. We will assess the effects of this novel preparative regimen on disease progression among the various lymphoma histologies. Short- and long-term transplant related complications with specific attention to pulmonary, hematologic and hepatic function based on our pilot study experience will be assessed.

The study will also focus on costimulatory receptors, namely, PD-1, CTLA-4, CD28, ICOS, OX40 and 4-1BB (CD137), and will be performed on blood samples collected at various time points before and after the AHSCT regimen, using either FACS analysis or mRNA Q-PCR. The results may contribute to a better understanding of immune factors important in outcome. To date, we have shown that the PD-1 molecule was up-regulated in HCT subjects before the development of CMV disease. Similar techniques will be used for the expression of the other costimulatory receptors. **NOTE THAT, DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT BE INCLUDED IN THE COSTIMULATORY MOLECULE ANALYSIS.**

Lastly, with the marked improvement in survival, coupled with an increase in the intensity of treatment for patients with malignancies, therapy-related AML or MDS (t-MDS/AML) has become a serious and growing clinical problem. The incidence of t-MDS/AML ranges between 6-18% following treatment of various malignancies such as Hodgkin disease and non-Hodgkin lymphoma (both after conventional chemotherapy and following bone marrow or stem cell transplantation), breast cancer, testicular and ovarian cancers and acute lymphoblastic leukemia.<sup>25-27</sup> Therefore, because of the need for continued prospective monitoring for long term therapy related complications such as myelodysplasia and therapy related AML, all patients will be co-enrolled on protocol 98117, 'Molecular Pathogenesis of Therapy Related Leukemia'.

## 2.0 STUDY OBJECTIVES

This is a phase II study designed to evaluate hematopoietic recovery, early and late transplant related toxicity, disease progression/relapse, progression free/relapse free survival, overall survival and therapy related MDS/AML among patients with poor risk/relapsed follicular lymphoma (grade1-3), mantle cell lymphoma, diffuse large B-cell lymphoma, and transformed low-grade lymphoma who undergo RIT based ASCT.

- 2.1 To estimate the progression free/relapse free survival and overall survival probabilities among patients with poor risk/relapsed follicular lymphoma (grade1-3), mantle cell lymphoma, diffuse large B-cell lymphoma, and transformed low-grade lymphoma who undergo RIT based ASCT.
- 2.2 To evaluate hematopoietic recovery, using neutrophil ( $ANC \geq 500 \times 10^3/\mu L$ ,  $ANC \geq 1000 \times 10^3/\mu L$ ) and unmaintained platelet ( $\geq 20 \times 10^3/\mu L$ ,  $\geq 100 \times 10^3/\mu L$ ) engraftment as primary criterion, following RIT based ASCT.
- 2.3 To characterize early and late pulmonary, cardiac and hepatic toxicities during the first 100 days post ASCT and again one year post ASCT.
- 2.4 To evaluate the response rate and the disease progression/relapse rate in patients treated with RIT based ASCT.
- 2.5 To evaluate long-term incidence of myelodysplasia and therapy related AML with this new preparative regimen.
- 2.6 To descriptively compare the outcomes of patients treated on this protocol to a comparable patient population treated with chemotherapy alone.
- 2.7 To perform exploratory studies on expression of costimulatory molecules before and after RIT based ASCT. Refer to Section 9.0 (Study Calendar) for costimulatory molecule assay time points. **NOTE THAT, DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT BE INCLUDED IN THE COSTIMULATORY MOLECULE ANALYSIS.**

## 3.0 STUDY DESIGN

This is an open-label clinical study of a new preparative regimen followed by autologous stem cell support in patients with relapsed- refractory- NHL. Patients with low and intermediate-grade NHL who have relapsed following conventional chemotherapy or have failed to achieve remission, or have poor risk disease and who are candidates for high-dose therapy and ASCT will be eligible for this study. All patients will receive Yttrium-90 in combination with high-dose BEAM followed by ASCT. Yttrium-90 will be given at a fixed dose of 0.4 mCi/kg and there will not be any dose escalation.

All patients will have peripheral blood stem cells collected with the target CD34+ of  $5.0 \times 10^6$ /kg. The mobilization regimen for stem cell collection will be at the discretion of the treating physician. Patients will undergo pre-therapy imaging studies on day -21 and therapy on day -14. BCNU will be given on day -7 and -6; cytarabine and VP-16 (etoposide) will be given between day -5 to day -2 and Melphalan on day -1. PBSC will be infused on day 0.

## 4.0 DRUG FORMULATION

### 4.1 Rituximab (Rituxan®)

#### a. *Drug Formulation and Procurement*

Rituxan is commercially available and jointly marketed by Biogen IDEC, Inc. and Genentech USA, Inc. Rituxan is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials. Single unit 100 mg carton contains one 10 mL vial of Rituxan (10 mg/mL). NDC 50242-051-21. Single unit 500 mg carton contains one 50 mL vial of Rituxan (10 mg/mL). NDC 50242-053-06.

#### b. *Drug Toxicity (See Rituxan package insert for more information [www.rituxan.com](http://www.rituxan.com))*

##### Warnings:

*Fatal Infusion Reactions:* Deaths within 24 hours of Rituxan infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Patients who develop severe infusion reactions should have Rituxan infusion discontinued and receive medical treatment.

*Tumor Lysis Syndrome (TLS):* Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with Rituxan.

*Severe Mucocutaneous Reactions:* Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with Rituxan treatment.

*Progressive Multifocal Leukoencephalopathy (PML):* JC virus infection resulting in PML and death has been reported in patients treated with Rituxan.

Infusion Reactions: Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first Rituxan infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). The incidence of infusion reactions was highest during the first infusion and decreased with each subsequent infusion.

Infectious Events: Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 — 588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

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

**Pulmonary Events:** 135 patients (38%) experienced pulmonary events in clinical trials. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical studies and post-marketing surveillance, there have been a limited number of reports of bronchiolitis obliterans presenting up to 6 months post-Rituxan infusion and a limited number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3 months post-Rituxan infusion, some of which resulted in fatal outcomes. The safety of resumption or continued administration of Rituxan in patients with pneumonitis or bronchiolitis obliterans is unknown.

**Immunogenicity:** The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading. In clinical studies of patients with low-grade or follicular NHL receiving single-agent Rituxan, human antichimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients and 3 had an objective clinical response. These data reflect the percentage of patients whose test results were considered positive for antibodies to Rituxan using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL).

*c. Drug Storage, Reconstitution and Stability*

Rituxan vials are stored in the refrigerator at 2-8°C (36-46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake. Refer to the “Preparation for Administration” section of the Rituxan package insert ([www.rituxan.com](http://www.rituxan.com)) for information on the stability and storage of solutions of Rituxan diluted for infusion.

## **4.2 Ibritumomab Tiuxetan (Zevalin®)**

*a. Drug Formulation and Procurement*

Zevalin is commercially available from Spectrum Pharmaceuticals. Each of the two Zevalin kits contains four vials that are used to produce a single dose of either In-111 Zevalin or Y-90 Zevalin, as indicated on the outer container label:

1. One (1) Zevalin vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.
2. One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present.
3. One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 28 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.
4. One (1) empty Reaction Vial, sterile, pyrogen-free.

