Lymphoma SPORE

University of Iowa/Mayo Clinic

The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study Of Single-Agent Rituximab Immunotherapy Versus Zevalin Radioimmunotherapy For Patients with New, Untreated Follicular Lymphoma Who Are Candidates for Observation

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Drug Availability
Commercial Agents: Rituximab and Zevalin

† Study contributor(s) not responsible for patient care.

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Biospecimens	[redacted]
Adverse Events (AdEERS, MedWatch, Non-AER	[redacted]

*No waivers of eligibility per NCI

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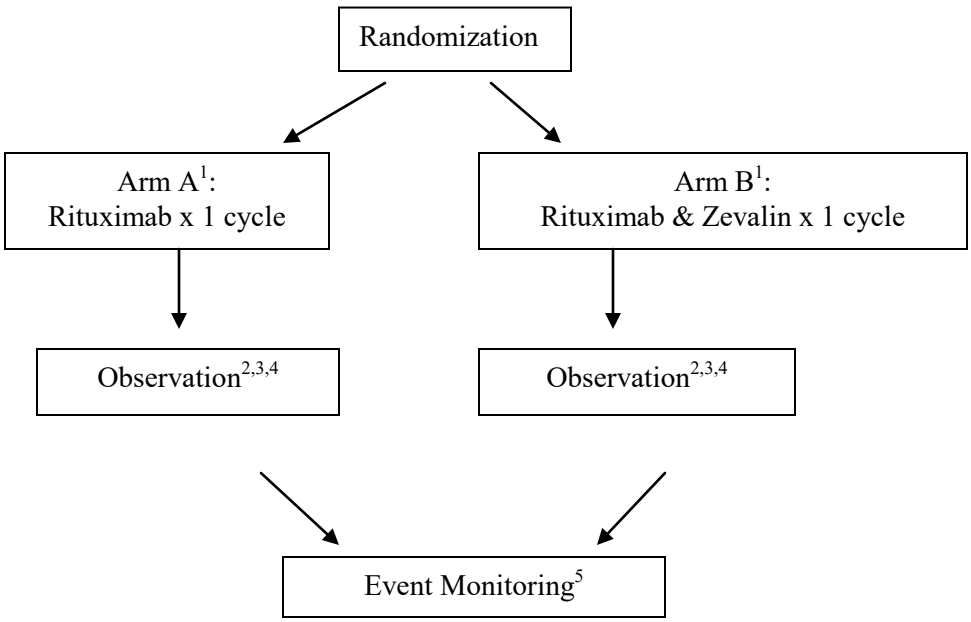
Schema



PD at any time
Subsequent treatment for lymphoma
Patient refusal
Failure to return for evaluation during observation

→ **Event Monitoring**

1. Cycle length = 3 months for Cycle 1 (assessment at 3 months)
2. Cycle length = 3 months for Cycles 2-4 (assessments at 6, 9, and 12 months)
3. Cycle length = 6 months for Cycles 5-8 (assessments at 18, 24, 30, and 36 months)
4. Cycle length = 12 months for Cycles 9-10 (assessments at 48 and 60 months)
5. 10 years after registering no further follow-up is necessary.

Generic name: 90 Yttrium Ibritumomab tiuxetan Brand name: Zevalin® Lymphoma SPORE abbreviation: Y2B8	Generic name: Rituximab Brand name: Rituxan® Lymphoma SPORE abbreviation: RITUX

1.0 Background

Non-Hodgkin lymphoma (NHL) is the 7th most common cancer in both men and women. Within NHL, follicular lymphoma (FL) is the second most common (diffuse large B-cell lymphoma is the most common). Typical teaching regarding FL incites the usual mantra of "treatable but not curable". However, a number of studies with very long-term follow-up demonstrate 20% of patients are cured.(1) We acknowledge that in these studies patients were not routinely scanned and biopsied throughout the many years of follow-up; however, the point is that they never manifested obvious recurrence and lived out their life and died without FL. Thus, they were "effectively cured".

The treatment of FL continues to evolve. For patients with new, untreated FL the standardized approach is to perform a history and physical, obtain basic laboratory tests, staging with a CT or PET/CT and a bone marrow aspiration and biopsy. A treatment plan is then formulated based initially on whether or not the patient requires chemotherapy. The commonly used criteria to start chemotherapy are the GELF criteria (2, 3) or the Follicular Lymphoma International Prognostic Index Score (FLIPI score). Patients who achieve a complete remission (CR) with initial therapy have a better outcome than those who merely achieve a partial remission (PR).(1)

1.1 **Patients who Need Chemotherapy**: Patients who have the need for chemotherapy are typically treated with rituximab/chemotherapy followed by either observation, two years of rituximab maintenance,(4) or a single dose of radioimmunotherapy (RIT).(5, 6) Rituximab and RIT both prolong time to progression (TTP) but their effects on overall survival (compared to observation followed by repeat treatment at time of relapse) are unknown. Bendamustine/rituximab (BR) produces higher overall response rates (ORR) and longer progression-free survival (PFS) with less toxicity than RCHOP.(7)There is currently no overall survival (OS) benefit from BR.

There are many clinical trials being performed for FL patients who meet the criteria for chemotherapy. ECOG 2408 is the current national trial in the cooperative groups. It is BR based with 2 years of rituximab maintenance. One arm contains BR + Velcade and one arm has Revlimid/Rituximab as maintenance. This study is predicted to reach accrual in 2014. It will not interfere with this proposal since patients must meet chemotherapy requirements. There also is an upfront Revlimid/rituximab trial.

1.2 **Patients Not Requiring Chemotherapy:** There is no movement yet to treat these patients with chemotherapy – **thus the main approaches used are observation, rituximab immunotherapy, or RIT**. The hypothesis is that patients with advanced but asymptomatic FL (AFL) are not reliably curable and since they may do well for years to wait for treatment. This approach of treatment nihilism dates back to the pre-rituximab days when the options were chemotherapy vs. observation. Since observation was shown to not reduce survival and since chemotherapy was toxic the choice was much simpler in favor of observation. The advent of immunotherapy and RIT changed the equation in that these treatments were mild, short in duration and effective. Thus, in 2014 *the real key issues in this group of AFL patients are preventing chemotherapy (with its inherent toxicity and risk of myelodysplastic syndrome), preserving QOL, preventing transformation to large cell lymphoma, and aiming to effectively cure a group of patients with initial therapy.*

