

**PHASE II TRIAL OF YTTRIUM-90-IBRITUMOMAB TIUXETAN (ZEVALIN®)
RADIOIMMUNOTHERAPY AFTER CYTOREDUCTION WITH ESHAP CHEMOTHERAPY
IN PATIENTS WITH RELAPSED FOLLICULAR NON-HODGKIN'S LYMPHOMA
(PROTOCOL # 106-P158; 009-004-ZEV)**

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Protocol Signature Page

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Protocol Version/Date:

28 August 2017

I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with FDA and ICH GCP guidelines and all other applicable regulatory requirements. I also will ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol.

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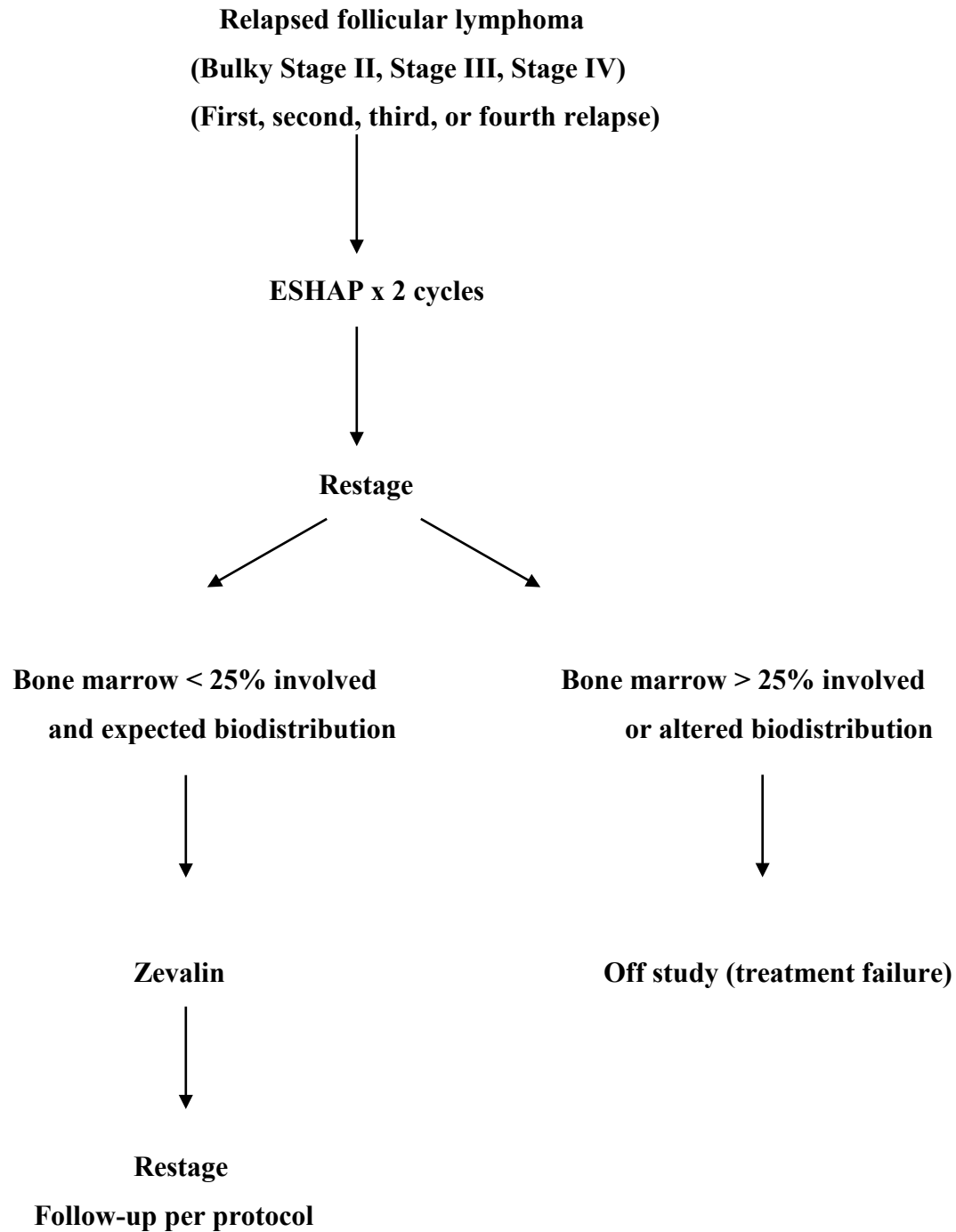
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Study Schema



1 BACKGROUND/RATIONALE

1.A Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas (NHL) are a diverse group of lymphoid neoplasms that collectively rank fifth in cancer incidence and mortality in the United States.^[1, 2] The incidence and prevalence of NHL has risen 150% over the past few decades.^[3, 4] The incidence of NHL increases with age and males are affected about 1.5 times more often than females.

The majority of non-Hodgkin's lymphomas is of B-cell origin and can be categorized according to the International Working Formulation (IWF) or the Revised European American Lymphoma (REAL) classification.^[5-7] The use of the WHO modified REAL classification of non-Hodgkin's lymphomas is strongly encouraged. The estimated median survival time for patients with follicular lymphoma is 7-10 years from initial diagnosis.^[8-13]

Transformation of low-grade NHL to a more aggressive subtype has been reported to occur in about 25% - 60% of patients over time.^[9, 10, 14,15] Patients with low-grade NHL usually present with advanced disseminated disease.^[11, 12, 16,17] Chemotherapy treatment with or without radiotherapy can lead to remissions; however, virtually all treated patients repeatedly relapse^[18] with shorter remissions following each subsequent course of chemotherapy.^[9-13, 19] Although there have been several additions to the oncologist's chemotherapy repertoire, no chemotherapeutic regimen has been shown to be superior to another in prolonging survival in follicular NHL,^[14, 20-22] and there has been little to no change in survival in the past 30 years.

Thus, follicular non-Hodgkin's lymphomas (NHL) pose a particularly difficult dilemma for clinicians and new treatment strategies are needed.

1.B Overview of Chemotherapy for Follicular Lymphoma

With the exception of a small fraction of patients (10% - 15%) with truly localized disease, as noted above most patients with indolent lymphoma do not achieve long-term remissions.^[23,24] Because conventional chemotherapy regimens have not been shown to improve survival in this disease compared with a policy of expectant therapy,^[23] many asymptomatic patients are followed with "watchful waiting." Symptomatic patients are commonly treated with oral alkylating agents (e.g., chlorambucil), or with an alkylating agent (cyclophosphamide) in combination with a vinca alkaloid and corticosteroids (CVP), but studies have not demonstrated a survival advantage for patients treated with these regimens.

Because of the curative potential of anthracycline-based regimens (e.g., CHOP) for aggressive NHL, CHOP has been tested extensively by the Southwest Oncology Group (SWOG) in patients with indolent lymphomas.^[25-28] Four hundred fifteen patients with low-grade malignant lymphomas were treated with CHOP (with or without BCG and/or levamisole) between 1972 and 1983 on SWOG-7204, SWOG-7426, and SWOG-7713. Approximately 90% of these patients achieved objective responses, including 61%-78% with complete remissions.^[25-27] With a median follow-up of 12.8 years, the median survival was 6.9 years.^[28] Toxicities included myelosuppression, nausea, paresthesias, infection, and cardiomyopathy (<5%). Unfortunately, these studies failed to demonstrate a plateau on the survival curves of patients treated with CHOP, indicating that by itself CHOP has little curative potential for indolent lymphomas, in contrast to its efficacy for diffuse large cell lymphomas.^[28] Whether cures with CHOP are possible for patients with follicular lymphomas remains controversial, with conflicting studies from several institutions.^[29-32] Nevertheless, all investigators agree on the necessity of developing better treatment for patients with indolent lymphomas.

Newer chemotherapy agents (fludarabine, 2-chlorodeoxyadenosine) have shown considerable activity in patients with relapsed low-grade lymphomas; however, no study has demonstrated that these drugs are curative in indolent lymphomas or that survival is prolonged by their use. SWOG-9501 investigated the combination of fludarabine plus mitoxantrone in patients with newly diagnosed follicular lymphomas. This regimen was well tolerated and produced a high response rate, but the survival curves do not appear superior to those obtained with other regimens, including CHOP.^[33] Other chemotherapy regimens which have been found to be effective for relapsed indolent lymphoma include ESHAP,^[34, 35] which has published response rates ranging from 36% to as high as 82%.

High-dose chemoradiotherapy with bone marrow or peripheral blood stem cell transplantation is commonly employed for treatment of patients with relapsed lymphomas of all types. Preliminary data from the Dana Farber Cancer Institute suggest the disease-free survival after transplantation for follicular lymphomas relates to the quality of initial morphological remission obtained and the ability to decrease the number of cells bearing clonal rearrangements of the bcl-2-oncogene (which is present in 80% of newly diagnosed follicular lymphomas).^[36] However, the curability of indolent lymphomas with stem cell transplantation and the advisability of performing this procedure are controversial.

1.C Monoclonal Antibody Therapy of B-Cell Non-Hodgkin's Lymphoma

Attempts to treat B-cell malignancies with immunotherapy using monoclonal antibodies reactive against B-cell antigens, began over a decade ago.^[37-41] In early studies using murine monoclonal antibodies, responses were limited by the development of human anti-mouse antibody (HAMA), by the relative inability of mouse antibodies to recruit human immune effector mechanisms for tumor killing, and by down-regulation of the target antigen.^[42] Efficacy could also be limited by circulating free antigen.

Recent approaches that have been taken to improve the clinical outcome of immunotherapy include:

- use of chimeric, humanized, or PRIMATIZED[®] antibodies to reduce antibody immunogenicity (HAMA);
- choice of target antigen that does not modulate, internalize, and/or shed from the cell surface;
- use of new high-yield manufacturing procedures allowing higher dosing levels;
- use of radioimmunoconjugates and other immunotoxins.

1.C.1 Rituximab

Rituximab (Rituxan[®], MabThera[®]) is a chimeric IgG1 kappa monoclonal antibody, with mouse variable and human constant regions. It specifically recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas.^[43] The CD20 antigen is a suitable target for treatment of B-cell lymphomas because it does not circulate in the plasma as free protein that could block targeting of an antibody to lymphomas,^[44] does not internalize upon anti-CD20 antibody binding, and does not shed from the cell surface after antibody binding.^[45]

In vitro studies have demonstrated that rituximab binds human complement and lyses lymphoid B-cell lines through CDC (complement dependent cytotoxicity) and antibody-dependent cellular cytotoxicity. Rituximab has also been shown to have antiproliferative effects in tritiated thymidine incorporation assays and to directly induce apoptosis, while other anti-CD19 and CD20 antibodies do not.^[46]

Rituximab (Rituxan[®]) is licensed in the United States as therapy for patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma (NHL) (See the appropriate

Appendix for the Package Insert); in Europe, rituximab (MabThera®) is licensed as therapy for patients with stage III-IV follicular lymphoma who are chemo resistant or are in their second or subsequent relapse after chemotherapy. In an open-label, single arm, multi-center pivotal trial, 166 patients with relapsed disease received four weekly infusions of 375 mg/m² rituximab.^[47] Ninety-one percent of patients (151 of 166) were evaluable for efficacy and an overall response rate of 50% with 6% CR and 44% PR was achieved. Median time to progression for responders was 13.2 months.^[48, 49] Other studies have demonstrated the activity of rituximab in patients with both treated and untreated lymphomas.^[50, 51] Despite the encouraging clinical results and success of rituximab, 40%-50% of patients with indolent lymphomas and 60%-70% of patients with aggressive lymphomas fail to respond to single-agent rituximab, only 5%-10% of patients attain complete remissions, and the median duration is only approximately 1 year. Consequently, many investigators have begun exploring methods of enhancing the potency of antibodies, including combining them with chemotherapy and conjugating them to toxins or radionucleotides.

Czuczman conducted a pilot trial administering CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) with rituximab to 40 patients with indolent lymphoma. Objective remissions were observed in 38 patients (95%), including 22 CRs (55%), with a median time-to-treatment failure of more than 29 months.^[52] In SWOG 9800, 85 evaluable patients with previously untreated advanced stage indolent lymphoma who were treated with 6 cycles of CHOP followed by four doses of rituximab were reported by Maloney et al.^[53] to have an overall response rate of 72% with 54% complete remissions and a 2-year progression-free survival rate of 74%. CHOP plus rituximab is currently being further evaluated in previously untreated advanced indolent lymphoma in SWOG 0016, a randomized phase III trial (SWOG 0016) comparing CHOP plus rituximab with CHOP plus Iodine-131 Tositumomab (Bexxar).

1.D Radioimmunotherapy of Lymphoma

Radiolabeled monoclonal antibodies are efficacious in treating NHL for the following reasons: lymphocytes and lymphoma cells are inherently sensitive to radiotherapy^[54]; the local emission of ionizing radiation by radiolabeled antibodies may kill cells with or without the target antigen in close proximity to the bound antibody; and penetrating radiation may obviate the problem of limited access in bulky or poorly vascularized tumors.

Early investigations of therapeutic radiolabeled antibodies for B-cell lymphoma were performed with iodinated antibodies.^[55-60] (Detailed below in **Section 1.D.1**) However, the development and improvement of methods for attaching metal chelating groups to proteins have made it possible to study other potentially useful radioisotopes such as ⁹⁰Yttrium (⁹⁰Y). (Detailed below in **Section 1.D.2**.) ⁹⁰Yttrium has several advantages over ¹³¹I and for these reasons, has been selected for this study.

As a pure, high-energy, beta-emitting isotope, ⁹⁰Y can deliver more energy to the tumor (2.3 MeV versus 0.6 MeV of beta energy for ¹³¹I) and the longer pathlength ($\chi^{90} = 5$ mm versus 1 mm for ¹³¹I)^[61] may allow tumor cells in the vicinity of the antibody-bound cell to be killed without direct binding of the antibody.^[62] These characteristics may be especially advantageous in the treatment of poorly vascularized tumors. The shorter half-life of ⁹⁰Y (2.7 days versus 8 days for ¹³¹I) approximates the biological half-life of the radiolabeled antibody, which may minimize toxicity to nontarget organs. Because ¹³¹I emits penetrating gamma rays (0.35 MeV), patients receive an increased whole body dose. In addition, patients require the following: 1) shielding to protect hospital staff, 2) restrictions in travel, activities, the use of bedroom and bathroom facilities to limit exposure to family and the public, and 3) possible hospitalization. Furthermore, dehalogenation of ¹³¹I leads to accumulation of free iodine in the

thyroid, posing the risk of hypothyroidism; this risk is present in patients treated with prophylactic potassium iodide as well. The isotope, ^{90}Y , is a pure beta emitter and can therefore be given on an outpatient basis without patient restrictions.

While the beta emitter, ^{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 efficiency.^[63-66] Characteristics of ^{90}Y and ^{131}I are summarized in Table 1.

Table 1.
Comparative Properties of ^{90}Y and ^{131}I

Properties	^{90}Y	^{131}I
Energy	Beta emitter (2.3 MeV)	Gamma (0.36 MeV)/Beta (0.6 MeV) emitter
Path Length	5 - 10 mm	1 - 2 mm for beta component
Administration	Always outpatient	Can require hospitalization
Half-life	64 hours	192 hours

1.D.1 Iodine-131 Anti-B1 Antibody Clinical Experience

In the initial Phase I/II, open-label study of non-myeloablative doses of Iodine-131 anti-B1 antibody for the treatment of patients with B-cell NHL of all histologic types,^[67-69] 59 patients were enrolled. Twenty-eight patients had low-grade NHL, 14 had transformed low-grade NHL, 15 had intermediate-grade NHL, and 2 had high-grade NHL. The median time from diagnosis was 45 months, the median number of prior therapies was four, 88% had stage III or IV disease, 36% had bulky disease, 51% had an elevated LDH, and 24% had failed bone marrow transplant (BMT). Patients received one to three dosimetric doses followed by a therapeutic dose. The dosimetric dose(s) involved the IV administration of 5 mCi of Iodine-131 anti-B1 antibody to determine the rate of whole body clearance so that a whole body radiation dose (cGy) could be calculated. Each dosimetric dose was preceded by 0, 95, or 475 mg of unlabeled antibody. Therapeutic dose-escalation was initiated at 25 cGy and adjusted in 10 cGy increments until the maximum tolerated dose (MTD) was reached. Fifty-three of the 59 patients received a therapeutic dose. The MTD was 75 cGy for patients who had not undergone BMT. Based on all data published in August 2000, a response was observed in 42/59 (71%) patients and a complete response (CR) was observed in 20/59 (34%) patients. The median progression free survival (PFS) was 12 months for responders and 20.3 months for those who achieved a CR. Seven of the 59 patients were in CR at time of publication. Responses were observed in 50% of post-BMT patients and 52% of bulky disease patients. A response was observed in 24/28 (86%) patients and a CR was observed in 13/28 (46%) patients with low-grade NHL. A response was observed in 11/14 (79%) patients and a CR was observed in 7/14 (50%) patients with transformed low-grade NHL. Dose-dependent pharmacokinetics were observed. The mean tumor dose was 14.5 times the whole body dose. The dose-limiting toxicity was hematologic: three patients developed a platelet count $< 10,000$ cells/mm³ and two patients had an absolute neutrophil count (ANC) < 100 cells/mm³. The most prevalent non-hematologic toxicities were transient, mild to moderate fever, nausea, asthenia, and chills. Ten of 59 (17%) patients developed human anti-murine antibodies (HAMA).

In the Phase II, multicenter, (dosimetry validation) open-label study of non-myeloablative doses of Iodine-131 anti-B1 antibody for the treatment of patients with low-grade B-cell lymphomas and

transformed low-grade lymphomas, [70] 37 patients had low-grade NHL and 10 had transformed low-grade NHL. The median time from diagnosis was 41 months, the median number of prior therapies was four, 91% had Stage III or IV disease, 44% had bulky disease, 44% had an elevated LDH. Patients received one dosimetric dose followed by a therapeutic dose. The dosimetric dose involved the IV administration of 450 mg of unlabeled antibody and 35 mg (5 mCi) of Iodine-131 anti-B1 antibody to determine the rate of whole body clearance so that a whole body radiation dose (cGy) could be calculated. The therapeutic dose involved IV administration of 450 mg of unlabeled antibody and 35 mg of Iodine-131 anti-B1 antibody with radioactive Iodine-131 titrated to deliver 75 cGy. Forty-five of the 47 patients received a single dosimetric and therapeutic dose of Iodine-131 anti-B1 antibody as described in the protocol. A response was observed in 27/47 (57%) patients and a complete response (CR) was observed in 14/47 (30%) patients. The median duration of response was 248 days (95% confidence interval: 136 days to upper limit not reached) and median duration of CR was not reached (95% with ongoing responses ranging from 245-606 days. A CR was observed in 9/37 (24%) patients with low-grade NHL. A response was observed in 6/10 (60%) patients and a CR was observed in 5/10 (50%) patients with transformed NHL. The mean tumor dose was 10.6 times the whole body dose. The dose-limiting toxicity was hematologic: five patients developed a platelet count <10,000 cells/mm³ and, mild to moderate asthenia, nausea and fever. Only one of 46 (2%) patients developed HAMA following treatment as assessed by centralized validated HAMA assay.

Press and colleagues studied myeloablative doses of the same radioiodinated antibody (anti-B1, Coulter Pharmaceuticals) with autologous stem cell support in Phase I and II trials in Seattle. [71,72] Twenty-nine patients with multiple relapsed B cell lymphomas were treated with single agent I-131-anti-CD20 (B1) antibody (2.5 mg/kg, 280 to 785 mCi) followed by autologous hematopoietic stem cell rescue between 2/90 and 7/94. Objective responses occurred in 86% of patients, including 79% complete responses. Early toxicities included Grade 4 myelosuppression in all patients, Grade 2-3 nausea in 8 of 29, and fatal sepsis in one. Reversible cardiopulmonary failure was the dose-limiting non-hematopoietic toxicity (2 pt.), occurring at an estimated absorbed lung dose of 27 Gy. Overall survival and progression-free surviving patients had long-term objective impairment of performance status or cardiopulmonary function, though one patient with a pre-existing anthracycline-induced cardiomyopathy remained on digoxin (with an ejection fraction of 69%) four years after radioimmunotherapy. No serious delayed cardiopulmonary complications occurred. Late toxicities were minimal, except for elevation of the thyroid stimulating hormone level in 59% of the subjects. Two patients who had been heavily pretreated with alkylating agents and external beam irradiation developed acute leukemia eight years after radioimmunotherapy. Two patients developed secondary solid neoplasms 3 years after treatment (1 noninvasive transitional cell carcinoma of the bladder; 1 metastatic colon cancer).

In SWOG 9911, 90 eligible previously untreated patients with advanced indolent lymphoma treated with six cycles of CHOP followed 4-8 weeks later by tositumomab/iodine I 131 tositumomab (anti-CD20 antibody) [73, 74] had an overall response rate to the entire treatment regimen of 90%, including 67% complete remissions and 23% partial remissions. Twenty-seven (57%) of the 47 fully evaluable patients who achieved less than a CR with CHOP had an improved remission status after tositumomab/iodine I 131 tositumomab. With a median follow-up of 2.3 years, the 2-year progression-free survival was estimated to be 81%, with a 2-year overall survival of 97%. Treatment was well tolerated. Reversible myelosuppression was the main adverse event and was more severe during CHOP chemotherapy than following radioimmunotherapy. As noted above, CHOP plus I-131 tositumomab is being evaluated further in advanced previously untreated indolent lymphoma in the randomized, phase III trial S0016.

1 D. 2 ⁹⁰Y Zevalin

a. Background

⁹⁰Y Zevalin is a unique compound composed of the following: a murine IgG1 kappa monoclonal antibody ibritumomab (IDEC-2B8); the linker chelator tiuxetan (isothiocyanatobenzyl MX-DTPA); and the radioisotope ⁹⁰Y that is securely chelated via the linker. Like its unlabeled chimeric counterpart, rituximab, ⁹⁰Y Zevalin targets the CD20 antigen present on 95% of B cell lymphomas.^[75] ¹¹¹In Zevalin is the ¹¹¹Indium-labeled murine monoclonal antibody used for imaging and dosimetry. Rituximab, a chimeric mouse/human antibody, is given initially to clear peripheral B lymphocytes and optimize biodistribution of the radiolabeled antibody.

In single-dose safety studies with ibritumomab (IDEC-2B8) performed in mice and guinea pigs, no overt toxicity was seen within seven days of dosing. Tumor localization studies with ¹¹¹In Zevalin performed in athymic mice demonstrated that concentrations of ¹¹¹In Zevalin increased steadily in tumor, but did not accumulate in blood or other tissues. Biodistribution studies performed in mice with ⁹⁰Y Zevalin demonstrated minimal bone accumulation (< 1.5% injected dose/gram after 3 days).

b. Zevalin® Clinical Experience

Zevalin radioimmunotherapy has been evaluated in seven clinical trials (see Table 2). The first two trials (106-01 and 106-02) differed from subsequent trials in the following ways:

- The murine ibritumomab antibody was used instead of the chimeric rituximab antibody as the cold antibody infused prior to Zevalin
- Dosing was based on total mCi rather than mCi/kg
- Stem cells were collected prior to radioimmunotherapy

Because of these differences, 106-01 and 106-02 have been excluded from the integrated safety summary.

Table 2.
Summary Zevalin Clinical Trials

Study	Type	Patient Population	Description	No. of Patients	⁹⁰ Y Zevalin Intended Dose
106-01 106-02	Phase I/II	Low- or intermediate-grade B-cell lymphoma	Dose-escalating	18	10 - 50 mCi
106-03	Phase I/II	Low- or intermediate-grade or mantle cell NHL	Dose-escalating	51	0.2, 0.3, 0.4 mCi/kg
106-04	Phase III Randomized	LG/F/T NHL	Zevalin vs.Rituximab control	73 70	0.4 mCi/kg N/A
106-05	Phase II	LG/F/T NHL mild thrombocytopenia	Single arm	30	0.3 mCi/kg
106-06	Phase III Nonrandomized	Rituximab refractory follicular NHL	Prior treatment served as control	57	0.4 mCi/kg
106-98	Open label	LG/F/T NHL	Open label	138	0.3-0.4 mCi/kg

b.1 Summary of Safety Results

The safety profile of Zevalin is summarized for patients who received ^{90}Y Zevalin as a mCi/kg dose in five clinical trials (106-03, 106-04, 106-05, 106-06, 106-98; N = 349). Results revealed that adverse events (AEs) are primarily hematologic with Grade 4 neutropenia, thrombocytopenia, and anemia occurring in 30%, 10% and 4.0% of patients, respectively. Most nonhematologic AEs were Grade 1 or 2 and the incidence was comparable to that seen with rituximab therapy. Median serum immunoglobulins remain largely within the normal range and a low incidence of severe infection was noted despite a 6-month reversible depletion of B cells. Incidence of HAMA/HACA is low and a HAMA or HACA response did not result in unusual toxicity. Myelodysplasia has been reported for 1.4% of patients, well within the expected background rate for this heavily pretreated patient population. [x, 76]

b.2 Summary of Efficacy Results

Knox administered Yttrium-90-labeled anti-CD20 antibodies to 18 patients with relapsed B cell lymphomas (4 treated with Y-90-tositumomab antibody and 14 with ibritumomab tiuxetan) in escalating single doses of 13.5 to 50 mCi.^[77] Six complete remissions and seven partial responses were observed (overall response rate, 72%), with a median response duration of 6 months. Four patients developed human anti-mouse antibodies (HAMA). Grade 4 myelosuppression was seen at doses above 50 mCi of 7-90, but no other serious toxicities were observed.