*b. Drug Toxicity (See Zevalin package insert for more information [www.zevalin.com](http://www.zevalin.com))*

**Warnings:**

**Fatal Infusion Reactions:** Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the Zevalin® therapeutic regimen. These fatalities were associated with

an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion. Patients who develop severe infusion reactions should have Rituximab, In-111 Zevalin, and Y-90 Zevalin infusions discontinued and receive medical treatment.

*Prolonged and Severe Cytopenias:* Y-90 Zevalin administration results in severe and prolonged cytopenias in most patients. The Zevalin therapeutic regimen should not be administered to patients with  $\geq 25\%$  lymphoma marrow involvement and/or impaired bone marrow reserve.

*Severe Cutaneous and Mucocutaneous Reactions:* Severe cutaneous and mucocutaneous reactions, some with fatal outcome, have been reported in association with the Zevalin therapeutic regimen. Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further component of the Zevalin therapeutic regimen and should seek prompt medical evaluation.

The most serious adverse reactions caused by the Zevalin therapeutic regimen include prolonged and severe cytopenias, infections (predominantly bacterial in origin), hemorrhage while thrombocytopenic (resulting in deaths), and allergic reactions (bronchospasm and angioedema). In addition, patients who have received the Zevalin therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of Rituximab. In postmarketing reports, cutaneous and mucocutaneous reactions have been associated with the Zevalin therapeutic regimen. Please refer to the BOXED WARNINGS and WARNINGS sections of the package insert for detailed descriptions of these reactions. 17 of 40 Isolated reports of extravasation with subsequent infusion site reaction, like dermatitis, desquamation and site ulcer have been received. In addition, isolated post-marketing reports have been received showing that Zevalin-associated radiation might cause damage to lymphoma-surrounding tissue and complications due to lymphoma swelling (see PRECAUTIONS in the package insert). The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity.

*c. Drug Storage, Reconstitution and Stability*

Store at 2-8°C (36-46°F). Do not freeze. The radiolabeled solutions should be used within 6 hrs and should be held at 2-8°C until administered.

**4.3 Etoposide (Vepesid<sup>®</sup>, VP-16) (epipodophyllotoxin, etoposide, 4'-demethyl-9(4,6-o-β) d-ethylidene-glycopyranoside).**

*a. Drug Formulation and Procurement*

Etoposide is commercially available from various manufacturers, 100 mg/5 ml solution in 100 mg, 500 mg vials.

*b. Drug Toxicity*

Myelosuppression, primarily granulocytopenia, is the dose-limiting toxicity. Gastrointestinal toxicity at high doses includes nausea, emesis and mucositis. Reversible hepatotoxicity may occur at very high doses. The acute side effects of occasional bronchospasm and hypotension are avoided by slow intravenous administration.

*c. Drug Storage, Reconstitution and Stability*

The contents of the ampule are diluted with 50 volumes of NaCl solution for injection, USP, and administered by slow intravenous infusion. Patients will receive the drug through a central venous catheter at a rate of 100 mg/m<sup>2</sup>/1 hour.

**4.4 Carmustine (BiCNU<sup>®</sup>) (1, 3-bis-(2-chloroethyl) 1- nitrosourea) (NSC-409962)**

a. *Description*

BCNU is a lipid soluble agent, which has alkylating properties plus an isocyanate metabolite, which interferes with DNA and RNA synthesis.

b. *Toxicology*

*Human toxicities:* The major toxicity of BCNU at this dose is myelosuppression. Transient abnormal liver function tests occur infrequently but are self-limited. Fatal hepatic necrosis has been described with much higher doses (1200 mg/m<sup>2</sup>) and in patients with accumulated dosage. Renal toxicity has been described with chronic administration of BCNU. As with pulmonary toxicity, the dose per course and schedule of drugs may be important co-variables along with the total accumulated dose. Rarely, seizures and obtundation have been reported in patients with brain tumors treated with BCNU, but this was presumed to be due to tumor rather than drug toxicity.

c. *Pharmacology*

*Kinetics:* IV BCNU is rapidly degraded to active metabolites. 60% to 70% is excreted in the urine in 96 hours and 10% as respiratory CO<sub>2</sub>. Because of the high lipid solubility, it crosses the blood-brain barrier readily.

*Formulation:* BCNU is an alkylating agent which is supplied by Bristol Laboratories as a lyophilized powder (100 mg vial) containing no preservatives. Due to its water insolubility, it is to be reconstituted with the diluent provided (3-ml absolute ethanol) followed by 27-ml sterile water to a final concentration of 3.3 mg/ml in 10% ethanol.

*Storage and Stability:* Stability upon reconstitution (less than 8% potency is lost) is 8 hours at room temperature or 40 hours if refrigerated and protected from light when stored in the original amber vial. BCNU solution may be further diluted to a concentration of 0.2 mg/ml with 5% dextrose or 0.9% sodium chloride injection, USP, and will be stable for 48 hours if refrigerated and an additional 8 hours at room temperature under normal room fluorescent light. BCNU has a low melting point requiring refrigeration at all times prior to reconstitution. Do not use if an oil film is present at the bottom of vial.

*Administration:* BCNU should be administered by IV drip over 1 to 2 hours. Unpublished data suggest decreased availability when administered in plastic infusion containers.

*Supplier:* BCNU is commercially available and should be purchased by a third party.

#### 4.5 **Melphalan (L-phenylalanine mustard, L-PAM, Alkeran)**

a. *Drug Formulation and Procurement*

In common with other nitrogen mustards, melphalan reacts with DNA to produce either DNA-DNA or DNA-protein cross-linked products, probably by binding at the N-7 position of guanine. Melphalan is commercially available by Burroughs Wellcome Company.

b. *Drug toxicity*

The dose-limiting toxicity of melphalan is myelosuppression. Other toxicities after IV melphalan include mucositis, nausea, vomiting and diarrhea. Alopecia is generally seen only with high doses associated with bone marrow transplant settings. Rarely reported reactions include pulmonary fibrosis, skin rash, vasculitis, and allergic reactions. With high dose chemotherapy, gastrointestinal toxicity becomes dose limiting. At such high doses, elevated transaminases, syndrome of inappropriate antidiuretic hormone secretion, depression, interstitial pneumonitis, and hepatic veno-occlusive disease have been reported. Acute nonlymphocytic leukemia and myeloproliferative syndromes may occur as secondary cancers from any alkylating agent such as melphalan. Amenorrhea, permanent in many cases, has been noted with melphalan used in premenopausal women undergoing adjuvant therapy for breast cancer. Azoospermia would be expected, but is not well documented in the literature.

c. *Drug Storage, Reconstitution and Stability:*

Melphalan is provided in sterile vials containing 50 mg lyophilized drug as the hydrochloride salt. It is formulated with 20 mg povidone per 50 mg vial. Sterile diluent is supplied, which contains per 10 ml: sodium citrate 0.20 g, propylene glycol 6 ml, ethanol (95%) 0.52 ml, sterile water q.s. 10 ml. Reconstitute each 50 ml vial by rapidly injecting 10ml diluent provided. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5mg/ml solution. Intact vials are stored at room temperature (15-30°C) protected from light. Once reconstituted with the diluent provided, the solution is chemically and physically stable at room temperature for 90 minutes. Melphalan, when reconstituted with the diluent provided and subsequently diluted in NS to a concentration of 0.1-0.45mg/ml is chemically and physically stable for 60 minutes at room temperature. Do not refrigerate. Reconstituted, undiluted melphalan has been administered via central line using doses of 70-200mg/m<sup>2</sup> over 2 to 20 minutes.