Why some patients choose observation over rituximab or RIT is not clear. This is likely due in part by patient and physician input. The number of AFL patients in the United States being observed has dropped to about 18% since the institution of rituximab but this figure was derived from all new FL patients.(8) It is clear that ***observation*** remains a recognized standard (***a*** standard not necessarily ***the*** standard) for these patients. Immunotherapy with ***rituximab*** has eroded support for observation, although to date, no OS benefit exists for early treatment. In this patient population, studies have shown that four doses of rituximab (no maintenance) can produce approximately a 75% ORR with 6 - 33% CR and in some patients a very long time to next chemotherapy (TTNT).(9, 10) Preliminary results from the RESORT ECOG trial in this same patient population showed an ORR of 71% after 4 doses of rituximab with approximately a 15% CR. Scheduled maintenance after induction is not better than rituximab when needed as far as prolonging survival.(11) Ardeshna et al(12) studied 379 patients with AFL by randomizing them between observation versus rituximab induction or rituximab induction followed by maintenance every two months for two years. They subsequently closed the rituximab induction only group beginning a new treatment rather than progression free survival. The primary endpoint was so that it became a two arm study – observation versus rituximab maintenance. There were 84 patients who received rituximab induction alone. 46% of patients in the observation group were still free of treatment at three years compared to 88% in the maintenance rituximab group being free of retreatment at three years. 78% of those in the rituximab induction group retreatment free at three years. Thus, at the three-year mark, rituximab induction only and rituximab maintenance were similar and both were superior to observation as far as preventing treatment at three years. Quality-of-life scores with regard to mental adjustment and coping were improved in those who receive maintenance rituximab. This study supports the use of rituximab monotherapy for patients with AFL. It still does not completely settle the issue of whether these patients should receive rituximab maintenance after rituximab induction. There was no difference in overall survival nor time to transformation. With respect to maintenance rituximab versus rituximab induction without maintenance, again there was no difference in overall survival or histologic transformation or time to start a new therapy. There was however an improvement in progression free survival with rituximab maintenance compared to rituximab induction only.

An additional finding of the study was an improvement in quality of life in patients who were treated with rituximab compared to those who are simply observed. It is likely that this study will continue to support the use of treatment in the AFL population although it does not mandate treatment sense survival was not impacted. The improvement in quality of life will again be tested in LS138D.

RIT with ***Zevalin*** or Bexxar is also a well-tolerated option for this patient population. As of February, 2014 Bexxar will no longer be marketed commercially; thus, Zevalin (Spectrum Pharmaceuticals) is the only RIT agent commercially available in the US. Kaminski et al(13) demonstrated a 95% response rate using a single dose of Bexxar with 60% of patients being disease-free at 10 years in a group of patients that likely contained these types of patients. A recent publication by Scholz et al (14) found a similar result with Zevalin. It is particularly reassuring that there were no cases of MDS in either of

these two studies. Kaminski et al. did report one additional case of MDS in their original cohort that occurred at eight years from RIT and this patient did have additional chemotherapy after RIT(15) (and personal communication October 2012). Therefore, the risk of MDS in patients who have never had any chemotherapy appears to be negligible. In contrast, the CR rate is very high with RIT, the treatment is very well tolerated, and RIT offers a well-tolerated, non-chemotherapy option for these patients.

Illidge et al(16) recently reported a study of Zevalin radioimmunotherapy in patients with new, untreated follicular lymphoma who met GELF criteria. This patient population thus differs from the AFL trial in that the patient's did have GELF criteria. It is similar to the AFL trial in that patients were previously untreated and received radioimmunotherapy only. The other difference is that the Illidge study also used two sequential doses of Zevalin. The study treated 72 patients and 94% responded with a CR rate of 58% (42/72). Nine patients improved with subsequent follow-up achieving an ORR of 96% and a CR rate of 69%. The estimated three-year PFS is 58% and OS 95%. The median PFS is 40.2 months. Thirty of the 72 patients have progressed and 24 of the 72 have required further treatment.

A second recently reported study by Ibatici et al.(17) treated 50 patients with stage II "bulky" stage III or IV FL with a single treatment course of Zevalin. The median age was 60 years and 14% had elevated LDH. The ORR was 94% and the CR rate was 86% with a median follow-up of 38.8 months. The median PFS has not yet been reached. The three-year estimated PFS was 63% and the 3-year OS was 90%. No cases of secondary hematological malignancies have been observed.

It is important to note that this study included patients who met GELF criteria and those that did not meet GELF criteria. The median PFS and OS for the 19 patients (40%) who fulfilled GELF criteria was 21.9 months and 50 months, respectively. In the other 29 patients who did not meet GELF criteria the median PFS and OS has not yet been reached. The estimated 3-year OS and PFS in patients without GELF criteria were 97% and 75%, respectively. These data support the premise of this study that patients who do not meet GELF criteria should have a very high CR rate and a long TTP. It is also likely that patients with these characteristics you receive rituximab will also do better; therefore, it is still not clear which approach is best.

Ongoing Clinical Studies: It has been felt by many investigators to be impossible to do a randomized study in this AFL patient population; thus, there are no current trials open in the US at this time.

It is been demonstrated that patients with FL who achieve CR have a chance at very long-term survival and likely approximately 20% are effectively cured.(1) Whether FL is "curable" is a contentious subject as discussed above. Because of the long survival of these patients and the development of novel agents it is reasonable to try and take advantage of the discovery of an early stage asymptomatic patient, achieve CR with a non-chemotherapy regimen, and then observe. *Avoiding chemotherapy for ≥5 years with a non-toxic, non-chemotherapy regimen would be considered meaningful to patients, physicians, and health care providers.*

1.3 **Hypothesis**: Treatment of patients with asymptomatic FL with Zevalin RIT will produce a higher CR rate than rituximab alone, and a higher % of patients progression-free at 3 and 5 years. The rationale for these parameters is that this treatment is low toxicity, brief, and will produce valuable remission time and effectively cure a percentage of these patients.

An additional important parameter is the time to chemotherapy (TTC). This parameter is important but can be years to measure. Patients who achieve a CR are in turn less likely to need chemotherapy. In addition, if the patient enters CR then transformation is less likely. Indeed, patients treated with rituximab have a lower chance of transformation than those observed;(18) thus supporting the view that less tumor, less chance of transformation.

1.4 **Translational research**:

Beta-2 microglobulin and LDH: this combination of factors has recently been shown to be prognostic in follicular lymphoma.(19) Patients with a normal beta-2 microglobulin had improved response to chemotherapy given with RIT consolidation in that study. We will evaluate this combination as prognostic factors in this prospective trial.

