A PHASE II STUDY OF R-CHOP AND IBRITUMOMAB TIUXETAN (ZEVALIN®) FOR ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA

Principal Investigator:	Paul A. Hamlin, M.D.*
Co Principle Investigator:	Andrew D. Zelenetz, M.D., Ph.D.*
Responsible Investigators:	Craig Moskowitz, M.D.* Neeta Pandit-Tasker, M.D.* Steven Horwitz, M.D.* Joseph Jurcic, M.D.* John Gerecitano, MD* Tarun Kewalramani, M.D.* Ariela Noy, M.D.* M. Lia Palomba, M.D.* Carol S. Portlock, M.D.* David Straus, M.D.*
Cardiology:	Nancy Roistacher, MD
Nuclear Medicine:	Steven Larson, M.D. Neeta Pandit-Tasker, M.D.*
Immunology Pharmacy:	Scott Freswick, Pharm.D.
Radiochemistry:	Ron Finn, Ph.D.
Hematopathology:	Daniel Filippa, M.D. Julie Feldstein, M.D.

MEMORIAL SLOAN-KETTERING CANCER CENTER
1275 York Avenue
New York, NY 10021

COLLABORATING INSTITUTIONS:
MD ANDERSON CANCER CENTER - University of Texas

Principle Investigator: Maria Alma Rodriguez, MD*
1515 Holcombe Boulevard, #68
Houston, TX, 77030
phone: 713.792.2860 *fax:* 713.794.5656
mrodriguez@notes.mdacc.tmc.edu

Responsible Investigators (Consenting individuals)

Luis Fayad, MD
Frederick Hagemeister, MD
Larry Kwak, MD, PhD
Peter McLaughlin, MD
Sattva Neelapu, MD
Barbara Pro, MD
Jorge Romaguera, MD
Felipe Samaniego, MD
Anas Younes, MD

DRUG MANUFACTURERS:

Biogen Idec, Inc.. Pharmaceuticals Corporation
3030 Callan Road
San Diego, CA 92121
Phone 858-431-8500
Fax 858-431-8887

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Fax 805 499 9472

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1.0 PROTOCOL SUMMARY

This is a multi-institutional, non-randomized, open-label, phase II study of 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by ^{90}Y-ibritumomab tiuxetan, a ^{90}Y-labeled anti-CD20 murine antibody, in patients 60 years or older with previously untreated high risk diffuse large B-cell lymphoma.

In part I of the study, patients will receive R-CHOP chemotherapy at standard doses every 21 days for a total of 6 cycles with pegfilgrastim (or G-CSF) and prophylactic Darbepoetin alfa support.

In part II of the study, patients will receive a loading dose of rituximab, 250 mg/m^2, over 3-5 hours on Day 0. This is followed by an imaging dose of ^{111}In ibritumomab tiuxetan. Two or three gamma camera images will be taken at 2-24 hours, 48-72 hours, and, if needed, 90-120 hours after injection of ^{111}In ibritumomab tiuxetan. On Day 7, a second loading dose of rituximab 250 mg/m^2 over 3-5 hours will be given, immediately followed by ^{90}Y-ibritumomab tiuxetan. Patients with baseline platelet counts ≥150,000 will receive a 0.4 mCi/kg dose, and patients with platelet counts of 100,000-149,000 will receive a 0.3 mCi/kg dose. The dose is given via slow IV push over 10 minutes.

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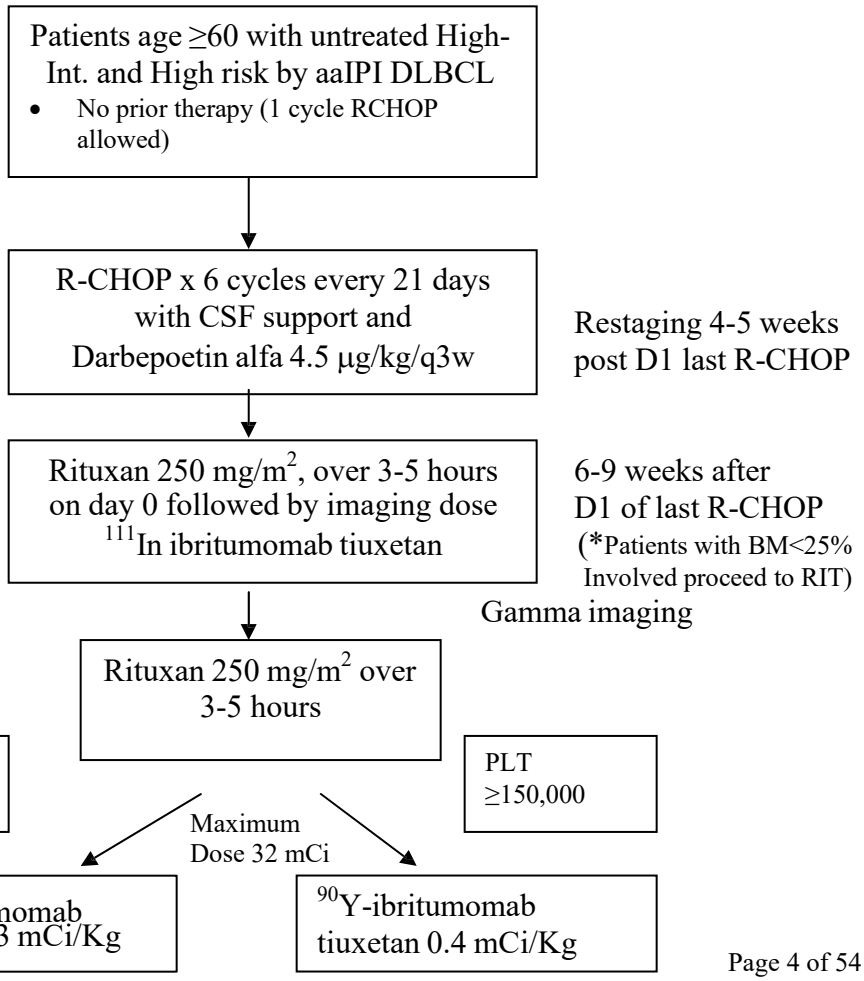


2.1 OBJECTIVES AND SCIENTIFIC AIMS

The primary efficacy endpoints for this study evaluating the sequential administration of 6 cycles of R-CHOP with pegfilgrastim (or G-CSF) and Prophylactic Darbepoetin alfa support followed by ^{90}Y-ibritumomab tiuxetan for patients 60 years of age or older with previously untreated high-intermediate or high risk by the age adjusted International prognostic index (aaIPI = 2 or 3, respectively) diffuse large B-cell lymphoma are to determine:

- progression free survival (PFS)
- overall survival (OS)

The primary safety endpoints are to determine:

- the incidence of adverse experiences
- hematologic toxicity (white blood cell, hemoglobin, and platelet nadir; transfusion requirements)
- cardiac toxicity – the incidence of LV dysfunction and cardiomyopathy as assessed by echocardiography

The secondary efficacy endpoints of the study are to determine:

- the predictive value of detecting minimal residual disease by molecular techniques for future relapse/recurrence
- the treatment response rate for R-CHOP
- Event free survival (EFS)
- The packed red blood cell transfusion requirements, change in hemoglobin (Hgb) from baseline, and incidence of anemia (CTC grading) with Prophylactic Darbepoetin alfa support. Hgb response and correction with darbepoetin alfa is defined as: an increase of ≥2.0 gm/dl from baseline and an Hgb ≥12.0 g/dl, respectively, in the absence of RBC transfusion in the preceding 21 days.
- A comparison of baseline FACT-An QOL scores with subsequent evaluations will be performed to correlate the impact of darbepoetin alfa on this QOL measure.
- The conversion rate to CR with ^{90}Y-ibritumomab tiuxetan for patients with a PR post R-CHOP
- the effects of sequential R-CHOP and ^{90}Y-ibritumomab tiuxetan on hematopoietic progenitor cells as determined by stem cell assays performed by Dr. Malcolm Moore's laboratory.

3.0 BACKGROUND AND RATIONALE

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a potentially curable subtype of non-Hodgkin's lymphoma (NHL) with an increasing frequency in elderly patients. In the International NHL Prognostic Factors Project, age was found to be an important adverse prognostic factor, affecting both relapse-free and overall survival. For elderly patients in that study, 5-year survival rates for low, low intermediate, high-intermediate, and high risk disease were 56%, 44%, 37%, and 21%, respectively (see table).[1] Other smaller, earlier studies have also confirmed the poor prognosis seen in elderly patients.[2-5] The reasons for the poor outcomes in elderly patients are unclear. DLBCL may be inherently more biologically aggressive in elderly patients than in younger patients. Co-morbid conditions in the elderly often complicate treatment, leading to poorer outcomes.[6] Increased treatment-related toxicities are seen in the elderly, and can be life-threatening (e.g., neutropenic sepsis) or can lead to dose reductions which result in lower dose intensity and a higher rate of treatment failure.[7,8]

Table 4 Age-Adjusted index, patients >60 (n=761)[1]

Risk	# of risk Factors	% of patients	CR Rate (%)	RFS (%) At 2 yrs.	RFS (%) At 5 yrs.	OS (%) @ 2yr	OS (%) @ 5yr
Low	0	18	91	75	46	80	56
Low-Int.	1	31	71	64	45	68	44
High-Int	2	35	56	60	41	48	37
High	3	16	36	47	37	31	21

Based on the Shipp data (1) for patients >60 years of age, CR rates range from 36-91% depending on the aaIPI group. For patients with High Intermediate and High Risk disease, only 56% and 36% respectively will attain a CR with CHOP therapy. Of these patients attaining a CR, between 59% and 63% will relapse by 5 years despite obtaining an initial CR. Attempts to improving this scenario have been the focus of many subsequent trials.

Supportive care advances with CHOP

Several efforts have been made at improving treatment outcomes in elderly patients with DLBCL. The use of hematopoietic growth factors with CHOP chemotherapy has shown promise in the management and prevention of febrile neutropenia. The NCCN recommends all patients aged 70 years or older and treated with CHOP chemotherapy receive prophylactic pegfilgrastim or G-CSF support. In a retrospective series of 50 consecutive elderly patients with DLBCL treated with CHOP and G-CSF, Donnelly et al reported a high dose intensity and response, with overall survival rates comparable to the cohort of patients under the age of 60 used to established the age-adjusted International Prognostic Index (IPI).[9] Improved response rates and dose-intensity were also reported in a recent prospective cohort of 20 elderly patients.[10]

Less information is available on the impact of anemia following chemotherapy. Traditional cutoffs for transfusion have included hemoglobin (Hgb) <8g/dl in the absence of coronary artery disease and <10g/dl in the presence of coronary artery disease to prevent myocardial ischemia. More recent evidence in non-hematologic malignancies suggests amelioration of cancer related fatigue and quality of life declines with maintenance of Hgb levels between 11-13 g/dl. [11]. The NCCN has recommended elderly patients receiving chemotherapy have Hgb maintained ≥12g/dl. Maintenance of functionality in the elderly population is paramount, with deterioration of ADLs leading to dependence, inability to receive additional therapy, and potentially requiring institutionalization.