#### **4.6 Cytosine Arabinoside (Cytarabine, Ara-C, cytosar)**

##### *a. Drug Formulation and Procurement*

Deoxycytidine analogue, which is metabolized to Ara-CTP, a substance that inhibits DNA polymerase. It is S-phase-specific, and thus affects DNA synthesis. It has an initial half-life of about 15 minutes, with a secondary phase of about 2 hours. Rapidly catabolized by hepatic cytidine deaminases to Ara-U. Ara-C is commercially available.

##### *b. Drug Toxicity*

*Acute DLT – severe leukopenia and thrombocytopenia.* Nausea and vomiting may be dose limiting at higher doses. Other adverse reactions include immunosuppression, anorexia, stomatitis, mild oral ulceration, flu-like syndrome with fever and alopecia. Diarrhea, fever, somnolence, conjunctivitis, ataxia, encephalopathy, or veno-occlusive disease can also develop. Chronic administration may cause mild gonadal dysfunction.

##### *c. Drug Storage, Reconstitution and Stability*

A freeze-dried powder available in 100 mg and 500 mg vials with diluent, which contains 0.9% benzyl alcohol in water. The unreconstituted form of the drug is stable at room temperature for at least two years. Reconstitute with 5 ml of diluent to 100-mg vial and 10 ml to the 500-mg vial. Also available in 1g and 2g vials without diluent. Reconstitute with 10 ml and 20-ml sterile water or bacteriostatic water. The reconstituted solution is stable at room temperature for 48 hours. Commercially available from various manufacturers in 100 mg, 1 g and 2 g vials.

#### **5.0 STAGING CRITERIA**

The Ann Arbor staging criteria will be used. Stage is determined based on extent of disease at the time of diagnosis.

**Ann Arbor Classification (AJCC Manual for Staging of Cancer, 6th ed. 2002)**

STAGE I	Involvement of a single lymph node region (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE).
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIE,S).
STAGE IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). The location of Stage IV disease is identified further by specifying the site according to the notations listed below.

A = Asymptomatic

B = Fever, sweats, weight loss > 10% of body weight

S=spleen; L=pulmonary (lung); M=bone marrow; H=hepatic; Pcard=pericardium; P=pleura; W=waldeyer's (tonsil, naso-oropharynx); O=osseous (bone); GI=gastrointestinal; D=skin; Softis=soft tissue; Thy=thyroid

## 5.1 Definitions of Disease Sensitivity

Patients are grouped into one of three groups based on sensitivity of disease:

1. Induction failure: patients who did not achieve a CR or PR from induction chemotherapy;
2. Resistant Relapse: patients who did not achieve a CR or PR from the most recent standard salvage chemotherapy;
3. Sensitive Relapse: patients who did achieve a CR or PR from the most recent standard salvage chemotherapy.

## 5.2 Poor Risk Disease Criteria

Patients are classified as having poor risk disease if they meet one or more of the following criteria

1. Age-adjusted international prognostic index (IPI) High (3 risk factors) or High-Intermediate (2 risk factors) based on the following risk factors: stage III-IV, elevated serum lactate dehydrogenase level (LDH) and ECOG performance status 2-4.
2. Patients with follicular lymphoma (grade 1-3) or diffuse large B-cell lymphoma who fail to achieve a complete remission after adequate induction chemotherapy regimen(s).
3. Patients with mantle cell lymphoma histology will be considered poor risk. This will include patients in first complete remission.
4. Patients with transformed lymphoma including those in first remission will be considered poor risk.

## 6.0 INCLUSION CRITERIA

**6.1** Age  $\geq$  18

**6.2** All patients must have biopsy proven diagnosis of low- and intermediate-grade NHL working formulation B, C, D, E, F, and G; including mantle cell lymphoma. Patients with transformed lymphoma are also eligible.

**6.3** Demonstrated monoclonal CD20 positive B-cell population in lymph nodes and/or bone marrow

**6.4** Patients must have relapsed after achieving a complete or partial response to prior therapy, have never responded to prior therapy or have poor risk disease (see definition, section 5.2)

**6.5** Patients with prior bone marrow involvement must have bone marrow aspiration and biopsy within 60 days prior to stem cell collection which shows  $\leq$ 10% lymphomatous involvement of total cellularity. Alternatively, patients with prior bone marrow involvement should have a normal bone marrow study

which shows  $\leq 10\%$  lymphomatous involvement within 28 days before salvage chemotherapy.

- 6.6 Normal renal function test with serum creatinine of  $< \text{ULN}$ , and a creatinine clearance of  $\geq 60$  ml/min (measured or calculated)
- 6.7 Adequate pulmonary function as measured by FEV1  $> 60\%$  of predicted measured, or a DLCO  $\geq 50\%$  of predicted measured
- 6.8 Cardiac ejection fraction of  $> 50\%$  by echocardiogram or MUGA scan. The LVEF from the prestudy ECHO or MUGA may be used for eligibility purposes, even if the prestudy stress test indicates a lower LVEF.
- 6.9 Adequate liver function tests with a bilirubin of  $\leq 1.5 \times \text{ULN}$  and SGOT or SGPT  $\leq 2 \times \text{ULN}$
- 6.10 Negative human immunodeficiency virus antibody
- 6.11 ECOG performance status = 0 or 1; KPS  $\geq 80$
- 6.12 No active CNS disease or prior history of CNS disease
- 6.13 Patients must have recovered from last therapy and should be at least four weeks from systemic chemotherapy on the day of administration of Y2B8.
- 6.14 After the last systemic *therapeutic* chemotherapy (Cytoxan, administered only for stem cell mobilization is not considered therapeutic) and prior to initiation of high dose treatment, the patient should have a baseline CT scan and PET scan done. An FDG/CT scan is sufficient (however, if clinically indicated, an additional diagnostic CT may be ordered). EXCEPTION: If scans were done and were negative for disease just prior to priming chemotherapy (therapeutic or nontherapeutic) and subsequent stem cell harvest, they do not need to be repeated prior to initiation of high dose treatment.