Bcl-2 mutations: Our group (Correia, Nowakowski, Kaufmann, Feldman) have recently described the functional and adverse prognosis of FL patients whose tumors have exon 2 bcl-2 mutations (Correia C et al submitted for publication). The rate of single nucleotide variants (SNV) was 53% (20/38). This was confirmed in an additional sample of 11 cases where 73% (8/11) also had SNV's. It is unknown what the incidence of these mutations are in AFL patients. We would anticipate that it would perhaps be lower and we postulate that if present, these patients may have a worse prognosis. This trial provides an opportunity to test this hypothesis in a group with lower risk disease.

Serum Cytokine Levels-IL-12: We measured IL-12 levels in patients with follicular lymphoma and found that those patients with higher pretreatment IL 12 (>0.56 ng/mL) had a shorter progression free survival.(20) This will be evaluated in this prospective study.

Tumor microenvironment: Malignant B cells from biopsies of tumors in patients with lymphoma do not play a passive role but instead clearly drive the differentiation and function of intratumoral T cells (**Figure 1** from (21). Malignant B cells have been found to express multiple ligands responsible for inducing regulatory T cells (Treg cells) and suppressing other intratumoral effector cells. Lymphoma B cells have been found to express CD70, and CD70/CD27 signaling promotes the induction of FoxP3- positive Treg cells. (22) Malignant cells also express PD-L1, and interactions with PD1 expressed on intratumoral immune cells results in immune suppression.(23, 24) B cells from lymphoma biopsies have been found to secrete chemokines and cytokines responsible for further immune suppression. CCL22 secreted by lymphoma B cells is involved in chemotaxis and migration of intratumoral Treg cells that express the receptor CCR4, which results in recruitment of Treg cells to the tumor microenvironment.(22) Treg cells recruited to sites of lymphoma have been shown to suppress both effector CD8+ T cells and intratumoral CD4+ cells.(22, 25) Cytokines and chemokines such as IL12 and

CXCL10 produced by the malignant B cells also have a role in regulating effector T-cell function.(20, 26) However, IL-12 has been shown to induce T-cell exhaustion, resulting in ineffective T cells that are unable to proliferate or lyse target B cells.(20) Overall, malignant B cells skew the T-cell balance within lymph nodes promoting Treg cells and inhibiting effector T cells or TH17 cells.(27)

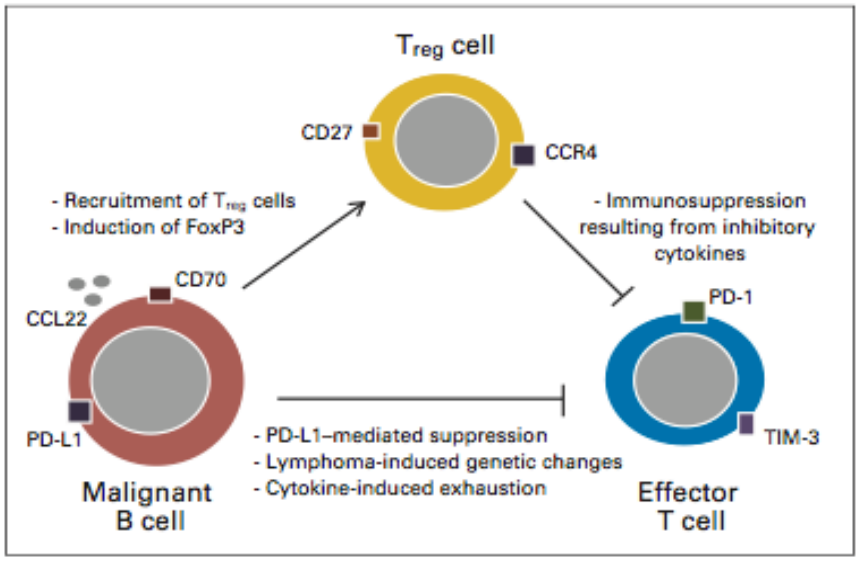


Fig 1. Mechanisms whereby malignant B cells modulate the function of intratumoral T cells. CCL22, chemokine (C-C motif) ligand 22; CCR4, chemokine (C-C motif) receptor 4; FoxP3, forkhead fox P3; PD-1, programmed cell death–1; PO-L1, programmed death ligand 1; TIM3 - T-cell immunoglobulin and mucin domain 3; T_{reg} cells, regulatory T cells.

2.0 Goals

2.1 Primary

2.11 Test the hypothesis that a single dose of Zevalin RIT will increase the CR rate over that achieved with standard rituximab in patients with untreated asymptomatic FL.

2.2 Secondary

2.21 Test the hypothesis that Zevalin RIT will improve progression-free survival.

2.22 Test the hypothesis that Zevalin RIT will improve time to next (any) therapy and time to next chemotherapy.

2.3 Correlative Research

2.31 Study the incidence of exon 2 bcl2 mutations in patients with AFL.

2.32 Measure Tregs and tissue monocytes in on-study FL tumor tissue

2.33 Measure serum cytokines and vitamin D at on study and month 6.

2.34 Evaluate beta-2 microglobulin plus LDH score as a prognostic factor.

2.35 Measure ALC, AMC, and ALC/AMC ratio at on study and after treatment.

2.36 Compare quality of life as measured by the FACT-Lym between arms.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of follicular lymphoma grades I, II diagnosed within 12 months (365 days) prior to registration. NOTE: The day of biopsy should be used as Day 1 of diagnosis for this calculation.

3.13 Stage I, II, III, or IV disease. NOTE: Stage I disease are eligible only if the disease is not amenable to external beam radiation therapy.

3.14 No indication for chemotherapy; candidate for observation.

3.15 Measureable disease by tumor imaging with at least one lesion ≥1.5 cm in at least one dimension.

3.16 Previously untreated. NOTE: This includes any chemotherapy or immunotherapy or RIT. Patients who received corticosteroids for diseases other than lymphoma are eligible as long as prednisone dose is ≤10 mg/day.

3.17 Low tumor burden as defined by GELF criteria (2):
- No tumor mass (nodal or extranodal) ≥7 cm in one dimension on CT
- Fewer than 3 (2 or less) nodal masses >3 cm
- No systemic or B symptoms
- No splenomegaly greater than 16 cm by CT scan
- No risk of organ compression – ureteral, orbital, neurological, gastrointestinal
- No leukemic phase (>5.0 x 10^9/L circulating FL cells in the blood as detected by CBC with differential and smear)
- No cytopenias – ANC <1000 or platelets <100,000

3.18 Meet standard criteria for RIT:
- <25% marrow involvement with FL
- No evidence of myelodysplasia

3.19a ECOG Performance Status (PS) 0, 1, or 2 (Appendix I).