In a multi-center Phase I/II trial dose-finding study (106-03), Witzig et al treated 51 patients with relapsed or refractory non-Hodgkin's lymphoma with Ibritumomab Tiuxetan (Y2B8, Zevalen®).^[78] Eligibility criteria included an ANC > 1,500/mm³, platelets \geq 100,000/mm³ and bone marrow involvement < 25%. Median age was 60 years. Patients had a median of two prior regimens (range, 1-7). In the phase I portion of the trial, patients received either 100 or 250 mg/m² of unlabeled rituximab (to clear peripheral B-cells and improve biodistribution) followed by Indium-111-ibritumomab tiuxetan (5 mCi on Day 1 for imaging and Y-90-ibritumomab tiuxetan 0.2, 0.3, or 0.4 mCi/kg on Day 8. The optimal dose of unlabeled rituximab was determined to be 250 mg/m² and 0.4 mCi/kg was the maximally tolerated dose of Yttrium-90. In an intent-to-treat analysis the overall response rate was 67%, including 26% CRs and 41% PRs. Thirty-four patients with low grade lymphoma achieved an 82% overall response rate (26% CRs, 56% PRs), 43% of 14 aggressive lymphomas responded, and none of the three patients with mantle cell disease responded. Estimated time to progression for intent to treat was 12.9 months and estimated median duration of response was 11.7 months. Hematologic toxicity was dose-limiting. Thrombocytopenia was the most common hematologic event. Hematologic toxicity was transient and reversible. Only one patient developed an immune response.

Witzig et al ^[79,80] (106-04) conducted a randomized phase III trial in 143 patients with relapsed or refractory low-grade, follicular, or CD 20+ transformed NHL. Patients received either ibritumomab tiuxetan, 0.4 mCi/kg (maximum of 32 mCi) or rituximab, 375 mg/m² weekly for 4 weeks. Eligibility required an ANC \geq 1,500/mm³, a platelet count \geq 100,000/mm³, and bone marrow involvement < 25%. As assessed by International Workshop Response Criteria, ^[81] patients who received ibritumomab tiuxetan achieved an overall response rate (ORR) of 80% (73 patients) compared with 56% (70 patients) for patients on the rituximab arm (p = 0.002). Complete response (CR) rates were 30% for the ibritumomab tiuxetan group and 16% for the rituximab group (p = 0.04), with an additional 4% of

patients in each arm achieving an unconfirmed CR. The estimated (Kaplan-Meier) median duration of response was 14.2 months versus 12.1 months, respectively ($p = 0.6$) and time to progression (TTP) was 11.2 versus 10.1 months, respectively ($p = 0.173$). For the 113 patients with follicular histology (113 of the 143 patients), the overall response rate was 86% in the 90-Y- ibritumomab tiuxetan group versus 55% in the rituximab group ($P < 0.001$), and the estimated median TTP was 12.6 months for the 90-Y-ibritumomab tiuxetan group and 10.2 months for the rituximab group ($P = 0.062$). The estimated median DR for patients with follicular lymphoma patients treated with 90-Y ibritumomab tiuxetan was 18.5 months versus 12.1 months for the rituximab control group ($P = 0.371$). Durable responses of ≥ 6 months were 64% versus 47% ($P = 0.030$), respectively. Although the differences in duration of response and TTP were not significant between arms, ORR and CR were significantly higher in the ibritumomab tiuxetan group. Time to progression was longer in CR/CRu patients treated with 90-Y-ibritumomab. Within the group of patients with follicular lymphoma 74% had DR ≥ 6 months, 59% ≥ 9 months, and 47% ≥ 12 months on the 90-Y-ibritumomab tiuxetan arm. Reversible hematologic toxicity was seen in patients treated with ibritumomab tiuxetan.

In an open-label trial, ^[82, 82a] 54 patients with follicular lymphoma were accrued to learn whether patients who had failed to achieve a partial remission or CR (complete response) to rituximab or had a response that lasted less than 6 months would respond to radioimmunotherapy with Y-90-ibritumomab tiuxetan. The median age was 54 years and patients had received a median of four prior regimens. Forty-four percent of patients had bulky disease (defined as ≥ 7 cm) and 32% had bone marrow involvement. Using the International Workshop Response Criteria, the overall response rate was 74% with Y-90-ibritumomab tiuxetan and the complete response rate was 15%. The duration of response was 7.7 months for ibritumomab tiuxetan compared to 4 months for prior rituximab in these patients ($p < 0.001$). Median time to progression had not been reached at the time of the report.

A fourth study, based on findings in the phase I portion of Study 106-03, confirmed the safety of the dose of 0.3 mCi/kg (11 MBq/kg) (maximum 32 mCi (1.2 GBq) in patients with mild thrombocytopenia (100,000 to 149,000 platelets/mm³) and demonstrated significant clinical activity in this population with an 83% ORR (37% complete response, 6.7% complete response unconfirmed, and 40% partial response as assessed by International Workshop Criteria). ^[83] Patients with follicular lymphoma had an overall response rate of 92%, and estimated median TTP of 10.8 months (12.6 months for responders).

Long-term follow-up information for the patients with B-cell NHL from the four registrational trials of Zevalin conducted between 1996 and 1999 has become available.

In 2002, Gordon et al ^[84] reported on long-term follow-up of the patients with diffuse mixed and diffuse large cell lymphoma (all of whom had had prior CHOP or CHOP-like regimens) treated in the phase I/II study. The median age of this group was 58 years and the overall response rate was 58% (33% CRs). At 35.5 months of follow-up (range, 2.4-40+ months), the median duration of response had not been reached. Toxicity was primarily hematologic with Grade 4 neutropenia in 17% and thrombocytopenia in 8%. Hematologic toxicity was reversible.

More recently ^[85] follow-up for the entire group of 51 patients in the phase I/II study was reported. The overall response rate (ORR) in all patients was 73% (51% CR/Cru, 22% PR). The ORR in patients with follicular lymphoma was 85% and 58% in patients with diffuse large B-cell lymphoma. Median time to progression (TTP) in responders was 12.6 months and DR was 11.7 months. Median TTP and duration of response (DR) for CR/Cru patients were 13.4 months and 12.4 months,

respectively. Median TTP and DR for CR/Cru patients treated at the 0.4 mCi/kg (14.8 MBq/kg) dose were 28.3 and 27.5 months, respectively. Median TTP and DR for patients in CR who were treated at the 0.4 mCi/kg (14.8 MBq/kg) dose was 45.0 and 44.0 months, respectively. Median TTP in DLBCL patients was 4.6 months in all 12 patients, including 7 responders and 5 nonresponders. Median DR in the seven responders was 49.8 months. The reason for the large difference between TTP and DR in DLCL group is that the rapid progression in the nonresponders lowered the median TTP. Median follow-up in this study is 28.5 months for all patients and 63 months for ongoing responders. Nine patients (24% of responding patients) (five with FL and four with DLCL) had a TTP of more than 3 years. Five of the 9 patients (14% of all responders) (3 with FL and 2 with DLCL) are still in remission (DR range, 60-70+ months).

Schilder et al ^[86] provide long-term follow-up data for the 211 patients with B-cell NHL treated in the four registrational trials of 90-Y ibritumomab conducted between 1996 and 1999. Of these patients, 153 patients (73%) had follicular lymphoma (FL). With ongoing follow-up, long-term durable responses (> 12 months) were reported for 37% of all 211 patients and for 39% of patients with follicular lymphoma. Median DR and TTP for long-term responder patients were 28 months (range, 11-80) and 29 months (range, 12-82), respectively, with a median follow-up of 50 months (range, 13-82). The median DR to the last prior therapy for LTR patients was 12 months. The CR and CRu among LTR patients was 65%, and the median DR and TTP were 29 and 31 months, respectively, for CR/CRu patients. In ongoing responders, the median DR is 52 months (range, 48-80). Compared to the overall LTR patients, LTR patients with FL had similar disease characteristics, DR, TTP, and CR/CRu rates. Failure to respond to the therapy given immediately prior to treatment with Zevalin did not appear to affect the ability to achieve long-term responses with the agent.

c. Summary of Dosimetry Results

Dosimetry has been performed on a total of 205 patients. A central analysis of the dosimetry data was completed for 179 of those patients. Initial MIRDose3 estimates of radiation absorbed dose to uninvolved organs and red marrow, completed at the clinical site, were used to determine patient eligibility for RIT. All patients studied with dosimetry met the protocol defined criteria for proceeding with ⁹⁰Y Zevalin treatment, with estimated radiation absorbed doses below the maximum allowable of 2000 cGy for uninvolved organs and 300 cGy for red marrow. Subsequent to ⁹⁰Y Zevalin treatment, a central dosimetry analysis was performed by a collaboration between Oak Ridge Associated Universities (ORAU) and the Mayo Clinic. This provided a uniform analysis of the patient blood and imaging data.

A 5 mCi tracer dose of ¹¹¹In Zevalin was used for imaging and dosimetry. The radiation absorbed doses from ¹¹¹In Zevalin and ⁹⁰Y Zevalin were estimated from blood and imaging data obtained during the week following ¹¹¹In Zevalin injection. The radiation absorbed doses from ¹¹¹In Zevalin were minimal. The median estimated radiation absorbed doses from 5 mCi ¹¹¹In Zevalin were 15 cGy to spleen, 11 cGy to liver, 5 cGy to lungs, 3 cGy to kidneys, and 2 cGy to red marrow. The radiation absorbed doses from ⁹⁰Y Zevalin were more significant. The median radiation absorbed doses from ⁹⁰Y Zevalin were 742 cGy to spleen, 450 cGy to liver, 211 cGy to lungs, 23 cGy to kidneys, and 62 cGy to red marrow. The mean whole blood effective half-life of ⁹⁰Y Zevalin was 27 +/- 5 hours.

Hematologic toxicity did not correlate with any of the dosimetric or pharmacokinetic parameters analyzed, including blood derived red marrow dose, sacral image-derived red marrow dose, total body dose, blood effective half-life, or blood AUC. Patients were effectively screened for safe treatment using clinical selection criteria including percent bone marrow involvement with NHL (< 25%), baseline

platelet count ($> 100,000$ cells/mm³). Patients were treated safely using individualized dosing based on patient weight and platelet count.

These findings indicate that dosimetry is not necessary for the safe administration of ⁹⁰Y Zevalin in this defined patient population.

1.E Rationale for Current Protocol

As detailed above, radioimmunoconjugates are effective treatments in relapsed/refractory follicular lymphoma when used as single agents and can result in prolonged disease control. These remissions can be extremely durable in patients with the greatest reduction in tumor burden. Radioimmunoconjugates used as consolidative treatment following a course of initial chemotherapy for patients with newly discovered follicular lymphoma produce durable remissions and appear to have changed the overall survival in this disease for the first time in 30 years.

Subset analyses of I-131 tositumomab studies have shown that the response rate is greater in individuals with decreased disease burden. In the University of Michigan experience of 59 patients treated for relapsed NHL, those with non-bulky disease had a higher response (82%) than did those with bulky disease (52%). Complete response was better in patients with no bulk vs. bulky disease, 37% vs. 29% respectively. [87] A multicenter phase III study published in 2001 demonstrated similar results. This study showed that patients with decreased tumor burden had improved response (81%) vs. patients with greater tumor burden (39%). [88] Finally, a recently published study of I-131 tositumomab in recurrent indolent and transformed B-cell NHL showed again the importance of reduced tumor volume. In this study patients with decreased tumor mass had a 100% overall response rate (ORR) vs. a 60% ORR in patients with increased tumor mass. [89]

Long-term outcome information for patients with relapsed/refractory indolent lymphoma treated with Y-90-ibritumomab tiuxetan indicates that durable long-term responses (> 5 years) can be obtained in a significant proportion of patients with follicular lymphoma and that improvements in CR rates improve TTP. [85, 86]

The recent analysis by the Southwest Oncology Group of long-term outcomes obtained in sequential Southwest Oncology Group clinical trials for previously untreated indolent lymphoma since 1974, [90] clearly demonstrates the impact of monoclonal antibody therapy in the management of follicular lymphoma. In this analysis, all previously untreated, advanced stage follicular lymphoma patients treated with three sequential treatment approaches (CHOP chemotherapy +/- non-specific immunostimulants (SWOG 7426 and 7713, 1974-1978); ProMACE-MOPP +/- interferon (SWOG 8809, 1988-1994); and CHOP followed by monoclonal antibody (MoAb) therapy (SWOG 9800 [CHOP-Rituximab] and SWOG 9911 [CHOP-I-131 tositumomab, 1998-2000) were evaluated for 4-year progression free survival (PFS) and 4-year overall survival (OS) by treatment strategy. Results are shown below in Tables 3a and 3b.

TABLE 3a.**Progression-Free Survival by Treatment Strategy**

TREATMENT	N	DEATH/PROGRESSION	4-YR PFS
CHOP + MoAb	179	75	61%
ProMACE	425	290	48%
CHOP	356	257	46%

TABLE 3b.**Overall Survival by Treatment Strategy**

TREATMENT	N	DEATH	4-YR OS
CHOP + MoAb	179	18	91%
ProMACE	425	189	79%
CHOP	356	226	69%

These results demonstrate that PFS remained unchanged until the recent studies that utilized CHOP followed by a monoclonal antibody for initial treatment. In contrast to PFS, OS has increased with each subsequent treatment strategy. These data are consistent with the hypotheses that initial therapy with chemotherapy followed by a monoclonal antibody has significant impact on PFS ($p = 0.005$) and OS ($p < 0.0001$).^[90]

Our hypothesis is that radioimmunoconjugates significantly change outcome for patients with follicular lymphoma when given in the situation of minimal residual disease. We propose to test this hypothesis prospectively in previously treated patients using a phase II trial design evaluating the combination of ESHAP chemotherapy (methylprednisolone, etoposide, cisplatin, cytarabine) followed by Zevalin. For this prospective test of cytoreduction of the tumor burden followed by radioimmunoconjugate therapy, an outpatient formulation of ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) will be used as a means of reducing the mass of disease. We propose to use this regimen for a few reasons. First, ESHAP has very good efficacy as a salvage regimen in treating relapsed low-grade lymphomas. One study^[35] showed a 75% ORR and 36% CR rate in patients with relapsed disease.

Second, although ESHAP is very active in low-grade NHL, it is not often utilized by community oncologists as a salvage regimen. Therefore, most pretreated patients have not seen these agents and therefore their lymphomas should be responsive to ESHAP. After treatment with two cycles of preparative ESHAP most patients should have minimal residual disease and therefore have higher response to Zevalin. It is our hypothesis that tumor mass reduction with standard chemotherapy in relapsed follicular lymphoma will result in a significant prolongation of time to progression following Zevalin therapy, changing the natural history of relapsed disease.

The TTP and OS results of this study will be compared with reported outcomes in published trials of Zevalin alone to assess whether there is sufficient improvement to merit further study of this approach in this setting. We have designed the trial to detect an increase in 1-year PFS from a historical value of 50% to 67.3%, which corresponds to an increase in median TTP from 12 months to 21 months.

2 OBJECTIVES

2.A Primary Objectives

- 2.A.1 To evaluate the 1-year progression-free survival (PFS) of patients with relapsed follicular non-Hodgkin's lymphoma (NHL) treated with ESHAP chemotherapy for cytoreduction (2 cycles) followed by Ibritumomab tiuxetan (Zevalin) radioimmunotherapy.
- 2.A.2 To evaluate the median TTP of patients with relapsed follicular NHL treated with ESHAP chemotherapy for cytoreduction (2 cycles) followed by Ibritumomab tiuxetan (Zevalin) radioimmunotherapy.

2.B Secondary Objective

- 2.B.1 To evaluate the overall (ORR) and complete response rates (CR) of patients with relapsed follicular NHL treated with ESHAP chemotherapy for cytoreduction (2 cycles) followed by Ibritumomab tiuxetan (Zevalin) radioimmunotherapy.

3 STUDY DESIGN

3.A Treatment Summary

After informed consent has been obtained, patients will undergo screening to assure eligibility for the study. After two cycles of ESHAP have been given, patients will be restaged to determine response. Patients with residual involvement of more than 25% of bone marrow after the two cycles of ESHAP will be taken off treatment and followed for time to progression and survival. Patients experiencing disease stabilization or reduction with less than 25% residual bone marrow involvement will undergo imaging for biodistribution. If biodistribution is acceptable, then patients will receive the Zevalin treatment and undergo a second disease evaluation for response assessment. Thereafter, patients will be followed at 6 month intervals (Short-term follow-up) for 2 years, and then annually (Long-Term follow-up) for an additional 3 years

3.B Study Duration

The estimated active accrual period for this study is 5 years. After completion of treatment, patients will be followed for 5 years to allow determination of study endpoints.

4 STUDY POPULATION

4.A Inclusion Criteria

- 4.A.1 All patients must have a history of relapsed follicular non-Hodgkin's lymphoma. Patients must be in first, second, third, or fourth relapse.
- 4.A.2 Lymphomas must express the CD20 antigen as demonstrated by either flow cytometry or immunoperoxidase staining of paraffin sections using anti-CD20 antibodies.

- 4.A.3 Patients must have bulky Stage II, Stage III, or Stage IV extent of disease by the Ann Arbor classification (see Appendix F). Bulky disease is defined as any tumor measuring 10.0 cm or greater or occupying \geq one-third of the chest diameter.
- 4.A.4 All patients must have bidimensionally measurable disease (as defined in Appendix D) documented within 28 days prior to C1, Day 1.
- 4.A.5 Pathology Review: Adequate sections from the diagnostic specimen or core needle biopsies which are large enough to show architecture (bone marrow biopsies and fine-needle aspirates are insufficient) is desirable. At a minimum, a report documenting the diagnosis is required.
- 4.A.6 Patients must have a unilateral or bilateral bone marrow aspirate and biopsy performed within 28 days prior to Cycle 1, Day 1.
- 4.A.7 Patients must have a CT or PET scan of chest, abdomen, and pelvis within 28 days prior to Cycle 1, Day 1.
- 4.A.8 Patients must have an LDH and β -2 microglobulin within 28 days prior to Cycle 1, Day 1.
- 4.A.9 Patients must have received prior chemotherapy for lymphoma.
(Patients must have had at least 1, but no more than 4 prior chemotherapy regimens for lymphoma. This includes investigational agents and/or other antibody therapy. All prior therapy must have been completed at least 3 weeks prior to registration. Patient who previously received rituximab must have completed this therapy 6 weeks prior to registration. If rituximab is given as a single agent after relapse, it is considered a separate regimen and will be counted as such. If the rituximab is given in combination for either the first or second relapse or as consolidation after a chemotherapy regimen without an intervening relapse, it will be considered part of the combination regimen and counted as one prior therapy. Patients must have recovered from any prior-therapy-related toxicities prior to Cycle 1, Day 1.)
- 4.A.10 All patients must have a Zubrod performance status of 0, 1, or 2 (see Appendix B).
- 4.A.11 Patients must be 18 years old or older.
- 4.A.12 Patients must have absolute neutrophil count (segmented neutrophils and bands) \geq 1,500 / μ L and platelets $>$ 100,000/ μ L within 28 days prior to Cycle 1, Day 1 unless decreased counts have been shown to be due to marrow involvement with NHL.

NOTE: For progression to treatment with Zevalin: Patients must have $<$ 25% bone marrow involvement with lymphoma as determined after cycle 2 of ESHAP. For patients without bone marrow involvement, there must be adequate bone marrow reserves as defined under EXCLUSION. (These criteria must be strictly met for adequate patient safety.)

Additionally, patients must have:

- serum creatinine value ≤ 2.0 and total bilirubin ≤ 2.0 .
 - Platelet counts $\geq 150,000/\text{mm}^3$, these patients will receive a dose of 0.4 mCi/kg of Zevalin
 - Platelet counts from $100,000/\text{mm}^3$ to $149,000/\text{mm}^3$, these patients will receive a 0.3 mCi/kg dose of Zevalin
- 4.A.13 Patients with renal insufficiency or renal failure (serum creatinine > 2.0 mg/dL; creatinine clearance < 50 ml/min) are not eligible for this study. A serum creatinine or creatinine clearance must be obtained within 28 days prior to Cycle 1, Day 1.
- 4.A.14 Pregnant or nursing women may not participate. Women or men of reproductive potential must agree to use an effective contraceptive method as determined by the treating physician from the time of Cycle 1, Day 1 to 6 months after receiving the Zevalin.
- 4.A.15 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for 5 years.
- 4.A.16 If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day. **In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.**
- 4.A.17 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and federal guidelines.
- 4.A.18 Expected survival ≥ 3 months

4.B Exclusion Criteria

- 4.B.1 Patients with impaired bone marrow reserve, as indicated by one or more of the following:
- Platelet count $< 100,000$ cells/ mm^3
 - Hypocellular bone marrow (cellularity $\leq 10\%$)
 - Marked ($\geq 10\%$) reduction in bone marrow precursors of one or more cell lines (granulocytic, megakaryocytic, erythroid) (beyond that which would be expected for the patient's age and bone marrow cellularity)
 - History of failed stem cell collection
- 4.B.2 Prior radioimmunotherapy

- 4.B.3 Presence of CNS lymphoma. Patients must not have clinical evidence of central nervous system (CNS) involvement by lymphoma.
- 4.B.4 Patients with abnormal liver function: total bilirubin > 2.0 mg/dL
- 4.B.5 Patients with abnormal renal function: serum creatinine > 2.0 mg/dL or creatinine clearance < 50 ml/min.
- 4.B.6 Patients who have received prior external beam radiation therapy to > 25% of active bone marrow (involved field or regional)
- 4.B.7 Patients who have received G-CSF or GM-CSF therapy within 2 weeks prior to treatment
- 4.B.8 Serious nonmalignant disease or infection which, in the opinion of the investigator and/or the sponsor, would compromise other protocol objectives
- 4.B.9 Major surgery, other than diagnostic surgery, within 4 weeks
- 4.B.10 Patients with pleural effusion

4.C Number of Patients to be Enrolled

All patients who receive at least one dose of chemotherapy ESHAP will be considered evaluable and will be included in the analysis. Fifty-two evaluable patients are needed. Although it is considered highly unlikely that a patient who has given consent (enrolled) for treatment would not be treated, if this were to occur, an additional patient would be enrolled to meet the goal of 52 evaluable patients.

4.D Patient Enrollment Procedure

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will be accepted. All patients will be registered centrally with the Clinical Research Coordinator based in the Arizona Cancer Center at 520-694-9053. The Clinical Research Coordinator will assign each patient a sequential number. Prior to registration, the fully signed informed consent must be presented and all inclusion and exclusion criteria will be reviewed with the registering investigator or designee. All source documentation needed to confirm eligibility must be available for this review.

5 STUDY PROCEDURES

5.A Screening/Baseline Evaluations

Unless otherwise specified, the following evaluations must be performed within 28 days prior to C1, D1:

- 5.A.1 Medical history, including documentation of all prior lymphoma treatments and documentation of the rationale for treatment of the patient's lymphoma with Zevalin

- 5.A.2 Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).
- 5.A.3 Disease Assessment
- Total of all measurable indicator lesions
 - CT or PET scan of the chest, abdomen and pelvis is recommended for baseline response evaluation.
- 5.A.4 Laboratory tests including:
- Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT (AST), SGPT (ALT)
 - Serum beta-2-microglobulin
 - Pregnancy test (serum) for women of childbearing potential
 - Hepatitis B screen (encouraged by Good Medical Practice, but not required)
- 5.A.5 Unilateral or Bi-lateral bone marrow biopsy and aspirate for histology and determination of percent bone marrow involvement
- 5.A.6 Bone marrow cytogenetics (Results are not required prior to enrollment). This can also be done with the repeat Bone Marrow biopsy and aspirate at Cycle 2, Day 29. This does not have to be done at each Bone Marrow biopsy and aspirate, but does need to be completed at either, Baseline or Cycle 2, Day 29.
- 5.A.7 Pathology Review: All patients registered on this study are encouraged to undergo pathology review. The purpose of this review is to verify the histologic diagnosis of an indolent non-Hodgkin lymphoma and that the patients are CD20 positive. Any excess tissue will be retained by the Arizona Cancer Center (unless the patient denies consent).

a Pathology materials are to be submitted to:

Lisa Rimsza, M.D.
Department of Pathology
The University of Arizona Cancer Center
1501 N. Campbell Avenue
Tucson, AZ 85724-0001
Phone: (520) 626-2212

b The following materials would constitute best available material for review:

- Representative H&E stained slides from the diagnostic biopsy. (Note: Needle aspirates are not adequate for this submission. Consult Dr. Rimsza if adequacy of the specimen is in question.)
- One representative paraffin block which will be conserved (no more than eight additional slides will be cut).
- One copy of the pathology report.