Erythropoietin given weekly has been shown to significantly increase Hgb levels, decrease transfusion requirements, and improve functional status and fatigue. 14% and 19% of patients in the GELA study had grade 3 or 4 anemia with R-CHOP and CHOP therapy, respectively.[12] Although data for grade I and II anemia with CHOP are largely unreported, one study of 174 patients reported a 49% incidence of grade I/II anemia and 17% grade III **[13]**. The maintenance of adequate Hgb levels is desirable, but erythropoietin therapy necessitates weekly injections. Darbepoetin Alfa (Aranesp) is a biochemically distinct form of recombinant human erythropoietin, containing additional sialic acid residues that prolong the serum half-life. [14] Darbepoetin alfa has been demonstrated to have a dose dependent relationship and can feasibly be administered on a reduced frequency schedule with combination chemotherapy, still retaining efficacy benefits.[15]

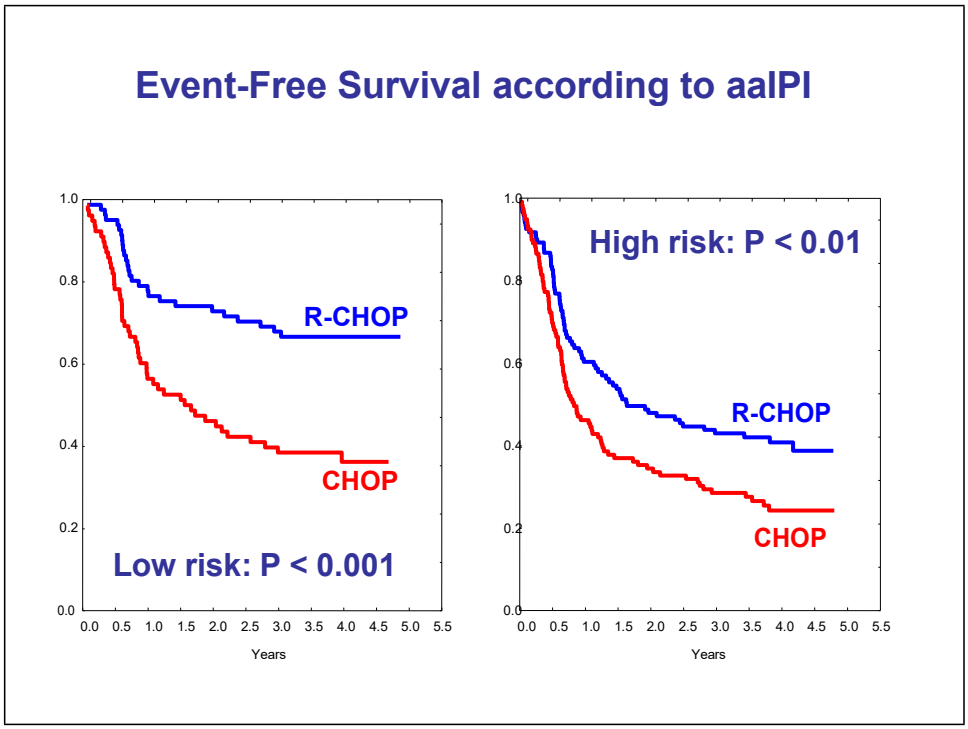
D. Kotasek et. Al. reported updated results of a randomized, double-blind, placebo controlled, phase I/II dose finding study of Aranesp administered once every three weeks in solid tumor patients. **[16]** 259 patients were randomized to receive either Aranesp (doses: 4.5-15 μg/kg/q3wk) or placebo. Results for the first four dosing cohorts were reported, demonstrating a 51% response rate at the 4.5 μg/kg/q3wk dose, with a mean change in hemoglobin of 0.6 gm/dl and a 52% response rate at the 6.75 μg/kg/q3wk dose, with a mean change in hemoglobin of 1.2 gm/dl. Increasing the dose to 9.0 and 12 μg/kg/q3k results in a dose response increase in the response rate and change in hemoglobin (61%/1.3 gm/dl and 71%/2.6gm/dl respectively). The ability to administer darbepoetin alfa in concert with R-CHOP would prove both cost effective regarding resource allocation and improve patients convenience by deceasing the number of hospital visits (from every week to every three weeks). Subsequently, Reardon et. Al. (ASH #3783, Blood 102(11), Nov 16,2003), p20B) reported on 112 patients effectively treated with 300 micrograms every 3 weeks. We plan to investigate the ability of Aranesp, delivered at a more convenient dosing schedule q3 weeks in conjunction with R-CHOP, to ameliorate the anemia associated with chemotherapy and radioimmunotherapy.

Rituximab monoclonal antibody therapy

Anti-CD20 monoclonal antibody therapy has been one of the most important advances in the management of B-cell lymphoid malignancies over the past few years. Rituximab, a chimeric anti-C20 antibody, exerts its anti-tumor effect by directly inducing apoptosis, by activating complement, and by antibody dependent cell-mediated cytotoxicity. It has been shown to produce objective responses in approximately 50% of patients with relapsed or refractory low-grade or follicular NHLs.[17] In patients with relapsed or refractory aggressive lymphomas (including DLBCL), Coiffier and colleagues found a response rate of 31% when an 8-week course of rituximab is used.[18]

Coiffier et al recently reported 24 month median follow-up of the GELA study which randomized 399 elderly patients with newly diagnosed DLBCL to receive either 8 cycles of CHOP or CHOP with rituximab (R-CHOP). Sixty percent of the patients had age-adjusted international prognostic index (aaIPI) high-intermediate or high-risk disease. The complete response rates in the R-CHOP cohort were significantly higher (76% vs. 63%), and at a median followup of 18 months the event-free survival (62% vs. 43%) and overall survival (73% vs. 61%) was also significantly improved, with statistical significance continuing at 24 months [12,19].

The GELA data was updated at ASH 2003 and continues to hold true with 4 years median followup (Figure below). Event free survival for high-risk patients by IPI is roughly 45% at 48 months. Consequently, the magnitude of rituximab's benefit appears to be less in the high-risk groups compared with the low risk groups.. These results are encouraging, and represent an important advance in the management of elderly patients with DLBCL. However, significant room for improvement remains.



(Coiffier, ASH 2003)

Toxicity of R-CHOP

The addition of Rituximab to CHOP chemotherapy was well tolerated and not associated with significant increases in toxicity. The grade 3 and 4 adverse events were consistent with expected toxic effects of CHOP, occurring with similar frequency. Hematologic toxicity was not associated with increased neutropenic infections (12% R-CHOP vs 20% CHOP) nor increased grade 3 or 4 anemia (14% R-CHOP vs 19% CHOP). [12]. Increased cardiac toxicity (47% for R-CHOP vs. 35% for CHOP) predominantly reflected increased grade 1 events related to rituximab infusion (24% RCHOP vs 13% CHOP) with an equivalent incidence of grade 3 and 4 events (8 %) in both groups.[12]

Anthracycline induced cardiomyopathy remains a rare but serious dose related consequence of therapy with doxorubicin. The risk of cardiomyopathy has been reported to be increased in patients > age 70, with hypertension, with coronary artery disease, and with combination chemotherapy. Elderly patients are likely to experience congestive heart failure at a lower cumulative dose.[20] Given the unknown cardiotoxicity of sequential R-CHOP and RIT, we will prospectively evaluate echocardiographic determinations of LV function.

Radioimmunotherapy

Radioimmunotherapy represents an emerging therapeutic modality that involves the conjugation of radionuclides to monoclonal antibodies in an attempt to enhance tumor cell kill and treatment outcomes. The monoclonal antibody maintains its anti-tumor efficacy and is augmented by the addition of a beam of gamma or beta radiation directed at tumor tissue adjacent to the target binding site. In the case of lymphoid malignancies, the radionuclides most commonly conjugated to anti-CD20 antibodies are iodine-131 (^{131}I) and yttrium-90 (^{90}Y). Limitations of I^{131} use include hypothyroidism and the inconvenience of gamma radiation, which necessitates isolation precautions for several days following its administration. Potential advantages of ^{90}Y include ease of administration since it is a pure beta emitter, which facilitates outpatient administration, and a longer path length of 5-10 mm, which results in improved cell kill in adjacent tumor tissue. While ^{90}Y provides therapeutic advantages, it cannot be used for imaging. The gamma emitter ^{111}In has been successfully used as an imaging agent prior to the ^{90}Y-labeled antibody. A dose of 5 mCi ^{111}In-labeled antibody is one that balances safety and imaging efficacy [21-24], allowing for the determination of expected biodistribution with the therapeutic dose.

Ibritumomab tiuxetan is a murine immunoglobulin G1 kappa monoclonal antibody (ibritumomab) covalently bound to MX-DTPA (tiuxetan) that chelates the radioisotope ^{90}Y. In a phase I/II trial involving patients with relapsed or refractory low-grade or transformed low-grade NHL, the maximum tolerated dose (MTD) was 0.4 mCi/kg (or 0.3 mCi/kg for patients with baseline platelet counts of 100,000-149,000). The overall response rate for the 51 patients treated at the MTD was 67% (26% CR, 41% PR). For patients who transformed to intermediate-grade disease (n=14), the overall response rate was 43%.[25] These results appear superior to immunotherapy alone when used in a similar patient population. The final results of a phase III study were presented at the ASH 2000 meeting which randomized 143 patients with relapsed or refractory low-grade or transformed low grade NHL to receive rituximab or ^{90}Y- ibritumomab tiuxetan. The overall response rate was 80% in the radioimmunotherapy arm vs. 56% in the rituximab arm (p=0.002), and the CR rate was significantly improved (30% vs. 16%, p=0.04). Response durations did not significantly differ between the two arms.[26]

The effect of radioimmunotherapy on stem cell precursors is currently not known. Preliminary reports from the Mayo Clinic have demonstrated the feasibility of administering additional chemotherapy for relapse post Zevalin, as well as reporting 5/6 successful peripheral blood stem cell mobilizations following Zevalin (all patients regaining adequate counts post ASCT).[27] We plan to evaluate stem cell progenitor assays before and after radioimmunotherapy in this group of transplant ineligible patients (see Appendix D).

Hypothesis

The number of elderly patients and the incidence of NHL in this population continue to increase annually. Elderly patients (age >60) have a poorer prognosis with standard

CHOP chemotherapy compared with younger patients and historically have been under-represented in clinical trials. The data from the GELA demonstrate that the addition of immunotherapy (rituximab) to CHOP may improve outcomes in elderly patients with DLBCL. Supportive care measures such as G-CSF and Prophylactic Darbepoetin help to maintain dose intensity and minimize toxicity. Elderly patients age >65 and many aged 60-65 are not candidates for potentially curative second-line transplant regimens should they have relapsed or refractory disease. Therefore, it is paramount that new regimens be designed to improve upon the quality and durability of the upfront treatment. Preliminary data show superior response rates with radioimmunotherapy over standard immunotherapy when used alone in low-grade and transformed NHL, raising the possibility that combinations with chemotherapy could improve results.

In follicular lymphoma, where BCL-2 represents a useful marker to assess for minimal residual disease, patients with PCR positive CRs (molecular residual disease) who are were treated with rituximab following CHOP and subsequently achieved PCR negativity had superior freedom from recurrence compared with those patients never achieving PCR negativity (57% vs 20%; $p<0.001$). [28] This lends credence to the premise that relapses result from residual but clinically undetectable disease. In a similar vein, the presence of minimal residual disease in intermediate and high grade lymphoma patients following ASCT, as detected by PCR IgH gene rearrangements, was associated with relapse in 6/6 cases, while 13/13 PCR negative patients remained in CR [29] We plan to prospectively evaluate the prognostic significance of minimally residual disease present after R-CHOP and RIT (See Appendix C) and to give additional therapy in the form of RIT to in hopes of targeting minimal residual disease and improving durable remissions.

Consequently, we hypothesize that the addition of targeted consolidative radioimmunotherapy following R-CHOP treatment may decrease future relapses and improve survival. We propose a phase II study evaluating the feasibility, efficacy, and safety of a sequential program of R-CHOP with pegfilgrastim or G-CSF and Prophylactic Darbepoetin alfa support followed by consolidation with ^{90}Y-ibritumomab tiuxetan. We will prospectively evaluate for molecular evidence of minimally residual disease, correlating this data with future outcome, and assess the impact of this regimen on bone marrow progenitor cells. The safety of RIT following R-CHOP will also be investigated.

4.0 STUDY DESIGN

This is a multi-institution, non-randomized, open-label, phase II study of 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by ^{90}Y-ibritumomab tiuxetan, a ^{90}Y-labeled anti-CD20 murine antibody, in patients 60 years or older with high risk (aaIPI 2 or 3), previously untreated diffuse large B-cell lymphoma.

In part I of the study, patients will receive R-CHOP chemotherapy at standard doses every 21 days for a total of 6 cycles with G-CSF growth factor support. In addition,

prophylactic Darbepoetin alfa will be administered every 3 weeks throughout the duration of this study. After the 4th and 6th cycles, patients will be assessed for treatment response. Intrathecal chemotherapy prophylaxis will be given for patients deemed at risk. Bone marrow examinations will also be performed to assess for minimal residual disease (See Appendix C) and hematopoietic progenitor cell assays (See Appendix D). Patients with a confirmed or unconfirmed complete response and patients with a partial response (who continue to be ineligible for autologous stem cell transplantation) will proceed to the radioimmunotherapy (RIT) part (part II) of the study. Pre-RIT, patients will be re- staged and must have a bone marrow biopsy with <25% involvement by lymphoma, adequate cellularity, and preserved cardiac function. Earlier work has shown that rituximab levels are not immediately cleared from tumor binding sites. [30]. Consequently, ^{90}Y-ibritumomab tiuxetan therapy will be delayed 6-9 weeks after completion of R-CHOP in order to expose more CD20 binding sites. Rituximab and B-cell levels will be measured following R-CHOP and prior to RIT.

In part II of the study, 6-9 weeks (42-63 days) after D1 of the last R-CHOP cycle, patients will receive a loading dose of rituximab, 250 mg/m^2, over 3-5 hours on Day 0. This is followed immediately by a 10 minute IV push infusion of 1.6 mg of ^{111}In ibritumomab tiuxetan (containing 5 mCi of ^{111}In). Imaging will be obtained 2-24 hours following ^{111}In ibritumomab tiuxetan infusion. Whole body anterior and posterior images will be acquired. Imaging will be repeated at 48-72 hours. The ^{111}In imaging will be done to ensure expected biodistribution, rather than tumor dosimetry. Additionally, since this study is evaluating the role of ^{90}Y-ibritumomab tiuxetan following chemotherapy in patients who may be in clinical remission, tumor uptake is not required for patient eligibility for ^{90}Y-ibritumomab tiuxetan administration. On Day 7, a second loading dose of rituximab 250 mg/m^2 over 3-5 hours will be given, immediately followed by ^{90}Y-ibritumomab tiuxetan. Patients with baseline platelet counts ≥150,000 will receive a 0.4 mCi/kg dose, and patients with platelet counts of 100,000-149,999 will receive a 0.3 mCi/kg dose. The dose is given via slow IV push over 10 minutes.