3.19b The following laboratory values obtained ≤ 28 days prior to registration:

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin >10.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN) or if total bilirubin is >1.5 x ULN, the direct bilirubin must be ≤ ULN
- Alkaline phosphatase ≤3 x ULN
- Aspartate transaminase (AST) ≤3 x ULN
- Creatinine ≤2 x ULN

3.19c Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.19d Provide informed written consent.

3.19e Willing to travel to a radioimmunotherapy site for Zevalin, if necessary.

3.19f Willing to return to the enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19g Willing to provide blood samples at baseline for correlative research purposes and tissue for central pathology review (see Sections 6.2, 14.0, and 17.0).

3.19h <25% bone marrow involvement of cellular marrow with lymphoma as determined by bilateral bone marrow aspirate and biopsy. NOTE: The percent involvement should be estimated by the hematopathologist using all of the biopsy material.

3.19i Has insurance coverage or is willing to pay for protocol therapy (rituximab x 4 or Zevalin x 1)

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception for at least three months after completing study treatment.

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into

this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Patients known to be HIV positive and currently receiving antiretroviral therapy.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent that would be considered as a treatment for the lymphoma.

3.26 Active other malignancy requiring treatment that would interfere with the assessments of response of the lymphoma to protocol treatment and would interfere with follow-up assessments through year 5.

3.27 Presence of CNS lymphoma.

3.28 Known to have lymphoma related to HIV or AIDS. NOTE: These patients are excluded because it is unknown what effects prolonged B-cell depletion will have on these patient's immune system.

3.29a Abnormal renal function (serum creatinine >2 x ULN).

3.29b Received prior external beam radiation therapy for another reason to >25% of active bone marrow (see form in Appendix IV).

3.29c Serious non-malignant disease such as active infection or other condition which in the opinion of the investigator would compromise other protocol objectives.

3.29d Major surgery other than diagnostic surgery ≤4 weeks prior to registration.

3.29e Any evidence of myelodysplastic syndrome or marrow chromosomal changes suggesting myelodysplasia (-7, -5 etc).

3.29f Corticosteroid therapy at the time the patient enters the protocol. NOTE: Patients using prednisone or its equivalent for adrenal failure or using ≤10mg of prednisone/day for other benign causes are accepted.

3.29g Follicular grades IIIA or IIIB are not eligible.

3.29h Marrow cellularity ≤15% (as determined on all bone marrow samples).

3.29i Seropositive for or active viral infection with hepatitis B virus (HBV):

- HBsAg positive

- HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

Notes:

- Subjects who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative are eligible.
- Subjects who are seropositive because of HBV vaccination are eligible (HBV surface antibody positive, HBV core antibody negative, and HBV surface antigen negative).

3.29j Active infection with hepatitis C virus (HCV).

4.0 Test Schedule

Tests and procedures	Baseline (Prior to Registration)	Active Monitoring*			
		Cycle 1		**Observation**	
	≤28 days prior to reg.	Week 5,6, 7 post Zevalin for Arm B pts only	Month 3 post Day 1 of treatment[11,12]	Month 6 post Day 1 of treatment[11,12]	Months 9, 12, 18, 24, 30, 36, 48, 60 post Day 1 of treatment[11,12]
History and exam, weight, PS	X			X	
Height	X				
Tissue confirmation of FL grade I or II from routine diagnostic tissue ≤365 days prior to registration[8]	X				
Adverse event assessment	X		X	X	
Hematology: WBC, ANC, ALC, AMC, Hgb, PLT	X	X[9]	X	X	X
Lactate dehydrogenase (LDH) - include ULN	X			X	X
Chemistry: Creatinine, Glucose, SGOT (AST), Alk phos, Ca, T. Bili, uric acid	X			X	
Beta-2 microglobulin (B2M)	X			X	
Direct bilirubin[3]	X				X
Serum pregnancy test[1]	X				
Bone marrow biopsy – unilateral or bilateral	X[5]			X[6]	
Tumor Measurement/Evaluation of indicator lesion (CT, MRI, etc.) CT Scan chest, abdomen and pelvis or PET/CT; measurements should be by CT or the CT portion of a PET/CT. May use MRI in situations that identify lesion more clearly than CT[2]	X			X	X (months 12, 24, 36, 48, 60)
Research tissue [R]	X[4]				
Research bloods[7, R]	X			X	
Hepatitis B and C screen[10]	X				
Quantitative serum immunoglobulins: IgG, IgA, IgM	X[5]				
QOL (FACT-Lym)	X[13]		X[13]	X[13]	X[13]

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. Use the same method throughout the study. See Section 11.0 for response criteria.
3. To be done only if the total bilirubin is abnormal.

4. Patients will be requested to submit paraffin embedded tumor for research purposes. This is optional and the patient can participate in the study without providing this sample. Patients at Mayo Clinic will be requested to provide an optional fresh research biopsy.
5. Bone marrow and immunoglobulins acceptable within 180 days prior to registration.
6. Repeat bone marrow only in patients with an initial positive bone marrow
7. Research bloods at baseline (visit 1/screening) and end of six months (visit 2/End of Cycle 2) only. The baseline samples can be collected after the patient consents but prior to starting treatment.
8. Patient can be registered with local pathology review; central review will be done on all cases (see Section 17.0).
9. CBCs should be drawn weekly or until ANC $\geq$ 1000 and platelets $\geq$ 50,000 at physician discretion.
10. Hepatitis B surface antigen (HbsAg) and antibody to Hepatitis B core (anti-HBc); Hepatitis C antibody. All patients must be screened prior to registration. Those patients who have evidence of chronic or acute infection with either hepatitis B or C may not be treated on this protocol.
11. $\pm$ 1 week.
12. Data at the Month 3 visit is entered as Cycle 1. Data at the Month 6, 9, and 12 visits are entered as Cycle 2, 3, and 4, respectively. Data at the Month 18, 24, 30, and 36 visits are entered as Cycle 5, 6, 7, and 8, respectively. Data at the Month 48 and 60 visits are entered as Cycle 9 and 10, respectively.
13. Patient questionnaire booklet must be used; copies are not acceptable for this submission. Booklet for baseline visit should be completed prior to starting treatment. Patient should be given a booklet to complete in clinic prior to review of the patient's treatment response and discussions of patient's general health since last treatment evaluation.