5.B Evaluations During ESHAP Treatment Period

For the purpose of toxicity assessment, the treatment period will include the time from the first ESHAP infusion to 30 days following Zevalin infusion. Evaluations during the 2 cycles of ESHAP are outlined in Appendix A.

5.B.1 ESHAP Cycle 1, Day 1

- a. Begin ESHAP Treatment (Please refer to Section 7A for ESHAP administration)

5.B.2 ESHAP Cycle 2, Day 1

- a. History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).
- b. Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine
- c. Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.

5.B.3 ESHAP Cycle 2, Day 29

- a. History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).
- b. Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine
- c. Unilateral or Bi-lateral bone marrow biopsy and aspirate for histology and determination of percent bone marrow involvement
- d. Bone marrow cytogenetics. Does not have to be done at each Bone Marrow biopsy and aspirate, but does need to be completed at either, Baseline or Cycle 2, Day 29.
- e. Disease Assessment:
 - Total of all measurable indicator lesions.
 - CT or PET scan of the chest, abdomen and pelvis
- f. Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.

5.C Evaluations During the Zevalin Imaging & Treatment Period

Ibritumomab Tiuxetan Indium (^{111}In Zevalin) regimen is administered 4 – 6 weeks after completion of ESHAP.

5.C.1 Day 1

- a. History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status are to be performed within 28 days of Rituximab & Zevalin administration. (Appendix B).
- b. Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.
- c. Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine

The above mentioned tests and assessment are to be performed within 28 days of Rituximab & Zevalin administration.

- d. Rituximab Infusion (250 mg/m²) & ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) infusion. (Please refer to section 7.B for detailed treatment administration)

5.C.2 Days 2, 3, 4 and 5

- a. Gamma Scan: A scan is to be performed at 48-72 hours after ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) infusion. Another optional scan may be performed at 90-120 hours after ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) infusion.

CAUTION WILL BE TAKEN IN THE HANDLING OF ALL RADIOACTIVE SAMPLES ACCORDING TO STANDARD PROCEDURES AND PRACTICES AT THE CLINICAL SITE.

The purpose of ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) imaging is twofold:

- To evaluate biodistribution of whole body gamma camera images
- To assess whether biodistribution is acceptable to proceed with ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) radioimmunotherapy.

The biodistribution of ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) 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. Images should be acquired using a large field of view gamma camera quipped with a medium energy collimator. Whole body anterior/posterior planar images should be acquired using a large field-of-view gamma camera and medium energy collimators. Suggested gamma camera settings: 256 x 1024 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min for the 48-72 hour scan, and 7-10 cm/min for subsequent scans.

➤ Expected biodistribution:

- Activity in the blood pool areas (heart, abdomen, neck, and extremities) may be faintly visible.
- Moderately high to high uptake in normal liver and spleen.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel.
- Non-fixed areas within the bowel lumen that change position with time; delayed imaging as described above may be necessary to confirm gastrointestinal clearance.

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. Tumor visualization on the ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) scan is not required for ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) therapy.

➤ Altered biodistribution

- Intense localization of radiotracer in the liver and spleen and bone marrow indicative of reticuloendothelial system uptake
- Increased uptake in normal organs (not involved by tumor) such as:
 - Diffuse uptake in normal lung more intense than the liver.
 - Kidneys with greater intensity than the liver on the posterior view.
 - Fixed areas (unchanged with time) of uptake in the normal bowel greater than uptake in the liver.
 - In less than 0.5% of patients receiving ^{111}In Zevalin (Ibritumomab Tiuxetan Indium), prominent bone marrow uptake was observed, characterized by clear visualization of the long bones and ribs.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) dose. The safety and efficacy of the administration of ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) in patients with prominent marrow uptake is not known. Possible causes of prominent bone marrow uptake, such as bone marrow involvement by lymphoma, increased marrow activity due to recent hematopoietic growth factor administration, and increased reticuloendothelial uptake in patients with HAMA and HACA, should be considered. Re-assessment of biodistribution after correction of underlying factors should be performed. ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) should not be administered to patients with persistently prominent marrow uptake on the repeat biodistribution scans.

5.C.3 Day 7, 8 or 9

- a. Rituximab Infusion & ^{90}Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) Infusion (Please refer to section 7.B for detailed treatment administration)

5.C.4 Day 35 (+/- 7 days)

- a. Laboratory tests including:

Complete blood count (CBC) with differential and platelet count. To be done every week until any count abnormalities have passed nadir.

5.D Restaging

5.D.1 3 Months Post- ⁹⁰Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) Infusion

The following tests/evaluations will be obtained 3 months (+/- 7 days) post ⁹⁰Y Zevalin Infusion:

- a. History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).
- b. Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine
 - LDH
- c. Disease Assessment:
 - Total of all measurable indicator lesions.
 - CT or PET scan of the chest, abdomen and pelvis
- d. Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.

5.E Follow-Up Evaluations

5.E.1 Short-Term Follow-Up Period

- a. The following tests/evaluations will be obtained at 6-month intervals (+/- 7 days) for a period of 2 years (24 months) following the Zevalin:
 - History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).
 - Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine
 - LDH
 - Disease Assessment (Only required at 6-month intervals for a period of 2 years (24 months) following Zevalin):
 - Total of all measurable indicator lesions.
 - CT or PET scan of the chest, abdomen and pelvis (Restaging of disease by CT scan is recommended every 6 months up to Month 24, then annually until year 5).

5.E.2 Long-Term Follow-Up Period

a. The following tests/evaluations will be obtained annually (+/- 30 days) for an additional 3 years after the completion of the Short-Term Follow-Up period:

- History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).
- Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine
 - LDH
- Disease Assessment:
 - Total of all measurable indicator lesions.
 - CT or PET scan of the chest, abdomen and pelvis

Once the patients have completed the Short-Term Follow-Up period they will continue to be followed for 3 years on an annual basis (+/- 30 days) for survival and disease status. Patients should be followed by physical exam and, if clinically indicated by Good Medical Practice, CT or PET scans. Patients will be followed for 3 years or until patient starts alternate treatment or is removed from study to allow determination of study endpoints.

5.F Disease Progression Evaluations/Off-Study

Patients who develop disease progression during the treatment period and who do not begin other anti-cancer therapy will continue to be followed for routine safety and efficacy for a total of 30 days following any discontinuation of treatment for any cause.

5.F.1 Tests to be Performed When a Patient is Determined to Have Disease Progression or is Removed from the Study for any Reason

The following tests will be performed within 4 weeks after a patient has demonstrated progression of disease, or removed from study:

It is strictly mandated that patients not be given other myelosuppressive anti-neoplastic agents until recovery from hematologic nadir.

These tests do not have to be repeated if they were performed within 7 days prior to documentation of disease progression.

- a. History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).
- b. Laboratory tests including:
 - Complete blood count (CBC) with differential and platelet count
 - Serum chemistries - BUN, creatinine

- LDH
- c. Disease Assessment (if patient is removed from the study for a cause other than progressive disease):
 - Total of all measurable indicator lesions.
 - CT or PET scan of the chest, abdomen and pelvis
- d. Toxicity Assessment: Adverse Events (AE) are to be recorded on an ongoing basis until resolved or determined to be permanent. All AEs are to be documented on appropriate source documents at the clinical site and in the patient's case report form.

6 DRUG INFORMATION

6.A. ESHAP Regimen Drug Information

6.A.1. Cisplatin (CDDP) (Platinol®) (NSC-119875)

a. DESCRIPTION

Cis-diamminedichloroplatinum (Patinol or cisplatin) is a heavy metal complex and is water-soluble. It is a white lyophilized powder with a molecular weight of 300.1.

b. TOXICOLOGY

Human Toxicology: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are alopecia, seizures, loss of taste and allergic reactions. Tetany may occur due to hypomagnesemia and/or hypocalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, papilledema, cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Kinetics: After a single IV dose, increased concentration is found in the liver, kidneys and a small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25-49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 43% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of actions are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates into CNS poorly.

Formulation: Cisplatin is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of Sterile Water for Injection USP, respectively. Cisplatin is also available as an aqueous solution, 1 mg/ml, in 50 or 100 ml vials.

Storage and Stability: The intact vials may be stored at room temperature (15-25 degrees C) for the lot life indicated on the package. Do not refrigerate. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. The reconstituted solution is stable for 20 hours at room temperature, although, due to lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2 NS (precipitate occurs in D5w).

Administration: In this protocol, cisplatin will be given immediately after preparation as an intravenous infusion over a 60 minute period. **Needles or intravenous sets containing aluminum parts that may come in contact with cisplatinum (Platinol) should not be used for preparation or administration, as a black precipitate is formed with 30 minutes.**

Supplier: Cisplatin is commercially available for purchase by a third party.

6.A.2 Cytosine Arabinoside (Ara-C) (Cytarabine) (Cytosar U) (NSC-63878)

a. DESCRIPTION

Ara-C is chemically 4-amino-1-S-D-arabino-furanosyl-2 (1H)-primidinone. Ara-C is metabolized to its active form, ara-CTP. The ara-CTP functions as an inhibitor of DNA polymerase. Ara-C exhibits cell phase specificity, killing cells

undergoing DNA synthesis (S phase) and may also block cells from progressing to S phase from G1. Extensive chromosomal damage, including chromatid breaks, occurs. Ara-C appears to be most effective in tumors with high growth fraction.

b. TOXICOLOGY

Human Toxicology: Side effects of ara-C include myelosuppression, nausea, vomiting, diarrhea, anorexia, anal ulceration, stomatitis, rash, headache, fever, myalgia, malaise, bone pain, chest pain, hepatic and renal dysfunction, and alopecia. Central nervous system toxicity, i.e., significant cerebral and cerebellar dysfunction, progression to coma, has been seen with high doses. Severe cardiomyopathy has been reported with high dose ara-C in combination with cyclophosphamide. Progressive ascending paralysis has occurred in two patients receiving IV and intrathecal ara-C. Marked keratoconjunctivitis has also occurred with high doses.

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever. Paraplegia and meningitis has been reported with intrathecal administration. Ara-C given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. If used intrathecally if high dose therapy is used, do not use a diluent containing benzyl alcohol.

Ara-c can cause fetal harm when administered to a pregnant woman, however, there are no adequate and well-controlled studies in pregnant women.

c. PHARMACOLOGY

Kinetics: Ara-C is metabolized by deoxycytidine kinase and related kinases to nucleotide triphosphate, which is an active inhibitor of DNA polymerase. Deoxycytidine prevents or delays cytotoxic activity. The active form is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. The balance of kinase and deaminase levels appears to be an important factor in sensitivity/resistance of the cell to ara-C. After IV injection, plasma disappearance of ara-C is biphasic. Initial half-life is 10 minutes, delayed half-life is 1-3 hours. After 24 hours, 80% is excreted in the urine as its inactive metabolite, ara-U. After a single IV administration of ara-C, levels in CSF are low. With intrathecal administration, half-life is 2 hours. There is little conversion to ara-U because of low CSF levels of deaminase. Drug interaction of ara-C has been reported with digoxin, gentamycin and fluorocytosine.

Formulation: Ara-C is supplied as a sterile powder in 100 mg and 500 mg vials for injection. Ara-C is also available in 1 and 2 gram vials. The drug should be reconstituted with sterile water for injection.

Storage and Stability: The sterile powder should be stored at room temperature 15 degrees to 30 degrees C (59-86 degrees). The resulting solution has a stability of 48 hours if stored at ROOM TEMPERATURE. Do not use if even a slight haze

develops. The reconstituted solution may be further diluted in 5% Dextrose or sodium chloride injection.

Administration: Ara-C is usually administered by continuous IV infusion, but IV bolus and subcutaneous use have their place in treating certain leukemic responses (i.e., maintenance or remission).

Supplier: Ara-C is commercially available and therefore should be purchased by the third party.

6.A.3 Etoposide (VP-16) (Vespesid) (Ethylidene-Lignan P.) (NSC-141540)

a. DESCRIPTION

Chemistry: VP 16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, and has antineoplastic properties in experimental animals, and in man. The empiric formula C₂₉H₃₂O₁₃ has a molecular weight of 588.

Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of titrated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L1210 system, activity was schedule-dependent, having greater effect with a twice-weekly administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated 1210.

b. TOXICOLOGY

Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, Leukopenia, and lymphoid involution occur in mice, rats, and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immunosuppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell-mediated immunity).

Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12 – 16 days from the initiation of therapy. Bone marrow

suppression is mainly manifested as granulocytopenia, with thrombocytopenia transient modest nausea, vomiting and diarrhea, are common. Other reactions could include aftertaste, rash, pigmentation, pruritis, abdominal pain, constipation and dysphagia. Occasional alopecia is reported. VP-16 does not produce phlebitis, or nephrotoxicity. Rarely, anaphylactic-like reactions have been reported, as well as, hypotension. Hypotension can be managed by infusing the drug over at least a 30-minute period. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of VP-16 administration. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other anti-neoplastic agents. VP-16 can cause fetal harm when administered to pregnant women.

Pregnancy and Lactation: Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. In these studies, etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity. Fetal abnormalities included decreased weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. No information is available on excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Kinetics: After IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4 – 11 hours. Drug does not accumulate in plasma following daily administration of 100 mg/M² for 4 – 5 days. Drug crosses blood-brain barrier poorly. Recovery after IV administration of radiolabeled etoposide in the urine ranges from 42 – 67% and feces from 0 – 16%. The mutagenic and genotoxic potential has been established in mammalian cells.

Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in Sterile Multiple Dose Vials for injection. The pH of the yellow clear solution is 3 – 4. Each ml contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. VP-16 must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/ml it is stable for 48 hours.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported.

Administration: VP-16 has a minimum infusion time of 30 minutes to reduce hypotension. In this protocol, VP-16 will be given over 60 minutes.

Supplier: VP-16 is commercially available for purchase by a third party.

6.A.4 Methylprednisolone sodium succinate (Solu-Medrol)

a. DESCRIPTION

Methylprednisolone is a glucocorticoid that is given intravenously.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with methylprednisolone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Kinetics: Methylprednisolone is extremely soluble in water. It is well-suited for intravenous use and high levels are obtained rapidly. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Methylprednisolone	Dexamethasone	Prednisone	Hydrocortisone	Cortisone
4 mg	0.75 mg	5 mg	20 mg	25 mg

Formulation: Several formulations are available. Act-O-Vial® comes in 40 mg/mL, 125 mg/2 mL, and 500 mg/4 mL. Another available formulation is 500 mg/8 mL.

Storage and Stability: The unconstituted product may be stored at room temperature 20° to 25° C. The product in solution can also be stored at room temperature. The solution must be used within 48 hours. The product must be protected from light.

Administration: Methylprednisolone is administered by the intravenous route.

Supplier: Methylprednisolone is commercially available and should be purchased by third party.

6.B Rituximab Drug Information

6.B.1 DESCRIPTION

Rituximab is a mouse/human chimeric monoclonal antibody consisting of human IgG1 heavy and kappa light chain constant regions with murine variable regions from the murine IgG1 kappa anti-human CD20 monoclonal antibody rituximab. The rituximab antibody is produced by a Chinese hamster ovary transfectoma.

6.B.2 TOXICOLOGY

Human Toxicology: Single doses of up to 500 mg/m² and weekly x 4 doses of 375 mg/m² have been administered without dose limiting toxicity. Adverse events are most common during the initial antibody infusion and usually consist of Grade 1, or 2 fever (73%), asthenia (16%), chills (38%), nausea (19%), vomiting (11%), rash (14%), and tumor site pain (3%). Grade 1 or 2 hypotension (8%) may be treated with IV fluids. Hematologic toxicity is usually mild and reversible. Transient decreases in the WBC or platelet count have been observed – especially in patients with high levels of circulating tumor cells or bone marrow involvement. Two patients have had late-onset Grade 4 neutropenia at four and ten months that was attributed to an unknown cause, were transient and resolved. Infections (Grade 1 and 2) have not been related to dose level. Symptoms are generally associated with the initial antibody infusions and diminish in frequency with each successive infusion.

Infusion Reaction: An infusion-related symptom complex consisting of fever and chills/rigors has occurred in the majority of patients during the first rituximab infusion. Other frequent infusion-related symptoms include nausea, urticaria, fatigue, headache, pruritis, bronchospasm, dyspnea, sensation of tongue or throat swelling (angioedema), rhinitis, vomiting, hypotension, flushing, and pain at disease sites. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen).

Tumor Lysis Syndrome: Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk for developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed.

Other viral infections: The following additional serious viral infections, either new, reactivated, or made more severe have been reported in some patients receiving rituximab in combination with chemotherapy. These viral infections include JC virus (which can lead to progressive multifocal leukoencephalopathy [PML], a rare and often fatal disease), cytomegalovirus (CMV), herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to 18 months after discontinuation of the rituximab and resulted in death. Because there are no warning

signs of PML, you should contact your study doctor immediately if you experience major changes in vision or unusual eye movements, loss of balance or coordination, or periods of disorientation or confusion. You should also contact your study doctor right away if you have a persistent cough, fever, chills, congestion, or any flu-like symptoms while receiving rituximab (or several months after discontinuation of rituximab therapy). These symptoms may be signs of a serious infection.

The following risks were updated per the Cancer Therapy Evaluation Program's (CTEP), National Cancer Institute (NCI) Action Letter dated June 16th, 2010.

Likely

- Fever
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)
- Chills

Less Likely

- Lack of enough red blood cells (anemia)
- Thickening of blood/serum as found in Waldenstrom's macroglobulinemia (a cancer of certain blood cells)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Belly Pain
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Swelling of the arms and/or legs
- Fatigue or tiredness
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat and difficulty breathing.
- Infection
- Awakening of viruses which have been latent/dormant
- Infection in HIV positive patients
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Decrease in the total number of white blood cells (leukocytes)
- Increased blood sugar level
- Decreased blood level of calcium
- Decreased blood level of potassium
- Joint pain
- Back pain

- Muscle pain
- Pain in the area of the tumor
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Abnormal drowsiness or sluggishness, an unusual lack of energy
- Convulsion or seizure
- Sudden or traumatic injury to the kidney
- Stuffy or runny nose, sneezing
- Sudden constriction of the small airways to the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Decrease in the oxygen supply to a tissue
- Inflammation of the lungs that may cause difficulty breathing and can be life threatening
- Sore throat
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Swelling of body tissue underneath the skin
- Hives
- Sudden reddening of the face and/or neck
- High blood pressure
- Low blood pressure

Rare, but Serious

Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.

- Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure.
- Disease affecting brain tissue, caused by a virus (specifically the JC virus: Jacob Cruetzfeld virus).
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs.
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer).
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer).

Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification.

Note: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.B.3 PHARMACOLOGY

Pharmacokinetics: In prior studies patients treated at the 375 mg/m² dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the T_{1/2} following the first antibody infusion was 59.8 hours (11.1 – 104.6 hr) with a C_{max} of 271 mcg/mL.

Formulation: Rituximab antibody will be provided on 100 mg (10mL) and 500 mg (50ml) pharmaceutical grade vials at a concentration of 10 mg of protein per mL (actual concentration should be noted on the product label).

Storage and Stability: Rituximab should be stored at 2 - 8°C. Do not freeze or store at room temperature. The product is a protein- **HANDLE GENTLY AND AVOID FOAMING**. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the denaturing of the product proteins.

Administration: Prepare the rituximab infusion solution as follows:

1. If a delay in administration of the infusion occurs after the product is prepared, the properly identified container may be kept refrigerated at 2 - 8°C for up to six hours.
2. Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.
3. Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.
4. Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile, pyrogen-free 0.9% sodium chloride solution, USP (saline solution). The final concentration of rituximab in saline solution should be a maximum of 1 mg/mL. Mix by inverting the bag gently. **DO NOT USE A VACUUM APPARATUS** to transfer the product from the syringe to the plastic bag.
5. Place an IV administration set into the outflow port of the bag containing the infusion solution.
6. **NOTE: DO NOT USE** evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.

The administration of rituximab will be accomplished by slow IV infusion. **CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.** IV pumps such as the IMED 960 may be used with the rituximab infusion. **DO NOT INFUSE CONCOMITANTLY** with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered. This will saturate the filter and tubing.

6.C Ibritumomab (IDEC-2B8) Drug Information

6.C.1 Origin of the Ibritumomab (IDEC-2B8) Cell Line

The murine anti-CD20 monoclonal antibody 2B8.H11.G3.G9, ibritumomab (IDEC-2B8), is an IgG₁ kappa antibody. The selection of the monoclonal antibody ibritumomab was based upon observations that: ibritumomab specifically recognized and bound 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; ibritumomab exhibited no cross-reactivity with T-lymphocyte populations.

Ibritumomab was previously expressed by a murine hybridoma cell line and produced in hollow-fiber bioreactors. Currently, ibritumomab is produced in Chinese hamster ovary (CHO) cells in suspension culture. The CHO-expressed ibritumomab 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.

6.C.2 Investigational Drug Nomenclature

- Biogen Idec, Incorporated code designation: Zevalin (Ibritumomab tiuxetan)
- Generic name: Ibritumomab tiuxetan
- IND numbers: BB-IND 4850 - Zevalin
- MF number: BB-MF 7087 - Zevalin

6.C.3 Clinical Formulation

The radiolabeling kit is provided by Biogen Idec and all components are tested to be sterile and pyrogen-free. The kit consists of the following components:

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

6.C.4 Storage

The radiolabeling kits should be stored in a secure refrigerator at 2 - 8°C. Zevalin solutions are stable at 2 - 8°C for up to 8 hours for ⁹⁰Y Zevalin and up to 12 hours for ¹¹¹In Zevalin following their preparation. Due to the relatively short half life of the ⁹⁰Y isotope, if not used soon after calibration time, the actual dose will have decayed and will require recalculation. For proper Rituxan storage instructions see the package insert in the appropriate Appendix.

6.C.5 ¹¹¹In Zevalin and ⁹⁰Y Zevalin Treatment Protocol

The ¹¹¹In and ⁹⁰Y isotope order form must be completed and faxed to the designated isotope vendor preceding the initial Rituxan infusion. Patients will receive an initial infusion of 250 mg/m² Rituxan. (¹¹¹In Zevalin, ⁹⁰Y-Zevalin, and Rituximab will not be provided by Biogen Idec

Incorporated). Immediately following, patients will receive a fixed dose of 5.0 mCi of ^{111}In Zevalin. If the biodistribution is altered such that the safety risk would be unacceptable, the patient will be taken off study and not proceed with ^{90}Y Zevalin radioimmunotherapy. On Day 7, 8 or 9, patients must receive a second infusion of 250 mg/m² of Rituxan and either 0.4 mCi/kg or 0.3 mCi/kg of Zevalin based on most recent platelet counts. The exact dose of Zevalin will be based on the patient's weight during the most recent evaluation according to Table 4. **The maximum dose is not to exceed 32 mCi of ^{90}Y .**

Table 4.
Dosing of Zevalin

Platelet Counts $\geq 150,000/\text{mm}^3$	Platelet Counts $100,000/\text{mm}^3$ to $149,000/\text{mm}^3$
0.4 mCi $^{90}\text{Y}/\text{kg}$ Dose will be calculated using actual body weight Not to exceed 32 mCi (Maximum Dose)	0.3 mCi $^{90}\text{Y}/\text{kg}$ Dose will be calculated using actual body weight Not to exceed 32 mCi (Maximum Dose)

6.C.6 Zevalin Adverse Events

For an extensive review of adverse events refer to the Investigational Brochure. Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with ZEVALIN. In all cases, the ZEVALIN regimen included two doses of RITUXAN. See the RITUXAN package insert for specific adverse event (AE) information for that product.

Table 5 lists most common nonhematologic adverse events in $\geq 5\%$ of patients. The table does not include hematologic AEs of neutropenia, thrombocytopenia, and anemia (See Table 6, Hematologic Toxicity).