Patients will be followed weekly during RIT. The nadir with ^{90}Y ibritumomab tiuxetan is expected starting week 6-8. Patients will then be assessed for treatment response at week 12-13. Bone marrow examinations to assess for minimal residual disease and hematopoietic progenitor cell assays will be repeated.

FACT-anemia quality of life (QOL) evaluations will be performed at baseline, at Part I restaging (between cycles 4&5), post/chemotherapy/pre-RIT restaging, and following RIT (week 12-13). Correlation of FACT-anemia scores with hematologic parameters and impact of RIT will be assessed.

The primary efficacy endpoints for this study are to determine the progression free survival (PFS) and overall survival (OS) of the sequential administration of 6 cycles of R-CHOP with pegfilgrastim (or G-CSF) and Prophylactic Darbepoetin alfa support followed by ^{90}Y-ibritumomab tiuxetan for patients 60 years of age or older with previously untreated diffuse large B-cell lymphoma.

The secondary efficacy endpoints of the study are to determine the predictive value of detecting minimal residual disease by molecular techniques for future relapse/recurrence, the treatment response rate for R-CHOP, the packed red blood cell transfusion requirements, incidence of anemia, and change in hemoglobin (Hgb) from baseline with Prophylactic Darbepoetin alfa support, impact of anemia and darbepoetin alfa use on QOL measures, impact of RIT on QOL measures, cardiotoxicity as assessed by echocardiography, the conversion rate to CR with ^{90}Y-ibritumomab tiuxetan for patients with a PR post R-CHOP, the effects of sequential R-CHOP and ^{90}Y-ibritumomab tiuxetan on hematopoietic progenitor cells.

The safety endpoints are to determine the incidence of adverse experiences, hematologic toxicity (e.g., white blood cell, hemoglobin, and platelet nadir) anduse of supportive care.

5.0 THERAPEUTIC AGENTS

5.1 Cyclophosphamide

5.1.1 Description, Pharmacology, Storage and Preparation

Cyclophosphamide, a nitrogen mustard derivative, is a polyfunctional agent. The drug is a monohydrate, white crystalline powder and is soluble in water and in alcohol. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. It is eliminated primarily in the form of metabolites; however, 5-25% of the dose is excreted in urine as unchanged drug. The elimination half-life after oral administration is 3-12 hours. The preparation and storage of cyclophosphamide should follow the manufacturer's recommendations.

5.1.2 Toxicities

Toxicities from cyclophosphamide consist of nausea and vomiting, anorexia, diarrhea, abdominal discomfort, alopecia, skin rash, leukopenia, thrombocytopenia, anemia, hemorrhagic cystitis, interstitial pneumonitis, and urinary bladder fibrosis. Cyclophosphamide causes dose-limiting myelosuppression and hemorrhagic cystitis. Myelosuppression consists of leukopenia and thrombocytopenia. Leukopenia nadir and time of recovery usually occur at 8-14 days and 18-25 days, respectively. Development of hemorrhagic cystitis is dependent on the dose of cyclophosphamide and the duration for therapy. Prophylactic measures, including forced diuresis and hydration, have been shown to be effective in preventing bladder toxicity.

Secondary malignancies, mostly bladder carcinomas and acute leukemias, have been shown to be associated in patients treated with cyclophosphamide alone or in conjunction with other agents or modalities. Occurrence of secondary malignancies may occur several years after treatment.

Cyclophosphamide decreases serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine, especially in very ill patients receiving large intravenous doses of cyclophosphamide. If a patient is to receive anesthesia, the anesthesiologist should be notified if the patient has received cyclophosphamide within 10 days of the procedure.

Cyclophosphamide is a know teratogen and impairs oogenesis and spermatogenesis. Sterility may occur in both sexes and may be irreversible.

5.2 Doxorubicin

5.2.1 Description, Pharmacology, Storage and Preparation

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. It exerts its action by intercalating between base pairs of the DNA double helix and by inhibition of topoisomerase II, causing double strand DNA breaks. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Rapid plasma uptake occurs after slow biliary metabolism and excretion. The majority of the drug is protein bound and independent of plasma concentration. Doxorubicin has a terminal half-life of 20-48 hours. The preparation and storage of doxorubicin should follow the manufacturer's recommendations.

5.2.2 Toxicities

The dose-limiting toxicity of doxorubicin is irreversible cardiotoxicity. Signs and symptoms of cardiotoxicity are cardiac arrhythmias, decreased left ventricular ejection fraction, congestive heart failure, and cardiorespiratory decompensation such as dilatation of the heart, pleural effusion, and venous congestion. Doxorubicin administration should not exceed cumulative lifetime doses of 550 mg/m^2. Myelosuppression consisting of leukopenia is common, with a nadir of 10-14 days. Other adverse effects include nausea, mucositis, stomatitis, alopecia, extravasation, hyperpigmentation of nail beds, red-orange discoloration of urine, and erythematous streaking of veins.

There is inadequate information as to what effect doxorubicin has on fertility in males. Doxorubicin falls into U.S. Food and Drug Administration Pregnancy Category D

5.3 Vincristine

5.3.1 Description, Pharmacology, Storage and Preparation

Vincristine is a naturally occurring vinca alkaloid. Vincristine sulfate is the salt of a dimeric alkaloid from *Catharanthus roseus*, the common periwinkle plant. Vincristine sulfate is a white, off-white, or slightly yellow hygroscopic, amorphous, or crystalline powder that is freely soluble in water and slightly soluble in alcohol. It is reconstituted to a

concentration of 1 mg/mL. Vincristine exerts its effects by inhibiting mitosis, causing an arrest of cell division in the metaphase stage. Vincristine is metabolized in the liver by the hepatic cytochrome P450 in the CYP3A family. Vincristine has a triphasic pattern of elimination occurring at 5 minutes, 2.3 hours, and 85 hours. The terminal half-life of vincristine ranges between 19 and 155 hours. About 80% of the injected dose appears in the feces and 10-20% is found in the urine. The preparation and storage of vincristine should follow the manufacturer's recommendations.

5.3.2 Toxicities

Patients receiving vincristine commonly experience alopecia. One dose-limiting side effect is peripheral neurotoxicity, as manifested by neuritic pain, paresthesias, decrease in deep tendon reflexes, foot drop, jaw pain, back pain, constipation, and paralytic ileus. These symptoms may disappear with a reduction in dosage. Vestibular and auditory damage can also occur and are usually manifested as dizziness, nystagmus, or loss of hearing.

Vincristine may result in azoospermia in males. Vincristine is a U.S. Food and Drug Administration's Pregnancy Category D

5.4 Prednisone

5.4.1 Description and Pharmacology

Prednisone is a synthetic glucocorticoid. It is often used to enhance the effects of other cancer agents when used in combination. Given in pharmacologic doses, prednisone exerts anti-inflammatory and immunosuppressive effects on the blood and lymphatic system. At the cellular level, prednisone appears to halt DNA synthesis by mediating the inhibition of glucose transport or phosphorylation. In consequence, this causes a decrease in available intracellular energy and thereby impedes mitotic division. Prednisone is rapidly absorbed from the gastrointestinal tract when administered orally and has a short duration (3-4 hours) of pharmacologic effects. Animal studies demonstrate that it is rapidly distributed to muscles, liver, skin, intestine, and kidneys upon ingestion.

5.4.2 Toxicities

Prednisone exerts numerous effects on the body: euphoria, mood swings, fluid retention, adrenocortical insufficiency, muscle pain or weakness, muscle wasting, increased susceptibility to infections, hypokalemia, hypercortisolism, amenorrhea, glucose intolerance, hyperglycemia, nausea, vomiting, anorexia, increased appetite, weight gain, gastric ulceration, ulcerative esophagitis, insomnia, headache, restlessness, increased motor activity, impaired wound healing, osteopenia, osteoporosis, avascular necrosis, skin atrophy and thinning, acne, and increased sweating.

Patients must be instructed to use glucocorticoids cautiously if they have any infections, impending surgery, hypothyroidism, cirrhosis, mental instability, congestive heart failure, peptic ulcer disease, diverticulitis, nonspecific ulcerative colitis, recent intestinal anastomoses, seizures, osteoporosis, herpes simple infections of the eye, and thromboembolic disorders.

5.5. Neupogen® (Filgrastim, G-CSF) and Neulasta(TM) (pegFilgrastim or pegylated filgastrim)

5.5.1. Description and pharmacology- Neupogen:
NEUPOGEN® is a human protein, which is involved in the promotion of the growth and maturation of granulocytic progenitors and the stimulation of functional activity.
Formulation: Available as a recombinant DNA product supplied as 1 or 2 ml vials containing clear colorless sterile protein solution.
Storage: It can be stored at 2-6°C and is stable for at least 30 months.

5.5.2. Description and pharmacology- Neulasta:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim
Formulation: 6 MG/0.6 ML SOL. A single fixed dose of 6 milligrams (mg) subcutaneously, given once per chemotherapy cycle, is effective and is recommended.
Storage: The manufacturer recommends storage of Neulasta(TM) syringes at 2 to 8 degrees C (36 to 46 degrees F), avoidance of freezing or shaking, and leaving syringes in the carton provided until time of use to protect from light (Prod Info Neulasta(TM), 2002).

5.5.3. Toxicity:
Bone pain, exacerbation of preexisting autoimmune disorders, transient and reversible changes in alkaline phosphatase, uric acid and LDH.
Contraindications: Prior hypersensitivity to Escherichia coli-derived proteins, filgrastim, or pegfilgrastim

5.5.4. Supplier: Amgen, Inc.

5.6. Rituximab

For a complete description of rituximab, please refer to the Rituxan→ Package Insert in **Appendix A**.

A very rare side effect is an infection of the brain called progressive multifocal leukoencephalopathy (PML). It is almost always fatal

5.7. ^{90}Y and ^{111}I-Ibritumomab Tiuxetan

5.7.1. Origin of the IDEC-2B8/ibritumomab cell line

The murine anti-CD20 monoclonal antibody 2B8.H11.G2.G9 (ibritumomab tiuxetan) is an IgG_1 kappa antibody. The selection of the monoclonal antibody ibritumomab tiuxetan was based upon the observations that: ibritumomab tiuxetan specifically recognizes and binds to human B-cell lines and normal human peripheral blood lymphocytes in the same relative proportion as the highly characterized and commercially available anti-CD20 antibodies anti-Leu16 and B1; anti-Leu16 and B1 were effectively inhibited by approximately equal concentrations of ibritumomab tiuxetan ; Ibritumomab tiuxetan exhibited no cross-reactivity with T-lymphocyte populations.

The ibritumomab tiuxetan antibody was previously expressed by a murine hybridoma cell line and produced in hollow-fiber bioreactors. Currently, ibritumomab tiuxetan is produced in Chinese hamster ovary (CHO) cells in suspension culture. The CHO-expressed ibritumomab tiuxetan antibody differs from the murine hybridoma product in that one amino acid (at position 238 in the heavy chain) has been changed from a lysine to a methionine. The CHO master Cell Bank has been fully characterized and found to be negative for mycoplasma, infectious virus, and replicating viruses. Types A and C retroviral particles were observed by electron microscopy.

5.7.2. Investigational Drug Nomenclature
IDEC Pharmaceuticals code designation: IDEC-Y2B8 (IDEC 106); IDEC-2B8-MX-DTP (IDEC-129), IDEC-In2B8 (IDEC-105)
Generic name: ^{90}Y-ibritumomab tiuxetan, ^{111}In-ibritumomab tiuxetan
IND numbers: BB-IND 4850 – IDEC-Y2B8/IDEC-In2B8
MF number: BB-MF – IDEC-Y2B8/IDEC-In2B8

5.7.3. Clinical Formulation
For a complete description of the preparation and dispensing of ^{90}Y and ^{111}I-Ibritumomab tiuxetan, please refer to **Appendix G**. The radiolabeling kit is provided by Biogen Idec, Inc.. and all compartments are tested to be sterile and pyrogen-free. The kit consists of the following components:

- 2 mL glass vial containing 2 mL (3.2 mg) of IDEC-Y2B8-MX-DTPA at 1.6 mg/mL in low metal normal saline
- 2 mL glass vial containing 2 mL low metal 50nM sodium acetate
- 10 mL glass vial containing 10 mL formulation buffer (PBS containing 7.5% human serum albumin and 1mM DTPA, pH 7.2)
- 10 mL glass vial (empty)

5.7.4. Storage
The radiolabeling kits should be stored in a secure refrigerator at 2-8°C. Ibritumomab tiuxetan solutions are stable at 2-8°C for up to 8 hours following preparation. Ibritumomab tiuxetan solutions are stable at 2-8°C for up to 12 hours following preparation. Due to the relatively short half-

life of the ^{90}Y and ^{111}In isotopes, if not used soon after calibration time, the actual doses will have decayed and will required recalculation.