R. Research funded (see Section 19.0).

5.0 Stratification Factors

5.1 Diagnosis: < 3 months vs. 3-12 months.

5.2 Beta-2 Microglobulin (using institutional values): normal vs. abnormal.

5.3 Lactate Dehydrongenase (using institutional values): normal vs. abnormal.

6.0 Registration Procedures

6.1 To register a patient, access the Lymphoma SPORE web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up is available between 8 a.m. and 4:30 p.m. Central Time (Monday through Friday) by phone at [redacted]

The instructions for registration/randomization application are available on the Lymphoma SPORE secured web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a Lymphoma SPORE subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm that the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the Lymphoma SPORE Registration Office [redacted] If the patient was fully registered, the Lymphoma SPORE Registration Office staff can access the information from the centralized database and confirm the registration.
- In the registration/randomization application, select the *Show Subject* button to verify that the patient registration data is retrievable.
- Enter the registration/randomization application and, using the Lymphoma SPORE subject ID, confirm the patient appears in the registration/randomization application.

6.2 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19g and 14.0).

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to have additional tissues collected from their diagnostics biopsy submitted for research.
- Patient has/has not given permission to obtain the optional fresh research tissue biopsy prior to starting treatment. **(Mayo patients only)**

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Prior to accepting the registration, registration application will verify the following:
- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of lymphoma by the Lymphoma SPORE.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for Lymphoma SPORE to give his/her sample(s) to researchers at other institutions.

6.6 Treatment cannot begin prior to registration and must begin ≤ 21 days after registration.

6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Treatment on this protocol must commence at the University of Iowa Holden Comprehensive Cancer Center or the Mayo Clinic Cancer Center under the supervision of a physician investigator registered with NCI Pharmaceutical Management Branch (PMB) and the Lymphoma SPORE Operations Office.

6.9b Blood draw kit is available on site.

6.9c Patient questionnaire booklet is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule – Arm A: Rituximab

Agent	Dose	Route	Day	Cycle Length
Rituximab[1]	375 mg/m^2/day	IV	1, 8, 15, 22	3 months

1. Substitution of a rituximab biosimilar covered by patients' insurance plan is acceptable for Arm A.

The following pre-medications are suggested prior to rituximab: acetaminophen 650-1000 mg PO 30 minutes prior to rituximab and every 4 hours as needed for infusion related reactions, diphenhydramine 50 mg PO 30 minutes prior to rituximab, diphenhydramine 25 mg IV every 4 hours as needed for infusion related reactions, meperidine 25 mg IV push as needed for rigors, may repeat x 1 dose if first dose is ineffective

7.2 Treatment Schedule – Arm B: Zevalin

Agent	Dose	Route	Day	Cycle Length
Rituximab[1]	250 mg/m^2/day	IV	1, 8	3 months
Zevalin	0.3 mCi/kg or 0.4 mCi/kg**	IV	8*	

* Administer within 4 hours of completion of rituximab infusion.

** Maximum dose = 32 mCi. Dose at 0.4 mCi/kg for patients with platelet counts greater than or equal to 150,000/mm^3 and at 0.3 mCi/kg for patients with platelet counts 100,000 to 149,000/mm^3

1. Substitution of a rituximab biosimilar covered by patients' insurance plan is not allowed for Arm B.

The following pre-medications are suggested prior to rituximab: acetaminophen 650-1000 mg PO 30 minutes prior to rituximab and every 4 hours as needed for infusion related reactions (maximum of 4000 mg in 24 hours), diphenhydramine 50 mg PO 30 minutes prior to rituximab, diphenhydramine 25 mg IV every 4 hours as needed for infusion related reactions, meperidine 25 mg IV push as needed for rigors, may repeat x 1 dose if first dose is ineffective.

7.3 For this protocol, patients randomized to Zevalin can be treated either at the enrolling site or referred to Mayo Clinic Rochester, Arizona, or Florida for the Day 1, 8 rituximab and Zevalin on Day 8. The enrolling site is also permitted to provide Day 1 rituximab if this is prearranged and coordinated with the Zevalin site. This can be arranged by calling the study [redacted] after the patient has been registered.

8.0 Dosage Modification Based on Adverse Events

8.1 There are no dose modifications in this study.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Patients may receive allopurinol at the discretion of the treating physician.

9.3 It is very unlikely that the patient would require blood products or growth factors. However, the patient may be administered hematopoietic growth factors (erythropoietin, GM-CSF, G-CSF, pegfilgrastim, oprelvekin) at the discretion of the treating physician. These should not be used prophylactically. The use of these agents should be recorded.

9.4 Rituximab reactions: Patients who experience rituximab reactions may receive oral or IV corticosteroids in order to enable completion of rituximab therapy. Suggested doses are 100 mg of hydrocortisone IV or 50-100 mg methylprednisolone (Solu-Medrol) IV pre-rituximab or to treat a rituximab reaction that does not respond to diphenhydramine and acetaminophen. Patients who experience a reaction that requires IV steroids may be pretreated with corticosteroids at the next dose.

9.5 Patients found to have immunoglobulin deficiency on pre-treatment testing may receive IVIG at physician discretion and per recommended guidelines.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a MedWatch report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 **Expected vs. Unexpected**

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 **Assessment of Attribution**

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 Expedited Reporting Requirements for CIP Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. Submit form to the FDA, [redacted]

Reporting Serious Adverse Events to Acrotech Biopharma: The Investigator must notify Acrotech Biopharma of any event that meets one of the criteria for an SAE within 24 hours of first knowledge. For the initial report, please complete a standard MedWatch form and email to [redacted] with all relevant documentation (laboratory tests, hospital admission/discharge summary, etc.). Please assure that patient identifiers are redacted from all documentation, except for patient initials and date of birth.

Acrotech Biopharma:

SAE Email: [redacted]

10.41 Special Situations for Expedited Reporting

EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements. Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/Adverse Events Form]; see footnote 1.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.[1]
Blood and lymphatic system disorders	Anemia	≤ Grade 4
Investigations	White blood cell decreased	≤ Grade 4
	Lymphocyte count decreased	≤ Grade 4
	Neutrophil count decreased	≤ Grade 4
	Platelet count decreased	≤ Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.5 Other Required Reporting

10.51 **Persistent or Significant Disabilities/Incapacities**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 **Death**

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benigh, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy

(and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White blood cell decreased	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response Considerations

Definitions for clinical response for patients with lymphoma are from the Cheson et al. Revised Response Criteria for Malignant Lymphoma .(28) Lymph node measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. Measurement of lymphadenopathy will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative

Response is based on CT alone or the CT component of PET/CT or MRI where applicable.

Response criteria, modified from Cheson et al. 2007.