Table 5
Incidence of Nonhematologic[†] Adverse Events in $\geq 5\%$ of Patients in Clinical Trials with ZEVALIN Regimen During the Treatment Period*(N = 349)

	All Grades N (%)	Grade 3/4 N (%)
Any Adverse Event	318 (91.1)	70 (20.1)
Body as a Whole	280 (80.2)	41 (11.7)
Asthenia	149 (42.7)	9 (2.6)
Infection	100 (28.7)	16 (4.6)
Chills	82 (23.5)	1 (0.3)
Fever	58 (16.6)	2 (0.6)
Abdominal Pain	54 (15.5)	9 (2.6)
Pain	44 (12.6)	3 (0.9)
Headache	43 (12.3)	2 (0.6)
Throat Irritation	33 (9.5)	0 (0.0)
Back Pain	27 (7.7)	2 (0.6)
Flushing	20 (5.7)	0 (0.0)
Cardiovascular System	58 (16.6)	12 (3.4)
Hypotension	22 (6.3)	3 (0.9)
Digestive System	168 (48.1)	10 (2.9)
Nausea	107 (30.7)	2 (0.6)
Vomiting	41 (11.7)	0 (0.0)
Diarrhea	31 (8.9)	1 (0.3)
Anorexia	27 (7.7)	0 (0.0)

	All Grades N (%)	Grade 3/4 N (%)
Hemic and Lymphatic System	50 (14.3)	12 (3.4)
Ecchymosis	25 (7.2)	1 (0.3)
Metabolic and Nutritional Disorders	79 (22.6)	12 (3.4)
Peripheral Edema	28 (8.0)	2 (0.6)
Musculoskeletal System	63 (18.1)	2 (0.6)
Arthralgia	26 (7.4)	2 (0.6)
Myalgia	23 (6.6)	1 (0.3)
Nervous System	94 (26.9)	7 (2.0)
Dizziness	35 (10.0)	1 (0.3)
Respiratory System	125 (35.8)	11 (3.2)
Dyspnea	47 (13.5)	7 (2.0)
Increased Cough	36 (10.3)	0 (0.0)
Rhinitis	22 (6.3)	0 (0.0)
Skin and Appendages	96 (27.5)	2 (0.6)
Pruritus	32 (9.2)	1 (0.3)
Rash	29 (8.3)	1 (0.3)
Special Senses	25 (7.2)	1 (0.3)
Urogenital System	21 (6.0)	1 (0.3)

*Treatment period is the time interval from first infusion to 30 days after ZEVALIN treatment.

†Hematologic toxicities of neutropenia, thrombocytopenia, and anemia are shown in Table 6.

Note: All adverse events are included, regardless of relationship.

The following adverse events occurred in $\geq 1\%$ but $< 5\%$ of patients during the treatment period: bronchospasm (4.9%), insomnia (4.9%), constipation (4.6%), angioedema (4.3%), urticaria (4.0%), anxiety (3.7%), dyspepsia (3.7%), increased lactic dehydrogenase (3.7%), sweats (3.7%), petechia (3.4%), sinusitis (3.2%), night sweats (3.2%), enlarged abdomen (2.9%), epistaxis (2.9%), hyperglycemia (2.9%), tachycardia (2.9%), hyperesthesia (2.6%), bone pain (2.6%), neck pain (2.6%), paresthesia (2.6%), conjunctivitis (2.3%), dehydration (2.3%), depression (2.3%), hypertension (2.3%), malaise (2.3%), increased SGOT (2.3%), skin disorder (2.3%), allergic reaction (2.0%), increased BUN (2.0%), leg cramps (2.0%), dry mouth (2.0%), melena (2.0%), pancytopenia (2.0%), somnolence (2.0%), gastrointestinal disorder (1.7%), hypocalcemia (1.7%), tumor pain (1.7%), increased alkaline phosphatase (1.7%), increased SGPT (1.7%), voice alteration (1.7%), increased creatinine (1.4%), edema (1.4%), pleural effusion (1.4%), rectal hemorrhage (1.4%), myasthenia (1.4%), stomatitis (1.4%), decreased weight (1.4%), agitation (1.1%), amblyopia (1.1%), dysphagia (1.1%), dysuria (1.1%), gastrointestinal hemorrhage (1.1%), gum hemorrhage (1.1%), hypokalemia (1.1%), hypoproteinemia (1.1%), urinary incontinence (1.1%), lymphadenopathy (1.1%), axilla pain (1.1%), injection site pain (1.1%), palpitation (1.1%), vasodilation (1.1%), and abnormal vision (1.1%).

All Grade 3 and 4 events occurring in $< 5\%$ of patients (except for those noted in Table 5) consisted of pancytopenia (1.7%), allergic reaction (1.1%), dehydration (1.1%), gastrointestinal hemorrhage (0.9%), hyperglycemia (0.9%), melena (0.9%), tumor pain (0.9%), increased alkaline phosphatase (0.6%), ascites (0.6%), constipation (0.6%), increased lactic dehydrogenase (0.6%), increased SGPT (0.6%), malaise (0.6%), apnea (0.6%), bilirubinemia (0.6%), hypoxia (0.6%), deep thrombophlebitis (0.6%), hypochromic anemia (0.3%), angioedema (0.3%), anxiety (0.3%), depression (0.3%), hypoproteinemia (0.3%), increased SGOT (0.3%), insomnia (0.3%), neck pain (0.3%), pleural effusion (0.3%), somnolence (0.3%), tachycardia (0.3%), urticaria (0.3%), anemia hemolytic (0.3%), arterial anomaly (0.3%), arrhythmia (0.3%), arthritis (0.3%), cachexia (0.3%), convulsion (0.3%), coronary artery disorder (0.3%), easy bruisability (0.3%), lung edema (0.3%), pulmonary embolus (0.3%), encephalopathy (0.3%), granulocytosis (0.3%), congestive heart failure (0.3%), hematemeses (0.3%),

subdural hematoma (0.3%), hepatic failure (0.3%), hypercalcemia (0.3%), hyperuricemia, (0.3%), increased prothrombin (0.3%), myocardial ischemia (0.3%), jaundice (0.3%), kidney failure (0.3%), migraine (0.3%), neuritis (0.3%), intestinal obstruction (0.3%), eye pain (0.3%), respiratory disorder (0.3%), supraventricular tachycardia (0.3%), vaginal hemorrhage (0.3%), and increased venous pressure (0.3%).

Hematologic Events: Hematologic toxicity has been frequently observed in clinical trials, and is dose-limiting. Table 6 presents the incidence and duration of Grade 3 and 4 hematologic toxicity for patients with mild thrombocytopenia at baseline who were treated at 0.3 mCi/kg (11.1 MBq/kg), and for those with normal baseline platelet count treated at 0.4 mCi/kg (14.8 MBq/kg), up to the maximum dose of 32 mCi (1184 MBq).

Table 6
Hematologic Toxicity

	Median Nadir	Patients with Grade 3 Toxicity	Patients with Grade 4 Toxicity	Days Within Grade 3 or 4* (Median for all Patients)	Days Within Grade 3 or 4* (Median for Patients with Grade 3 or 4 Nadir)
0.3 mCi/kg; 11.1 MBq/kg dose (maximum 32 mCi; 1184 MBq)					
ANC (cells/mm ³)	600	40%	35%	23.0	29.0
Platelets (/mm ³)	24,000	66%	14%	29.0	34.5
Hemoglobin (g/dL)	10.0	12%	8%	0.0	14.0
0.4 mCi/kg; 14.8 MBq/kg dose (maximum 32 mCi; 1184 MBq)					
ANC (cells/mm ³)	800	28%	30%	14.0	22.0
Platelets (/mm ³)	41,000	52%	10%	15.0	24.0
Hemoglobin (g/dL)	10.5	14%	3%	0.0	14.0

*ANC < 1000 cells/mm³, platelets < 50,000/mm³, and hemoglobin < 8.0 g/dL

Infectious Events: During the first 3 months after initiating ZEVALIN therapy, 28.7% (100/349) of patients developed infections, which were Grade 1 or Grade 2 in 24% (84 patients). Nine (2.5%) patients developed Grade 3 infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection. Grade 4 infections were reported for 2.0% (7 patients) and comprised sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6.0% (21 patients) developed infections, which were Grade 1 or Grade 2 in 3% (12 patients). Six patients (2.0%) had Grade 3 infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. Three patients (1.0%) had Grade 4 infections comprising bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: A total of 1.7% of patients (6/349) developed secondary malignancies following treatment with ZEVALIN. One (0.3%) patient developed a Grade 1 meningioma, and 5 (1.4%) developed myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).

NOTE: Past-marketing experiences of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis were reported in patients who received received the Zevalin® therapeutic regimen, which includes Rituximab, In-111 Zevalin® and Y-90 Zevalin®. Some of these events were fatal. The onset of the reactions was variable: in some cases acute, days in others, and delayed (3-4 months). Biogen Idec has, therefore, revised the BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS sections of the Prescribing Information for Zevalin® to describe severe cutaneous or mucocutaneous reactions in patients receiving Zevalin®. Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the Zevalin® therapeutic regimen and should seek prompt medical evaluation.

7 TREATMENT PLAN

All patients who qualify for this study will receive chemotherapy with ESHAP followed by treatment with Zevalin

7.A ESHAP REGIMEN DOSING

ESHAP chemotherapy: Patients will receive 2 cycles of cytoreductive chemotherapy according to the schedule described below. (Table 7)

TABLE 7
ESHAP CHEMOTHERAPY PLUS ZEVALIN

DRUG	DOSE	ROUTE	DAYS	INTERVAL
Etoposide	40 mg/m ² / day	IV infusion over 1 hour	1,2,3,4	q 28 days for 2 cycles
Methylprednisolone	250 mg/day	IV push	1,2,3,4	q 28 days for 2 cycles
Cytarabine	2000 mg/m ²	IV infusion over 2 hours	4	q 28 days for 2 cycles
Cisplatin	25 mg/m ² /day	IV infusion at 1mg/min	1,2,3,4	q 28 days for 2 cycles

- The cycle length will be 28 days if bone marrow recovery allows. If recovery requires an additional week, then the second cycle will be postponed for a week.
- Either pegfilgastrim or filgastrim may be given at the investigator's discretion.

7.B RITUXIMAB , ¹¹¹IN ZEVALIN, AND ⁹⁰Y ZEVALIN ADMINISTRATION

The rituximab + ibritumomab tiuxetan regimen is given 4-6 weeks after completion of the second cycle of ESHAP. Treatment can be completed within 7 - 9 days in an outpatient setting

TABLE 8
Rituximab , ¹¹¹In Zevalin, AND ⁹⁰Y Zevalin Administration

AGENT	DOSE	ROUTE	DAYS	NOTES
Rituximab	250 mg/m ²	Slow IV	1, then 7, 8 or 9	Give prior to ¹¹¹ In Zevalin
¹¹¹ In Zevalin	5 mCi	Slow IV push over 10 minutes	1	Give within 4 hours after rituximab
⁹⁰ Y Zevalin	Depends on platelet count (see Section 7.B.3)	Slow IV push over 10 minutes	7, 8, or 9	Give within 4 hours after rituximab

7.B.1 Rituxan & ¹¹¹In Zevalin Administration

1.6 mg of ¹¹¹In Zevalin (5.0 mCi of ¹¹¹In) will be used for radioimaging. The imaging dose of ¹¹¹In Zevalin will be administered by a 10-minute slow IV push injection immediately following the infusion of Rituxan. ¹¹¹In Zevalin may be directly injected by stopping the flow from the IV bag and injecting the radiolabeled antibody directly into the line. A 0.22 micron filter must be on line between the patient and the infusion port. Flush the line with at least 10 mL of normal saline after ¹¹¹In Zevalin has been injected. (See Appendix H).

- a. Oral premedication (2 tablets [325 mg] of acetaminophen and 50 - 100 mg oral diphenhydramine hydrochloride) may be administered 30 - 60 minutes prior to starting each infusion of rituximab.

7.B.2 Radioimaging Schedule

Imaging (see Appendices H & I) will be conducted at the clinical site on each patient prior to receiving ⁹⁰Y Zevalin. Within 48-72 hours following the ¹¹¹In Zevalin administration, whole body anterior and posterior images of the patient must be acquired. If desired, a second image can be obtained at 90 - 120 hours to support the decision. If the patient has an altered biodistribution, the patient will be taken off study before proceeding to ⁹⁰Y Zevalin radioimmunotherapy.

- a. Whole-body gamma camera images to assess biodistribution of ibritumomab tiuxetan are obtained as described below after the first infusion of rituximab followed by In-111 ibritumomab tiuxetan.

Scan 1	Hours 48 -72
Optional Scan	Hours 90 - 120

- b. If ibritumomab tiuxetan biodistribution is acceptable, therapy continues on Day 7, 8, or 9 with a second infusion of rituximab followed by Y-90 ibritumomab tiuxetan as noted in Table 8.
- c. **Altered biodistribution:** Y-90 ibritumomab tiuxetan should not be administered to patients with altered biodistribution of In-111 ibritumomab tiuxetan. The expected biodistribution of In-111 ibritumomab tiuxetan includes easily detectable uptake in the

blood pool areas 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 image; and 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. Altered biodistribution of In-111 ibritumomab tiuxetan can be characterized by diffuse uptake in normal lung more intense than the liver on the posterior view of the second or third day image; or intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.

7.B.3 Rituxan & ⁹⁰Y Zevalin Administration

⁹⁰Y Zevalin will be administered following the second Rituxan infusion Day 7, 8 or 9 (See Appendix H). Each patient will receive one therapeutic dose of Zevalin according to the dosing schema (see Table 4 or Section 7.B.3b).

Please note: Patients with platelet counts from 100,000/mm³ to 149,000/mm³ will receive 0.3 mCi/kg and patients with platelet counts \geq 150,000/mm³ will receive 0.4 mCi/kg, **not to exceed 32 mCi ⁹⁰Y Zevalin**. ⁹⁰Y Zevalin will be administered intravenously as a slow IV push over 10 minutes. ⁹⁰Y Zevalin 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. Flush the line with at least 10 mLs of normal saline after ⁹⁰Y Zevalin has been infused. (See Appendix H for radioincorporation methods)

There is no provision for additional treatment courses for patients entered into this protocol.

- a. Oral premedication (2 tablets [325 mg] of acetaminophen and 50 - 100 mg oral diphenhydramine hydrochloride) may be administered 30 - 60 minutes prior to starting each infusion of rituximab.
- b. Y-90 ibritumomab tiuxetan should be dosed at 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with platelets counts \geq 150,000/mm³ and at 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet counts of 100,000 - 149,000/mm³. **The prescribed, measured and administered dose of Y-90 ibritumomab tiuxetan must not exceed the absolute maximum allowable dose of 32.0 mCi (1,184 MBq), regardless of the patient's body weight. Do not give Y-90 ibritumomab tiuxetan to patients with a platelet count < 100,000/mm³.**
- c. Radiation Safety Precautions are minimal: No isolation required. Observe the following guidelines for 7 days after Y-90 Zevalin Patients should wash their hands thoroughly after urination. The use of a condom is recommended during sexual intercourse to avoid transfer of body fluids. Avoid deep kissing. Throughout therapy and for up to 12 months following treatment, effective contraception is recommended.

- d. Granulocyte colony stimulating factors may be given at the discretion of the treating physician to prevent or mitigate unacceptable granulocytopenia associated with fever, or granulocytopenia less than 500 granulocytes/ μ L. The use of G-CSF must be documented on the treatment summary form. Any toxicities associated with G-CSF must also be documented on the adverse event form.

8 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

This study will utilize the CTC (NCI Common Toxicity Criteria) Version 3.0 for toxicity and Adverse Event reporting. A copy of the CTC Version 3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). **All appropriate treatment areas should have access to a copy of the CTC Version 3.0.**

8.A ESHAP Toxicities & Dose Modification

In the case of multiple toxicities, dose modifications should be based on the most severe dose-limiting toxicity.

8.A.1 Hematologic Toxicity:

The ESHAP regimen should be given as described in Section 7.A if the granulocytes are $> 1,500$ cells/ μ L and the platelets are $> 100,000$ cells/ μ L by the time the next cycle is due. If the blood counts have not recovered, treatment should be delayed by an additional week and counts repeated unless low peripheral counts are due to tumor. If, after 2 weeks, counts have not yet recovered, the patient should be treated at 75% of the last dose received of etoposide and cytarabine.

8.A.2 Grade 3 or 4 Infection:

(NCI Common Toxicity Criteria Version 3.0) due to chemotherapy-related neutropenia requires a decrease in the doses of etoposide and cytarabine to 75% of the last dose received. Re-escalation is at the discretion of the treating physician. In this study, filgrastim or peg-filgrastim may be administered to prevent neutropenia at the discretion of the treating physician.

The use of filgrastim or peg-filgrastim must be documented on the treatment flow sheets. Any toxicities associated with either of these agents must also be documented on the treatment flow sheets.

8.A.3 Impaired Renal Function:

All patients with serum creatinine levels ≤ 1.3 or creatinine clearance (CrCl) > 60 mL/min will receive full doses of all drugs. If the creatinine is 1.4 – 2.0 or the CrCl is 30 – 60 mL/min then the doses of cytarabine, etoposide, and cisplatin should all be reduced by 50%. A creatinine clearance of < 30 mL/min will require holding all treatment. Re-escalation to full dose is at the discretion of the treating physician if the serum creatinine level drops to ≤ 1.3 or the CrCl ≥ 50 mL/min.

TABLE 9

Cytarabine, Etoposide & Cisplatin Reductions According to Renal Function

<u>CrCl</u>	<u>Etoposide Dose</u>	<u>Cytarabine Dose</u>	<u>Cisplatin Dose</u>
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> 60 mL/min	100%	100%	100%
30-60 mL/min	50%	50%	50%
10-30 mL/min	0%	0%	0%
< 10 mL/min	0%	0%	0%

8.A.4 Neuropathy:

Patients experiencing Grade 3 cisplatin neuropathy (e.g., loss of motor function) will have the dose reduced by 50% for all further cycles of ESHAP. Patients experiencing Grade 4 neuropathy will have the cisplatin omitted from all further cycles of ESHAP. Patients experiencing Grade 3 cytarabine neuropathy with ESHAP cycle 1 will have the dose reduced by 50% for cycle 2. Patients experiencing Grade 4 or worse cytarabine neuropathy will have the cytarabine omitted from all further cycles.

8.B Rituximab Antibody Toxicities & Dose Modifications

8.B.1 Fevers:

Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. If Grade 3 fever (or Grade 2 fever with rigors) or Grade 2 rigors are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when fever resolves to Grade 2 or less and rigors to Grade 1 or less, the infusion should be continued, initially, at 1/2 the previous rate. Following the antibody infusion, the IV line should be kept open for medications, as needed.

8.B.2 Hypersensitivity:

Hypotension, bronchospasm or angioedema have occurred as part of an infusion-related symptom complex. If a Grade 3 or greater hypersensitivity/allergic reaction occurs, rituximab infusion should be interrupted and may be resumed at a 50% reduction in rate when symptoms have completely resolved. Treatment with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be used at the physician's discretion. Precautionary hospitalization for patients experiencing severe infusion symptoms which do not resolve after discontinuation of the cycle is recommended.

8.B.3 Observation post Infusion

If there are no complications, the IV line may be discontinued after 1 hour of observation. If complications occur during the rituximab infusion, the patient should be observed for 2 hours after the completion of infusion. If a patient experiences a Grade 3 toxicity that persists until the next scheduled infusion, the patient must discontinue treatment until toxicities have resolved to Grade 2 or less. If treatment is delayed for more than 3 weeks, call the Study Coordinator.

8.B.4 Tumor Lysis Syndrome:

Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent

rituximab therapy may be administered in conjunction with prophylactic therapy for this syndrome. Contact the Study Coordinator prior to resuming treatment in these patients.

TABLE 10
Rituximab Infusion rate Adjustment

Fever	Rigors	Mucosal Congestion/ Edema	% Drop in Systolic BP	Infusion Rate Adjustment
Grade 1	Grade 1-2	Grade 1-2	30 – 49	Decrease By 50%
Grade ≥ 2	Grade ≥ 3	Grade ≥ 3	$\geq 50\%$	Stop infusion*

*Temporarily discontinue infusion until adverse experiences have reversed (generally 15 to 30 minutes) and then resume infusion at 25 – 50% of initial rate.

8.B.5 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections:

Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation. Patients with any evidence of active hepatic disease or known HBV infection should be managed as clinically appropriate and should only receive rituximab if they have control of the infection and are adequately informed of the risks. Patients who have never received vaccination for HBV, and have not had serologic testing for HBsAg, should be tested for surface antigen positivity.

In patients who develop progressive multifocal leukoencephalopathy (PML), rituximab should be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy and appropriate treatment, including antiviral therapy, should be considered. Physicians should consider PML in any patients presenting with new onset neurologic manifestations, particularly in patients with systemic lupus erythematosus (SLE) or lymphoid malignancies. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

8.B.6 Severe mucocutaneous reactions:

All patients on or off rituximab therapy should be closely monitored for signs and symptoms suggestive of severe cutaneous and mucocutaneous reactions. Should these symptoms arise, discontinue rituximab therapy (if applicable) and support as clinically indicated.

8.B.7 Cardiovascular events:

Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular events compared with the general population. Patients with RA should be monitored through the infusion, and rituximab should be discontinued in the event of a serious or life-threatening event.

8.B.8: Arrhythmias:

Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period. Patients

off rituximab therapy should be closely monitored for signs and symptoms suggestive of life-threatening cardiac events and supported as clinically indicated.

8.B.9 Bowel Obstructions and Perforation:

Complaints of abdominal pain, especially early in the course, should prompt a thorough diagnostic evaluation and appropriate treatment. If the patients experiences a bowel obstruction or perforation, discontinue rituximab therapy. Patients off rituximab therapy should be closely monitored for signs and symptoms suggestive of bowel obstruction and supported as clinically indicated.

8.B.10 Renal:

Discontinuation of rituximab should be considered for those patients with rising serum creatinine or oliguria.

8.C ¹¹¹In Zevalin & ⁹⁰Y Zevalin Toxicities & Dose Modifications

The ibritumomab tiuxetan (Zevalin) regimen may cause severe and potentially fatal infusion reactions that usually occur with the first rituximab infusion. Signs and symptoms may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of rituximab, ¹¹¹In Zevalin or ⁹⁰Y Zevalin administration. The infusion may be restarted at the physician's discretion.

During the administration of treatment, emergency support for anaphylaxis is to be readily available, including a try for epinephrine, diphenhydramine, hydrocortisone, a laryngoscope, and an endotracheal tube.

8.C.1 Use of Colony Stimulating Factors (CSF) and Platelet and Red Blood Cell Transfusions:

Colony Stimulating Factors (CSF) should be administered only in accordance with published ASCO guidelines. Use of CSF under these conditions will be at the discretion of the treating investigator, but must be recorded on the flow sheets.

Platelet transfusions should be administered only in patients with Grade 3 or 4 thrombocytopenia with obvious bleeding. The use of platelet and red cell transfusions under these conditions will be at the discretion of the treating physician, but must be recorded on the flow sheets.

For treatment or dose modification related questions, please contact Dr. Persky at (520) 626-8908.

Unexpected or fatal toxicities (including suspected reactions) must be reported to the Study Coordinator, the ACC DSMB, the IRB, Biogen Idec, and the FDA. The procedure for reporting adverse reactions is outlined in Section 9.

9 ADVERSE CLINICAL EVENT REPORTING

Throughout the course of the study, every effort should be made to remain alert to possible adverse experiences. Adverse events should be recorded using the toxicity criteria of the NCI Clinical Cooperative Groups and the Cancer Treatment Evaluation Program(Appendix C). Adverse events not listed in toxicity criteria should be rated as either mild, moderate, severe, maximal/life threatening as

Grades 1, 2, 3, 4 respectively. In the event of an adverse experience, appropriate medical intervention should be provided and if necessary, the investigational agent (Zevalin) should be discontinued.

All adverse events regardless of the relationship to the study drug(s) whether observed by the investigator or reported by the patient, will be recorded with details of the duration and intensity of each episode, the action taken with respect to test drug and the patient outcome, on an appropriate source document at the clinical site. The investigator will evaluate each adverse experience as to its relationship to the test drug and as to whether or not it was serious.

All abnormal laboratory results will be appraised by the investigator as to clinical significance. For any laboratory abnormality considered clinically significant, details should be recorded on an appropriate source document including the action taken with respect to the test drug and the patient outcome.

Adverse events occurring after the initiation of other anti-cancer therapy will not be followed, unless the therapy is initiated and the adverse event occurs within 30 days following the Zevalin drug infusion.

9.A Reporting of Serious Adverse Events to the Principal Investigator, ACC DSMB, the IRB and, if necessary, the FDA

Any serious or unexpected adverse event (including death) due to any cause whether or not related to the study drug(s) must be immediately reported to the principal investigator, ACC DSMB, the IRB and drug manufacturer. The Principal Investigator must immediately complete the SAE form and arrange to have it faxed in a timely manner to the Drug Safety and Risk Management Department of Biogen Idec Incorporated (877-462-1532). See Appendix E for SAE form.

It is the responsibility of the Investigator-Sponsor to **IMMEDIATELY REPORT ALL SERIOUS OR UNEXPECTED ADVERSE IMMEDIATELY TO THE IRB CHAIR (AS PER INSTITUTION POLICY) AND, IF APPROPRIATE, TO THE FDA BY COMPLETING AND SUBMITTING A MEDWATCH FORM (FDA FORM 3500A)**. The Investigator-Sponsor must promptly provide a copy of the MedWatch form to Biogen Idec at the same time it is submitted to the FDA. **Completed FDA 3500A reports should be faxed to the Drug Safety and Risk Management Department of Biogen Idec Incorporated (877-462-1532).** See Appendix E for additional information and a blank copy of the MedWatch form.