## 7.0 EXCLUSION CRITERIA

- 7.1 Presence of human anti-Zevalin antibody (HAZA).
- 7.2 Prior radioimmunotherapy
- 7.3 Failure to collect adequate number of CD34+ cells  $\geq 3 \times 10^6$  /kg
- 7.4 Abnormal cytogenetic study not related to the underlying lymphoma on the bone marrow aspirate sample prior to stem cell collection. If cytogenetics were not performed on the marrow aspirate prior to stem cell collection, cytogenetics on the peripheral blood may be performed.
- 7.5 Prior bone marrow transplantation
- 7.6 Prior malignancy except for:
  - adequately treated basal cell or squamous cell skin cancer
  - adequately treated noninvasive carcinoma
  - other cancer from which the patient has been disease-free for at least five years.
- 7.7 Active evidence of Hepatitis B or C infection; Hepatitis B surface antigen positive
- 7.8 Patients who have had prior radiation to the lung will be excluded from the study, although mediastinal irradiation will be permitted if minimal lung is in the treatment volume.
- 7.9 Patients who have received  $> 500\text{cGy}$  radiation to the kidneys will be excluded from the study.
- 7.10 Patients who are pregnant or lactating.

## 8.0 TREATMENT PLAN

Prior to receiving the Yttrium-90 the patient will undergo a blood draw for Rituxan levels and a pre-therapy imaging study with IDEC-In2B8 to confirm favorable localization of isotope, one week prior to the administration of the therapeutic dose. This will consist of an infusion of 5 mCi IDEC-In2B8 following 250 mg/m<sup>2</sup> Rituxan on day -21 followed by whole body gamma camera images obtained at approximately 1-24 hours post infusion, approximately 48-72 hours post infusion and an optional third scan at approximately 90-120 hours post infusion. Exceptions to this time frame will be made if the optional scan falls on a weekend day or a holiday. Rituxan 250 mg/m<sup>2</sup> will be administered on day -21 if Rituxan levels are  $< 10$  ug/ml (refer to Table 1 below). Blood samples will be obtained at approximately 0, 2 and 4-6 hours, as well as 1, 2, 3-4, 5 and 6 day(s) post infusion of the antibody. These samples will be used for analysis of antibody clearance and bone marrow dose estimation. Blood samples may be waived at the discretion of the PI. Patients with unfavorable biodistribution, such as localization to the spleen or failure in renal clearance of the isotopes, will

be excluded from the study due to the concerns of increase in toxicity.

If the patient does not show unfavorable biodistribution, Rituxan levels will be drawn on day -15 or on day -16 (refer to Table 1 below). A non-myeloablative dose of Yttrium-90 will be administered on day -14. If the Rituxan levels are <10 ug/ml then patients will receive Rituxan 250 mg/m<sup>2</sup> prior to the Yttrium-90 (refer to Table 1 below). Blood samples will be obtained at approximately 0, 2 and 4-6 hours, as well as 1, 2, 3-4, 5 and 6 day(s) post infusion of the antibody. These samples will be used for analysis of antibody clearance and bone marrow dose estimation. Blood samples may be waived at the discretion of the PI. High dose BEAM will be given between day -7 and day -1 followed by re-infusion of autologous peripheral stem cells.

Table 1. Guide for administration of Day -21 and Day -14 Rituxan:

Day -23 or -22) Rituxan level*	Give Day -21 Rituxan?	Day -16 or -15 Rituxan level*	Give Day -14 Rituxan?
≥10 ug/ml	No	≥10 ug/ml	No
<10 ug/ml	Yes	<10 ug/ml	Yes

\*Note: On Monday holidays, the Rituxan level will be drawn the Friday before. If the level is ≥15 µg/ml, another sample on Monday does not need to be drawn (because the level will not have decreased to less than 10 ug/ml by Monday). Additionally, if the value is <10 µg/ml, another sample on Monday again does not need to be drawn (because the patient will be receiving Rituxan according to the table above). However, if the value is ≥10 µg/ml but <15 µg/ml, then a Rituxan level draw will be repeated on Monday.

### 8.1 Outline of the preparative regimen

Day -23 or -22	Blood draw for Rituxan levels* See note below Table 1 above
Day-21	Pre-therapy imaging with 5 mCi IDEC-In2B8 following 250 mg/m <sup>2</sup> Rituxan or no Rituxan (depending on day -23 or -22 Rituxan levels; refer to table guide above)
Day -16 or -15	Blood draw for Rituxan levels* See note below Table 1 above
Day-14	IDEC-Y2B8 0.4 mCi/Kg following 250 mg/m <sup>2</sup> Rituxan or no Rituxan (depending on day -16 or -15 Rituxan levels; refer to table guide above). Note: Max dose is 40 mCi.
Day-7	BCNU 150mg/m <sup>2</sup>
Day-6	BCNU 150mg/m <sup>2</sup>
Day-5 to -2	Etoposide 100mg/m <sup>2</sup> BID for 4 days Ara-C 100mg/m <sup>2</sup> BID for 4 days
Day-1	Possible Rituxan 250 mg/m <sup>2</sup> (refer to guide table below). Then Melphalan 140mg/m <sup>2</sup>
Day 0	Peripheral Stem Cell Reinfusion
Day+5	Start G-CSF 5mcg/kg
Day +8	Rituxan 250 mg/m <sup>2</sup> (this will be administered regardless of previous Rituxan doses)

Table 2. Guide for administration of Day -1 and Day +8 Rituxan:

Received Rituxan Day - 21?	Received Rituxan Day - 14?	Give Rituxan Day - 1?	Give Rituxan Day +8?
No	No	Yes	Yes
Yes	Yes	No	Yes
Yes	No	No	Yes
No	Yes	No	Yes

## 8.2 Pre-Transplant Therapy

### a. Autologous Stem Cell Collection and Cryopreservation

Patients will have a permanent indwelling central venous catheter inserted and peripheral blood stem cells (PBSCs) will be collected via leukapheresis as conducted according to current standard operating procedures. (The HCT Manual SOP for Stem Cell Mobilization can be found at [http://www.coh.org/hct%5Fsop/docs/B.003.02\\_Mobilization\\_of\\_Peripheral\\_Blood.pdf](http://www.coh.org/hct%5Fsop/docs/B.003.02_Mobilization_of_Peripheral_Blood.pdf) accessibility verified on 04.February.2008). PBSCs will be collected after mobilization by: 1) growth factors i.e. G-CSF 10 µg/kg/d or 2) chemotherapy with growth factors. A minimum of 3.0 x 10<sup>6</sup>/kg CD34+ should be collected.

### Radioimmunotherapy

**8.31** On day -23 or -22, blood will be drawn for Rituxan levels (refer to Table 1 above). Patients with Rituxan levels <10ug/ml will receive Rituxan 250 mg/m<sup>2</sup> prior to the IDEC-In2B8 infusion.

On day -21, 5mCi IDEC-In2B8 will be given following 250 mg/m<sup>2</sup> Rituxan or no Rituxan (depending on day -23 or -22 Rituxan level as noted above.)