5.7.5. Toxicities

The adverse events described are summarized from the aggregated clinical experience with 349 patients enrolled on 5 trials and is reflected in the Product Information: Zevalin ™, ibritumomab tiuxetan (Biogen Idec, Inc.., 2/02)

Hematologic Toxicity: The most common side effects were hematologic. Hematologic toxicity was transient and reversible. 61% of patients with a platelet count of at least 150,000 cells/ mm^3 prior to therapy developed thrombocytopenia with a platelet count less than 50,000 cells/ mm^3; median 41,000 cells/ mm^3; 57% of patients developed neutropenia with an absolute neutrophil count (ANC) of less than 1000 cells/ mm^3 (median 800 cells/ mm^3). In patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/ mm^3), 78% developed severe thrombocytopenia (median platelet count 24,000 cells/ mm^3) and 74% developed severe neutropenia (median ANC 600 cells/ mm^3). Median time to platelet nadir was 53 days with a median duration of 35 days; median ANC nadir was at 62 days with a median duration of 22 days. Twenty-two percent of patients received platelet transfusions; 20% received red blood cell transfusions; 13% received filgrastim; and 8% received erythropoietin. Severe cytopenia extended beyond 12 weeks after administration of ibritumomab tiuxetan in less than 5% of patients.

Ibritumomab tiuxetan should not be administered to patients with 25% or greater lymphoma marrow involvement and/or impaired bone marrow reserve (prior myeloablative therapies); platelet count less than 100,000 cells/ mm^3; neutrophil count less than 1500 cells/ mm^3; bone marrow with 15% or less cellularity or marked reduction in bone marrow precursors; or patients with a history of failed stem cell collection. Ibritumomab tiuxetan therapy should not be considered in patients with a platelet count of less than 100,000 cells/ mm^3; dose reduction is required in patients with platelet counts of 100,000 to 150,000 cells/ mm^3.

In a Phase I/II study of n=51 patients **25** median nadirs for the 0.4 mCi/kg dose group were 50,000/mm^3 platelets, 1100 /mm^3 granulocytes and 9.9 g/dL hemoglobin. For patients in the 0.4 mCi/kg group whose nadirs fell below 50,000/mm^3 platelets, 1100/mm^3 granulocytes or 9.9 g/dL hemoglobin, the median time to recovery for these values was 14 days, 10.5 days, and 9.5 days, respectively. Five patients (10%) developed platelet nadirs <10,000/mm^3. Fourteen patients (27%) developed granulocyte nadirs <500/mm^3. Six patients received red blood cell transfusions, 3 received granulocyte colony-stimulating factor, and 10

patients received platelet transfusions. A significant correlation was noted between percent bone marrow involvement with NHL at baseline and hematologic toxicity.

Secondary Malignancies: Three cases of acute myelogenous leukemia, 2 cases of myelodysplastic syndrome, and 1 case of a grade 1 meningioma were reported.

Cardiovascular effects: Hypotension was reported in 6% of patients and was grade 3/4 in 1%; peripheral edema was reported in 8% and was grade 3/4 in 1%.

Central nervous system: The following nervous system adverse events were reported (% all grades, % grade 3/4): asthenia (43%, 3%), headache (12%, 1%), dizziness (10%, less than 1%), and insomnia (5%, 0%)

Gastrointestinal effects: The following gastrointestinal adverse events were reported (% all grades, % grade 3/4): nausea (31%, 1%), abdominal pain (16%, 3%), vomiting (12%, 0%), throat irritation (10%, 0%), diarrhea (9%, less than 1%), anorexia (8%, 0%), abdominal enlargement (5%, 0%), and constipation (5%, 0%).

Nausea, abdominal pain, and anorexia have been described by some non-Hodgkin's lymphoma patients (less than 10%) during or following the radioimmunotherapy protocol **25**. Some of these effects have been reported with rituximab mono-immunotherapy, and the contributing role of rituximab pretreatment is unclear.

Increases in serum bilirubin have been observed occasionally following the radioimmunotherapy protocol **25**. There have been no reports of clinical hepatotoxicity.

Respiratory effects: The following respiratory adverse events were reported (% all grades, % grade 3/4): dyspnea (14%, 2%), increased cough (10%, 0%), rhinitis (6%, 0%), and bronchospasm (5%, 0%)

Dermatologic effects: The following dermatologic adverse events were reported (% all grades, % grade 3/4): pruritus (9%, less than 1%), rash (8%, less than 1%), flushing (6%, 0%), and angioedema (5%, less than 1%).

Flushing, pruritus, and urticaria have been observed in some non-Hodgkin's lymphoma patients (less than 10%) during or following the radioimmunotherapy protocol **25**. These effects have been reported during rituximab mono-immunotherapy; the contribution of rituximab pretreatment is unclear.

Infectious Complications: In clinical trials (n=349), 29% of patients developed infections during the first 3 months after receiving ibritumomab tiuxetan therapy. Serious infections developed in 3% of patients and life-threatening infections developed in 2% of patients. In long-term follow-up from 3 months to 4 years after ibritumomab tiuxetan therapy, infections developed in 6% of patients with 2% serious infections and 1% life-threatening infections.[31]

Musculoskeletal effects: The following musculoskeletal adverse events were reported (% all grades, % grade 3/4): back pain (8%, 1%), arthralgia (7%, 1%), myalgia (7%, less than 1%).

Back pain and arthralgia have been described by some non- Hodgkin's lymphoma patients (less than 10%) during or following the radioimmunotherapy protocol **25**. These effects have been reported with rituximab monoimmunotherapy, and the contributing role of rituximab pretreatment is unclear.

Infusion Reactions: Fatal infusion-related reactions have occurred within 24 hours of rituximab infusion; 80% of fatal reactions were associated with the first rituximab infusion. Fatal reactions were associated with a symptom complex that included hypoxia, pulmonary infiltrates, ARDS, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Severe infusion reactions typically occur within 30 to 120 minutes after administration of rituximab and may include symptoms of hypotension, angioedema, hypoxia, and bronchospasm.

Medications for the treatment of anaphylactic and other hypersensitivity reactions should be available. Administration of rituximab and Indium-111 or Yttrium-90 ibritumomab tiuxetan should be discontinued and medical treatment should be administered to patients who develop severe infusion reactions.

In clinical trials (n=349), allergic reactions occurred in 2% of patients and were severe or life threatening in 1%, and severe or life-threatening apnea occurred in 1% of patients. Angioedema occurred in 5% of patients and was severe or life- threatening angioedema in less than 1% of patients; urticaria occurred in 4% of patients and was severe in less than 1% of patients.

Decreases in immunoglobulin levels (by at least 50%) have occurred rarely after therapy **25**

Geriatric Patients: In clinical trials (n=349), there were no differences in safety or effectiveness between patients 65 years of age and over (n=132), patients 75 years of age and over (n=41), and younger patients; greater

sensitivity of some older patients cannot be ruled out (Prod Info Zevalin(TM), 2002).

Dosimetry data collected from 56 patients in a phase I/II study were used to estimate the radiation dose to normal organs and bone marrow from ^{90}Y-ibritumomab tiuxetan treatment. Patients received ^{111}In-ibritumomab tiuxetan on Day 0, followed by a therapeutic dose of ^{90}Y-ibritumomab tiuxetan on Day 7. Following administration of ^{111}In-ibritumomab tiuxetan, periodic whole body images were performed acquiring anterior and posterior images. Time-activity curves for each organ were derived by drawing regions of interest. From the area under the curve, residence times were determined and entered into the MIRDOSE3 computer software program to estimate absorbed radiation dose of ^{90}Y-ibritumomab tiuxetan to each organ. An additional centralized dosimetry analysis was performed subsequently to provide a consistent analysis of data collected from the 7 clinical sites where the study was performed. In all patients, normal organ and red marrow radiation doses were estimated to be well under the protocol-defined upper limit of 2000 cGy and 300 cGy, respectively. Patients with spleen involvement by lymphoma were allowed to exceed the 2000 cGy upper limit. Estimated median tumor absorbed dose as determined by data in 18 tumors in 9 patients was 1712 cGy (range 575-6710). The estimated absorbed radiation dose to organs, by dosing group, is shown in the Table below.

Estimated ^{90}Yttrium (0.4 mCi/kg) Absorbed Radiation Dose to Organs (N=30)

	Liver	Spleen	Lungs	Bladder Wall	Red Marrow	Bone Surfaces	Kidneys	All Other Organs
Patients (N)	35	30	35	35	35	35	35	35
Median (cGy)	358	709	275	73	63	56	43	43
Range (cGy)	173-779	300-2448	136-442	38-158	30-120	28-96	24-61	24-61

5.8Darbepoetin alfa

5.8.1 Other Names:
Aranesp™

5.8.2 Description:
Darbepoetin alfa is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Darbepoetin alfa is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3. The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Because of this increased carbohydrate content, darbepoetin alfa has a 3-fold longer circulating mean residence time and 3- to 4-fold greater biological activity in animal models compared with rHuEPO. Details of these clinical trials as well as the chemistry, pre-clinical pharmacology, pharmacokinetics and toxicology of darbepoetin alfa are contained in the darbepoetin alfa investigator's brochure.

5.8.3 Packaging and Formulation:
HSA-free (polysorbate) darbepoetin alfa will be manufactured and packaged by Amgen. Darbepoetin alfa will be provided as a clear, colorless, sterile protein solution containing x µg of darbepoetin alfa per mL (to be defined by Amgen) and the following excipients: 0.05 mg polysorbate 80, 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.2 ± 0.2. The vials supplied will contain approximately 1.0 mL of study medication and are for single-dose use only.

5.8.4 Labeling:
Information presented on the label for study medication will comply with the local regulatory requirements.

5.8.5 Storage Conditions and Stability:
The supplied darbepoetin alfa must be stored in a refrigerator. The stability of darbepoetin alfa has been demonstrated for at least 24 months when stored at a temperature between 2° to 8°C (36° to 46°F). Further stability testing is ongoing. Exposure to temperatures above or below this range and vigorous shaking should be avoided because this may denature the protein. Vials of darbepoetin alfa must not be used if any particulate matter or discoloration is observed.

5.8.6 Expiration Dating:
As per standard practice for experimental biologic pharmaceuticals, Amgen will conduct periodic stability assays to monitor product stability and determine appropriate expiration dating of the study drug. The appropriate Amgen representative shall communicate this information to the investigator.

5.8.7 Darbepoetin alfa (Aranesp®) will be administered at a dose of 300 micrograms (mcg) every 3 weeks for anemic patients. Anemia will be defined as Hgb< 11.0 g/dL. Non-Anemic patients (Hgb≥ 11.0gm/dL) will be monitored and initiate Darbepoetin alfa if they become anemic.

5.8.8 Dose Adjustments:

- Dose escalation is permitted after 6 weeks (2 doses). The dose should be escalated to 500mcg q3w if the Hgb remains below 10.0 g/dL and the increase in Hgb from baseline is less than 1.0 g/dL after 6 weeks. Physician discretion regarding dose escalation should be exercised if the Hgb is above 10g/dL; for example, if after 6 weeks of treatment the Hgb is below the baseline value.
- The dose should should be held if the Hgb is ≥ 11.5 g/dl. A target hemoglobin of 11-11.5 g/dl is sought.
- Any other dose modifications should be made in accordance with the modified Aranesp® package insert as follows:
    - If Hgb increases by more than 1.0 g/dL in a 2-week period (or 1.5 g/dL in a 3-week period) immediately preceding the next dose, the dose should be reduced by approximately 40%.
    - If Hgb ≥ 11.5 g/dl at the time of the next dose, the planned doses should be temporarily withheld until the Hgb falls to less than 11.0 g/dL. At this point Aranesp® should be reinitiated at a dose approximately 40% below the previous dose.

5.8.9 Overdose:
There is no clinical experience of overdose with darbepoetin alfa.

5.8.10 Preparation and Administration:
Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing darbepoetin alfa and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw the desired volume of solution into the syringe.

- Do not shake darbepoetin alfa. Vigorous shaking may denature darbepoetin alfa, rendering it biologically inactive.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

- Do not dilute darbepoetin alfa.

- Do not administer darbepoetin alfa in conjunction with other drug solutions.

- Darbepoetin alfa is packaged in single-use vials and contains no preservative. Discard any unused portion. Do not pool unused portions.

5.8.11 Availability:
Darbepoetin alfa is being supplied by Amgen, Inc.

5.8.12 Drug Shipment, Re-Supply, and return:
A completed and signed Drug Request Form must be faxed, at least 3 days prior to the expected delivery date, to Clinical Logistics, Amgen, Inc., 805-499-9697. The study drug will be shipped to the investigator's institution; the quantity amount and condition of the drug received should be documented on the proof of receipt letter. The proof of receipt letter should be faxed to Amgen Clinical Logistics at the number indicated on the letter and the original retained in the pharmacy files.