Serious adverse events occurring after initiation of other anti-cancer therapy do not need to be reported, unless the therapy is initiated and the event occurs within 30 days following the infusion of the study drug or the event is felt to be related to the study drug. An exception to this is the occurrence of myelodysplastic syndrome, leukemia, or other malignancy, which should be reported immediately.

10 CONCOMITANT MEDICATIONS

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, anti-emetics, etc., where applicable. **It is strictly mandated that patients not be given other myelosuppressive anti-neoplastic agents until recovery from hematologic nadir.**

Patients receiving concurrent oral anticoagulant therapy should have this medication discontinued when the platelet counts fall below 30,000 cells/mm³. Oral anticoagulant therapy may be resumed upon signs of platelet recovery, at the discretion of the investigator.

11 REMOVAL OF PATIENTS FROM THIS STUDY

11.A Criteria for Discontinuation of a Patient's Study Participation

The date of discontinuation and reason(s) for patient discontinuation from the study will be recorded in the CRF. All evaluations which are required at the final study visit must be conducted for each patient who discontinues treatment, regardless of the reason (see Section 5.F.1).

- Disease Progression: Patients will be taken off study if they have progressive disease (PD) or clinically significant deterioration at any time during the study.
- Personal Reasons: Patients may choose to withdraw from the study at any time.
- Clinical Judgment of the Investigator: A patient may be withdrawn from the study, if in the opinion of the investigator, it is not in the patient's best interest to continue.
- Requiring other anti-neoplastic therapies

12 STATISTICAL CONSIDERATIONS

12.A Study Design

This is a two- institution phase II trial to determine the efficacy and safety of the ESHAP-Zevalin combination therapy for the management of relapsed (CD 20+) follicular lymphoma. Patients must have received at least one, but no more than 2 prior treatments for follicular lymphoma.

The primary objective of this phase II clinical trial is to evaluate the 1-year progression-free survival (PFS) of patients with relapsed follicular NHL treated with ESHAP chemotherapy for cytoreduction (2 cycles) followed by Y-90 ibritumomab tiuxetan (Zevalin) radioimmunotherapy, compared to what would be expected historically for patients treated with Zevalin without prior cytoreduction. For this patient population, a 1-year PFS of 67.3% will be considered highly encouraging, compared to an historical rate around 50%. These values correspond to approximate median times to progression of 21 months and 12 months, respectively, assuming exponential survival.

12.B. Sample Size

The planned sample size of 52 evaluable patients is based on testing the null hypothesis that the true 1-year PFS is $\leq 50\%$, versus an alternative hypothesis that the true rate is $\geq 67.3\%$ with this therapeutic approach. Based on the number of patients seen at the Arizona Cancer Center with relapsed follicular lymphoma requiring treatment, the anticipated accrual rate is 2 patients per month. It is estimated that accrual to the study would be completed within 26 months. All patients who receive at least one dose of chemotherapy will be considered evaluable and included in the analysis. In the unlikely event that an enrolled patient does not receive treatment, an additional patient will be registered.

12.C Method of Analysis

The following are the design characteristics based on a chi-square test for one binomial population at the one-sided 0.10 significance level. If the true PFS is $\leq 50\%$, then there is a maximum probability of 0.10 of concluding that this treatment approach is sufficiently promising that it should be accepted for further study (false positive rate). Alternatively, if the true PFS is $\geq 67.3\%$, then the maximum probability of

rejecting this treatment approach for further study in this setting is 0.10 (false negative rate), equivalent to a power of 90%.

At the end of the trial, the observed PFS and response rates will be reported, along with appropriate confidence limits. Kaplan-Meier methods will be used to estimate the survival curve of time-to-progression. Promising results at the conclusion of this trial will justify further study in a larger trial.

13 STUDY ADMINISTRATION

13.A Review and Consent Requirements

13.A.1 Institutional Review Board (IRB)

The investigator will supply all necessary documents to be submitted to the IRB and will ensure that the institution has a properly structured research committee. The University of Arizona Human Subjects Protection Program will be the IRB of record. Documentation of initial and ongoing reviews, submission of serious adverse event reports, study amendments and revisions, and consent form modifications will be required. This documentation is to be forwarded to:

- Consent Forms:

Lora Inclan
Clinical Research Coordinator
The University of Arizona Cancer Center – North Campus
Room 2111
3838 N. Campbell Ave.
Tucson, AZ 85719

- Regulatory Documents:

Kara Heard
Lymphoma Program Regulatory Coordinator
The University of Arizona Cancer Center, Room 1955
1515 N. Campbell Ave
Tucson, AZ 85724

13.A.2 Patient Information and Informed Consent

Written informed consent will be obtained for this study from all patients. The investigator or his/her staff will explain the nature of the study and the risks involved to each patient prior to his/her inclusion in the trial. The patient will also be informed that he/she is free to withdraw from the study at any time. Original, signed informed consent forms for patients registered from the University of Arizona Cancer Center will be kept at The University of Arizona Cancer Center, North Campus, room 2111.

13.B Registration Procedure

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will be accepted. All patients will be registered centrally with the Clinical Research Coordinator based at 520-694-9053 prior to the initiation of treatment. The Clinical Research Coordinator will assign each patient a sequential number prior to registration. The fully signed informed consent must be presented and all inclusion and exclusion criteria will be reviewed with the registering investigator or designee. All source documentation needed to confirm eligibility must be available for this review. A second phone registration is required prior to the initiation of Zevalin® to confirm eligibility and dose of therapy.

13.C Study Records – Data Collection & Recording

Study-specific data forms are to be found in the Clinical Research Services clinical database. All forms are to be submitted centrally to the Clinical Research Coordinator at the University of Arizona Cancer Center at baseline, completion of ESHAP cycle 1, completion of ESHAP cycle 2, restaging at Cycle 2, Day 29, completion of Zevalin®, and at the follow-up intervals specified in Appendix A, including at time of relapse/progression, second malignancy, or death.

13.D Patient Confidentiality

The information obtained as a result of this research is confidential and all efforts must be made to ensure that the patient's anonymity will be maintained. All records, evaluation forms, and reports will be identified by an identification code to maintain confidentiality. A log of patients' codes, names and addresses will be kept separately. All records are to be kept in locked files.

13.E Monitoring

This research study is an investigator-sponsored trial. The Arizona Cancer Center has an NCI-approved Data and Safety Monitoring Plan for clinical research. Data and systems for participating in the study will be monitored according to procedures outlined in that plan, with centralized patient screening and registration, submission and review of data, and initial verification of data as summarized below.

Protocol Data and Safety Monitoring Plan (Medium Risk)

Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are **not** designated as high risk per NCI and the IND is not held by the investigator.

Data and Safety Monitoring Plan:

1. Identification of the DSMB obligated for oversight responsibilities:

The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

2. Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

3. Monitoring progress and data review process:

Routine monitoring of subject data will be conducted at least every six months.

The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;

- Subject eligibility - 50% of cases, up to two subjects;
- Data review - 50% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed within two weeks of the routine monitoring visit; a copy will be maintained in the study file. A query/finding form will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF). Source documentation supporting the CRF data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms *[other forms, depending on study]* should be completed with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

4. Process to implement study closure when significant risks or benefits are identified:

This study may be prematurely terminated, if in the opinion of the investigator there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient complete and/or evaluable data

5. Description of adverse events and reporting procedures:

ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and will address:

- Grade
- Relationship to study drug(not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- 1) Results in death;
- 2) Is life-threatening;
- 3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
- 4) Results in disability persistent or significant disability/incapacity, or;
- 5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and DSMB Coordinator. All serious adverse events, regardless of attribution, and any deaths will be reported within 5 days of notification of the event to the University of Arizona Human Subjects Protection Program.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

6. Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Monitoring and protocol compliance;
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least every six months.

7. Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.

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APPENDIX A
STUDY CALENDAR
4/1/2010

STUDY CALENDAR Page 1

Required Studies	Baseline	ESHAP Treatment			Ibritumomab Tiuxetan (Zevalin) Regimen [∞]			
Visits (weeks or days)	Within 28 days prior to C1, D1	Cycle 1 Day 1	Cycle 2 Day1	Cycle 2 Day 29	Day 1	Day 2,3,4,5	Day 7, 8, or 9	Day 35
PHYSICAL								
History / Physical / vital signs ^α	X		X	X	X ∩			
Height / Weight / BSA / PS	X		X	X	X ∩			
Disease Assessment	X			X				
Toxicity Assessment	X		X	X	X ∩			
LABORATORY								
CBC / differential / platelets	X		X	X	X ∩			X ^Σ
Serum Creatinine / BUN	X		X	X	X ∩			
AST/ ALT/ Alk. Phos/ T. Bilirubin [^]	X							
LDH	X							
BHCG [†]	X							
Beta 2- microglobulin	X							
Hepatitis B screen [*]	X							
Pathology Review [£]	X							
Bone marrow cytogenetics [¥]	X			X				
Bone marrow aspiration and Bx	X			X				
SCANS								
CT or PET Chest	X			X				
CT or PET Abdomen	X			X				
CT or PET Pelvis	X			X				
Gamma Scan						X [≠]		
TREATMENT								
ESHAP		X	X					
Rituximab 250 mg/m2					X		X	
Ibritumomab Tiuxetan Indium (¹¹¹ In Zevalin)					X			
Ibritumomab Tiuxetan Yttrium-90 (⁹⁰ Y Zevalin)							X	

α Vital Signs consist of BP, temperature and pulse

† Baseline for women of childbearing potential

≠ A scan is performed at 48-72 hours after ¹¹¹In Zevalin. Another optional scan may be performed at 90- 120 hours after ¹¹¹In Zevalin.

∞ ¹¹¹In Zevalin is administered 4-6 weeks after completion of ESHAP.

^ Required at Baseline and Encouraged to repeat as clinically indicated by Good Medical Practice.

***** Encouraged by Good Medical Practice, but not required.

¥ Bone Marrow cytogenetics can be done at either Baseline or C2,D29, but must be done at least once.

£ Pathology Review consists of a basic review of a pathology report. If possible submit: Representative H&E stained slides from the diagnostic biopsy, one representative paraffin block and one copy of the pathology report.

Σ Starting Day 35 (+/- 7 days) a CBC w/ Diff and Platelet count should be done every week until nadir.

∩ Within 28 days prior to Rituximab & Zevalin administration..

STUDY CALENDAR Page 2

Required Studies	Restaging	Short-Term Follow-Up				Long-Term Follow-Up	Off-Study [#]
Visits (weeks or days)	3 mos post ^{90Y} Zevalin	6 mos post Zevalin	12 mos post Zevalin	18 mos post Zevalin	24 mos post Zevalin	Follow-Up: Annually for 3 years [£]	Disease Progression or Removed from Study (within 4 weeks)
PHYSICAL							
History / physical / vital signs ^α	X	X	X	X	X	X	X
Height/Weight /BSA/PS	X	X	X	X	X	X	X
Disease Assessment	X	X		X		X	X
Toxicity Assessment	X	X	X	X	X	X	X
LABORATORY							
CBC/differential/platelets	X	X	X	X	X	X	X
Serum Creatinine/BUN	X	X	X	X	X	X	X
LDH	X	X	X	X	X	X	X
X-RAYS AND SCANS							
CT or PET chest	X	X		X		X	X
CT or PET Abdomen	X	X		X		X	X
CT or PET pelvis	X	X		X		X	X

Ω After completion of post Zevalin restaging, follow-up exams and tests are to be repeated every 6 months for 2 years, and then annually for up to 3 years.

Off-Study Tests to be Performed When a Patient is Determined to Have Disease Progression or is Removed from the Study for any Reason. These tests will be performed within 4 weeks after a patient has demonstrated progression of disease, or removed from study. These tests do not have to be repeated if they were performed within 7 days prior to documentation of disease progression.

α Vital signs consist of BP, temperature and pulse

£ Follow-up should occur every 6 months (+/- 30 days) for 2 years after the completion of the Short-Term Follow-Up period.

† Continued Follow-Up should occur annually (+/- 30 days) for survival and disease status. Patients should be followed by physical exam and, if clinically indicated by Good Medical Practice, CT scans. Patients will be followed for 3 years or until patient starts an alternate treatment or is removed from study to allow determination of study endpoints.

APPENDIX B

PERFORMANCE STATUS SCALE

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

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APPENDIX C
ADULT TOXICITY CRITERIA
COMMON TOXICITY CRITERIA (CTC)

**Common Terminology Criteria for Adverse Events v3.0
(CTCAE)**

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word '*Select*' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE

Grade 2 Moderate AE

Grade 3 Severe AE

Grade 4 Life-threatening or disabling AE

Grade 5 Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
 - This AE is to be used in the situation where a death
1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
 2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Please refer to <http://ctep.cancer.gov/reporting/ctc.html> for specific Adverse Event grading and reporting.

APPENDIX D

INTERNATIONAL WORKSHOP STANDARDIZED RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMAS

1. RESPONSE CLASSIFICATIONS

The definition of “complete disappearance” of clinically detectable disease varies. Patients considered disease-free have been defined by variables including complete blood count (CBC), clinical and radiologic findings, and sizes of lymph nodes, spleen, and liver. Additionally, the lack of bone marrow involvement may be required. Some investigators have set a minimal duration for the absence or reduction of disease before the response is confirmed^[1-11]. In some, responses are reclassified retrospectively.

Because of the considerable variation in the literature, specific, standardized guidelines for response assessment were recently established in a 1998 report from an International Workshop conducted at the NCI. Recommendations were presented to ensure accurate and objective evaluation of the presence or lack of disease, and comparability among clinical trials. The recommended criteria were based on lymph node biopsy and bone marrow evaluation and considered as anatomic definitions. Categories were included for CR, CR/unconfirmed (CRu), PR, and relapse/progression ^[12]. Flow cytometric, cytogenetic, and molecular studies were not included in response definitions (Table 1).

Table 1
International Workshop Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal Normal	Normal Normal	Normal > 75% decrease	Indeterminate Normal or indeterminate
PR	Normal Normal Decrease in liver/spleen	Normal ≥ 50% decrease ≥ 50% decrease	Normal ≥ 50% decrease ≥ 50% decrease	Positive Irrelevant Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Adapted from Cheson et al., 1999^[12]

In addition, definitions were recommended for end points of interest in clinical trials, including survival (overall, event-free, progression-free, and disease-free), as well as response duration, time to next treatment, and cause-specific death (Table 2).

Table 2
International Workshop Definitions of End Points for Clinical Trials

End Point	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death from any cause	Entry onto trial
Event-free survival	CR, CRu, PR	Failure or death from any cause	Entry onto trial
Progression-free survival	All patients	Disease progression or death from NHL	Entry onto trial
Disease-free survival	CR, CRu	Time to relapse	First documentation of response
Response duration	CR, CRu, PR	Time to relapse or progression	First documentation of response
Time to next treatment	All patients	Time when new treatment is needed	Entry onto trial
Cause-specific death	All patients	Death related to NHL	Death

Adapted from Cheson et al., 1999^[12]

2. MEASURES OF DURATION

- Time to Progression: measured from the date of first study treatment to the first date when progressive disease is documented.
 - a. Progressive Disease (PD)-Free Interval (Duration Of Response): measured, in a responder, from the date when a CR, CCR or PR is first noted to the first date at which progressive disease is observed. An ongoing PD-free interval occurs when there is a responder for whom progressive disease has not been noted.

3. MEASURABLE LESIONS

- Measurable lesions will be assessed **bidimensionally** at baseline for determining the efficacy of study treatment. Measurable lesions must be measured at baseline by the method which will be used for routine tumor measurement during the study. The patient must have at least one lesion of 2 cm or larger in its longer diameter.

4. DEFINITION OF MEASURABLE DISEASE

- b. The extent of disease is measurable if the patient has one or more lesions that are clearly demarcated and may be represented with clearly defined margins as measured in centimeters. These measurements will be bidimensional (two longest perpendicular measures per lesion) meeting the minimum requirement: 1) at least 1.5 cm in a single dimension for all lesions and 2) at least 2.0 cm in a single dimension for at least one lesion. All other lesions will be followed as evaluable disease.

5. MEASUREMENT OF LESIONS

- c. Measurable lesions must be measured at baseline by the method that will be used for routine measurements during the study. Each measurable lesion will be consistently measured bidimensionally for the duration of the study. In addition,

the routine method of measurement for any measurable lesion, e.g., X-ray, CT scan, etc. will remain the same for each evaluation throughout the course of the study. Measurements will be performed using a ruler or calipers and will be recorded in centimeters.

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APPENDIX E

- SAE Reporting documents
- MedWatch forms



SERIOUS ADVERSE EVENT FORM (SAE)

SAE Case Reference

Biogen Idec **use only**

Section A:

Patient Number: _____	Patient Initials: _____	Site Number: _____	Protocol Number: _____
DOB: _____ (MM/DD/YY)	Patient Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female		Principal Investigator: _____
Date reported to Biogen Idec: _____ (MM/DD/YY)		Report Type: <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up <input type="checkbox"/> Final	
Onset date of event: _____ (MM/DD/YY)			

Section B:

CRITERIA FOR SERIOUS CLASSIFICATION

Please check all that apply:

<input type="checkbox"/> Death _____ (MM/DD/YY) Autopsy performed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Life-Threatening <input type="checkbox"/> New / Prolonged Hospitalization _____/_____/_____ Admission Date Discharge Date <input type="checkbox"/> Persistent / Significant Disability / incapacity	<input type="checkbox"/> Important medical events (may jeopardize the patient and may require medical/surgical intervention to prevent above outcomes) <input type="checkbox"/> Congenital anomaly / Birth defect <input type="checkbox"/> Other: specify _____
--	---

Section C:

STUDY DRUG

Investigational Drug Name: * _____	First Treatment date: _____ (MM/DD/YY)
Date of most recent treatment: _____ (MM/DD/YY)	Dose, Frequency, Route: _____
Action taken on Study Drug due to Adverse Event: (check one)	
<input type="checkbox"/> None <input type="checkbox"/> Dose increased <input type="checkbox"/> Dose reduced <input type="checkbox"/> Interrupted <input type="checkbox"/> Discontinued <input type="checkbox"/> IV rate increased <input type="checkbox"/> IV rate decreased	
Did Adverse Event abate after stopping drug? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A	

Did Adverse Event reappear after reintroduction?


☐ Yes

☐ No

☐ Unknown


☐ N/A

**If Investigational Drug is a combination therapy, specify other suspect component in Sections D and E*


 SERIOUS ADVERSE EVENT FORM (SAE)		SAE Case Reference # _____ Biogen Idec use only	
Patient Number: _____	Patient Initials: _____	Site Number: _____	Protocol Number: _____
Section D: Combination Therapy (Second Component)			
Investigational Drug Name: * _____		First Treatment date: _____ (MM/DD/YY)	
Date of most recent treatment: _____ (MM/DD/YY)		Dose, Frequency, Route: _____	
Action taken on Study Drug due to Adverse Event: (check one)			
<input type="checkbox"/> None <input type="checkbox"/> Dose increased <input type="checkbox"/> Dose reduced <input type="checkbox"/> Interrupted <input type="checkbox"/> Discontinued			
<input type="checkbox"/> IV rate increased <input type="checkbox"/> IV rate decreased			
Did Adverse Event abate after stopping drug?		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A	
Did Adverse Event reappear after reintroduction?		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A	
Section E: Combination Therapy (Third Component)			
Investigational Drug Name: * _____		First Treatment date: _____ (MM/DD/YY)	
Date of most recent treatment: _____ (MM/DD/YY)		Dose, Frequency, Route: _____	
Action taken on Study Drug due to Adverse Event: (check one)			
<input type="checkbox"/> None <input type="checkbox"/> Dose increased <input type="checkbox"/> Dose reduced <input type="checkbox"/> Interrupted <input type="checkbox"/> Discontinued			
<input type="checkbox"/> IV rate increased <input type="checkbox"/> IV rate decreased			
Did Adverse Event abate after stopping drug?		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A	
Did Adverse Event reappear after reintroduction?		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A	

Section F: DESCRIPTION OF THE SERIOUS ADVERSE EVENT						
(Include relevant medical history and intercurrent illness)						
Section G: EVALUATION OF THE SERIOUS ADVERSE EVENT						
Key						
RELATIONSHIP TO STUDY DRUG	GRADE	OUTCOME AT TIME OF REPORT				
1 = Probably Related	1 = Mild	1 = Resolved	4 = Worsened			
2 = Possibly Related	2 = Moderate	2 = Improved	5 = Not Available			
3 = Unknown	3 = Severe	3 = Unchanged	6 = Fatal			
4 = Not Related **	4 = Life Threatening					
ADVERSE EVENT (list primary diagnosis first, if possible - one per line) e.g. neutropenic fever	ONSET DATE (MM/DD/YY)	DATE STOPPED (MM/DD/YY)	RELATIONSHIP	GRADE	OUTCOME	

****Specify on "Other Comments" section other factors that may have contributed to the adverse event.**


		<p align="center">SERIOUS ADVERSE EVENT FORM (SAE)</p>		<p align="center">SAE Case Reference</p> <p align="center"># _____</p> <p align="center">Biogen Idec use only</p>	
<p>Patient Number: _____</p>		<p>Patient Initials: _____</p>		<p>Site Number: _____</p>	
				<p>Protocol Number: _____</p>	

[illegible][illegible]

 <div style="display: inline-block; vertical-align: middle; text-align: center;"> SERIOUS ADVERSE EVENT FORM (SAE) </div>		SAE Case Reference # _____ Biogen Idec use only			
Patient Number: _____	Patient Initials: _____	Site Number: _____	Protocol Number: _____		
Section J: CONCOMITANT THERAPY (ongoing or completed within one week prior to onset of event) Do Not Include Treatments for SAE					
Drug/Therapy	Start Date (MM/DD/YY)	Stop Date (MM/DD/YY)	Ongoing Y / N?	Dose/Route	Indication
Section K: OTHER COMMENTS					

I have reviewed the data contained in these pages and have found it to be accurate:

Principal Investigator's Signature	Date Signed ()
Name (<i>print</i>)	Title
Institution	Phone Number ()
	Fax Number

A. Patient Information			
1. Patient identifier (In Confidence)	2. Age at time of event: Or date of birth:	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight or lbs. kgs.
B. Adverse Event or Product Problem			
1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)			
2. Outcomes attributed to adverse event (check all that apply)			
<input type="checkbox"/> Death		<input type="checkbox"/> Disability	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital anomaly	
<input type="checkbox"/> Hospitalization – initial or prolonged		<input type="checkbox"/> Required intervention to prevent permanent impairment/damage	
<input type="checkbox"/> Other:			
3. Date of event (mo/day/yr) to		3. Date of this report (mo/day/yr)	
4. Describe event or problem: Please see page two for additional information of this event.			
Please see page three for laboratory data, including dates.			
6. Other relevant history, including preexisting conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.):			
 Submission of a report does not constitute an Admission that medical personnel, user facility, Distributor, manufacturer or product caused or Contributed to the event. FDA Form 3500A (6-93)			

C. Suspect Medication(s)		
Name (give labeled strength & mfr/labeler, if known)		
#1		
#2		
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration from/to (or best estimate))	
#1	#1	
#2	#2	
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced	
#1	1# <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply	
#2	2# <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply	
6. LOT # (if known):	7. Exp. Date (if known):	8. Event reappeared after reintroduction:
#1:	#1:	1# <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply
#2:	#2:	2# <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply
9. NDC # - for product problems only (if known)		
— —		
10. Concomitant medical products and therapy dates (exclude treatment of event)		
D. All Manufacturers		
1. Contact office – name/address (& mfring site for devices):		2. Phone number:
		3. Report Source: (check all that apply)
		<input type="checkbox"/> Foreign
		<input type="checkbox"/> Study
		<input type="checkbox"/> Literature
		<input type="checkbox"/> Consumer
		<input type="checkbox"/> Health professional
		<input type="checkbox"/> User facility
		<input type="checkbox"/> Company representative
		<input type="checkbox"/> Distributor
		<input type="checkbox"/> Other:
4. Date received by manufacturer	5. NDA # IND # PLA #	
	Pre-1938 <input type="checkbox"/> Yes	
6. If, IND, protocol #	OTC product <input type="checkbox"/> Yes	
7. Type of report (check all that apply)	8. Adverse event term(s)	
<input type="checkbox"/> 7-day <input type="checkbox"/> 15-day		
<input type="checkbox"/> 10-day <input type="checkbox"/> periodic		
<input type="checkbox"/> Initial <input type="checkbox"/> follow-up #		
9. Mfr. report number		
E. Initial Reporter		
1. Name, address & phone #		
2. Health professional? <input type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation	4. Initial reporter also sent report to FDA? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number"

Form Approved: OMB No. 0910-0291 Expires 12/31/94 See OMB statement below	
Mfr. report #	
UF/ Dist report #	
FDA use only	

Form Approved: OMB No. 0910-0291 Expires 12/31/94 See OMB statement below	
Mfr. report #	
UF/ Dist report #	
FDA use only	



FDA Form 3500A (6-93)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

“An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number”

APPENDIX F

ANN ARBOR STAGING CRITERIA

Ann Arbor Classification (AJCC Manual for Staging of Cancer, 5th edition, 1997)

- STAGE I** Involvement of a single lymph node region (I) or localized involvement of a single extralymphoatic organ or site (IE)
- STAGE II** Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm
- STAGE III** Involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE) by involvement of the spleen (IIIS) or both (IIISE).
- STAGE IV** Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

A = Asymptomatic

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

“**BULKY**” is defined as a mediastinal mass > 1/3 of the maximum chest diameter (ie, internal dimension of the thoracic cavity measured at its widest point per radiograph) or any other mass \geq cm in maximum diameter.