- a. Prior to receiving the Yttrium-90 the patient will undergo a pre-therapy imaging study with IDEC-In2B8 to confirm favorable localization of isotope, one week prior to the administration of the therapeutic dose. The objective of the imaging study is to confirm the expected biodistribution as an additional safety measure. Patients with unfavorable distribution (altered biodistribution) will be excluded from the study due to the concerns of increase in toxicity. Altered biodistribution on imaging is rare, which includes 1) Diffuse uptake in normal lung, more intense than the cardiac blood pool on the first day image or more intense than the liver on the second or third day image; 2) Kidneys with greater intensity than the liver on the posterior view of the second or third day image; 3) Intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.
- b. Rituxan, 250 mg/m<sup>2</sup>, is to be administered by slow intravenous infusion having been diluted to 1-4 mg/ml in saline. Initial infusion should be through a dedicated line at a rate of 50 mg/hr, or 100 mg/hr if the patient has had prior Rituxan. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments (or 100 mg/hr increments if the patient has had prior Rituxan) every 30 minutes to a maximum rate of 400 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The infusion can be continued at one-half the previous rate when symptoms abate. The calculated dose will be based on actual body weight.
- c. IDEC-In2B8 Administration - 2 mg of IDEC-In2B8 (5.0 mCi of <sup>111</sup>In) will be administered for the pre-therapy imaging portion of the protocol. The imaging dose will be administered over 10 minutes by slow IV injection immediately following the infusion of Rituxan (if Rituxan is given). A 0.22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-In2B8 has been infused.
- d. As stated in 8.31.a, if the patient has unfavorable (altered) bio-distribution as documented by pre-therapy imaging study, he/she will be taken off-study.

- 8.32** On day -16 or -15, blood will be drawn for Rituxan levels (refer to Table 1 above). Patients with Rituxan levels <10ug/ml will receive Rituxan 250 mg/m<sup>2</sup> prior to the IDEC-Y2B8 infusion.

On day -14, Yttrium-90 0.4mCi/Kg will be given following 250 mg/m<sup>2</sup> Rituxan or no Rituxan (depending on day -16 or -15 Rituxan level as noted above.)

- a. Rituxan, 250 mg/m<sup>2</sup>, is to be administered by slow intravenous infusion having been diluted to 1-4 mg/ml in saline. Initial infusion should be through a dedicated line at a rate of 100 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 100 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The infusion can be continued at one-half the previous rate when symptoms abate. The calculated dose will be based on actual body weight.
- b. IDEC-Y2B8 Administration – IDEC-Y2B8 0.4 mCi/kg will be administered for the therapy portion of the protocol. A 0.22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-Y2B8 has been infused. The calculated dose will be based on actual body weight. Max dose: 40 mCi.

#### **8.4 Chemotherapy**

- a. BCNU will be administered intravenously at dose of 150 mg/m<sup>2</sup> on day-7 and 150 mg/m<sup>2</sup> on day-6, based on adjusted ideal body weight. BCNU will be diluted with normal saline or 5% dextrose/water and administered over 4 hours. Patients will be premedicated with a sedative and antiemetics at the discretion of the primary M.D. All patients will receive loading dose of 1 gm of Dilantin on day-8 and continue 400 mg/day for 3 days beyond the last BCNU dose as seizure prophylaxis.
- b. VP-16 is to be administered twice daily on days -5,-4,-3 and -2 (total of 8 doses). Each dose of VP-16 is 100mg/m<sup>2</sup> and is calculated on adjusted ideal body weight. VP-16 100 mg/m<sup>2</sup> can be diluted to 0.4 mg/ml and infused over 1 hour. The volume of undiluted dose is ~ 10 ml Premeds will be given as per City of Hope SOP. If necessary, diuretics may be given. The intravenous hydration should be continued before, during, and after the VP-16.
- c. Ara-C is to be administered twice daily on days -5,-4,-3 and -2 (total of 8 doses). Each dose of Ara-C is 100mg/m<sup>2</sup> and is calculated based on adjusted ideal body weight. Infuse each dose over 2 hours. Ara-C will be mixed in D5W or NA. The volume of undiluted dose is ~ 2 ml. Appropriate antiemetics and sedatives should be given before the infusion begins.
- d. Melphalan 140 mg/m<sup>2</sup> is to be administered on day -1. The dose is calculated according to adjusted ideal body weight. IV hydration will be continued with normal saline at a rate of 200cc/hour and KCL 15 meq/L for a total of at least 24 hours. Administer per COH standard practice.  
  
Prior to Melphalan administration on day -1, so that all patients will receive the same amount of Rituxan, Rituxan 250 mg/m<sup>2</sup> will be given for certain patients only: If the patient received Rituxan on both day -21 and day -14, or if the patient received Rituxan on one of those two days, Rituxan on day -1 will not be given.(refer to the guide table in Sec 8.1)
- e. Rituxan 250 mg/m<sup>2</sup> will be given to all patients on day +8, regardless of prior Rituxan levels and whether or not they received Rituxan on day -21 and/or day -14. (refer to the guide table in Sec 8.1).

#### **8.5 Peripheral Stem Cell Reinfusion**

PBSCs will be thawed and infused according to standard guideline at approximately 24 hours after completion of melphalan.

#### **8.6 Growth Factor Therapy**

All patients will receive rh-G-CSF, 5 mcg/kg/day IV beginning on day +5, after PBSC infusion and continue daily until discontinued as per treating MD discretion.

## **8.7 Supportive Care**

All patients will be housed in private rooms during the period of granulocytopenia.

### *a. Hyperalimentation*

All patients will receive appropriate hyperalimentation as soon as necessary after admission. This will be determined by the treating physician.

### *b. Platelet Transfusion*

1. Indication. Platelets are transfused to prevent bleeding and an attempt is made to keep the circulating level greater than 20,000/mm<sup>3</sup> at all times. This goal may be changed by the attending physician as clinically indicated.
2. Irradiation. All blood products (except the autologous stem cells) are irradiated with 1,500 cGy prior to infusion.

*c. Prophylaxis of Infections:* Trimethoprim-sulfamethoxazole or an alternate PCP prophylaxis will be administered from day -8 to day -2. Prophylaxis should be re-instituted when graft function is stable as determined by the treating physician. Prophylaxis should be continued for at least 6 months post transplant. Antifungal therapy should be initiated on day 0 or +1 and continued daily until granulocytopenia resolves. The choice of antifungal will be at the discretion of the treating physician.

### *d. Treatment of Infections*

Treatment of patients on this protocol is not intended to restrict the freedom of the managing physician to treat suspected or documented infections. In neutropenic patients, however, the following guidelines should be followed.

1. All febrile, neutropenic patients should be treated with IV antibiotic(s), the choice of which should be guided by the patient's clinical history, institutional practices and subsequent culture results.
2. Patients with documented, invasive fungal infection or with persistent, unexplained fevers while neutropenic and on broad-spectrum antibiotic therapy should receive appropriate antifungal therapy.