At the end of the study, or as directed, all study drug vials, including unused, partially used, or empty vials, will be returned to Amgen. The vials should be counted and placed in a box clearly marked with EXTRAMURAL on the outside of the box and sealed with tamper evident tape. Accompanying paperwork should be attached to the outside of the box. Ship to:
Amgen Inc.
Returned Clinical Drug, Room 124A
One Amgen Center Drive
Thousand Oaks, CA 91320.

5.8.13 Toxicity:
Aranesp™ is contraindicated in patients with:

- uncontrolled hypertension

- known hypersensitivity to the active substance or any of the excipients

5.8.14 Potential risks and discomforts:
Darbepoetin alfa is generally well tolerated. Some of the side effects reported in clinical studies were in subjects with kidney disease, dialysis treatment, or cancer with and without chemotherapy, and may not have been not be due to darbepoetin alfa treatment. These events were more common in subjects with chronic kidney disease than in subjects with cancer.

Darbepoetin alfa injections can be associated with stinging at the injection site, and rare allergic reactions (e.g., skin rash, itching and hives or more serious allergic reactions). There is a possibility that darbepoetin alfa may be associated with an increased risk of cardiac events (e.g. heart attack), circulatory events (worsening of blood pressure, stroke, or blood clots) and seizure or even death. The higher risk of cardiac events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. In one Epoetin alfa study in subjects with chronic kidney disease receiving dialysis, who also suffered from heart disease, there was a higher risk of death and thrombosis associated for those subjects who were assigned to maintain hemoglobin levels of 14.0 ± 1.0 g/dL. The reason for the increased death rate is not understood. Despite the overall outcome of the study, within each group, higher hemoglobin values were associated with better survival.

5.8.15 Allergic responses:
There may be a risk of developing an allergic reaction to darbepoetin alfa. Rare allergic symptoms following darbepoetin alfa treatment (eg, skin rash, itching and hives) have been reported, primarily in chronic renal failure patients. It is possible for more serious allergic reactions to occur. These possible reactions include a whole body rash, shortness of breath, wheezing, sudden drop in blood pressure, swelling around the mouth or eyes, rapid pulse or sweating.

5.8.16 Pregnancy and lactation:
There are no adequate and well-controlled studies in pregnant women (pregnancy category C), therefore, darbepoetin alfa should not be used during pregnancy. In addition, it is not known if darbepoetin alfa is excreted in human milk, therefore, lactating mothers should stop lactating in order to take part in this study.

5.8.17 Drug Interactions:
No formal drug interaction studies of darbepoetin alfa with other medications commonly used in CRF patients have been performed.

5.8.18 Geriatric Use:
Of the 1598 CRF patients in clinical studies of darbepoetin alfa, 42% were

age 65 and over, while 15% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

6 CRITERIA FOR PATIENT ELIGIBILITY

Please note copies of source documentation confirming eligibility for patients enrolling at outside institutions must be provided to MSKCC at the time of registration. Please fax to: 212-557-0786 (see section 15)

6.1. Patient Inclusion Criteria

6.1.1 Patients must have reached their 60th birthday by the time of enrollment. Patients age 60-65 must be deemed ASCT ineligible at the time of enrollment.

6.1.2 Patients must have an initial diagnosis of diffuse large B-cell lymphoma that is confirmed by one of the hematopathologists at the treating institution. Any of the following subtypes of DLBCL as described in the WHO Classification [33] are eligible: centroblastic, immunoblastic, T-cell/histiocyte-rich, lymphomatoid granulomatosis type, anaplastic large B-cell, plasmablastic, mediastinal, or intravascular large B-cell lymphoma. Lymphomas with discordant histology (small cells in the bone marrow) and a DLBCL diagnosis will be eligible for enrollment. All patients must have an initial diagnostic specimen that is CD20-positive.

6.1.3 Patients must have at least Ann Arbor Stage II disease and not have disease confined to an involved field radiation port.

6.1.4 Patients must have high-intermediate or high-risk DLBCL as defined by an Age-Adjusted IPI (aaIPI) score of 2 or 3 (with 1 point each assigned for a ECOG>1 / KPS≤ 70%, LDH>1x normal, and Stage III or IV)

6.1.5 Patients must not have received prior chemotherapy, biologic therapy, or radiation therapy. Patients who have received steroids for ≤14 consecutive days are eligible. Patients with a history of prior intravenous contrast allergy are permitted to receive steroids as a premedication. However, patients who have already received a single cycle of R-CHOP at standard dosages and otherwise meet all eligibility requirements will be allowed enrollment. These patients will start therapy with cycle number two of R-CHOP provided all pretreatment evaluations meet protocol criteria.

6.1.6 Karnofsky performance status of at least 50% (see Appendix B).

6.1.7 Patients must have a total bilirubin of 2.0 mg/dL or less at the time of study enrollment. The patient may have a bilirubin >2.0 mg/dL if he/she has a history of Gilbert's disease.

6.1.8 Patients must have adequate renal function defined as a serum creatinine of 1.5 mg/dL or less at the time of study enrollment. Patients with a serum creatinine of 1.6 mg/dL or greater are still eligible if their 12 or 24-hour creatinine clearance is measured at >50 mL/min. Patients who do not meet either criteria but have renal insufficiency that is believed to be directly caused by lymphomatous involvement of the kidneys or renal collecting system are eligible.

6.1.9 Patients must have a cardiac ejection fraction of 50% or greater as determined by echocardiogram.

6.1.10 Patients must have HIV antibody test drawn within 4-6 weeks of enrollment; results may be pending provided there is no history of known risk factors or clinical suspicion of HIV.

6.1.11 Patients must have no concurrent uncontrolled medical problems that would preclude administration of chemotherapy or radioimmunotherapy.

6.1.12 Patients receiving therapeutic doses of Coumadin may be considered eligible for therapy. Given the potential for thrombocytopenia on this study, the patient's coagulation studies will be closely monitored. (See section 9.0)

6.1.13 Patients must have no prior history of radiotherapy or chemotherapy for a cancer diagnosis within the last 5 years.

6.1.14 Patients must have bi-dimensionally measurable disease at the time of study entry, defined as at least one lymph node ≥2.0 x 2.0 cm on physical examination, CT scan, or PET scan.

6.1.15 Bone Marrow cellularity at entry must be greater than 15% as determined by a treating institution's hematopathologists or specified as normocellular (~40%) or hyper cellular on the bone marrow biopsy report.

6.1.16 Patients must have no known brain or leptomeningeal metastases at the time of study enrollment.

6.1.17 Patients must be capable of providing written informed consent.

6.2. Patient Exclusion Criteria

6.2.1 Patients who have not reached their 60th birthday at the time of study entry or who are ages 60-65 and deemed potential future transplant candidates.

6.2.2 Patients with any lymphoma subtype other than diffuse large B-cell lymphoma, discordant lymphomas with a DLBCL component are ineligible. Composite lymphomas and patients with primary effusion lymphomas are ineligible.

6.2.3 Patients with Stage I or limited Stage II disease (i.e., disease confined to an involved field radiation port).

6.2.4 Patients with Low or Low-Intermediate risk disease as defined by aaIPI scores of 0 or 1.

6.2.5 Patients who have received prior treatment of any kind for their lymphoma, including chemotherapy, radiation therapy, or biologic therapy. For the

purposes of this trial, corticosteroids will not be considered prior therapy. However, patients who have already received a single cycle of R-CHOP at standard dosages and otherwise meet all eligibility requirements will be allowed enrollment. These patients will start therapy with cycle number two of R-CHOP provided all pretreatment evaluations meet protocol criteria. Patients with a history of prior severe intravenous contrast allergy are permitted to receive steroids as a premedication.

6.2.6 Karnofsky performance status of less than 50%.

6.2.7 Patients with a total bilirubin > 2.0 mg/dL without a history of Gilbert's disease.

6.2.8 Patients with a serum creatinine >1.5 mg/dL or creatinine clearance <50 mL/min as a result of medical renal disease.

6.2.9 Cardiac ejection fraction of <50% by echocardiogram.

6.2.10 HIV-positivity.

6.2.11 Concurrent uncontrolled medical problems (including uncontrolled hypertension)

6.2.12 Unstable angina pectoris, recent acute myocardial infarction (within 3 months of randomization), or congestive heart failure (> NYHA class II)

6.2.13 Subjects with an active seizure disorder. Subjects with a previous history of seizure disorders will be eligible for the study, if they have had no evidence of seizure activity, and they have been free of anti-seizure medication for the previous 5 years.

6.2.14 Patients with a history of radiotherapy or chemotherapy for a cancer diagnosis within the last 5 years.

6.2.15 Patients with less than 15% bone marrow cellularity as determined by MSKCC hematopathologists.

6.2.16 Brain or leptomeningeal metastases at the time of study enrollment

6.2.17 Patients incapable of providing written informed consent.

7 RECRUITMENT PLAN

Patients will be recruited to this trial by members of the Lymphoma Service listed as Clinical Investigators at each participating institutions. Information regarding this study will be made available on the MSKCC Internet Web site. This study will be offered to all eligible patients referred to MSKCC, regardless of gender or ethnicity. Clinical Investigators on the study are expected to discuss with the patient his/her diagnosis, prognosis, risks and benefits of study participation, as well as treatment alternatives (i.e., standard treatment options) and their risks and benefits. All patients will be required to sign a statement of informed consent that conforms to local IRB guidelines.

8 PRETREATMENT EVALUATION

8.1. History and physical examination including height, weight, and vital signs within 7 days of study entry.
8.2. Karnofsky performance status within 7 days of study entry.
8.3. Complete blood count with differential within 7 days of study entry.
8.4. Screening profile (include electrolytes, BUN, creatinine, total bilirubin, AST, alkaline phosphatase) and serum lactate dehydrogenase (LDH) within 7 days of study entry. Erythropoietin level, Ferritin, Iron, TIBC, B12 and Folate levels within 4-6 weeks of entry.
8.5. Completion of a FACT-Anemia QOL scale within 7 days of study entry. Patients will self-administer the FACT-anemia test. See appendix K.
8.6. CT scans of chest, abdomen, and pelvis within 4-6 weeks of study entry. If a patient has palpable neck adenopathy, a CT scan of the neck must also be performed within the same time period.
8.7. PET scan within 4-6 weeks of study entry.
8.8. Echocardiogram within 4-6 weeks of study entry.
8.9. EKG
8.10. 12 or 24-hour urine collection for creatinine clearance for patients with a creatinine >1.5 mg/dL.
8.11. HIV-1 antibodies drawn within 4-6 weeks of study entry.
8.12. Unilateral bone marrow biopsies within 4-6 weeks of study entry.
8.13. Peripheral blood (MSKCC Only) – nine 2-mL purple top tubes: 2 for minimal residual disease studies (to Dr. Zelenetz' lab, K1011, see Appendix C), 7 tubes for progenitor cell studies (to Dr. Moore's lab, RRL717, see Appendix D)
8.14. Bone marrow aspirate within 4-6 weeks of study entry (MSKCC Only) – five 2-mL pulls in purple top tubes. Two tubes will be sent to Dr. Zelenetz' lab in K1011 (see Appendix C). Two tubes will be sent to Dr. Moore's lab in RRL 717 for progenitor cell studies (see Appendix D) and one tube will be sent to the flow cytometry lab for CD34+ count.
8.15. Additionally, bone marrow evaluation for cytogenetics must be performed prior to RIT (preferably at baseline study, although post RCHOP is also acceptable). Abnormal cytogenetics by karyotype analysis that are consistent with myelodysplasia will exclude patients from radio-immunotherapy. (All Institutions)
8.16. Patients being enrolled after previously receiving a single cycle of RCHOP will not be required to have the following tests: baseline minimal residual disease studies, progenitor cell analysis, CD34 Flow study. Minimal residual disease studies may be omitted for the duration of the trial. Progenitor cell analysis may commence following cycle #1 as dictated in the trial.

9 TREATMENT PLAN

9.1. Chemotherapy Phase

9.1.1 R-CHOP Chemotherapy

R-CHOP will be given at the following doses:

- Rituximab 375 mg/m^2 IVPB with premedications (see below)

- Cyclophosphamide 750 mg/m^2 IVPB
- Doxorubicin 50 mg/m^2 IV push
- Vincristine 1.4 mg/m^2 IV push (not to exceed 2 mg per cycle)
- Prednisone 100 mg po qd, either from Days 1-5 or 2-6

The first Rituximab dose will be given over 3-5 hours to minimize the risk of infusion-related reactions. Subsequent doses may be given over a minimum of 2 hours as tolerated.

Premedications for Rituximab include acetaminophen 650 mg po and diphenhydramine 50 mg IVPB given at least 30 minutes prior to infusion. Chlorpheniramine 4 mg po may be substituted for diphenhydramine.