APPENDIX G

GUIDELINES FOR THE ESTABLISHMENT OF RADIONUCLIDE DOSE CALIBRATOR SETTINGS USING MDS NORDION YTTRIUM-[90] CHLORIDE

#1. DOSE CALIBRATOR SETUP FOR ^{90}Y : Please use the following two worksheets (pages 2 and 3), along with the manufacturer's reference manual, to establish dose calibrator dial settings for assaying ^{90}Y . Dial settings for ^{90}Y are established using MDS Nordion ^{90}Y as a standard. MDS Nordion ^{90}Y is accompanied by an Activity Concentration Sheet stating the radioactivity concentration of the product at 1200h ET on the intended day of use. The radioactivity concentration is determined by a liquid scintillation technique traceable to the National Institute of Standards and Technology (NIST). This traceability has been established by both MDS Nordion and NIST performing assays on the same ^{90}Y sample and achieving agreement to within plus or minus 5%.

#2. GEOMETRY CHANGES: You must establish a new dial setting when you change dispensing equipment. This applies to a change in needle size, a change in syringe type, or a change in the reaction vial within the dose calibrator. A change in the type of container and/or the orientation of the container within the dose calibrator is a change in geometry. When using beta-emitting radionuclides a change in geometry will influence the dose calibrator reading.

#3. ACCURACY: The accuracy of liquid transfer from the MDS Nordion ^{90}Y vial using syringes commonly available in nuclear medicine departments is adequate, but not optimal. Gravimetric or volumetric methods can enhance the accuracy of the transfer (Coursey et al, Nucl Med Biol 1993; 20:693-9).

#4. USE OF WORKSHEETS: The worksheets on pages 2 and 3 are only for the *initial* determination of the dial settings used to assay ^{90}Y . Dial settings must be established for 10 mL of ^{90}Y Zevalin in a Zevalin reaction vial, or the range of ^{90}Y Zevalin volumes assayed in a 10 mL syringe. Once the dial settings are established, keep these worksheets as a reference for future use. An example of the range of dial settings used for a range of ^{90}Y Zevalin volumes in a 10 mL syringe is provided on page 4.

#5. DAILY CALIBRATION CHECK: On a daily basis, the dose calibrator response for each frequently used dial setting must be checked with a long-lived dose calibrator source. Suggested isotopes are ^{137}Cs , ^{57}Co , ^{60}Co , or ^{133}Ba . Consult your health physicist.

#6. INITIAL ISOTOPE CALIBRATION NUMBER: The radionuclide dose calibrator manufacturer must be contacted for the initial dial setting for working with ^{90}Y .

^{90}Y Decay Factor Table

Hours before 1200 h EST on the intended day of use:

	0	1	2	3	4	5	6	7	8
0	1	1.011	1.022	1.033	1.044	1.056	1.067	1.079	1.090
0.25	1.003	1.013	1.025	1.036	1.047	1.058	1.070	1.082	1.093
0.50	1.005	1.016	1.027	1.039	1.050	1.061	1.073	1.084	1.096
0.75	1.008	1.019	1.030	1.041	1.053	1.064	1.076	1.087	1.099

Hours after 1200 h EST on the intended day of use:

	0	1	2	3	4	5	6	7	8
0	1	0.989	0.979	0.968	0.958	0.947	0.937	0.927	0.917
0.25	0.997	0.987	0.976	0.966	0.955	0.945	0.935	0.925	0.915
0.50	0.995	0.984	0.973	0.963	0.953	0.942	0.932	0.922	0.912
0.75	0.992	0.981	0.971	0.960	0.950	0.940	0.930	0.920	0.910

To use the decay table, find the number of hours in the top and left-hand columns of the grids, then find the corresponding decay factor.

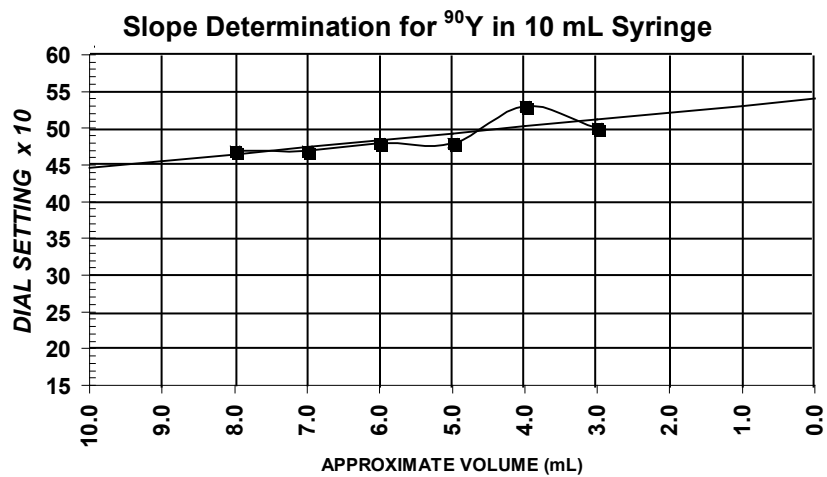
**GUIDELINES FOR THE ESTABLISHMENT OF RADIONUCLIDE DOSE CALIBRATOR
SETTINGS USING MDS NORDION YTTRIUM-[90] CHLORIDE: WORKSHEET #1
(ZEVALIN REACTION VIAL)**

1. The <u>Activity Concentration Sheet</u> provided with each MDS Nordion ⁹⁰ Y vial includes data based on 1200h ET on the intended day of use. Use the ⁹⁰ Y decay table on page 1 to determine the current MDS Nordion ⁹⁰ Y activity concentration, adjusting for time zone changes. (Example: At 1400h ET, 2 hours post-calibration, the decay factor is 0.979. If the <u>Activity Concentration Sheet</u> reports 84.0 mCi/mL, the current activity concentration is 84.0 mCi/mL x 0.979 = 82.2 mCi/mL).		_____ mCi/mL
2. Using the activity concentration determined in Step #1, calculate the volume for 40 mCi. (Example: 40 mCi ÷ 82.2 mCi/mL = 0.49 mL). Draw up the appropriated volume for 40 mCi into a 1 mL syringe with a removable needle.		_____ mL
3. Change the needle on the 1 mL syringe. Place the 1 mL syringe in the dose calibrator. A 1 mL syringe holder may be required from your dose calibrator manufacturer to center the syringe in the unit. Adjust the dial setting until the dose calibrator indicates 40 mCi (take into account any multiplier that may be required by the calibrator). Record as Dial Setting A.		<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Dial Setting _____ (Δ)• </div>
4. Transfer 40 mCi into a reaction vial.		
5. Wash residual activity from the 1 mL syringe into the reaction vial with normal saline. (Two 0.5 mL aliquot transfers will remove most of the retained activity in the needle/syringe hub).		_____ mL
6. Place the 1 mL syringe into the dose calibrator and assay for residual activity.		_____ mCi
7. Subtract the residual activity in the 1 mL syringe determined in step #6 from 40 mCi to determine the activity transferred into the reaction vial (Example: 40.0 mCi - 0.2 mCi = 39.8 mCi).		_____ mCi
8. Add normal saline to the reaction vial to a total volume of 10.0 mL. (Note: 10.0 mL minus volume transferred in step #2 and step #5 equals the volume to add).		_____ mL
9. Place the 10 mL reaction vial into the dose calibrator and adjust the dial setting until the display shows the activity determined in step #7. Record as Dial Setting B. Record the reaction vial type and date performed.		<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Dial Setting _____ </div> Reaction Vial Type: _____ Date: _____

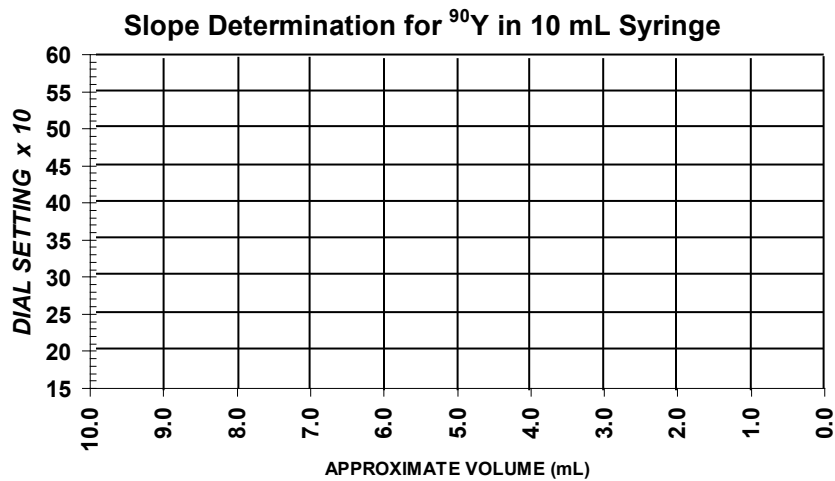
**GUIDELINES FOR THE ESTABLISHMENT OF RADIONUCLIDE DOSE CALIBRATOR SETTINGS USING
MDS NORDION YTTRIUM-[90] CHLORIDE: WORKSHEET #2
(10 ML SYRINGE)**

1. The <u>activity concentration sheet</u> provided with each mds nordion ⁹⁰ Y vial includes data based on 1200h ET on the intended day of use. Use the ⁹⁰ Y decay table on page 1 to determine the current mds nordion ⁹⁰ Y activity concentration, adjusting for time zone changes. (example: at 1400h ET, 2 hours post-calibration, the decay factor is 0.979. If the <u>activity concentration sheet</u> reports 84.0 mCi/mL, the current activity concentration is 84.0 mCi/mL x 0.979 = 82.2 mCi/mL).	_____ mCi/mL
2. Using the activity concentration determined by step #1, calculate the volume for 40 mci. (example: 40 mCi ÷ 82.2 mCi/mL = 0.49 ml). Draw up the appropriate volume for 40 mCi into a 1 mL syringe with a removable needle.	_____ mL
3. Change the needle on the 1 mL syringe. Place the 1 mL syringe in the dose calibrator. A 1 mL syringe holder may be required from your dose calibrator manufacturer to center the syringe in the unit. Adjust the dial setting until the dose calibrator indicates 40 mCi (take into account any multiplier that may be required by the calibrator). Record as dial setting a.	<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Dial Setting _____ </div>
4. Transfer 40 mCi into a reaction vial.	
5. Wash residual activity from the 1 mL syringe into the reaction vial with normal saline. (two 0.5 mL aliquot transfers will remove most of the activity retained in the needle and syringe hub).	_____ mL
6. Place the 1 mL syringe into the dose calibrator and assay for residual activity.	_____ mCi
7. Subtract the residual activity in the 1 mL syringe determined in step #6 from 40 mCi to determine the activity transferred into the reaction vial (example: 40.0 mCi - 0.2 mCi = 39.8 mCi).	_____ mCi
8. Add normal saline to the reaction vial to a total volume of 10.0 mL. (note: 10.0 mL minus volumes transferred in step #2 and step #5 equals the volume to add).	_____ mL
9. Calculate the activity that will be contained in 1 mL aliquots (example: 39.8 mCi/10mL, 35.8 mCi/9mL, 31.8 mCi/8mL, etc.).	
10. Using a 10 mL syringe, sequentially remove 1 mL aliquots of ⁹⁰ Y solution from the reaction vial. Assay the syringe in dose calibrator after each aliquot is removed. Adjust dial setting for each volume assayed until the display shows the corresponding activity calculated in step #9. Record each dial setting.	<div style="border: 1px solid black; padding: 5px;"> Dial Settings (B): 10 mL _____ 5 mL _____ 9 mL _____ 4 mL _____ 8 mL _____ 3 mL _____ 7 mL _____ 2 mL _____ 6 mL _____ 1 mL _____ </div>
11. Plot dial setting versus syringe volume onto graph paper (see example on page 4). If the slope is flat for the range of volumes, use only one dial setting to assay ⁹⁰ Y activity. If the slope is decending or ascending, use corresponding dial settings for each volume, regardless of activity.	
12. Record the syringe type and size configuration and date completed.	Syringe Type and Size: _____ Date: _____

Dose Calibrator Set-Up for ^{90}Y : Example Plot



Dose Calibrator Set-Up for ^{90}Y



APPENDIX H

BIOGEN IDEC INCORPORATED PREPARATION AND DISPENSING INFORMATION FOR ^{111}In Zevalin and ^{90}Y Zevalin

CAUTION: New Drug -- Limited by Federal Law to Investigational Use Only

DESCRIPTION:

ZevalinTM (ibritumomab tiuxetan) is a murine monoclonal anti-CD20 antibody that will be radiolabeled with Indium-111 or Yttrium-90.

Note: ^{111}In Zevalin or ^{90}Y Zevalin should not be administered until the patient has received the second Rituxan infusion.

I. Components of the Zevalin (ibritumomab tiuxetan) Kit and Preparation of ^{111}In Zevalin and ^{90}Y Zevalin

A. Radioisotopes: ^{111}In and ^{90}Y used for preparing ^{111}In Zevalin and ^{90}Y Zevalin, will be obtained from vendors identified by Cell Therapeutics. All lots of isotopes must be sterile, pyrogen-free and be supplied in septum vials designed to maintain these conditions.

B. Radiolabeling Kit Components: For clinical studies, conjugated Zevalin (ibritumomab tiuxetan) will be radiolabeled with either ^{111}In for imaging or ^{90}Y for therapy using a radiolabeling kit. The radiolabeling kit is provided by Biogen Idec to the clinical site or radiopharmacy. All kit components are tested for sterility and pyrogenicity.

The kit is stored at 2 - 8°C (35 - 45°F) and consists of the following components:

- 1) Three mL glass septum vial containing 2 mL (3.2 mg) Zevalin (ibritumomab tiuxetan) in low-metal normal saline at 1.6 mg/mL
- 2) Three mL glass septum vial containing 2 mL low-metal 50 mM sodium acetate
- 3) Ten mL glass septum vial containing 10 mL formulation buffer (1X PBS containing 7.5% human serum albumin and 1 mM DTPA, pH 7.2)
- 4) Ten mL glass septum reaction vial (empty)

C. See the appropriate Appendix for corrected geometry of dose calibrator for Y-[90].

D. Preparation of ^{111}In Zevalin: Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves shall be utilized in the preparation and determination of the radiochemical purity assay of ^{111}In Zevalin. The radiolabeling of ^{111}In Zevalin shall be done according to the following directions using the radiolabeling kit described above.

- 1) Before radiolabeling, bring refrigerated Zevalin (ibritumomab tiuxetan) cold kit to room temperature, 25° C (77° F).
- 2) Clean the rubber stopper of all cold kit vials and the ¹¹¹In chloride vial with a suitable alcohol swab and allow to air dry.
- 3) Place the ¹¹¹In Zevalin reaction vial in a suitable dispensing shield.
- 4) Using a 1 mL syringe, transfer sodium acetate to the reaction vial. The volume of sodium acetate added is equivalent to 1.2 times the volume of ¹¹¹In chloride.
- 5) With a 1 mL syringe, aseptically transfer 5.5 mCi of ¹¹¹In chloride to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times, do not shake.
- 6) Using a 3 mL syringe, transfer 1.0 mL Zevalin (ibritumomab tiuxetan) to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times. Do not shake.
- 7) Incubate the ¹¹¹In Zevalin reaction vial at room temperature for thirty minutes. Labeling more than or less than thirty minutes may result in inadequate radiochemical purity.
- 8) Using a 10 mL syringe with a large bore needle (18 - 20 G), draw formulation buffer that will result in a total volume of 10 mL when all components are added to the reaction vial. The initial volume in the reaction vial is the volumes calculated in Steps 4, 5, and 6. Ten mL minus the volumes in 4, 5, and 6, will be the volume of formulation buffer to add.
- 9) At the end of the thirty-minute incubation period, add the formulation buffer to the reaction vial. Gently add the formulation buffer down the side of the reaction vial. Do not foam, shake or agitate the mixture.
- 10) Assay the ¹¹¹In Zevalin reaction vial in a suitably calibrated dose calibrator.
- 11) If not immediately administered to the patient, store the reaction vial containing the ¹¹¹In Zevalin at 2° to 8° C (26° to 46° F) and use within 12 hours.
- 12) The percent radiochemical purity of the prepared ¹¹¹In Zevalin should be determined before administration to the patient according to the procedure in Section II.
- 13) DO NOT EXCEED THE MAXIMUM ALLOWED DOSE OF 5 mCi ¹¹¹In Zevalin.

E. **Preparation of ⁹⁰Y Zevalin:** Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves shall be utilized in the preparation and determination of the radiochemical purity assay of ⁹⁰Y Zevalin. The radiolabeling of ⁹⁰Y Zevalin shall be done according to the following directions using the radiolabeling kit described above.

- 1) Before radiolabeling, bring refrigerated Zevalin (ibritumomab tiuxetan) cold kit to room temperature 25° C (77° F).
- 2) Clean the rubber stopper of all cold kit vials and the ⁹⁰Y chloride vial with a suitable alcohol swab and allow to air dry.
- 3) Place the ⁹⁰Y Zevalin reaction vial in a suitable dispensing shield.
- 4) Using a 1 mL syringe, transfer sodium acetate to the reaction vial. The volume of sodium acetate added is equivalent to 1.2 times the volume of ⁹⁰Y chloride.
- 5) With a 1 mL syringe, aseptically transfer 40 mCi of yttrium-[90] chloride to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times, **do not shake**.
- 6) Using a 3 mL syringe, transfer 1.3 mL Zevalin (ibritumomab tiuxetan) to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times. **Do not shake**.
- 7) Incubate the ⁹⁰Y Zevalin reaction vial at room temperature for five-minutes. Labeling more than or less than five minutes may result in inadequate radiochemical purity.
- 8) Using a 10 mL syringe with a large bore needle (18 - 20 G), draw formulation buffer that will result in a total volume of 10 mL when all components are added to the reaction vial. The initial volume in the reaction vial is the volumes calculated in Steps 4, 5, and 6. Ten mL minus the volumes in 4, 5, and 6, will be the volume of formulation buffer to add.
- 9) At the end of the five-minute incubation period, add the formulation buffer to the reaction vial. Gently add the formulation buffer down the side of the reaction vial. Do not foam, shake, or agitate the mixture.
- 10) Assay the ⁹⁰Y Zevalin reaction vial in a suitably calibrated dose calibrator.
- 11) If not immediately administered to the patient, store the reaction vial containing ⁹⁰Y Zevalin at 2° to 8° C (36° to 46° F) and use within eight hours.
- 12) The percent radiochemical purity of the prepared ⁹⁰Y Zevalin should be determined before administration to the patient according to the procedure in Section II.
- 13) **CAUTION: DO NOT EXCEED THE MAXIMUM ALLOWED DOSE OF 32 mCi.**

II. CLINICAL RELEASE TESTING FOR ¹¹¹IN ZEVALIN AND ⁹⁰Y ZEVALIN

Release assay is performed at the clinical site ¹¹¹In Zevalin and ⁹⁰Y Zevalin.

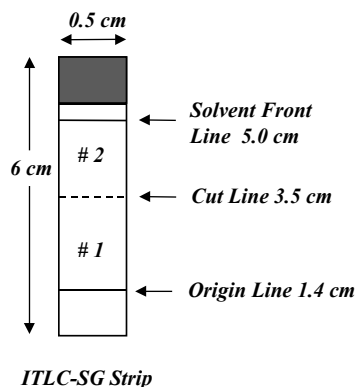
Radiochemical Purity: This assay insures that an acceptable percentage of the radioisotope is chelated by the antibody conjugate. An instant thin-layer chromatographic assay using a commercial kit (Biodex) is available for use. In this assay, conjugated

antibody remains at the origin whereas tiuxetan or DTPA-chelated indium/yttrium advances with the solvent front. The amount of radioactivity remaining at the origin bound to the antibody conjugate is expressed as a percentage of the total amount of radioactivity applied to the strip. See instructions below Steps #1 - #8.

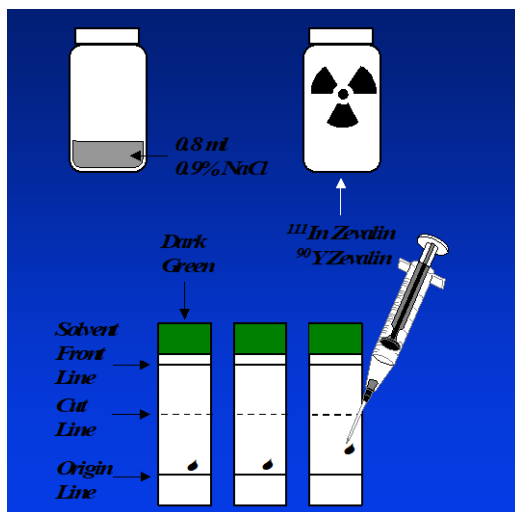
The Radiochemical Purity by Instant Thin Layer Chromatography (ITLC) shall be done according to the following procedure at room temperature:

1. Required materials not supplied:

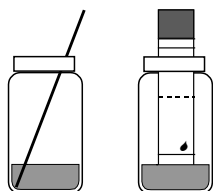
- 1 mL insulin syringe with a 25 - 26 G needle
- ITLC-SG, or Biodex "Tec-Control" kit, part number 151-770
- Single or multichannel analyzer



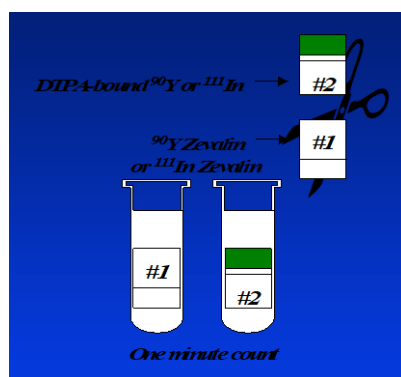
2. Set region of interest of single or multichannel analyzer to incorporate channels 140-1000 keV for ^{90}Y or 140 -300 keV for ^{111}In .
3. Using a 1 mL insulin syringe, place a hanging drop (7 - 10 μL) onto the ITLC-SG strip at its 1.4 cm mark "origin." Spot one strip at a time and run the procedure on three ITLC-SG strips. A 1:100 dilution may be necessary if the instrument deadtime is appreciable.



4. Fill developing chamber with 0.8 mL of bacteriostatic free 0.9% NaCl. The volume of 0.9% NaCl should not touch the 1.4 cm “origin” line.
5. Place ITLC-SG strip into developing chamber and allow the solution to migrate past the 5 cm “Solvent Front” line. Do not allow ITLC-SG strip to adhere to the side of the developing chamber. See illustration below.



6. Remove ITLC-SG strip and cut in half at the 3.5 cm “Cut-Line.” Count each half of the ITLC-SG strip in a multi-channel or single channel analyzer counter for one-minute (cpm).



Subtract background counts and use corrected counts.

7. Calculate the radiochemical purity % as follows:

$$(Radiochemical\ purity\ \%) = \left(\frac{(cpm\ \#1)}{(cpm\ \#1) + (cpm\ \#2)} \right) \times 100$$

8. Repeat process two times and take the average percentage of the radiochemical purity (RCP).

The release specification for the average radiochemical purity is $\geq 95\%$ for both ^{111}In Zevalin and ^{90}Y Zevalin.

III. RECOMMENDED HANDLING AND ADMINISTRATION OF ^{111}In ZEVALIN AND ^{90}Y ZEVALIN

1. Refer to the appropriate section of the clinical trial protocol for details about the dose and dose schedule. Note: Patients will receive an imaging dose of 5 mCi ^{111}In Zevalin. Patients with most recent platelet counts from 100,000/mm³ to 149,000/mm³ will be treated with a 0.3 mCi/kg dose of ^{90}Y Zevalin. Patients with most recent platelet counts $\geq 150,000/\text{mm}^3$ will be treated with 0.4 mCi/kg dose of ^{90}Y Zevalin.
2. **Vials should be stored with proper shielding at 2 - 8°C (35 - 45°F).** Do not freeze or store at room temperature. The drug is a protein -- HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the de-naturing of the product proteins.
3. All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.
4. ^{111}In Zevalin and ^{90}Y Zevalin may be directly injected 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.