Response Category	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease.	Regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes and regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	No change in size of previous lesions on CT		
PD (Relapse/ Progressive disease)	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete response; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial response; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

11.11 **Complete Response (CR)**. The designation of CR requires all of the following:

11.111 Complete disappearance of all detectable clinical evidence of disease and definitely disease-related symptoms if present before therapy.

11.112 All lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment. .

11.113 The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

11.114 If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

11.12 **Criteria for Partial Response (PR)**. The designation of PR requires all of the following:

11.121 At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following:

- they should be clearly measurable in at least 2 perpendicular dimensions
- if possible they should be from disparate regions of the body
- they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

11.122 No increase should be observed in the size of other nodes, liver, or spleen.

11.123 Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

11.124 With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

11.125 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

11.126 No new sites of disease should be observed.

11.127 CT criteria should be used

11.13 **Criteria for Stable Disease (SD)**

11.131 A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR (see above), but does not fulfill those for progressive disease (see below).

11.132 There must be no change in the size of the previous lesions on the post-treatment CT scan.

11.14 **Relapsed Disease (after CR)/Progressive Disease (PD) (after PR, SD):**
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

11.141 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

11.142 At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

11.143 At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

12.0 Descriptive Factors

12.1 Follicular Lymphoma International Prognostic Index 2 (FLIPI2) (29) low risk (0 risk factors) vs. intermediate risk (1 or 2 risk factors) vs. high risk (3-5 risk factors)

Risk Factors	0 points	1 point
β2-microglobulin	≤ ULN	> ULN
Longest diameter of the largest involved node	≤ 6 cm	> 6 cm
Bone marrow involvement	No	Yes
Hemoglobin Level	≥12 g/dL	<12 g/dL
Age	≤60 years	>60 years

Total number of risk factors = sum of the number of points for each prognostic factor

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients will be evaluated per the test schedule during cycle 1 of treatment.

13.2 After treatment, patients will be observed at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months from day 1 of treatment.

13.3 Criteria for removing patients from treatment and initiating observation.

13.31 Requested withdrawal or patient non-compliance.

13.4 Patients who have progressive or relapsed disease, receive subsequent treatment for lymphoma, refuse further observation, or fail to return for evaluation during observation will go to event monitoring.

13.5 At 5 years from day 1 of treatment, all patients still on observation will go to event monitoring every 12 months until 10 years from time of registration per Section 18.0.

13.6 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

The patient may continue protocol treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will continue treatment (if no safety concerns), observation, and event monitoring as specified for all patients (or will be taken off study, if applicable).

- If the patient received treatment, the patient will continue treatment (if no safety concerns), observation, and event monitoring as specified for all patients.
- If the patient never received treatment, On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. The patient may continue protocol treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will continue treatment (if no safety concerns), observation, and event monitoring as specified for all patients.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Visit 1 (Screening/Baseline)	Visit 2 (End of 6 months/ End of Cycle 2)	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping[1]
Plasma cytokines, Tumor Treg and Monocyte content, Vitamin D, and Blood molecular markers (Section 14.3)	Mandatory	Whole Blood	ACD (yellow)	8.5 mL (2)[2]	X	X	No	Ambient temperature NO cold pack required
	Mandatory	Whole Blood	EDTA (purple)	10 mL (1)	X	X	No	
	Mandatory	Whole Blood	None (red)	10 mL (1)	X	X	No	

[1]After all samples have collected according to kit instructions, ship all specimens according to shipping instructions (see Section 14.24 for detailed shipping instructions).
[2]Mayo Clinic Rochester only: Samples will be collected in three 6 mL tubes.

14.2 Blood/Blood Products Handling

14.21 **Kits are required for this study for non-Mayo Rochester sites.**

The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Participating institutions may obtain kits by e-mailing [redacted] E-mail requests should include the site address, contact information and number of kits being requested.

Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow 3 to 4 business days to receive the kits.**

14.22 Label specimen tubes with the protocol number, the patient's initials (last, first, middle), study patient ID number (if available) and date of blood collection.

14.23 Collect all peripheral blood according to specific kit instructions (see Appendix III) and table above.

14.24 Shipping

Specimens must be shipped the same day they are drawn.

Ship ACD, EDTA, and no additive (red top) whole blood tubes in their respective Styrofoam boxes; no cold pack is required but may be used. Avoid freezing of specimen. The Fed Ex airbills is pre-addressed.

Ship specimens via Priority Overnight service on **Monday – Thursday Preferred** (Friday only if you must) directly to:

Predolin Biobank
[redacted]

Please send email message to [redacted] The message should include the study name, sample type, Fed Ex airbill tracking number, contact name and telephone number. Phone calls if necessary to [redacted]

Shipping costs will be covered by the study if these kits and Fed Ex airbills are used for shipping specimens. Each kit contains the required tubes.

14.3 Background and Methodology

14.31 **Plasma cytokines:** Plasma cytokine levels will be measured using a standard 30-plex ELISA (Invitrogen, Camarillo, CA) as previously described.(26) Thirty

cytokines will be analyzed using the Luminex- 200 system. Data will be acquired using STarStation software (Applied Cytometry, Dinnington, Sheffield, UK).

14.32 **Tumor Treg and Monocyte content:** This will be measured using standard IHC methods and subsets enumerated by the study pathologist.

14.33 **Vitamin D:** 25(OH)D and 1,25(OH)D concentrations will be performed using the on-study, pretreatment research serum sample in the [redacted] under the direction of [redacted] The normal range and that laboratory is 25-80 ng/ML. Patients will be classified as "insufficient" if the level is less than 25 ng/ML.

14.34 **Blood molecular markers:** Serum, plasma, and blood mononuclear cells will be cryopreserved and used by the SPORE investigators for markers of prognosis and markers to predict response. Specific assays and sample calculations will be determined using the approval system in the SPORE and will follow standard Mayo and Iowa procedures for sample request and approval.

14.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Rituximab (Rituxan®, C2B8)

15.11 **Background**: Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

15.12 **Formulation**: Commercially available for injection, solution [preservative free]: 10 mg/mL (10 mL, 50 mL) [contains Polysorbate 80].

15.13 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store vials at refrigeration temperature, do not freeze or shake. Protect vials from direct sunlight. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/mL with 0.9% NaCL or D_5W. Gently invert the bag to mix the solution; do not shake. Solutions for infusion are stable at

2ºC to 8ºC for 24 hours and at room temperature for an additional 24 hours.