R-CHOP will be repeated every 21 days for a total of 6 cycles. The next cycle of R-CHOP can be given when the absolute neutrophil count is at least 1000/mm^3 and the platelet is at least 75,000/mm^3.

Tumor lysis prophylaxis: During cycle one only, prophylactic Allopurinol is recommended to prevent tumor lysis syndrome in patients with high tumor burden (bone marrow involvement or LDH>500). Patients should receive 600mg PO 24 hrs. prior to the first rituximab, and continue 300 mg po daily for at least 7 days after cycle #1 of R-CHOP. Additional measures such as IV hydration or urinary alkalinization may be implemented as clinically necessary.

Anti-emetic medications, including dexamethasone, will be given as per hospital guidelines on Day 1 of each cycle.

Patients with B12 or Folate deficiency should be commenced on appropriate repletion therapy (B12 1000 mcg SQ q month, folic acid 1 mg po qd). Patients with iron deficiency (eg. Ferritin <10 mcg/L; TSAT<15%, low iron, and high TIBC) should commence FeSO4 supplementation. Dosing and route as per treating physician.

For patients requiring therapeutic anticoagulation with coumadin while on study, PT/PTT/INR studies should be followed closely with appropriate adjustments made by the treating physician. Patients should be considered for low-molecular heparin when appropriate, given the potential for fewer drug interactions.

Granulocyte colony-stimulating factor will be given with each cycle. Neulasta 6mg SQ 24 hours after chemotherapy is preferred

(at MSKCC), although GCSF at 300 µg for patients <70kg and 480 µg for patients ≥70 kg SQ starting at day 5 and continuing to day 12 remains acceptable. Doses may be adjusted at the discretion of the treating physician and should follow institutional procedure.

Darbepoetin alfa (Aranesp®) will be administered at a dose of 300 micrograms (mcg) every 3 weeks for anemic patients. Anemia will be defined as Hgb< 11.0 g/dL. Non-Anemic patients (Hgb≥ 11.0gm/dL) will be monitored and initiate Darbepoetin alfa if they become anemic.

Dose Adjustments:

- Dose escalation is permitted after 6 weeks (2 doses). The dose should be escalated to 500mcg q3w if the Hgb remains below 10.0 g/dL and the increase in Hgb from baseline is less than 1.0 g/dL after 6 weeks. Physician discretion regarding dose escalation should be exercised if the Hgb is above 10g/dL; for example, if after 6 weeks of treatment the Hgb is below the baseline value.
- The dose should not be escalated if the Hgb is within the Hgb target range of 11-11.5 g/dL.
- Any other dose modifications should be made in accordance with the Aranesp® package insert as follows:
    - If Hgb increases by more than 1.0 g/dL in a 2-week period (or 1.5 g/dL in a 3-week period) immediately preceding the next dose, the dose should be reduced by approximately 40%.
- If Hgb ≥ 11.5 g/dl at the time of the next dose, the planned doses should be temporarily withheld until the Hgb falls to less than 11.0 g/dL. At this point Aranesp® should be reinitiated at a dose approximately 40% below the previous dose.
- The following events should prompt discontinuation of darbepoetin alfa:
    - Uncontrolled hypertension
    - Deep vein thrombosis

Central Nervous System prophylaxis is recommended for all individuals with 1) evidence of bone marrow involvement with large cells on blind bone marrow biopsy, 2) radiographic evidence of more than one site of lytic bone involvement, or evidence of bone marrow involvement, 3) testicular involvement, 4) two or more sites of non-contiguous extranodal involvement. Either of the following two regimens, or a combination thereof, is recommended:

- Methotrexate, 12 mg administered intrathecally weekly for 6 treatments during the R-CHOP course,
- Cytasine Arabinoside, 60 mg administered intrathecally weekly for 6 treatments during the R-CHOP course.

9.1.2 R-CHOP Schedule/Dose Modifications

- If a patient has an absolute neutrophil count <1000/mm^3 or platelet count of <100,000/mm^3 on a scheduled treatment day, or if the patient develops febrile neutropenia, the next cycle of R-CHOP may be delayed up to 14 days as indicated. The retreatment platelet count should be consistent with each individual institutional guidelines (with a minimum cut-off of at least >75,000/mm^3.)

- Vincristine doses may be reduced by 50% for Grade 2 neurotoxicity and may be discontinued for Grade 3 or 4 neurotoxicity

- Dose reductions to R-CHOP chemotherapy for comorbidity or potential toxicity should be made at the discretion of the treating physician and may occur with Cycle #1 if necessary. Vincristine may be omitted in entirety from cycle 1 if potential GI toxicity outweighs potential benefit in the opinion of the treating MD. Prednisone may be given for control of symptoms prior to the start of chemotherapy (maximum 14 consecutive days).

9.2. Radioimmunotherapy Phase

9.2.1 Criteria to Proceed to Radioimmunotherapy Phase of Study

- Patients must have < 25% intratrabecular space bone marrow involvement on a post-R-CHOP bilateral bone marrow biopsy, to be performed 4-6 weeks post R-CHOP and within 4 weeks of starting the radioimmunotherapy phase.
- Patients must have greater than 15% cellularity of bone marrow as determined by MSKCC hematopathologists
- Patients must have baseline cytogenetics that is not consistent with myelodysplasia (performed on a bone marrow aspiration prior to the initiation of Radioimmunotherapy). FISH abnormalities associated with MDS, whether or not morphologic or cytogenetic evidence of MDS is present, will also preclude Phase II treatment with RIT. These patients will remain on study to be followed for outcome.
- Patients must have post-R-CHOP restaging studies within 4-5 weeks of completing R-CHOP showing that their disease has not progressed from the time of study entry. Patients with confirmed or unconfirmed complete response and patients with partial responses who are not transplant eligible are allowed to proceed.

- Pre-radioimmunotherapy phase Karnofsky performance status of at least 60%.
- Patients must not have received any pegfilgrastim (or G-CSF) within the 2 weeks (14 days) and no Darbepoetin alfa within the 21 days (3 weeks) preceding day 0 of the radioimmunotherapy phase.
    - Darbepoetin Alfa may be administered during the radioimmunotherapy phase of treatment starting week #3 at the discretion of the treating physician. Drug will be supplied by Amgen for this purpose. The protocol does not mandate colony stimulating factors during the RIT phase.
- Patients must have acceptable hematologic function within 2 weeks of receiving the first loading dose of rituximab. Acceptable hematologic function is defined as an absolute neutrophil count $\geq 1500/mm^3$, hemoglobin ≥ 8.0 g/dL, and platelets $\geq 100{,}000/mm^3$ in the absence of hematopoietic growth factors for at least 14 days.
- Patients must have no evidence of clinically significant pleural effusions prior to receiving the first loading dose of rituximab.

9.2.2 Rituximab and 111In-ibritumomab tiuxetan/^{90}Y-ibritumomab tiuxetan

- Day 0 of the Radioimmunotherapy Phase must begin between 6 and 9 weeks (42-63 days) after Day 1 of the last cycle of R-CHOP.
- Rituximab administration:
  See Rituxan Package Insert (**Appendix A**).
- The CBC drawn on Day 0 will serve as the reference CBC for the dosing of the 90Y ibritumomab tiuxetan on Day 7. An additional CBC should not be drawn on day 7.
- On Day 0 of the Radioimmunotherapy Phase, patients will be premedicated with acetaminophen 650 mg po, diphenhydramine 50 mg po or chlorpheniramine 4 mg po, and Ativan 0.5 mg IV 30 minutes prior to beginning of Rituximab infusion. (Patients need not receive any of the above premedications if there is a prior history of an adverse reaction to any of them.) Following this, rituximab 250 mg/m2 will be infused.
- On Day 0, immediately following the infusion of rituximab, patients will receive a fixed dose of 1.6 mg (5.0 mCi) of ^{111}In-ibritumomab tiuxetan, given by slow IV push over 10 minutes.
- On Day 0-1, 2-24 hours after infusion of ^{111}In-ibritumomab tiuxetan, whole body gamma camera images will be taken.
- On Day 2-3, 48-72 hours after infusion of ^{111}In-ibritumomab tiuxetan, whole body gamma camera images will be taken.
- On Day 5-7, 90-120 hours after infusion on ^{111}In-ibritumomab tiuxetan, whole body gamma camera images will be taken, if deemed necessary.
- On Day 7 of the Radioimmunotherapy Phase, a second rituximab infusion at a dose of 250 mg/m2 will be given, using the same pre-

medications. The Day 7 rituximab dose may be delayed up to Day 14 if necessary.

- Dose calibration settings will be determined by the Division of Nuclear Medicine according to the methods described in **Appendix F**.
- ^{90}Y-ibritumomab tiuxetan will be administered immediately following the Day 7 rituximab infusion. Each patient will receive one therapeutic dose of ^{90}Y-ibritumomab tiuxetan. For patients weighing >80 kg, a maximum dose of 32 mCi will be given. For patients weighing ≤80 kg with platelet counts ≥150,000/mm^3, a dose of 0.4 mCi ^{90}Y/kg will be given. For patients weighing ≤80 kg with platelet counts <150,000/ mm^3, a dose of 0.3 mCi/kg will be given.
- ^{90}Y-ibritumomab tiuxetan will be administered intravenously as a slow IV push over 10 minutes. The drug may be directly infused by stopping the flow from the IV bag and injecting the radiolabeled antibody directly into the infusion port. A 0.22 micron filter must be on line between the syringe and the infusion port. (The 0.22 micron filter is not provided by Biogen Idec, Inc.. Pharmaceuticals). Flush the line with at least 10 mL of normal saline after ^{90}Y-ibritumomab tiuxetan has been infused. See **Appendix G** for radio incorporation methods.

10 EVALUATION DURING TREATMENT

10.1. Chemotherapy Phase (please refer to the Table below)

10.1.1 Cycles 2-6 of R-CHOP: History and physical examination, assessment of Karnofsky Performance Status, complete blood count, comprehensive panel and LDH on Day 1 of each cycle. Transfusion requirements and adverse experiences will be recorded at each evaluation.

10.1.2 Interim restaging: between cycles 4 and 5 of R-CHOP, a repeat CT scan of the chest, abdomen and pelvis and PET scan (if previously positive). Patients must have at least stable disease or better to be allowed to continue on study.

10.1.3 Between cycles 4 and 5 (prior to cycle 5's administration) patients will complete a FACT-anemia evaluation.

10.2. Post-Chemotherapy / Pre-Radioimmunotherapy Restaging Evaluation (all to be done 4-5 weeks after Day 1 of the last cycle of R-CHOP)

10.2.1 History, physical examination, and assessment of Karnofsky Performance Status

10.2.2 CBC with differential, comprehensive profile, LDH

10.2.3 CT scans of the chest, abdomen, and pelvis, and a PET scan (if previously positive).

10.2.4 FACT-anemia evaluation form to be completed prior to the initiation of radioimmunotherapy

10.2.5 Echocardiography and EKG evaluation

10.2.6 Peripheral blood (MSKCC Only) – nine 2-mL purple top tubes: 2 for minimal residual disease studies (to Dr. Zelenetz' lab, K1011, see **Appendix**

C), 7 tubes for progenitor cell studies (to Dr. Moore's lab, RRL717, see **Appendix D**).

10.2.7 Bone marrow aspirate studies (MSKCC Only) - five 2-mL pulls of bone marrow aspirate in purple top tubes will be drawn. Two tubes will be sent to Dr. Zelenetz' lab in K1011 (see **Appendix C**). Two tubes will be sent to Dr. Moore's lab in RRL 717 for progenitor cell studies (see **Appendix D**) and one tube will be sent to the flow cytometry lab for CD34+ count.

10.2.8 Bone marrow biopsy demonstrating ≤25% BM involvement. A bilateral bone marrow biopsy is preferred; if a unilateral bone marrow biopsy reveals <10% intratrabecular space involvement, a contralateral biopsy need not be performed. This is mandatory at all institutions

10.2.9 Bone marrow cellularity must be greater than 15% in order to proceed with Zevalin therapy.

	Chemotherapy Phase (I)								
	Base-Line	**Cycle 1[a]**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Restaging**	**Cycle 5**	**Cycle 6**	**Post-R-CHOP /Pre-RIT Restaging[b]**
History, Physical,KPS	X	X	X	X	X		X	X	X
CBC, diff	X	X	X	X	X		X	X	X
Comp.Profile, LDH	X	X	X	X	X		X	X	X
Erythropoietin level, ferritin, Fe, B12, Folate	X								
HIV testing	X[f]								
FACT-anemia[e]	X					X			X
CT C-A-P	X					X			X
PET	X					X			X
ECHO/EKG	X								X[C]
Peripheral blood (research)	X								
Bone marrow									X

Aspirate studies	**X[D]**								
Bone marrow biopsy	**X**								**X**
R-CHOP		**X**	**X**	**X**	**X**		**X**	**X**	

[a] History, Physical, KPS, and Labs must be performed within 7 days of 1st R-CHOP
[b]Restaging post R-CHOP to be completed 4-5 weeks following cycle #6.
[c]Echocardiography must be completed prior to initiation of radio-immunotherapy.
[d]Aspiration to include cytogenetic evaluation
[e]self administered FACT-anemia QOL questionnaire to be completed by the patient
[f]performed within 4-6 weeks of enrollment

10.3. Radioimmunotherapy Phase and Post-Radioimmunotherapy Monitoring

10.3.1 Days 0-7

10.3.2 The purpose of ^{111}In-ibritumomab tiuxetan imaging is to evaluate the biodistribution of whole body gamma camera images and to assess whether biodistribution is acceptable to proceed with ^{90}Y-ibritumomab tiuxetan administration.