NOTE: DO NOT USE evacuated glass containers that require vented administration sets because this causes foaming as air bubbles pass through the solution.

5. The administration of the radiolabeled drug will be accomplished by 10 minute IV injection and should be completed within the time specified in the protocol. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS BOLUS. Flush the line with at least 10 mLs of normal saline after radiolabeled product has been infused.

NOTE: IV pumps may be used with the ^{111}In Zevalin and ^{90}Y Zevalin injection. DO NOT INJECT CONCOMITANTLY with another IV solution or IV medications.

6. If a delay in administration occurs after the ^{111}In Zevalin or ^{90}Y Zevalin (in a properly identified container) is prepared, the radiolabeled product must be kept refrigerated after

preparation at 2 - 8°C (35 - 45° F) for up to twelve hours for ¹¹¹In Zevalin and eight hours for ⁹⁰Y Zevalin. If not used soon after the calibration time, the actual dose activity will have decayed and require recalculation.

FOR ADDITIONAL INFORMATION CONTACT:

Zevalin Support Services, Spectrum Pharmaceuticals, 1-866-298-8433, www.Zevalin.com

APPENDIX I

DATA ACQUISITION FOR ^{111}In ZEVALIN

Equipment and Materials

1. A dual-head gamma camera with medium energy collimators is highly recommended for the whole body planar imaging; however, a single-head gamma camera capable of whole body imaging may be used.
2. ^{111}In standards to be imaged on the whole body gamma camera.

Patient ^{111}In Zevalin Injection and Post Injection Imaging

Injected Activity

1. Just prior to infusion, verify and record the dose using a dose calibrator. Record the time and date.
2. Count the empty syringe after injection using the dose calibrator to determine residual activity to calculate and record the total activity injected.

Whole Body ^{111}In Zevalin Image Acquisition

1. Perform a whole body scan at 48 – 72 hours and optionally at 90 - 120 hours post ^{111}In Zevalin® injection. At 48 – 72 hours, the scan speed should be at 7 - 10 cm/min (30 minute scan), and at 90 – 120 hours, the scan speed should be 5 - 7 cm/min (40 minute scan).
2. Record the start times of the acquisitions on the data sheet.
3. Each set of images should include a standard of ^{111}In in a small plastic vial (such as a gamma-counting vial). A standard of approximately 50 μCi in 10 ml water should be made up prior to the 0 hr image and the same standard used with each planar image acquisition beginning after the dose is infused. Measure the exact standard activity in a dose calibrator and record the time and activity. This should correspond to the time of the start of the first scan. Place the standard on the imaging table approximately 10 cm from the body, lateral to the feet. Always place standard on the same side of the body for each scan. Scan the standard with each whole body image.

APPENDIX J

Amendment #1

(3/1/06)

Summary of Changes

- Face Page: University of Arizona/Arizona Cancer Center Co-Investigators: deletion of John Sweetenham, M.D., as he has left the institution, and addition of Leslie Andritsos, M.D. (Medical Oncology) and Lisa Gobar, M.D. (Nuclear Medicine); change of version date of the protocol to Amendment #1, March 1, 2006, and addition of sponsor protocol number 009-004-ZEV.
- Section 5.C (Evaluations During the ¹¹¹In Zevalin Imaging Period): revision to reflect deletion of 2-24-hour scan (see below).
- Section 6.C (Zevalin® Adverse Events) and Risk section of the Model Consent Form: Addition of new information relating to severe cutaneous and mucocutaneous adverse events observed in patients who received the Zevalin® regimen (post-marketing experiences of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis).
- Section 8.C (Toxicities to be Monitored and Dosage Modifications, Ibritumomab Tiuxetan Regimen): Addition of cautions for cutaneous and mucocutaneous reactions.
 - Section 7.B.1 Radioimaging Schedule: Decrease in the number of required whole-body gamma camera scans to assess biodistribution after the initial imaging dose on In-111 Zevalin® from two to one. Scan 1 at 2-24 hours has been deleted, leaving the scan to be administered 48-72 hours after the In-111 Zevalin®. As before, an optional subsequent scan may be performed to resolve ambiguities (90-120 hours after the initial imaging dose).
- Model Consent Form: Updated with regard to risks (as detailed above) and number of imaging scans
- Appendix H: Package Insert: addition of current Zevalin® Package Insert as H-2. **Added 4/18/06 Current NCI Composite Adverse Event and Potential Risks List**
- Appendix K: Updated Data Acquisition for 111-In Zevalin® (imaging times)

APPENDIX K
Amendment #2
(4/27/07)

Summary of Changes

- Face Page: University of Arizona/Arizona Cancer Center Co-Investigators: deletion of Leslie Andritsos, M.D., and addition of Daniel Persky, M.D. (Medical Oncology); change of version date of the protocol to Amendment #2, April 27, 2007.
- Section 4.A. Inclusion Criteria: 4.A.1: Change in wording to indicate that patients may be in first, second, third, or fourth relapse (expanded from “first or second relapse”. 4.A.9 Change in wording to “...Patients must have had at least 1, but no more than 4 prior chemotherapy regimens for lymphoma....”
- Section 5.B Evaluations During ESHAP Treatment and 5.C and 5.D Evaluations During post-Zevalin® follow-up and Appendix A: : Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), uric acid, glucose, and urinalysis will be obtained as clinically indicated, rather than required as part of the study. Restaging will occur 3 months (rather than 2 months) after completion of Zevalin®. Followup CT scans during the first 2 years after Zevalin® will be performed every 6 months, rather than every 3 months, unless clinically indicated. Thus, the revised CT schedule is at 6, 12, 18, and 24 months for 2 years and then every 6 months for 2 years, and then annually. The Zevalin® will be administered 4-6 weeks after completion of ESHAP (rather than 3-6 weeks). A required week 4 blood count after the Zevalin® treatment has also been added. The baseline anti-CD20 immunophenotyping in Appendix A has been deleted, as this will have been done as part of the original diagnostic testing before any treatment.
- Section 6.B and 6.C (Drug Information) and the Model Consent have been updated to include the new rituximab risk information received from the Study Sponsor and NCI (attached) for this study. The wording for the changes is that agreed upon by SWOG and the NCI for SWOG studies using rituximab or Zevalin® (which has rituximab as a component): revised wording regarding severe infusion and hypersensitivity reactions; new information on viral infections (including the possibility of progressive multifocal leukoencephalopathy related to JC virus), and gastrointestinal, cardiovascular, and renal toxicities; new cautions related to immunization, carcinogenesis, impairment of fertility, pregnancy, and nursing. **APPENDIX H updated (Rituximab package insert 2/2007 update added).**
- Section 8 (Toxicities to be Monitored and Dosage Modifications) has been revised to provide guidance for monitoring for the above-noted side effects).
- Model (Locally Approved) Consent Form: This has been updated with regard to risks (as detailed above), number of prior therapies allowed, and timing of Zevalin® and specific study procedures.

APPENDIX L

Amendment #3

(11/1/08)

Summary of Changes

- Updated: Cover Sheet, Version date, Table of Contents
- Inserted Protocol Signature Page
- Updated Study Duration to 5 years
- Re-paginated, Re-numbered Sections
- Updated Inclusion Criteria (All changes have been reflected in the Study Calendar: Apx. A):
 - 4.A.2 –REMOVED: *“A report providing confirmation of CD20 expression must be submitted per Section 5.A.”*
 - 4.A.4 – Changed: *“All patients must have bidimensionally measurable disease (as defined in Appendix D) documented within 1 month prior to registration. Patients with non-measurable disease (as defined in Appendix D) in addition to measurable disease must have all non-measurable disease assessed within 42 days prior to registration.”*

To: *“All patients must have bidimensionally measurable disease (as defined in Appendix D) documented within 28 days prior to Cycle 1, Day 1.”*
 - 4.A.5 – Changed: **“Pathology Review:** *Adequate sections from the diagnostic specimen or core needle biopsies which are large enough to show architecture (bone marrow biopsies and fine-needle aspirates are insufficient) must be available for submission as outlined in Section 5. Patients are also eligible for participation in Arizona Cancer Center tumor and serum specimen acquisition protocols.”*

To: *“Pathology Review: Adequate sections from the diagnostic specimen or core needle biopsies which are large enough to show architecture (bone marrow biopsies and fine-needle aspirates are insufficient) is desirable. At a minimum, a report documenting the diagnosis is required.”*
 - 4.A.6 –Changed: *“Patients must have a unilateral or bilateral bone marrow aspirate and biopsy performed within 42 days prior to registration.”*

To: *“Patients must have a unilateral or bilateral bone marrow aspirate and biopsy performed within 28 days prior to Cycle 1, Day 1.”*
 - 4.A.7 – Changed : *“Patients must have a CT scan of chest, abdomen, and pelvis within 1 month prior to registration.”*

To: *“Patients must have a CT scan of chest, abdomen, and pelvis within 28 days prior to Cycle 1, Day 1.”*
 - 4.A.8 – Changed: *“Patients must have an LDH and β -2 microglobulin within 1 month prior to registration.”*

To: *“Patients must have an LDH and β -2 microglobulin within 28 days prior to Cycle 1, Day 1.”*

- REMOVED: Formerly 4.A.10: “Patients may not have undergone bone marrow transplantation (BMT).”
- 4.A.13, Now 4.A.12- Changed: “...within 14 days prior to registration...”
To: “...within 28 days prior to Cycle 1, Day 1...”
- 4.A.14, Now 4.A.13 – Changed: “A serum creatinine or creatinine clearance must be obtained within 14 days prior to registration.”
To: “A serum creatinine or creatinine clearance must be obtained within 28 days prior to Cycle 1, Day 1.”
- REMOVED: Formerly 4.A.15: “Patients known to be HIV-positive are not eligible.”
- 4.A.18, Now 4.A.16 – Changed: “If Day 42 falls on a weekend or holiday, the limit may be extended to the next working day. **In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 6 weeks later would be considered Day 42. This allows for efficient patient scheduling without exceeding the guidelines.**”
To: “If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day. **In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.**”
- Updated Exclusion Criteria:
 - a., Now 4.B.1 – REMOVED: “Prior myeloablative therapies with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell (PBSC) rescue.”
Changed: “Hypocellular bone marrow (cellularity \leq 15%)”
To: “Hypocellular bone marrow (cellularity \leq 10%)”
 - c., Now 4.B.3 – REMOVED: “Any laboratory tests that are performed to assess clinical signs of CNS involvement must be negative within 42 days prior to registration.”
 - REMOVED - Formerly d.: “Patients with chronic lymphocytic leukemia (CLL)”
 - REMOVED – Formerly e.: “Patients with HIV or AIDS-related lymphoma”
 - REMOVED – Formerly f.: “Patients with pleural effusion”
- 4.D – Changed: “All patients will be registered centrally with the Study Coordinator based in the Arizona Cancer Center Lymphoma Program Office at 520-626-6786.”
To: “All patients will be registered centrally with the Clinical Research Coordinator based in the Arizona Cancer Center at 520-694-9053. The Clinical Research Coordinator will assign each patient a sequential number.”
- 5.A – Changed: “Unless otherwise specified, the following evaluations must be performed within 4 weeks prior to patient registration.”
To: “Unless otherwise specified, the following evaluations must be performed within 28 days prior to C1, D1:”
- 5.A.b, Now 5.A.2 – Changed: “Physical examination, including, performance status (Adult Common Toxicity Criteria; see the appropriate Appendix), and Tumor Assessment (see the appropriate Appendix)”

To: *“Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).”*

- 5.A.c, Now 5.A.3 – Changed: *“CT scan or MRI of the neck, chest, abdomen and pelvis is recommended for baseline response evaluation”*

To: *“Disease Assessment:*

- *Total of all measurable indicator lesions*
- *CT scan of the chest, abdomen and pelvis is recommended for baseline response evaluation.”*

- 5.A.d, Now 5.A.4 – Changed: *“Laboratory tests including:*
 - *Complete blood count (CBC) with differential and platelet count (within 2 weeks prior to patient registration)*
 - *Serum chemistries - glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, SGOT (AST), SGPT (ALT) (within 2 weeks prior to patient registration)*
 - *Serum beta-2-microglobulin*
 - *Urinalysis: routine dip stick*
 - *Pregnancy test (serum) for women of childbearing potential”*

To: *“Laboratory tests including:*

- *Complete blood count (CBC) with differential and platelet count*
- *Serum chemistries - BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT (AST), SGPT (ALT)*
- *Serum beta-2-microglobulin*
- *Pregnancy test (serum) for women of childbearing potential*
- *Hepatitis B screen (encouraged by Good Medical Practice, but not required)”*

- 5.A.e, Now 5.A.5 – Changed: *“Bi-lateral bone marrow biopsy or aspirate (within 6 weeks of patient registration) for histology and determination of percent bone marrow involvement.”*

To: *“Unilateral or Bi-lateral bone marrow biopsy and aspirate for histology and determination of percent bone marrow involvement.”*

- 5.A.f, Now 5.A.6 – Changed: *“Bone marrow cytogenetics must be performed within 6 weeks prior to patient registration. (Results are not required prior to enrollment.)”*

To: *“Bone marrow cytogenetics (Results are not required prior to enrollment). This can also be done with the repeat Bone Marrow biopsy and aspirate at Cycle 2, Day 29. This does not have to be done at each Bone Marrow biopsy and aspirate, but does need to be completed at either, Baseline or Cycle 2, Day 29.”*

- 5.A.g, Now 5.A.7 – Changed: *“All patients registered on this study will undergo pathology review.”*

To: *“All patients registered on this study are encouraged to undergo pathology review.”*

- 5.A.g.1, Now 5.A.7.a – Changed: *“Pathology materials are to be submitted within 30 days of registration to:”*

To: *“Pathology materials are to be submitted to:”*

REMOVED: *“An additional copy of the Protocol Specific Pathology Submission Form*

must be submitted each time submissions are made to Dr. Rimsza.”

- 5.A.g.2, Now 5.A.7.b – Changed: “*The following materials are to be submitted for review:*”

To: “*The following materials would constitute best available material for review:*”

- 5.B – Changed: “*For the purpose of safety assessments, the treatment period will include the time from the first ESHAP infusion to 12 weeks following Zevalin infusion (see Appendix A). Evaluations during the 2 cycles of ESHAP are outlined in Appendix A and include Day 1 Cycle 1 pre-treatment CBC, differential, and platelets and Day 2 and Day 29 history and physical examination, CBC, differential, and platelets, serum creatinine, and BUN. AST, ALT, alkaline phosphatase, and total bilirubin will be repeated as clinically indicated (4/27/07). Clinically significant changes should be recorded on the clinical events page of the CRF. On Day 29 of cycle 2 bone marrow aspiration and biopsy are repeated, as well as CT scans of the chest, abdomen, and pelvis.*

Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form. The onset of new adverse events as defined in Appendix E will be documented in the patient's case report form. In addition, any transfusions of blood and blood products are to be recorded in the patient's CRF.

In the event that a Grade 3 or 4 hematologic toxicity occurs at any time, blood samplings for follow-up evaluations should be performed as clinically indicated until the abnormality is resolved.”

To: “*For the purpose of toxicity assessment, the treatment period will include the time from the first ESHAP infusion to 30 days following Zevalin infusion. Evaluations during the 2 cycles of ESHAP are outlined in Appendix A.*

5.B.1 ESHAP Cycle 1, Day 1

- a. *Begin ESHAP Treatment (Please refer to Section 7A for ESHAP administration)*

5.B.2 ESHAP Cycle 2, Day 1

- a. *History & Physical examination, including vital signs (BP, temperature*

& pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).

- b. *Laboratory tests including:*

- *Complete blood count (CBC) with differential and platelet count*
- *Serum chemistries - BUN, creatinine*

- d. *Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.*

5.B.3 ESHAP Cycle 2, Day 29

- a. *History & Physical examination, including vital signs (BP, temperature*

& pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).

- b. *Laboratory tests including:*

- *Complete blood count (CBC) with differential and platelet count*

- Serum chemistries - BUN, creatinine

- g. *Unilateral or Bi-lateral bone marrow biopsy and aspirate for histology and determination of percent bone marrow involvement*
- h. *Bone marrow cytogenetics. Does not have to be done at each Bone Marrow biopsy and aspirate, but does need to be completed at either, Baseline or Cycle 2, Day 29.*
- i. *Disease Assessment:*
 - *Total of all measurable indicator lesions.*
 - *CT scan of the chest, abdomen and pelvis*
- j. *Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.*

• **5.C - Changed: "Evaluations During the ¹¹¹In Zevalin Imaging Period**

CAUTION WILL BE TAKEN IN THE HANDLING OF ALL RADIOACTIVE SAMPLES ACCORDING TO STANDARD PROCEDURES AND PRACTICES AT THE CLINICAL SITE.

Vital signs will be obtained every 15 minutes for the first hour during the Rituxan infusion, hourly during the remainder of the infusion, and immediately following the ¹¹¹In Zevalin infusion. If vital signs are unstable, they will be monitored at 5-minute intervals until stable.

48.A. Evaluations During the ¹¹¹In Zevalin Imaging Period

Vital signs will be obtained every 15 minutes for the first hour during the Rituxan infusion, hourly during the remainder of the infusion, and immediately following the ¹¹¹In Zevalin infusion. If vital signs are unstable, they will be monitored at 5-minute intervals until stable.

The purpose of ¹¹¹In Zevalin imaging is twofold:

- *To evaluate biodistribution of whole body gamma camera images*
- *To assess whether biodistribution is acceptable to proceed with ⁹⁰Y Zevalin radioimmunotherapy.*

The biodistribution of ¹¹¹In 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. Images should be acquired using a large field of view gamma camera quipped with a medium energy collimator. Whole body anterior/posterior planar images should be acquired using a large field-of-view gamma camera and medium energy collimators. Suggested gamma camera settings: 256 x 1024 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min for the 48-72 hour scan, and 7-10 cm/min for subsequent scans.

a. Expected biodistribution:

- *Activity in the blood pool areas (heart, abdomen, neck, and extremities) may be faintly visible.*

- Moderately high to high uptake in normal liver and spleen.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel.
- Non-fixed areas within the bowel lumen that change position with time; delayed imaging as described above may be necessary to confirm gastrointestinal clearance.

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. Tumor visualization on the ^{111}In Zevalin scan is not required for ^{90}Y Zevalin therapy.

b. Altered biodistribution

- Intense localization of radiotracer in the liver and spleen and bone marrow indicative of reticuloendothelial system uptake
- Increased uptake in normal organs (not involved by tumor) such as:
 - Diffuse uptake in normal lung more intense than the liver.
 - Kidneys with greater intensity than the liver on the posterior view.
 - Fixed areas (unchanged with time) of uptake in the normal bowel greater than uptake in the liver.
- In less than 0.5% of patients receiving ^{111}In Zevalin, prominent bone marrow uptake was observed, characterized by clear visualization of the long bones and ribs.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the ^{90}Y Zevalin dose. The safety and efficacy of the administration of ^{90}Y Zevalin in patients with prominent marrow uptake is not known. Possible causes of prominent bone marrow uptake, such as bone marrow involvement by lymphoma, increased marrow activity due to recent hematopoietic growth factor administration, and increased reticuloendothelial uptake in patients with HAMA and HACA, should be considered. Re-assessment of biodistribution after correction of underlying factors should be performed. ^{90}Y Zevalin should not be administered to patients with persistently prominent marrow uptake on the repeat biodistribution scans."

48.B. To: "Evaluations During the Zevalin Imaging & Treatment Period

48.C. Ibritumomab Tiuxetan Indium (^{111}In Zevalin) regimen is administered 4 – 6 weeks after completion of ESHAP.

5.C.1 Day 1

- History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).*
- Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form.*
- Laboratory tests including:*
 - Complete blood count (CBC) with differential and platelet count

- Serum chemistries - BUN, creatinine

d. Rituximab Infusion (250 mg/m²) & ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) infusion.
(Please refer to section 7.B for detailed treatment administration)

Vital signs will be obtained every 15 minutes for the first hour during the Rituxan infusion, hourly during the remainder of the infusion, and immediately following the ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) infusion. If vital signs are unstable, they will be monitored at 5-minute intervals until stable.

5.C.2 Days 2, 3, 4 and 5

a. Gamma Scan: A scan is to be performed at 48-72 hours after ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) infusion. Another optional scan may be performed at 90-120 hours after ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) infusion.

CAUTION WILL BE TAKEN IN THE HANDLING OF ALL RADIOACTIVE SAMPLES ACCORDING TO STANDARD PROCEDURES AND PRACTICES AT THE CLINICAL SITE.

The purpose of ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) imaging is twofold:

- To evaluate biodistribution of whole body gamma camera images
- To assess whether biodistribution is acceptable to proceed with ⁹⁰Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) radioimmunotherapy.

The biodistribution of ¹¹¹In Zevalin (Ibritumomab Tiuxetan Indium) 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. Images should be acquired using a large field of view gamma camera quipped with a medium energy collimator. Whole body anterior/posterior planar images should be acquired using a large field-of-view gamma camera and medium energy collimators. Suggested gamma camera settings: 256 x 1024 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min for the 48-72 hour scan, and 7-10 cm/min for subsequent scans.

➤ *Expected biodistribution:*

- Activity in the blood pool areas (heart, abdomen, neck, and extremities) may be faintly visible.
- Moderately high to high uptake in normal liver and spleen.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel.
- Non-fixed areas within the bowel lumen that change position with time; delayed imaging as described above may be necessary to confirm gastrointestinal clearance.

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. Tumor visualization on the ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) scan is not required for ^{90}Y Zevalin (Ibritumomab Tiuxetan Ytrium-90) therapy.

➤ *Altered biodistribution*

- *Intense localization of radiotracer in the liver and spleen and bone marrow indicative of reticuloendothelial system uptake*
- *Increased uptake in normal organs (not involved by tumor) such as:*
 - *Diffuse uptake in normal lung more intense than the liver.*
 - *Kidneys with greater intensity than the liver on the posterior view.*
 - *Fixed areas (unchanged with time) of uptake in the normal bowel greater than uptake in the liver.*
 - *In less than 0.5% of patients receiving ^{111}In Zevalin (Ibritumomab Tiuxetan Indium), prominent bone marrow uptake was observed, characterized by clear visualization of the long bones and ribs.*

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the ^{90}Y Zevalin (Ibritumomab Tiuxetan Ytrium-90) dose. The safety and efficacy of the administration of ^{90}Y Zevalin (Ibritumomab Tiuxetan Ytrium-90) in patients with prominent marrow uptake is not known. Possible causes of prominent bone marrow uptake, such as bone marrow involvement by lymphoma, increased marrow activity due to recent hematopoietic growth factor administration, and increased reticuloendothelial uptake in patients with HAMA and HACA, should be considered. Re-assessment of biodistribution after correction of underlying factors should be performed. ^{90}Y Zevalin (Ibritumomab Tiuxetan Ytrium-90) should not be administered to patients with persistently prominent marrow uptake on the repeat biodistribution scans.

5.C.3 Day 7, 8 or 9

a. Rituximab Infusion & ^{90}Y Zevalin (Ibritumomab Tiuxetan Ytrium-90) Infusion (Please refer to section 7.B for detailed treatment administration)

Vital signs will be obtained every 15 minutes for the first hour during the Rituxan infusion, hourly during the remainder of the infusion, and immediately following the ^{111}In Zevalin (Ibritumomab Tiuxetan Indium) infusion. If vital signs are unstable, they will be monitored at 5-minute intervals until stable.

5.C.4 Day 35 (+/- 7 days)

a. Laboratory tests including:

Complete blood count (CBC) with differential and platelet count. To be done every week until any count abnormalities have passed nadir.

- 5.C.1, Now 5.D – Changed:

48.C.1. “Evaluations/Tests During the Zevalin Treatment Period Up to Month 3

History and physical examination, including performance status, will be performed 8 weeks post Zevalin, along with repeat renal function tests (4/27/07), LDH, and CTs, X-rays for tumor assessment and rating of response to treatment. For patient with persistent bone marrow involvement prior to Zevalin®, a third biopsy/aspirate should be done post Zevalin® to document response.”

To:

“Restaging

48.D. 5.D.1 3 Months Post- ⁹⁰Y Zevalin (Ibritumomab Tiuxetan Yttrium-90) Infusion

The following tests/evaluations will be obtained 3 months (+/- 7 days) post ⁹⁰Y Zevalin Infusion:

- a. *History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA) & performance status (Appendix B).*
- b. *Laboratory tests including:*
 - *Complete blood count (CBC) with differential and platelet count*
 - *Serum chemistries - BUN, creatinine*
 - *LDH*
- e. *Disease Assessment:*
 - *Total of all measurable indicator lesions.*
 - *CT scan of the chest, abdomen and pelvis*

Toxicity Assessment: Adverse events are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form”

- 5.D, Now 5.E – Changed:

“Follow-Up Evaluations From Month 3 and Beyond

Post-Treatment Follow-Up Period

The following tests will be obtained at 3-month intervals for a period of 2 years following the Zevalin, every 6 months for years 3 and 4, and then annually.