## **8.8 Criteria for Removal from Protocol Treatment**

**8.81** Patients may withdraw from study at any time for any reason.

**8.82** All reasons for discontinuation of treatment must be documented in the flow sheets.

**8.83** All patients will be followed for survival until death. For patients who relapse/progress, the date of relapse/progression will be recorded, but these patients will no longer follow the study calendar for required restaging.

## 9.0 STUDY CALENDAR - PREPARATIVE REGIMEN AND PBSCT

### Pre-study through Day 0

REQUIRED STUDIES	Pre-Study	Day -23 or -22	Day -21	Day -16 or -15	Day -14	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
PHYSICAL													
H&PE	X@												X
LABORATORY													
CBC/Platelets	X			X									X
HAZA	X												
LDH	X												
LFTs	X												X
PT (or PT INR) /PTT	X												
Immunoglobulin levels	X												
CMV Titer	X												
Hepatitis Profile	X												
Herpes Simplex	X												
HIV Antibody	X												
BMbx%	X												
Creatinine Clearance	X												
Rituxan Level		X		X									
Costim Assays		X <sup>2</sup>				X <sup>2</sup>							
X-RAYS & SCANS													
CT Scans*	X												
EKG	X												
MUGA or ECHO	X												
DLCO/FEV1	X												
FDG-PET Scan	X												
TREATMENT													
Stem cell Collections	X												
Rituxan			X <sup>1</sup>		X <sup>1</sup>							X <sup>1</sup>	
IDEC-In2B8			X										
IDEC-Y2B8					X								
BCNU						X	X						
VP-16 & Ara-C								X	X	X	X		
Melphalan												X	
PBSCT													X
G-CSF													

@ Include KPS pre-study.

\* CT scans of C/A/P (and neck, if clinically indicated). Note: FDG/CT is sufficient; an additional diagnostic CT may be ordered if clinically indicated.

% Bone marrow aspiration and biopsy, cytogenetic study and immunophenotyping

1. If indicated, depending on pre-Imaging dose and pre-Therapy dose Rituxan levels; refer to protocol for details

2. Draw two 6ml and two 4ml heparinized tubes (green tops) for an amount of whole blood of about 20ml and send to Virology Lab, Familian Science Bldg, Rm C209D (x63392). **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED.**

## Day 1 through day 100

REQUIRED STUDIES	Day 5	Day 7	Day 8	Day 21	Day 30	Day 60	Day 90	Day 100
<b>PHYSICAL</b>								
H&PE					X	X		X
<b>LABORATORY</b>								
CBC/Platelets		X			X	X		X
HAZA						X		X
LDH					X	X		X
LFTs					X	X		X
Immunoglobulin levels					X			X
Costim Assays				X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	
<b>X-RAYS &amp; SCANS</b>								
CT Scans*					X <sup>1</sup>			X <sup>5</sup>
EKG								
MUGA or ECHO								
DLCO/FEV1								
FDG-PET Scan					X <sup>⊕</sup>			
<b>TREATMENT</b>								
Rituxan			X					
G-CSF	X <sup>#</sup>							

⊕ Repeat FDG PET will be done at Day 30 if previously positive; however, if positivity is not due to lymphoma, it does not need to be repeated.

\* CT scans of C/A/P (and neck, if clinically indicated). Note: FDG/CT is sufficient; an additional diagnostic CT may be ordered if clinically indicated.

# Continue G-CSF daily until discontinued as per treating MD discretion.

1. Day 30 CT not required if pt in CR at time of transplant.

\$ Day 100 CT scans are only required if a scan was not done at day 30.

2. Draw two 6ml and two 4ml heparinized tubes (green tops) for an amount of whole blood of about 20ml and send to Virology Lab, Familian Science Bldg, Rm C209D (x63392). Costim assay on Day 21 may be drawn within +/- 7 days and the one on Day 90 may be drawn within +/- 14 days. **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED.**

## Day 101 through year 5

REQUIRED STUDIES	Day 180	YR 1		YR 2	YR 3	YR 4	YR 5
<b>PHYSICAL</b>							
H&PE	X	X		X <sup>\$</sup>	X	X	X
<b>LABORATORY</b>							
CBC/Platelets	X	X		X			
HAZA	X	X					
LDH	X	X		X			
LFTs	X	X		X			
Immunoglobulin levels	X	X					
BM <sup>%</sup>		X		X	X	X	X
<b>X-RAYS &amp; SCANS</b>							
CT Scans*	X	X		X			X
EKG		X					
MUGA or ECHO		X					
DLCO/FEV1		X					
FDG-PET Scan		X					

\$ All late complications such as cataract formation and occurrence of second malignancies must be documented and reported

\* CT scans of C/A/P (and neck, if clinically indicated). Note: FDG/CT is sufficient; an additional diagnostic CT may be ordered if clinically indicated.

% Bone marrow aspiration and biopsy, cytogenetic study and immunophenotyping. Note: for patients with no history of bone marrow involvement by lymphoma, the bone marrow asp/bx is optional.

For required followup tests, acceptable windows are: +/-14 dys for Days 30 & 60, +/- 30 dys for Days 100 & 180, and +/- 60 days for Yr 1 and beyond.

## 10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

### Definitions

- a. **Measurable Disease:** Bidimensionally measurable lesions with clearly defined margins by: 1) medical photograph (skin or oral lesion), or plain x-ray with at least one diameter 0.5 cm or greater (bone lesions are not included) or, 2) CT, MRI or other imaging scan with both diameters greater than the distance between cuts of the imaging study, or 3) palpation with both diameters 2 cm or greater.
- b. **Evaluable Disease:** Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.
- c. **Non-Evaluable Diseases:** Pleural effusions, ascites, disease documented by indirect evidence only (e.g., by lab values).
- d. **Objective Response, To Be Recorded at Each Evaluation:** If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL is measurable and evaluable sites and lesions are assessed.

### 10.1

Revised Response Criteria for Malignant Lymphoma Response Definitions for Clinical Trials (Cheson et al)				
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT.	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT and PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed Disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

From "Revised Response Criteria for Malignant Lymphoma", B.D. Cheson, et. al. J Clin Oncol 25:579-586, 2007

## 10.2 Duration of Response

Defined as time from beginning of response (CR or PR) to disease relapse, disease progression, or last disease evaluation if patient in continued CR, PR.

## 10.3 Time to Relapse/Progression

Defined as time from RIT based ASCT to date of first observation of progressive disease or relapsed disease.

## 10.4 Survival and Engraftment Endpoints

- a. Overall survival. Defined as the time from transplant to death due to any cause. If a patient is alive, survival time is censored at the time of last follow-up.
- b. Relapse-free survival. Defined as the time from transplant to the first observation of relapsed disease or death due to any cause, whichever occurs first. If the patient has not relapsed or died, relapse-free survival is censored at the time of last follow-up.
- c. Progression-free survival. Defined as the time from transplant to first observation of progressive disease or death due to any cause, whichever occurs first. If the patient has not progressed or died, event-free survival is censored at the time of last follow-up.
- d. Engraftment. Engraftment will be monitored by measuring the duration and extent of myelosuppression as shown in days until ANC recovery ( $500,1000 \times 10^3/\mu\text{L}$ ) and unmaintained platelet recovery (20K,100K $\mu\text{L}$ ). The primary engraftment endpoint is defined as the first of three consecutive days on which the ANC is  $\geq 500 \times 10^3/\mu\text{L}$ . Patients who are deceased prior to day 28 post-ASCT will be considered inevaluable for engraftment.