10.3.3 The biodistribution of ^{111}In Zevalin should be assessed by a visual evaluation of whole body planar view anterior and posterior gamma images. A set of images at 48-72 hours after injection is required. To resolve ambiguities, optional images at other time points may be necessary. If the patient has an altered biodistribution, he/she will not receive ^{90}Y Ibritumomab tiuxetan and will be taken off study.

10.3.4 Expected biodistribution

- Easily detectable uptake in the blood pool areas (including but not limited to the heart, major abdominal blood vessels, vascular areas of the head, lungs and pelvis) on the first day image, with less activity in the blood pool areas on the second or third day image.
- Moderately high to high uptake in normal liver and spleen during the first day and the second or third day images.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image.
- Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor bearing areas in normal organs may be seen as areas of increased or decreased intensity. Those patients in CR or CRu would not be expected to have any tumor visualized.

10.3.5 Altered biodistribution

- 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.
- Kidneys with greater intensity than the liver on the posterior view of the second or third day image.

- Intense areas of uptake throughout the normal bowel comparable to the liver on the second or third day images.

10.3.6 Weeks 3-12

- History and physical examination, including performance status, will be performed at monthly intervals for 3 months following ^{90}Y-ibritumomab tiuxetan as indicated in the radioimmunotherapy calendar.
- CBC with differential and platelet will be obtained weekly for 12 weeks following administration of ^{90}Y-ibritumomab tiuxetan, or until the WBC, absolute neutrophil count, hemoglobin and platelet count have normalized. Transfusion requirements will be recorded at each evaluation.
- Comprehensive profile and LDH will be obtained at monthly intervals for three months following administration of ^{90}Y-ibritumomab tiuxetan.
- In the event that a Grade 3 or 4 hematologic toxicity occurs at any time, blood samplings for followup evaluations should be performed as clinically indicated until the abnormality is resolved. Twice or thrice weekly platelet counts, or more if clinically appropriate, should be utilized when platelets are below 50K.

10.3.7 Three (3) month evaluation (Week 12 or 13)

- History and physical examination
- Assessment of Karnofsky Performance Status
- CBC, Comprehensive profile and LDH
- FACT-an evaluation
- CT scan of the chest, abdomen, and pelvis, and PET scan (if previously positive)
- Repeat Echocardiogram to be performed between weeks 12-13.
- Peripheral blood (MSKCC Only) – nine 2-mL purple top tubes: 2 for minimal residual disease studies (to Dr. Zelenetz' lab, K1011, see **Appendix C**), 7 tubes for progenitor cell studies (to Dr. Moore's lab, RRL717, see **Appendix D**)
- Bone marrow aspirate studies (MSKCC Only) - five 2-mL pulls of bone marrow aspirate in purple top tubes will be drawn. Two tubes will be sent to Dr. Zelenetz' lab in K1011 (see **Appendix C**). Two tubes will be sent to Dr. Moore's lab in RRL 717 for progenitor cell studies (see **Appendix D**) and one tube will be sent to the flow cytometry lab for CD34+ count.
- Bilateral bone marrow biopsy, if pre-RIT bone marrow biopsy was positive.

10.3.8 Long term post-Radioimmunotherapy followup

- The same studies listed in Section 10.3.7 are performed at 6 months post-radioimmunotherapy, 12 months, and every 12 months thereafter for 2 years for patients in continued CR or CRu.
- Echocardiograms are not required after week12-13; PET is repeated only if previous study was positive and no evidence of progressive disease.

- A bone marrow aspirate for MRD studies will not be required if the patient has had less than a complete response to therapy or has relapsed. Bone marrow aspirate studies for MRD will be done for up to 2 years post-Radioimmunotherapy (MSKCC Only) - two tubes will be sent to Dr. Zelenetz' lab in K1011 (see **Appendix C**), and peripheral blood for MRD will be performed for up to 5 years.
- Peripheral blood or bone marrow aspirate for progenitor cell studies need not be performed.
- A bone marrow biopsy need only be repeated if the previous biopsy was positive.
- CT scans will be preformed at 3, 6, 12, 18, 24, 30, 36, 48 and 60 months Post RIT.

		Radioimmunotherapy Phase (II)													
Week #	**Pre-RIT***	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**12-13[1]**
History, Physical,KPS	X	X			X				X						X
CBC, diff	X	X			X	X	X	X	X	X	X	X	X	X	X
Comp.Profile, LDH	X				X				X						X
Rituxan level	X														
CT C-A-P	X														X
FACT-an															X
PET	X														X
ECHO	X														X
Bone marrow Aspirate studies	X														X[3]
Bone marrow biopsy	X														X[4]
Peripheral blood (research)	X														X[5]
Rituximab 250 mg/m2		X	X												
^{90}Y-ibritumomab tiuxetan			X												

* Pre-RIT studies overlap with the post-chemotherapy/pre-RIT studies on Part I table – studies do not need to be duplicated.

[1] These studies are repeated every 6 months for 5 years with the following exceptions: Echocardiograms are not required after week12-13; PET is repeated only if previous study was positive and no evidence of progressive disease.

[2] Bone marrow aspirate studies will be done for progenitor cell studies and MRD at week 12-13. At 6 months post RIT, 12 months post-RIT and yearly followup restaging periods for 2 years, bone marrow aspirate studies for MRD will only be performed on patients in continued CR. MSKCC ONLY

[3] A bone marrow biopsy need only be performed in patients with a positive bone marrow biopsy on pre-RIT evaluation. Once negative, repeat bone marrow biopsies are not required.

[4] Peripheral blood samples for cell progenitor studies and MRD studies will be performed at 3 months (week 12-13) and 6 months post radioimmunotherapy; subsequently, every 6 months stating at month 6 post-radioimmunotherapy (up to 5 years), the MRD studies will only be performed for patients in continued CR or CRu. MSKCC ONLY

11 ADVERSE EXPERIENCES

The toxicities of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and ^{90}Y-ibritumomab tiuxetan are listed in Section 5 of the protocol.

11.1. An objective of this study is to obtain information on the safety of the sequential administration of R-CHOP followed by ^{90}Y-ibritumomab tiuxetan for elderly patients with previously untreated DLBCL. It is the Investigator's obligation to report all adverse experiences (AE's), regardless of association with study drugs.

11.2. Definitions of AE's

11.2.1 Adverse Experience: An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and does not necessarily have to have a causal relationship or association with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or significant worsening of a pre-existing sign or symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered to be related to the medicinal product. Laboratory abnormalities should only be recorded as AE's if they are associated with clinical sequelae and/or require an intervention.

11.2.2 Serious Adverse Experience (SAE): An SAE is considered to be any experience occurring at any dose that results in any of the following outcomes: death, a life-threatening AE (at immediate risk of death from the experience as it occurred), in-patient hospitalization or prolongation of existing hospitalization, a persistent of significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death may be considered SAE's when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2.3 Expected Adverse Experience: Any AE that is identified in Section 5 is considered an expected AE.

11.2.4 Unexpected Adverse Experience: Any AE, the specificity of severity of which is not consistent with those listed in Section 5, is considered to be unexpected.

11.3. Reporting AE's

11.3.1 During the chemotherapy phase of treatment, only grade 3 and 4 toxicities will be recorded. During the RIT phase of treatment, all toxicities regardless of grade will be recorded. All AE's (serious and non-serious), regardless of relationship to study drug, are to be recorded on the AE Form (grade 3/4 toxicities) and Toxicity Form (grades 0-4) from the time of enrollment to 3 months after the administration of radioimmunotherapy, or until the administration of alternative therapy for the patient's disease, whichever comes first. Subsequent to this timeframe, only AE's that are considered by

the Investigator to be possibly related or probably associated with the administration of R-CHOP or ^{90}Y-ibritumomab tiuxetan are to be reported. The severity of AE's will be recorded on the case report form using the NCI Common Toxicity Criteria (version 2.0). These are found in **Appendix E** and on the internet at *http://ctep.info.nih.gov*. Laboratory abnormalities should be recorded as AE's only if they are associated with clinical sequelae and/or require intervention. Patient deaths at any time are to be recorded , with immediate notification to the lead investigator at MSKCC (death certificate or Death Notice to be sent)

11.4. Reporting SAE's

11.4.1 The Investigator is required to report all SAE's, regardless of cause or relationship to study drug, that come to the attention of the investigative site from the time of enrollment to 3 months after the administration of radioimmunotherapy, or until the administration of alternative therapy for the patient's disease, whichever comes first. Subsequent to this timeframe, only SAE's that are considered by the Investigator to be possibly related or probably associated with the administration of R-CHOP or ^{90}Y-ibritumomab tiuxetan are to be reported. Any SAE will be reported to the local institutions IRB. In addition, it will need to be sent to the other participating centers to report to their institution's IRB, Biogen Idec, Inc.. Pharmacovigilance and Amgen as soon as possible but no later than 7 days from the onset of the event.

- To the local institutional review board (IRB)
- To MSKCC (in the case of SAE's at collaborating institutions). To Paul A. Hamlin, MD (PI) Fax 646-422-2164 and Brett Wegner, RSA Fax: 212-557-0787
- Direct SAE reporting must be directed to Biogen Idec, Inc.. Pharmacovigilance at 877-866-IDEC (4332) (phone) or (617)679-2979 (fax).
- Direct SAE reporting must be directed to Amgen c/o International Clinical Safety 866-814-1889 (fax).

Phone reporting must be followed by a written report within 10 days using the SAE template from CRDB. A similar format will be provided to collaborating institutions for uniformity and will contain the following:

- The initials of the subjects, patient MRN#, MSKCC protocol # and title
- The date the event occurred
- A description of the SAE
- An explanation of how it was handled
- A description of the subjects condition
- Indication if the subject remains on study
- Indication if the event is considered related to the treatment
- Indication if an amendment will need to be made to the protocol and/or consent for as a result of the SAE
- Institutional procedure:

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

11.4.2 The Investigator will maintain documentation of each SAE in the Investigator's Brochure/Safety Report Binder (Biogen Idec, Inc..) at the site and should notify the IRB of the event in a timely manner. Information regarding resolution of an SAE, therapies, or procedures administered to treat the SAE and copies of the medical records, laboratory results, or the test results may be requested by Biogen Idec, Inc.. Pharmaceuticals.

11.4.3 Reporting Procedures for All Adverse Events (Amgen):
All fatal or life-threatening events considered related to study drug by the investigator must be reported to Amgen within (10) calendar days.

C/o International Clinical Safety
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Fax: 805-499-4495

The investigator should notify their Institutional Review Board (IRB) of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

12 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1. Definitions

Response and progression of disease will be evaluated in this study using a modification of the international criteria proposed by the Cheson et al.[34] Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (PET, CT, MRI, x-ray) . All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.2 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.2. Response Criteria

Response criteria will be assessed based on the post R-CHOP and Post ^{90}Y-ibritumomab tiuxetan evaluations. The criteria are as follows (GTD = Greatest Transverse Diameter; SPD = Sum of the Products of the Greatest Diameter):

12.2.1 Complete Remission (CR):

- No clinical, radiographic or diagnostic evidence of disease.
- No disease related symptoms.
- Abnormal biochemical values (eg. LDH) clearly attributable to lymphoma must have normalized.

- Lymph nodes, nodal masses regressed to "normal" size:
- If >1.5 cm before treatment, regressed to ≤ 1.5 cm in GTD.
- If 1.1 to 1.5 cm before treatment, regressed to ≤ 1 cm in GTD (or >75% in SPD).
- Spleen and all previously enlarged organs decreased in size. Spleen must not be palpable on exam
- Bone marrow free of disease on repeat aspirate and biopsy if initially positive.
- Normalization of PET scans.

12.2.2 Complete Remission/unconfirmed (CRU):

Patients meeting the above criteria for CR with the following exceptions:

- Residual node mass of >1.5 cm in GTD regressed by > 75% in SPD
- Individual nodes previously confluent regressed by >75% in SPD
- Indeterminate bone marrow (increased number or size of lymphoid aggregates without cytologic or architectural atypia.)