- a. *Serious adverse events, as well as any new or worsening drug related adverse events (see Appendix E.*
- b. *Interim medical history, physical examination and performance status (Adult Common Toxicity Criteria; Version 3.0)*
- c. *Serum chemistries: BUN, creatinine, LDH (4/27/07).*
- d. *CBC with differential and platelet count*
- e. *Restaging of disease and Response Evaluation by physical examination*

Restaging of disease by CT scan or MRI is recommended every 6 months for the first 2 years, every 6 months for years 3 and 4, and then annually. Bone marrow aspirate/biopsy should be repeated as clinically indicated.”

To:

48.E. “Follow-Up Evaluations

48.E.1. 5.E.1 Short-Term Follow-Up Period

- b. *The following tests/evaluations will be obtained at 3-month intervals (+/- 7 days) for a period of 2 years (24 months) following the Zevalin:*
- *History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).*
 - *Laboratory tests including:*
 - *Complete blood count (CBC) with differential and platelet count*
 - *Serum chemistries - BUN, creatinine*
 - *LDH*
 - *Disease Assessment (Only required at 6-month intervals for a period of 2 years (24 months) following Zevalin):*
 - *Total of all measurable indicator lesions.*
 - *CT scan of the chest, abdomen and pelvis (Restaging of disease by CT scan is recommended every 6 months up to Month 24, then annually until year 5).*

5.E.2 Long-Term Follow-Up Period

- a. *The following tests/evaluations will be obtained every 6 months (+/- 30 days) for an additional 3 years after the completion of the Short-Term Follow-Up period:*
- *History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).*
 - *Laboratory tests including:*
 - *Complete blood count (CBC) with differential and platelet count*
 - *Serum chemistries - BUN, creatinine*
 - *LDH*
 - *Disease Assessment:*
 - *Total of all measurable indicator lesions.*
 - *CT scan of the chest, abdomen and pelvis*

Once the patients have completed Long-term Follow-Up they will continue to be followed indefinitely on an annual basis (+/- 30 days) for survival and disease status. Patients should be followed by physical exam and, if clinically indicated by Good Medical Practice, CT scans. Patients will be followed indefinitely or until patient starts alternate treatment or is removed from study to allow determination of study endpoints.

- 5.E, Now 5.F – Changed:

“Disease Progression Evaluations/Off-Study

Patients who develop disease progression during the treatment period and who do not begin other anti-cancer therapy will continue to be followed for routine safety and efficacy for a total of 12 weeks following the Zevalin treatment.

Tests to be Performed When a Patient is Determined to Have Disease Progression or is Removed from the Study for any Reason

*The following tests will be performed within 4 weeks after a patient has demonstrated progression of disease. **It is strictly mandated that patients not be given other myelosuppressive anti-neoplastic agents until recovery from hematologic nadir.***

These tests do not have to be repeated if they were performed within 7 days prior to documentation of disease progression.

- Tumor assessment if patient is removed from the study for a cause other than progressive disease*
- Physical examination, interim medical history, and performance status*
- CBC with differential and platelet count*
- Serum chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, SGOT (AST), SGPT (ALT)*
- Urinalysis: routine dip stick*
- Follow-up of all ongoing related adverse events until resolved or determined to be permanent”*

To:

48.F. “Disease Progression Evaluations/Off-Study

Patients who develop disease progression during the treatment period and who do not begin other anti-cancer therapy will continue to be followed for routine safety and efficacy for a total of 30 days following any discontinuation of treatment for any cause.

48.F.1. 5.F.1 Tests to be Performed When a Patient is Determined to Have Disease Progression or is

48.F.2. Removed from the Study for any Reason

The following tests will be performed within 4 weeks after a patient has demonstrated progression of disease, or removed from study:

It is strictly mandated that patients not be given other myelosuppressive anti-neoplastic agents until recovery from hematologic nadir.

These tests do not have to be repeated if they were performed within 7 days prior to documentation of disease progression.

- History & Physical examination, including vital signs (BP, temperature & pulse), height, weight, Body Surface Area (BSA), and performance status (Appendix B).*
- Laboratory tests including:*
 - *Complete blood count (CBC) with differential and platelet count*
 - *Serum chemistries - BUN, creatinine*

- LDH

c. Disease Assessment (if patient is removed from the study for a cause other than progressive disease):

- Total of all measurable indicator lesions.
- CT scan of the chest, abdomen and pelvis

d. Toxicity Assessment: Adverse Events (AE) are to be recorded on an ongoing basis until resolved or determined to be permanent. All AEs are to be documented on appropriate source documents at the clinical site and in the patient's case report form."

- 6.B – Changed:

48.G. "Rituximab, 111-Indium Zevalin and 90-Y-Zevalin Information

6.B.1 Rituximab

For information formulation, administration and adverse events, see Rituximab package insert (Appendix H—updated February 2007) (4/27/07)

To:

"Rituximab Drug Information

6.B.1 DESCRIPTION

Rituximab is a mouse/human chimeric monoclonal antibody consisting of human IgG1 heavy and kappa light chain constant regions with murine variable regions from the murine IgG1 kappa anti-human CD20 monoclonal antibody rituximab. The rituximab antibody is produced by a Chinese hamster ovary transfectoma.

6.B.2 TOXICOLOGY

Human Toxicology: Single doses of up to 500 mg/m² and weekly x 4 doses of 375 mg/m² have been administered without dose limiting toxicity. Adverse events are most common during the initial antibody infusion and usually consist of Grade 1, or 2 fever (73%), asthenia (16%), chills (38%), nausea (19%), vomiting (11%), rash (14%), and tumor site pain (3%). Grade 1 or 2 hypotension (8%) may be treated with IV fluids. Hematologic toxicity is usually mild and reversible. Transient decreases in the WBC or platelet count have been observed – especially in patients with high levels of circulating tumor cells or bone marrow involvement. Two patients have had late-onset Grade 4 neutropenia at four and ten months that was attributed to an unknown cause, were transient and resolved. Infections (Grade 1 and 2) have not been related to dose level. Symptoms are generally associated with the initial antibody infusions and diminish in frequency with each successive infusion.

Infusion Reaction: An infusion-related symptom complex consisting of fever and chills/rigors has occurred in the majority of patients during the first rituximab infusion. Other frequent infusion-related symptoms include nausea, urticaria, fatigue, headache, pruritis, bronchospasm, dyspnea, sensation of tongue or throat swelling (angioedema), rhinitis, vomiting, hypotension, flushing, and pain at disease sites. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen).

Tumor Lysis Syndrome: Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk for developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed.

6.B.3 PHARMACOLOGY

Pharmacokinetics: In prior studies patients treated at the 375 mg/m² dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the $T_{1/2}$ following the first antibody infusion was 59.8 hours (11.1 – 104.6 hr) with a C_{max} of 271 mcg/mL.

Formulation: Rituximab antibody will be provided on 100 mg (10mL) and 500 mg (50ml) pharmaceutical grade vials at a concentration of 10 mg of protein per mL (actual concentration should be noted on the product label).

Storage and Stability: Rituximab should be stored at 2 - 8°C. Do not freeze or store at room temperature. The product is a protein- **HANDLE GENTLY AND AVOID FOAMING**. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the denaturing of the product proteins.

Administration: Prepare the rituximab infusion solution as follows:

7. If a delay in administration of the infusion occurs after the product is prepared, the properly identified container may be kept refrigerated at 2 - 8°C for up to six hours.
8. Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.
9. Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.
10. Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile, pyrogen-free 0.9% sodium chloride solution, USP (saline solution). The final concentration of rituximab in saline solution should be a maximum of 1 mg/mL. Mix by inverting the bag gently. **DO NOT USE A VACUUM APPARATUS** to transfer the product from the syringe to the plastic bag.
11. Place an IV administration set into the outflow port of the bag containing the infusion solution.
12. **NOTE: DO NOT USE** evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.

The administration of rituximab will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. IV pumps such as the IMED 960 may be used with the rituximab infusion. DO NOT INFUSE CONCOMITANTLY with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered. This will saturate the filter and tubing.”

- 6.B & 6.C, Now 6.C – Re-numbered, Information the same
- 9.A.1, Now 9.A – Changed: “It is the responsibility of the Investigator-Sponsor as the IND holder to **IMMEDIATELY REPORT ALL SERIOUS OR UNEXPECTED ADVERSE EVENTS...**”

To: “It is the responsibility of the Investigator-Sponsor to **IMMEDIATELY REPORT ALL SERIOUS OR UNEXPECTED ADVERSE EVENTS...**”

- 13.A.a, Now 13.A.1 – Changed:

“Review and Consent Requirements

a. Institutional Review Board (IRB)

The investigator will supply all necessary documents to be submitted to the IRB and will ensure that the institution has a properly structured research committee. The University of Arizona Human Subjects Protection Program and the University of Rochester IRB will be the IRB’s of record. Documentation of initial and ongoing reviews, submission of serious adverse event reports, study amendments and revisions, and consent form modifications will be required from all study sites. This documentation is to be forwarded to the Study Coordinator:

Ellen Chase, B.S.

Arizona Cancer Center, Room 1959

1501 North Campbell Avenue

Tucson, Arizona 85724”

To:

“Institutional Review Board (IRB)

The investigator will supply all necessary documents to be submitted to the IRB and will ensure that the institution has a properly structured research committee. The University of Arizona Human Subjects Protection Program will be the IRB of record. Documentation of initial and ongoing reviews, submission of serious adverse event reports, study amendments and revisions, and consent form modifications will be required. This documentation is to be forwarded to:

- *Consent Forms:*

Lora Inclan

Clinical Research Coordinator

Arizona Cancer Center

at UMC North, Room 2111

3838 N. Campbell Ave.

Tucson, AZ 85719

- *Regulatory Documents:*

Amanda Hutchison-Rzepka

Research Specialist, Pcpl.

Arizona Cancer Center, Room 1959

1515 N. Campbell Ave

Tucson, AZ 85724”

- 13.A.b, Now 13.A.2 – Changed:

“Original, signed informed consent forms for patients registered from the Arizona Cancer Center will be kept in the Arizona Cancer Center Data Management Office. Original signed consents for patients registered by the University of Rochester James P. Wilmot Cancer Center will be maintained at that center, with a copy forwarded to the Study Coordinator at the Arizona Cancer Center by fax at the time of registration.”

To:

“Original, signed informed consent forms for patients registered from the Arizona Cancer Center will be kept at The Arizona Cancer Center at UMC, North, room 2111.”

- 13.B – Changed:

“Registration Procedure

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will accepted. All patients will be registered centrally with the Study Coordinator based at 520-626-6786 prior to the initiation of treatment. Prior to registration, the fully signed informed consent must be presented and all inclusion and exclusion criteria will be reviewed with the registering investigator or designee. All source documentation needed to confirm eligibility must be available for this review. A second phone registration is required prior to the initiation of Zevalin® to confirm eligibility and dose of therapy.”

To:

48.H. “Registration Procedure

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will accepted. All patients will be registered centrally with the Clinical Research Coordinator based at 520-694-9053 prior to the initiation of treatment. The Clinical Research Coordinator will assign each patient a sequential number prior to registration. The fully signed informed consent must be presented and all inclusion and exclusion criteria will be reviewed with the registering investigator or designee. All source documentation needed to confirm eligibility must be available for this review. A second phone registration is required prior to the initiation of Zevalin® to confirm eligibility and dose of therapy.”

- 13.C, Now 13.E – Changed:

“Monitoring

This research study is an investigator-sponsored trial. The Arizona Cancer Center has an NCI-approved Data and Safety Monitoring Plan for clinical research. Data and systems for participating in the study will be monitored according to procedures outlined in that plan, with centralized patient screening and registration, submission and review of data, and initial verification of data as summarized below.

DATA SAFETY AND MONITORING PLAN

The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide general oversight for this trial to ensure patient safety, data integrity and protocol compliance. The Study Coordinator (based in the Southwest Oncology Group and the Lymphoma Programs) will coordinate data review and report preparation for this review.

Reports detailing clinical trial study status, serious adverse events, clinical outcomes (toxicities, responses), and audit findings from both sites will be submitted on at least a quarterly basis. Serious adverse events from both sites will also be reported to the DSMB on a weekly basis. The University of Arizona IRB will receive immediate notification of study serious adverse events and study progress reports at the time interval specified at initial review.

Procedures for centralized registration of patients on this study are detailed in Section 13B. All subjects registered to this study will be entered into the Arizona Cancer Center CRIS database for accrual and treatment status tracking. Adverse events will also be tracked. Patients from the University of Rochester will be assigned a unique number to preserve anonymity. In addition, a registration log will be maintained at both sites using Excel to keep track of study number, verification of consent, date of consent.

Case report forms, which include the registration form, the inclusion/exclusion criteria form, tumor measurement forms, response and survival assessment forms, adverse event forms, and serious adverse event forms should be completed with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff.

The Principal Investigator for each site will ensure the accuracy, completeness, legibility and timeliness of the data reported in these forms. Source documentation supporting the Case Report Form (CRF) data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Data and systems auditing will be performed at each of the two sites to ensure that the investigation is conducted according to protocol design and regulatory requirements. Audits will be performed every 6 months at the Arizona Cancer Center and annually at the University of Rochester by designated Arizona Cancer Center Quality Assurance representatives. An audit report will be completed within 2 weeks of the review and a copy will be maintained in the study file. A visit follow-up letter (if required) detailing outstanding data and/or issues to be addressed by the Principal Investigator and staff within 2 weeks of the monitoring visit will be given to the Principal Investigator for action. A monitoring form will also be completed by the monitor to request specific corrections to the case report forms and/or request clarification or additional source documentation. The study coordinator responsible for the study will be given a copy of this form for resolution of findings. The monitor form will be maintained with a copy of the visit report for follow-up at the next monitoring visit.

Once the study forms have undergone initial review with source documentation, data may be entered into the CRIS database by the study coordinator. All computer-based subject data are password-protected. It is designed to track data changes so that unintentional deletions in data are not made. The Arizona Cancer Center Quality Assurance

and Quality Control (QA/QC) Group will be responsible for monitoring the data entered in the database every 8-12 weeks or every 4th patient depending on frequency of enrollment.

Auditing will be carried out by the Arizona Cancer Center QA/QC Group to comply with Good Clinical Practice guidelines. The audits will include a review of subject informed consent; consistency between data points and source documents, adherence to protocol, accuracy of toxicity and response assessments, completeness and timeliness of serious adverse event reporting and general data quality. Although the primary endpoints in this study relate to progression-free survival and time to progression, determination of overall and complete response rates with this treatment is a secondary endpoint and confirmatory review of responses will be required.

REPORTING ADVERSE EVENTS

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Any and all adverse events will be recorded by the Principal Investigator using the adverse events record form..

A serious adverse event is any adverse event regardless of causality and: 1) results in death, 2) is life-threatening, 3) requires in-patient hospitalization or prolongation of an existing hospital stay, 4) results in disability, 5) is an important medical event, in the view of the investigator, that requires medical or surgical intervention to prevent one of the outcomes listed above. All serious adverse events, regardless of attribution, and any deaths will be reported immediately to the Principal Investigator/ Study Coordinator at 520-626-6786 and to the local IRB within 5 days of notification of the event. Serious adverse events will be reported on the SAE form. Serious adverse events will also be reported to Biogen Idec, Inc, as specified in Section 9 of this protocol.

All adverse events will be classified using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and will address:

- grade*
- relationship to study agent or causality/attribution (not related, unlikely, possible, probable, definitely)*
- date of onset, date of resolution*
- frequency of event (single, intermittent, continuous)*
- event outcome (resolved, ongoing, death)*
- action taken (none, medication, other)*

REPORTING TO AZCC DATA & SAFETY MONITORING BOARD (DSMB)

Quarterly reports will be sent to the Arizona Cancer Center Data and Safety Monitoring Board. These reports will include enrollment figures (# subjects consented, # screened, # screen failures, # passed), dates and results of data monitoring visits, a comprehensive list of all adverse events and patient status.”

To:

48.I. “Monitoring

This research study is an investigator-sponsored trial. The Arizona Cancer Center has an NCI-approved Data and Safety Monitoring Plan for clinical research. Data and systems for participating in the study will be monitored according to procedures outlined in that plan, with centralized patient screening and registration, submission and review of data, and initial verification of data as summarized below.

Protocol Data and Safety Monitoring Plan (Medium Risk)

*Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are **not** designated as high risk per NCI and the IND is not held by the investigator.*

Data and Safety Monitoring Plan:

8. Identification of the DSMB obligated for oversight responsibilities:

The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

9. Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

10. Monitoring progress and data review process:

Routine monitoring of subject data will be conducted at least every six months.

The first routine monitoring visit will include at a minimum:

- *Informed consent – 100% of cases enrolled;*
- *Subject eligibility - 50% of cases, up to two subjects;*
- *Data review - 50% of cases, up to two subjects.*

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed within two weeks of the routine monitoring visit; a copy will be maintained in the study file. A query/finding form will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF

and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF). Source documentation supporting the CRF data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms [other forms, depending on study] should be completed with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

11. Process to implement study closure when significant risks or benefits are identified:

Enter specifics per study phase here.

12. Description of adverse events and reporting procedures:

ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and will address:

- Grade
- Relationship to study drug(not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)

- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- 1) Results in death;*
- 2) Is life-threatening;*
- 3) Requires in-patient hospitalization or prolongation of an existing hospital stay;*
- 4) Results in disability persistent or significant disability/incapacity, or:*
- 5) Is a congenital anomaly/birth defect.*

Note: *A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.*

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and DSMB Coordinator. All serious adverse events, regardless of attribution, and any deaths will be reported within 5 days of notification of the event to the University of Arizona Human Subjects Protection Program.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

13. Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:

- *Study activity, cumulative and for the period under review;*
- *Safety (narrative description on non-serious and serious adverse events);*
- *Predetermined protocol early stopping rules for efficacy/futility;*
- *Monitoring and protocol compliance;*
- *Comments;*
- *Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.*

Data, safety and study progress will be reported to:

- *Human Subjects Protection Program (IRB) at least annually;*
- *Sponsor (if applicable) at least every six months.*

14. Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify, in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study."

- **APPENDICIES REMOVED:**

- Appendix E: Adverse Event Definitions, Documentation and Categories for Determining Relationship to Study Drug Administration
 - REPLACED WITH: Biogen Idec SAE forms & Medwatch Form
- WHO Modified REAL Classification of Non-Hodgkin's Lymphoma
- Rituxan package Insert
- Model Informed Consent
- Adjusted Ideal Body Weight Calculations and Use
- Case Report Forms

- **APPENDICIES ADDED:**

- Amendment 1 Summary of Changes
- Amendment 2 Summary of Changes
- Amendment 3 Summary of Changes

- **Calendar Changes (page 1):**

- *Day 35 column added under Ibritumomab Tiuxetan (Zevalin) Regimen*
- *Disease Assessment added to Baseline & C2, D29*
- *Toxicity Assessment added to Baseline; C2, D1; C2, D29, Day 1 of Ibritumomab Tiuxetan (Zevalin) Regimen*
- *CBC removed from C1, D1 and added to Day 35 of Ibritumomab Tiuxetan (Zevalin) Regimen*
- *Uric Acid/Glucose/Urinalysis row removed*
- *Hep B screen and Pathology Review separated into individual rows*
- *Bone Marrow cytogenetics added to C2, D29*
- *X rays as needed for tumor assessment row removed*
- *Gamma Scan changed from 2 to only 1*

- **Calendar Changes (page 2):**

- *3 months post Zevalin changed to Restaging 3 months post Zevalin*
- *Follow-up separated out into Short-term follow-Up and Long-Term follow-Up*
- *Continued Follow-Up: Annually column added*
- *Off-Study column added*
- *Disease Assessment removed from 9, 15 and 21 mos post Zevalin*

- *AST/ALT/Alk Phos/T.Bilirubin row removed*
- *Uric Acid/Glucose/Urinalysis row removed*
- *Beta 2 microglobulin, Hep B screen/pathology review, Bone Marrow cytogenetics and Bone marrow aspiration/bx rows removed*
- *X rays as needed for tumor assessment row removed*
- *Gamma scans row removed*
- *TREATMENT AND FOLLOWUP rows removed*

APPENDIX M
Amendment #4
(4/1//10)

Summary of Changes

- Updated: Cover Sheet: Amendment #4 Version Date 4/1/2010
- Updated Protocol Signature Page: Amendment #4 Version Date 4/1/2010
- Table of Contents: Pg. 5 Added Appendix M Amendment #4 Summary of Changes
- Section 4.A.7: Pg. 19 Added PET scan
- Section 5.A.3: Pg. 22 Added PET scan
- Section 5.B.3.e: Pg. 24 Added PET scan
- Section 5.C.1 Day 1: Pg. 24 History, Physical exam, BSA, performance status, toxicity assessment, lab tests “are to be performed within 28 days of rituximab & Zevalin administration.”
- Section 5.C.3 Day 7, 8 or 9: Pg. 26-27 Removed paragraph about obtaining vital signs every 15 minutes during rituxan infusion.
- Section 5.D.1: Pg. 27 Added PET scan
- Section 5.E.1: Pg. 28 Added PET scan
- Section 5.E.2: Pg. 28 Added PET scan
- Section 5.F.1.c: Pg. 29 Added PET scan
- Section 13.A.1: Pg. 51 Removed Amanda Hutchison Rzepka, Added Alex Thomas-regulatory documents.
- Appendix A Study Calendar: Pg. 62 Added PET to scans; added History, Physical exam, BSA, performance status, toxicity assessment, lab tests “are to be performed within 28 days of rituximab & Zevalin administration.”
- Appendix A Study Calendar: Pg. 63 Added PET to scans.
- Appendix H: Pg 89 Added Spectrum Pharmaceuticals. Removed Cell Therapeutics, Inc (CTI)
- Appendix M: Pg. 113 Added Appendix M Amendment #4 Summary of Changes

APPENDIX N
Amendment #5
(5/21//10)

Summary of Changes

- Updated: Cover Sheet: Amendment #5 Version Date 5/21/2010
- Updated Protocol Signature Page: Amendment #5 Version Date 5/21/2010
- Table of Contents: Pg. 5 Added Appendix N Amendment #5 Summary of Changes
- **Section 6.B.2 Added Other Viral Infections to the Rituximab Toxicology Section.**

APPENDIX O
Amendment #6
(6/28//10)

Summary of Changes

- Updated: Cover Sheet: Amendment #6 Version Date 6/28/2010
- Updated Protocol Signature Page: Amendment #6 Version Date 6/28/2010
- Table of Contents: Pg. 5 Added Appendix O Amendment #6 Summary of Changes
- Table of Contents: Pgs. 4-5 have been corrected to correspond with protocol page numbers
- Section 6.B.2 Risks section was updated per the Cancer Therapy Evaluation Program's (CTEP), National Cancer Institute (NCI) Action Letter dated June 16th, 2010.

APPENDIX P
Amendment #7
(1/7//13)

Summary of Changes

- Updated: Cover Sheet: Amendment #7 Version Date 1/7/2013, removed Co-PIs Daruka Mahadevan and Daniel Persky and added Soham D. Puvvada, MD; updated the Arizona Cancer Center name to "The University of Arizona Cancer Center"
- Updated Protocol Signature Page: Amendment #7 Version Date 1/7/2013
- Table of Contents: Revised numbering; Pg. 5 Added Appendix P Amendment #7 Summary of Changes
- 9.A: 2nd paragraph – Removed highlight
- 12.B: 4th sentence - Removed highlight
- Section 13.A.1: Pg. 51 Removed Alex Thomas, Added Ruth Cañamar- regulatory documents.
- Administrative changes: Reformatted document to be justified and single spacing throughout the entire document

APPENDIX Q

Amendment #8
(04/17/2017)

Summary of Changes

- Updated footers throughout protocol to Amendment #8: 04/19/2017
- Updated Cover Page: Amendment #8 dated 04/19/2017; removed Dr. Thomas Miller and Dr. Soham Puvvada as PI and Co-PI, respectively; added Dr. Daniel Persky as PI.
- Updated Protocol Signature Page: Amendment #8 dated 04/19/2017; updated Dr. Daniel Persky as PI.
- Updated Sections 3.A, 5.E.2, and Appendix A: Updated patient long-term follow-up from indefinitely to 5 years.
- Section 8C: Removed Dr. Thomas Miller's contact information and updated with Dr. Daniel Persky's contact information.
- Section 13.A.1: Removed Ruth Cañamar and added Kara Heard as current regulatory coordinator for lymphoma team.

APPENDIX R

Amendment #9
(08/28/2017)

Summary of Changes

- Updated footers and dates throughout protocol to Amendment #9: 08/28/2017
- Updated Sections 3A, 5.E.2 and Appendix A: Clarified that patients will continue long-term follow-up every 6 months for 2 years, then annually for 3 years. The scheduled assessments for the annual 3 year follow-up timepoints was updated to match the assessments performed every 6 months for 2 years.