## 11.0 STATISTICAL CONSIDERATIONS

### 11.1 Study Design, Sample Size Justification

This is a phase II study to evaluate progression-free survival (PFS) among four poor risk non-Hodgkin lymphoma histologies: follicular lymphoma (grade 1-3), mantle cell lymphoma, diffuse large B-cell lymphoma and transformed lymphoma. All patients enrolled in this study will be treated with  $^{90}\text{Y}$ -labeled anti-CD20 MAb (Yttrium- 90) in combination with high-dose BEAM (BCNU, cytarabine, etoposide and melphalan) followed by Autologous Stem Cell Transplant (ASCT).

When treated with BEAM chemotherapy alone, previously reported studies show two-year PFS estimates for each poor-risk subgroup as follows:

<b>Non-Hodgkin lymphoma Poor Risk Subgroups</b>	<b>2-Year PFS Probabilities<sup>1</sup>, Chemotherapy (BEAM) alone</b>
Follicular (grade 1-3)	45%
Mantle cell	35%
Diffuse large B-Cell	45%
Transformed	35%

<sup>1</sup>: Approximate values

Using PFS estimates from previously reported BEAM (chemotherapy alone) studies and City of Hope Z-BEAM/ASCT pilot studies, a total of 36 (evaluable) patients are required per stratum; however, the Diffuse Large B-Cell stratum will instead contain an additional 10, for a total of 46 (evaluable) patients in that stratum. Target accrual is thus 118 patients as the follicular and transformed lymphoma will be grouped together. An increase in two-year progression-free survival from historical estimates of 35% and 45% to 55% and 65% would be detectable with 80% power, if continuous follow-up were possible on all 36 patients. We anticipate it could take approximately 81 months to complete accrual on this study.

### 11.2 Phase II Monitoring

Early stopping rules are incorporated to monitor toxicity, however there will be no interim analysis for efficacy. Toxicities will be recorded using two distinct grading systems; the modified Bearman Scale (Bearman, S., et al, JCO, Vol 6, No 10 (Oct), 1988, pp1562-1568. See appendix II for details) and the NCI CTCAE 3.0 Scale.

Generally, the modified Bearman Scale will be used to define (grade) 'early stopping' events (toxicities), and the NCI CTCAE 3.0 Scale will be used for reporting adverse events. The only exception relates to how hematologic toxicities are graded and incorporated into the early stopping criteria. For hematologic toxicities, the CTCAE 3.0 Scale will be used. (The NCI CTCAE 3.0 can be found at <http://ctep.cancer.gov/reporting/ctc.html> accessibility verified on 26.March.2007) The table below will be consulted as relevant toxicities are encountered, so there will be no accrual-based interim analysis point.

Early Stopping Criteria: For each adverse outcome, stop if the cumulative number of patients reaches or exceeds the following limits:

Table of Early Stopping Criteria					
# of patients treated	# of patients expired due to treatment related causes that would stop the study*	# of patients with grade 3 toxicities that would require an evaluation for safety per Bearman Scale**	Probability that the early stopping rule will be invoked given a failure rate of:		
			10%	15%	20%
6	2	2	0.12	0.22	0.35
12	3	3	0.16	0.34	0.51
18	5	5	0.17	0.35	0.53
24	6	6	0.17	0.36	0.57
30	8	8	0.17	0.37	0.58
36	9	9	0.18	0.38	0.60

\* Note: The stopping rules are not statistically based; expected treatment related mortality should not exceed 25%.

\*\* Note: For hematologic toxicities: Any grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days per CTCAE 3.0 toxicity criteria should be counted toward the early stopping rule.

Any patient who receives treatment will be evaluable for toxicity. Each patient will be assessed periodically according to the treatment schedule for the development of any toxicity. The toxicity rule for safety will be assessed as each patient reaches day +30 post transplantation and day +100 post transplantation. If more than the specified number of patients (noted in the table above) have significant treatment related toxicities, then the safety of the study will be evaluated.

### 11.3 Analysis of Clinical Endpoints

Toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTC and nadir or maximum values for the laboratory measure) and time of onset. For grade 4 neutropenia, duration will be recorded. In accordance with the primary study objectives, we will perform descriptive statistical analyses on these data after the study is complete. Costimulatory profile data will be used for subjects for whom these data are available. Response rates and duration of response will be estimated. Confidence intervals for the response rate will be established by calculating the exact 95% confidence limits for a binomial parameter. Additional analyses will be conducted to evaluate the post transplant toxicity/complication profile, and incidence of therapy induced myelodysplasia (MDS)/acute myeloid leukemia (AML).

Descriptive statistics will be used to characterize the expression of six costimulatory molecules (PD-1, CTLA-4, CD28, ICOS, OX40 and 4-1BB) pre- post- RIT based ASCT. Exploratory analyses will also be performed to assess the impact of these molecules on the NK and T cells of lymphoma patients pre- post-RIT based ASCT. **NOTE THAT, DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT BE INCLUDED IN THE COSTIMULATORY MOLECULE ANALYSIS.**

The product-limit method of Kaplan and Meier will be utilized to estimate time-to-event endpoints such as progression-free survival, overall survival, and time to relapse. We also may consider alternative survival distributions such as the accelerated failure models for poor-risk subgroups. We will consider univariate Cox models for the analysis of potential prognostic factors of time-to-event endpoints, including such factors as histologic grade, age at transplant, and disease stage as independent variables, first performing diagnostics to confirm the validity of the proportional hazards assumption. Descriptive comparisons with recent historical data from similar patient populations will be made to evaluate differences in progression-free survival, overall survival, relapse/progression rate, and toxicities.

## **12.0 REGISTRATION GUIDELINES**

Once signed, informed consent has been obtained and all evaluations have been performed, patients will be entered on study after review of patient eligibility criteria by the assigned Clinical Research Associate (CRA) from the City of Hope Clinical Trials Office (CTO). Patients may be screened for registration by calling (626) 256-HOPE (4673) ext. 62468.

Eligible patients will be identified by the nurse coordinator/CRA who will register the patient with the City of Hope Clinical Trials Office (CTO) between 9:00 A.M. and 5:00 P.M. pacific standard time, Monday through Friday.

## **13.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE**

### **13.1 Confidentiality of Records**

The original data collection forms will be stored in secure cabinets in the CTO. All radioimmunotherapy associated data will be kept in the Department of Radioimmunotherapy.