12.2.3 Partial Remission (PR)

- ≥ 50% decrease in SPD of the six largest dominant nodes/nodal masses.
- No increase in size of other nodes, liver or spleen.
- Splenic and hepatic nodes regressed at least 50% in SPD
- No new sites of disease.
- Bone marrow and organs other than the spleen and liver cannot be considered for evaluation for PR because involvement at these sites is considered evaluable but not measurable.

12.2.4 Relapsed Disease (RD)

- In patients previously CR or CRU:
- New node
- Size of previously involved site has increase ≥ 50% in SPD.
- ≥ 50% increase in either: GTD of any previously identified node that was >1 cm in its short axis, or
  -SPD of more than one node.

12.2.5 Stable Disease (SD)

- Patients who have achieved less than a partial remission but who have not developed findings consistent with progressive disease.

12.2.6 Progressive Disease (PD)

- In patients previously PR or SD.
- ≥ 50% increase from nadir in SPD of any previously identified abnormal node.
- Appearance of any new lesion during or at the end of therapy.

Note:

- Patients with a global deterioration of their health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective

progression, even after discontinuation of treatment.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.3. Duration of Response

-

12.3.1 Progression-Free Survival

- Time to progression is defined as the time of enrollment to the first documented progression or death. Time-to-progression analyses will treat patient withdrawals and interventions for reasons other than progression or death as independent censoring.

12.3.2 Overall Survival

- Overall survival is defined as the time of enrollment to the time of death or time of last followup.

12.3.3 Event Free Survival

- Event free survival is defined as the time of enrollment to the first documented event, with events defined as: death, relapse, progressive disease, secondary malignancy, or toxicity attributed to therapy and requiring removal from study

12.4. Response Review

- Review of response will be confirmed and validated by a selected team of investigators from the Department of Medicine with expertise in running Phase II clinical trials, and will be available for independent review as requested by Biogen Idec, Inc.. Pharmaceuticals.

13 CRITERIA FOR REMOVAL FROM STUDY

13.1. Failure to meet the eligibility criteria to receive the Radioimmunotherapy Phase of the treatment program.

13.2. Progressive disease or stable disease during or following R-CHOP therapy.

13.3. Failure to receive the next cycle of R-CHOP within 35 days of the last prior cycle of R-CHOP.

13.4. Administration of selected alternative therapy (defined as corticosteroids, standard or investigational chemotherapy or biological therapy).

13.5. Lost to followup or failure to comply with necessary follow-up as indicated in the protocol.

13.6. Decision of the patient to withdraw from the study.

13.7. If, in the opinion of the Investigator, the patient would be at unacceptably high risk for life-threatening toxicities by continuing on the study.

13.8. Patient expires.

14 BIOSTATISTICS

14.1. Study Design

This is a phase II study. The main goal is to observe the clinical efficacy in elderly patients (60 years or older) with previously untreated high risk (aaIPI 2 or 3) diffuse large B cell lymphoma by assessing the induction regimen R-CHOP followed by ^{90}Y-ibritumomab-tiuxetan (Zevalin). 65 patients will be enrolled in this study.

Part I of this study is essentially standard chemotherapy in the elderly, recapitulating the R-CHOP GELA study. Approximately 2/3 of patients will achieve complete remission (CR) or partial remission (PR). Therefore, 43 patients are expected to be eligible for part II of this study. During Part II, Zevalin will be administered to those patients in CR/PR with adequate hematologic parameters.

Overall survival rates in the Shipp et al. IPI database [1] for age greater than 60 patients at 2 years were 48% for high-intermediate risk patients and 31% for high risk patients. 70% and 30% of patients had high-intermediate risk and high-risk disease, respectively. Thus, overall the survival rate at two years for high-intermediate and high risk groups combined in the Shipp et at. study is 43%. This overall survival rate represents all patients treated – OS data for patients achieving a CR/PR are not reported. The 43 patients in the second part of this study allow us to detect a 20% difference in overall survival at two years with type I error 0.1 and 0.90 power. An improvement in PFS/OS >20% will be deemed a positive study. PFS was not calculated in the Shipp et al. study, but a relapse free survival rate at 2 years for high-intermediae and high-risk groups combined is 55.8% and will be used as an estimate for PFS.

At the end of the study, Kaplan-Meier curves will be generated for overall survival, progression free survival and event free survival. As a second endpoint, the conversion rate to CR with ^{90}Y-ibritumomab tiuxetan for patients with a PR post R-CHOP can be estimated. The response rate by R-CHOP can be estimated within +/- 12%. Finally, the predictive value of minimal residual disease for overall and progression free survival, as detected by molecular techniques for disease relapse/recurrence, will be evaluated utilizing a log-ranked analysis.

In Part I, endpoints related to anemia will be evaluated in the setting of darbepoetin support. Descriptive statistics will report the incidence and severity of anemia, days of anemia, time to anemia, and change in hemoglobin from baseline. Hgb response and correction will be defined as: an increase of ≥2.0 gm/dl from baseline and an Hgb ≥12.0 g/dl, respectively, in the absence of RBC transfusion in the preceding 21 days.

QOL analysis will be performed utilizing the self-administered FACT-anemia questionnaire, a well-validated instrument in cancer studies [11,35,36] that incorporates the FACT-G general assessment with symptom specific scales for fatigue and anemia (FACT-an). Scoring will be performed according to the FACT-anemia scoring schema in Appendix K. The compliance rate at each assessment will be estimated by the ratio of completed questionnaires actually completed to the number of patients alive at each assessment. Summary statistics will be presented for each time point and correlation with baseline hemoglobin levels and change in hemoglobin levels with darbepoetin evaluated. The nature of missing data will be evaluated and an appropriate longitudinal analysis method will be used to analyze the quality of life scores.

14.2. Stopping Rule

14.2.1 The trial will be stopped early if there is a ≥15% incidence of prolonged hematologic toxicity at the 3 month evaluation post phase II RIT. Prolonged hematologic toxicity will be defined as a absolute neutrophil count <1.5 K/μl, Hgb ≤8 gm/dl, or platelets ≤100,000 for patients without evidence of recurrent disease. If >10 patients have prolonged hematologic toxicity at the 3 month evaluation post RIT, there will be 95% confidence that a ≥15% incidence of prolonged hematologic toxicity has been reached, necessitating early stopping of the protocol.

14.2.2 The trial will be stopped early and re-evaluated if the first five consecutive patients experience prolonged hematologic toxicity as defined above. If the first three consecutive patients experience prolonged hematologic toxicity, a decrease in dose to 0.3 mCi/Kg may be considered.

14.2.3 Additionally, the trial will be suspended and continued accrual will be re-evaluated if there are 4 or more patients among the first 20 patients who require hospitalization because of the administration of Zevalin.

14.2.4 To receive ^{90}Y-ibritumomab tiuxetan, patients must meet the criteria described in Section 9.1.4. The results of this study may not be applicable generally if a sizable fraction of patients does not go on to receive ^{90}Y-ibritumomab tiuxetan. If any 11 of the first 33 patients do not proceed to receive ^{90}Y-ibritumomab tiuxetan, the appropriateness of the sample size will be reviewed with the biostatics department at the time of the 11th patient. If necessary, the sample size will be adjusted and addressed in a protocol amendment.

14.3. Sample Size and Accrual Rate

Approximately 25-35 patients will be accrued per year. It is expected that the duration of the entire study should be approximately 3 years. MDACC may enroll a maximum of 20 patients.

15 SUBJECT REGISTRATION AND RANDOMIZATION PROCEDURES

Research Participant Registration

The following person(s) can obtain informed consent:

Principal Investigator:	Paul A. Hamlin, M.D.*
Co Principle Investigator:	Andrew D. Zelenetz, M.D., Ph.D.*
Responsible Investigators:	Craig Moskowitz, M.D.*
	Steven Horwitz, M.D.*
	John Gerecitano, MD*
	Joseph Jurcic, M.D.*
	Tarun Kewalramani, M.D.*
	Ariela Noy, M.D.*
	Owen O'Connor, M.D., Ph.D.*
	M. Lia Palomba, M.D.*
	Carol S. Portlock, M.D.*
	David Straus, M.D.*

The following person(s) can obtain informed consent at MDACC:

Principal Investigator:	Maria Alma Rodriguez, M.D.*
Responsible Investigators (Consenting individuals)	
	Luis Fayad, MD
	Frederick Hagemeister, MD
	Larry Kwak, MD, PhD
	Peter McLaughlin, MD
	Sattva Neelapu, MD
	Barbara Pro, MD
	Jorge Romaguera, MD
	Felipe Samaniego, MD
	Anas Younes, MD

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

For Participating Centers:

Central registration for this study will take place at Memorial Sloan-Kettering Cancer Center. All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

Once eligibilty has been established, the patient is assigned an MSKCC Clinical Research Database (CRDB) patient number. This number is unique to the patient and must be written on all data correspondence for the patient.

16 DATA MANAGEMENT ISSUES AND QUALITY ASSURANCE

16.1. A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2. Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and followup will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times of year, or more frequently if indicated. All documentation of AE's, records of study drug receipt and dispensation, and all IRB correspondence will be retained for at least 2 years after the investigation is completed.

16.3. The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan Kettering Cancer Center

16.4. For patients treated at participating institutions, the institution will be responsible for filling out MSKCC Case Report forms (CRFs) and submitting them to MSKCC (via fax) bimonthly. Blank case report forms will be sent to the data managers at each site (for photocopying and use). When a patient is off-study, MSKCC should be alerted within 14 days, and all forms need to be sent no later than 4 weeks after the off-study date. Participating centers must fax CRFs to (212) 557-0787 to the attention of Brett Wegner. Forms can also be mailed to the following: Memorial Sloan Kettering Cancer Center, Clinical Trials Office, Brett Wegner, 633 Third Ave – 15th Floor, New York, NY 10017

17 PROTECTION OF HUMAN SUBJECTS

17.1. Privacy

It is the responsibility of the Research Staff to ensure that Memorial Sloan-Kettering Cancer Center has on file a written acknowledgment of receipt by the subject of the Center's Notice of Privacy Practices. If the subject has not already done so, he/she must sign such an acknowledgment before participating in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2. Potential Risks

Potential risks and adverse experiences associated with the drugs in this study program are described in Section 5.

17.3. Potential Benefits

CHOP or R-CHOP is the treatment of choice for elderly patients with DLBCL. However, many patients who obtain a complete or partial response to therapy will relapse from their disease. While some older patients can be salvaged with high-dose chemotherapy and an autologous stem cell transplant, others are too advanced in age to tolerate this procedure. In such cases, salvage treatment is palliative. It is hoped that by treating patients in CR or PR following R-CHOP, the administration of ^{90}Y-ibritumomab tiuxetan will increase the cure rate by eliminating minimal residual disease, with minimal additional toxicity.

17.4. Provisions for Preventing and Treating AE's

Treatment of febrile neutropenia and cytopenia will be in accordance with MSKCC guidelines. Rituximab administration will be premedicated with acetaminophen and diphenhydramine (or chlorpheniramine), as well as Ativan to prevent infusion-related AE's. Infusion will be titrated as described in the Rituxan Package Insert (See **Appendix A**). In the event of an adverse reaction, the infusion will be stopped, the patient will be assessed, and treatment will be administered in accordance with standard medical practice. Patients will also receive standard anti-emetics as prophylaxis against nausea and vomiting with R-CHOP therapy.

17.5. Alternatives/Options for Treatment

Patients who refuse to participate in this study will be offered standard therapy, which includes CHOP or R-CHOP. Alternative chemotherapy regimens such as CEPP may be considered for patients in whom CHOP or R-CHOP would not be considered safe.

17.6. Costs

The patient will be responsible for all costs related to treatment and complications associated with R-CHOP chemotherapy. Biogen Idec, inc. Pharmaceuticals will provide Rituximab given during the Radioimmunotherapy Phase of the study. Biogen Idec, Inc.. Pharmaceuticals will provide the cost of ^{90}Y-ibritumomab tiuxetan and ^{111}In-ibritumomab tiuxetan , its preparation, and administration. Testing for minimal residual disease studies and progenitor cell studies will also be provided by Biogen Idec, Inc. The patient will be responsible for the costs of all scans, standard laboratory tests, and hospitalizations during the course of this study.

17.7. Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Only qualified individuals from MSKCC, the FDA, and Biogen Idec, Inc.. Pharmaceuticals will be able to review patient medical records. Neither the patients' names nor other identifying information will be used in reports or publications arising from this study.

18 INFORMED CONSENT PROCEDURES (see Appendix I)

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

Patients potentially eligible for this trial will be informed about the nature of their disease and the standard treatment options will be discussed. Enrollment in this trial will be offered and the expected benefits and potential risks involved with this treatment program, including risks associated with the various agents and procedures, will be explained. A written informed consent form reiterating these points will be provided for review. Patients wishing to enroll will be required to sign three copies of the consent form; one will be returned to the patient, one will be filed in the patient's chart, and one copy will be filed with the Clinical Trials Office. Individuals authorized to obtain written consent include Attending Physicians from the Lymphoma Service listed in Section 15.

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