15.14 **Administration:** Do not administer I.V. push or bolus. Refer to treatment section for specific infusion instructions. Suggested administration guidelines are:
Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hour.
Subsequent infusions: If patient did not tolerate initial infusion follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction; increase the rate by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.
Note: If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate.

Accelerated infusion rate (90 minutes): For patients with previously untreated follicular NHL and diffuse large B-cell NHL who are receiving a corticosteroid as part of their combination chemotherapy regimen, have a circulating lymphocyte count <5000/mm^3, or have no significant cardiovascular disease. After tolerance has been established (no grade 3 or 4 infusion-related event) at the recommended infusion rate in cycle 1, a rapid infusion rate may be used beginning with cycle 2. The daily corticosteroid, acetaminophen, and diphenhydramine are administered prior to treatment, then the rituximab dose is administered over 90 minutes, with 20% of the dose administered over the first 30 minutes and the remaining 80% is given over 60 minutes. If the 90-minute infusion in cycle 2 is tolerated, the same rate may be used for the remainder of the treatment regimen (through cycles 6 or 8).

15.15 **Pharmacokinetic information**:
Duration: Detectable in serum 3-6 months after completion of treatment; B-cell recover begins ~6 months following completion of treatment; median B-cell levels return to normal by 12 months following completion of treatment
Distribution: RA: 3.1 L; GPA/MPA: 4.5L
Absorption: Immediate and results in a rapid and sustained depletion of circulating and tissue-based B cells
Half-life elimination: Proportional to dose; wide ranges reflect variable tumor burden and changes in CD20 positive B-cell populations with repeated doses:
Following first dose: Mean half-life: 3.2 days
Following fourth dose: Mean half-life: 8.6 days
CLL: Median terminal half-life: 32 days
NHL: Median terminal half-life: 22 days
RA: Median terminal half-life: 18 days
GPA/MPA: 23 days
Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system

15.16 **Potential Drug Interactions**:
Increased Effect/Toxicity: Monoclonal antibodies may increase the risk for allergic reactions to rituximab due to the presence of HAC antibody. Antihypertensive medications may exacerbate hypotension.
Decreased Effect: Currently recommended not to administer live vaccines during rituximab treatment.

Herb/Nutraceutical Interactions: Avoid hypoglycemic herbs, including alfalfa, bilberry, bitter melon, burdock, celery, domain, fenugreek, grainier, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of rituximab). Monitor.

Immunosuppressants: Rituximab may enhance the adverse/toxic effects of pimecrolimus, tacrolimus and to a lesser extent of denosumab.

Rituximab may enhance the adverse/toxic effects of abatacept, belimumab, clozapine, dipyrone and tofacitinib.

15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe infusion reactions; Progressive multifocal leukoencephalopathy (PML); Tumor lysis syndrome leading to acute renal failure; and severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis).

Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema, hypertension
Central nervous system: Fatigue, chills, neuropathy, headache, insomnia, pain
Dermatologic: Skin rash, pruritus, night sweats
Endocrine & Metabolic: Weight gain
Gastrointestinal: Nausea, diarrhea, abdominal pain
Hematologic: Lymphocytopenia, anemia, leukopenia, neutropenia, thrombocytopenia, cytopenia, febrile neutropenia
Hepatic: ALT increased
Hypersensitivity: Angioedema
Immunologic: Antibody development
Infection: Infection, bacterial infection
Neuromuscular & skeletal: Weakness, muscle spasm, arthralgia
Respiratory: Cough, rhinitis, epistaxis
Miscellaneous: Infusion related reaction

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Hypotension, flushing
Central nervous system: Dizziness, anxiety, migraine, paresthesia
Dermatologic: Urticaria
Endocrine & metabolic: Hyperglycemia, increased lactate dehydrogenase

Gastrointestinal: Vomiting, dyspepsia
Infection: Viral infection, fungal infection
Neuromuscular & skeletal: Back pain, myalgia
Respiratory: Dyspnea, throat irritation, bronchospasm, upper respiratory tract infection, sinusitis

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Acute mucocutaneous toxicity, acute renal failure (associated with tumor lysis syndrome), acute respiratory distress, anaphylactoid reaction/anaphylaxis, angina, pectoris, aplastic anemia, arthritis (polyarticular), bone marrow depression, bronchiolitis obliterans, cardiac arrhythmia, cardiac failure, cardiogenic shock, encephalitis, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hypogammaglobulinemia (prolonged) hypoxia, increased serum immunoglobulins (hyperviscosity syndrome in Waldenstrom's macroglobulinemia), interstitial pneumonitis, intestinal obstruction, Kaposi's sarcoma (progression), laryngeal edema, lichenoid dermatitis, lupus-like syndrome, mucositis, myelitis, MI, nephrotoxicity, optic neuritis, pancytopenia, paraneoplastic pemphigus, pleurisy, pneumonia, pneumonitis, polymyositis, progressive multifocal leukoencephalopathy, pure red cell aplasia, reactivated pure red cell aplasia, reactivated tuberculosis, reactivation of HBV, reversible posterior leukoencephalopathy syndrome, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, toxic epidermal necrolysis, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral reactivation (includes JC virus [PML], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C), wheezing

15.18 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 **Nursing Guidelines:**

1. Do not administer as an IV push or bolus since it increases the risk of a hypersensitivity reaction.

2. Hypotension, bronchospasms, and angioedema have occurred in association with Rituxan infusion. Because of this it is recommended that patients be pre-medicated with acetaminophen and diphenhydramine before infusion. Stop infusion for severe reaction. Infusion may be restarted at 50% rate after resolution of symptoms. It is recommended that diphenhydramine, acetaminophen, epinephrine, bronchodilators, IV saline, and corticosteroids are available for immediate use in the event of a hypersensitivity reaction during administration.

3. Patients should be cautioned to withhold their anti-hypertensive medication for 12 hours prior to drug administration.

4. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituxan therapy and should be monitored throughout the infusion and immediate post-infusion period.

5. It has been found that patients with bulky disease (lesion >10 cm in diameter) have an increased incidence of adverse events. Monitor for signs and symptoms of tumor lysis syndrome, and acute renal failure.

6. An infusion-related symptom complex consisting of fever and chills/rigors occurs in the majority of patients during the first infusion. These reactions generally occur within 30 minutes to 2 hours of beginning the first infusion and resolve with slowing or stopping the infusion and giving supportive care. The incidence of adverse reactions decreased from 80% to 40% with subsequent infusions.

7. Cytopenias are common and can be long term. Monitor CBC. Instruct patient to report signs and symptoms of infection, excessive bruising and/or bleeding to the health care team.