### **13.2 Patient Consent Form**

At the time of registration, signed and dated copies of the patient Informed Consent form with the Experimental Subject's Bill of Rights must be available (for patient, chart, and CTO.)

## **14.0 DATA MANAGEMENT**

The Department of Biomedical Informatics maintains a clinical research database at the City of Hope National Medical Center, which allows for the storage and retrieval of patient data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key-entry, and verification. All patients are assigned a de-identified research participant number to assure patient confidentiality. Any publications or presentations will refer to patient by research participant number, not name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room and are maintained by the CTO. Access is restricted to personnel authorized by the CTO.

## **15.0 ETHICAL AND REGULATORY CONSIDERATIONS**

This study is to be approved by the Institutional Review Board according to City of Hope ethical and regulatory guidelines. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to

current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or other authorized users such as the National Cancer Institute (NCI), under the guidelines established by the Federal Privacy Act.

## 16.0 DATA SAFETY MONITORING PLAN: RISK LEVEL 3

### 16.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the “Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope”, <http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx> because it is a Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

### 16.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMC annually. In addition to the annual report, any early evaluations for safety and/or treatment related mortality will also be reported as these assessments are made (per guidelines set in sections 11.2 and 11.3 of the protocol). This report (the PMT report) will include a summary of accrual, adverse events and treatment related mortality.

### 16.3 Definitions

**Adverse event (AE)** - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

**Attribution** - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMC or by the IRB during the process of review.

**Expected Adverse Event** - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event that results in any of the following outcomes:*

- Death
- Is life-threatening event (places the subject at immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization;

- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect
- Secondary Malignancy, or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**Unanticipated problem (UP)** – Any incident, experience or outcome that meets all three of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

**Unexpected Adverse Event [21 CFR 312.32 (a)]** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

## 16.4 Reporting of Unanticipated Problems and Adverse Events

**Unanticipated Problems:** Unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at <http://www.coh.org/hrpp/Pages/hrpp-policies.aspx>. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (<http://iris.coh.org>).

Serious Adverse Events - **All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at <http://www.coh.org/hrpp/Pages/hrpp-policies.aspx> and Table 1 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (<http://iris.coh.org>).**

**Adverse Events** - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious adverse event or are not unanticipated problems will be reported only at the time of protocol continuation reports (see Table 1 below).

All toxicities, according to the CTCAE version 3.0 and the Modified Bearman Toxicity Scale, will be collected from day -21 to day 100. After day 100, all grade 3 and above toxicities according to the CTCAE version 3.0 (the Bearman Scale will not be used beyond day 100) will be collected, unless the toxicity is due to salvage therapy given after a relapse or progression post transplant. Grade 4 hematologic toxicities will not be considered reportable events with the

exception of grade 4 neutropenia associated with fever or infection and lasting beyond 3 weeks, and grade 4 neutropenia lasting for more than 28 days. All SAEs will be reported until the patient expires or withdraws from the study, except in cases when the SAE is clearly due to salvage therapy given after a relapse or progression post transplant.

**Table 1: City of Hope Adverse Event Reporting Timelines for the IRB and DSMC**

<b>Required Reporting Timeframe to IRB of Record</b>		
<b>Attribution</b>	<b>UNEXPECTED</b>	<b>EXPECTED</b>
	<b>Death</b>	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	<b>Grades 3 and 4 AND meeting the definition of a UP</b>	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	<b>Grade 1 and 2 AND meeting the definition of a UP</b>	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

<b>Required Reporting Timeframe to DSMC</b>		
<b>Attribution</b>	<b>UNEXPECTED</b>	<b>EXPECTED</b>
	<b>Death while on active treatment or within 30 days of last day of treatment</b>	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	<b>Death after 30 days of last active treatment/therapy</b>	
Possibly, Probably, Definitely	5 calendar days	No reporting required*
Unlikely, Unrelated	No reporting required*	No reporting required*
	<b>Grades 3 and 4 AND meeting the definition of “serious”</b>	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	5 calendar days	5 calendar days
	<b>Grade 1 and 2 AND resulting in “hospitalization”</b>	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

\*Such events are not required to be reported to the DSMC. These events should be included with the SAE/AE summary provided in the IRB Annual Continuation reports.

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## **Appendix I**

### **Common Terminology Criteria for Adverse Events (CTCAE) version 3.0**

<http://ctep.cancer.gov/forms/CTCAEv3.pdf>

## Appendix II

### Modified Bearman Toxicity Scale

	<b>Grade I</b>	<b>Grade II</b>	<b>Grade III</b>
<b>Cardiac Toxicity</b>	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
<b>Bladder Toxicity</b>	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
<b>Renal Toxicity</b>	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
<b>Pulmonary Toxicity</b>	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO <sub>2</sub> (> 10% from baseline) but not requiring mechanical ventilation or > 50% O <sub>2</sub> on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
<b>Hepatic Toxicity</b>	Mild hepatic dysfunction with bilirubin $\geq$ 2.0 mg/dL and $\leq$ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascitis or image documented ascitis > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function
<b>CNS Toxicity</b>	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding

<b>Stomatitis</b>	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
<b>GI Toxicity</b>	Watery stools > 500 mL but < 2,000 mL every day not related to infection	Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

## **Appendix III**

### **Additional Assays to be Performed on Previously Collected Samples**

#### **I. Rituxan Level Assays for IRB 01176 and IRB 07163**

This Phase II study includes serum Rituxan level assays performed pre-treatment, however the earlier Phase I study (IRB #01176) did not include this assay. Moreover, those patients having received this same Zevalin-BEAM + aHSCT regimen (not on clinical trial) and participating in the retrospective chart review protocol (IRB #07163) also did not have Rituxan level assays done on their pre-treatment blood samples.

We will perform Rituxan level analyses retrospectively, on leftover serum aliquots from previously-collected blood samples, which were drawn and used for the pre-treatment HAZA assay (one per patient) for those patients participating in the prior, Phase I study (IRB #01176) as well as those patients participating in the retrospective chart review protocol (IRB #07163). The total number of samples assayed will be 63 (38 for #01176 and 25 for #07163).

The information obtained from having the Rituxan level data on these additional patients will allow better analysis of potential correlations regarding pre-treatment circulating Rituxan levels and meaningful study outcomes, such as disease response.

#### **II. Additional Immunohistochemistry Staining on Pathology Specimens**

For each of the participating study subjects having a histology of DLBCL (including transformed histology), additional IHC staining on all previously collected diagnostic pathology specimens (including bone marrow, lymph nodes, and other tissue) will be done, in order to identify high risk molecular features and correlate with outcomes post Zevalin-BEAM (radioimmunotherapy) conditioning + autologous hematopoietic stem cell transplantation.

The markers include but are not limited to: CD10, bcl6, MUM1, MIB1, MUC1, MDR, p53, cyclin D2, and Bcl2.

The information obtained from having this data will aid in study of the potential role of these molecular markers in predicting disease outcome in the cohort of patients with DLBCL (including transformed histology) treated with Zevalin-BEAM (RIT) conditioning prior to aHSCT.