8. GI disturbances (Nausea, abdominal pain and less commonly diarrhea, vomiting, dyspepsia) headache, and weakness are common side effects. Treat as necessary. Monitor for effectiveness.

9. Adequate birth control measures should be used during therapy and for 12 months following therapy. Women should not breastfeed while drug is detectable in serum.

10. Endocrine and metabolic disturbances can be seen (hyper/hypoglycemia, hypocalcemia, hypocholesterolemia, hyperphosphatemia, hyperuricemia. Monitor labs and for signs or symptoms of these conditions. Treat accordingly.

11. There is the possibility of reactivation of Hepatitis B (HBV). Patients who are at high risk of hepatitis B virus should be screened prior to initiation of therapy, carriers of hepatitis B should be closely monitored.

15.2 **Ibritumomab (Zevalin)**

15.21 **Background**: Ibritumomab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. Ibritumomab binding induces apoptosis in B lymphocytes in vitro. It is combined with the chelator tiuxetan, which acts as a specific chelation site for either Indium-111 or Yttrium-90. The monoclonal antibody acts as a delivery system to direct the radioactive isotope to the targeted cells, however, binding has been observed in lymphoid cells throughout the body and in lymphoid nodules in organs such as the large and small intestines. Y-90 emits beta particles. Beta-emission induces cellular damage through the formation of free radicals (in both target cells and surrounding cells).

15.22 **Formulation**: Commercially available for injection, Kit, Intravenous [preservative free]: 3.2 mg/2 mL

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Do not exceed the Y-90 ibritumomab maximum allowable dose of 32 mCi; do not administer to patients with altered biodistribution (determined by imaging with In-111 ibritumomab). Use should be reserved to physicians and other professionals qualified and experienced in the safe handling of radiopharmaceuticals, and in monitoring and emergency treatment of infusion reactions. The contents of the kit are not radioactive until radiolabeling occurs. During and after radiolabeling, adequate shielding should be used with this product, in accordance with institutional radiation safety procedures. Radiolabeling of ibritumomab with Yttrium-90 must be performed by appropriate personnel in a specialized facility.

15.24 **Administration:** Inject slowly, over 10 minutes through a 0.22 micron low protein binding in-line filter. After injection, flush line with at least 10 mL normal saline. Y-90 ibritumomab: Establish free-flowing I.V. line prior to administration. Avoid extravasation; if signs or symptoms of extravasation occur, stop infusion and restart in another limb.

15.25 **Pharmacokinetic information**:
Duration: Beta cell recovery begins in ~12 weeks; generally in normal range with 9 months.
Distribution: To lymphoid cells throughout the body and in lymphoid nodules in organs such as the large and small intestines, spleen, testes, and liver
Metabolism: Has not been characterized; the product of yttrium-90 radioactive decay is zirconium-90 (nonradioactive); Indium-111 decays to cadmium-111 (nonradioactive).
Half-life elimination: Y-90 ibritumomab: 30 hours; Indium-111 decays with a physical half-life of 67 hours; Yttrium-90 decays with a physical half-life of 64 hours.
Excretion: A median of 7.2% of the radiolabeled activity was excreted in urine over 7 days.

15.26 **Potential Drug Interactions**:
Increased Effect/Toxicity: Ibritumomab may increase the levels of: Leflunomide; Natalizumab; Vaccines (Live); Vitamin K Antagonists

The levels/effects of Ibritumomab may be increased by: Anticoagulants; Antiplatelet Agents; Denosumab; Pimecrolimus: Tacrolimus (Topical); Trastuzumab

Decreased Effect: Ibritumomab may decrease the levels/effects of: BCG; Cardiac Glycosides; Sipuleucel-T; Vaccines; Vitamin K Antagonists.

Herb/Nutraceutical Interactions: Avoid Echinacea (may diminish therapeutic effect). Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have antiplatelet activity).

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: **Do not exceed the Y-90 ibritumomab maximum allowable dose of 32 mCi; do not administer to patients with altered biodistribution (determine by imaging with In-111 ibritumomab). Serious fatal infusion reactions may occur with the rituximab component of the therapeutic regimen. Delayed, prolonged, and severe cytopenias are common. Do not administer to patients with greater than or equal to 25% lymphoma marrow involvement, patients with impaired marrow reserve.**

Common known potential toxicities, > 10%:
Central nervous system: Fatigue
Gastrointestinal: Nausea, abdominal pain, diarrhea
Hematologic: Thrombocytopenia, neutropenia, anemia, leukopenia, lymphocytopenia, metastases, including acute myelogenous leukemia and Myelodysplastic syndrome
Neuromuscular & skeletal: Weakness
Respiratory: Nasopharyngitis, cough
Miscellaneous: Infection

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Hypertension
Central nervous system: Dizziness
Dermatologic: Night sweats, pruritus, skin rash
Gastrointestinal: Anorexia
Genitourinary: Urinary tract infection
Hematologic & oncologic: Petechia, bruise, severe cytopenia
Neuromuscular & skeletal: myalgia
Respiratory: Bronchitis, flu-like symptoms, rhinitis, pharyngolaryngeal pain, sinusitis, epistaxis
Miscellaneous: fever

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Anaphylactic reactions, arthritis, cerebral hemorrhage, cytogenetic abnormalities, encephalopathy, hematemesis, hemorrhage, hypersensitivity; infusion site erythema/ulceration, radiation injury/complications, meningioma, pulmonary edema, pulmonary embolism, radiation necrosis, stroke, subdural hematoma, tachycardia, vaginal hemorrhage

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

1. Drug does not emit gamma radiation, just Beta emissions that have only moderate penetrating power of a few millimeters. Therefore, radiation exposure to hospital personnel is minimal. The isotope can be administered in the outpatient setting. However, it is recommended that the treatment room be prepared for possible contamination in the event of spillage.

    - Absorbent pads should be placed under the infusion site and over the bed tables.
    - Direct the patient to wash their hands thoroughly after using the toilet.
    - Direct the patient to use condoms during sexual relations for one week following administration.

2. Administer through a free flowing IV line within 4 hours following completion of rituximab. After injection, flush line with at least 10 mL of normal saline.

3. Monitor patients closely for signs of extravasation. If extravasation is suspected, stop infusion immediately and restart in another limb.

4. Cytopenias are common, especially thrombocytopenia. Monitor CBC. Instruct patient to report any sign of infection, unusual bruising or bleeding to the health care team.

5. Monitor for cutaneous reactions.

6. Patients may experience fatigue.

7. Gastrointestinal side effects including nausea, abdominal pain, and diarrhea have been seen. Treat symptomatically and monitor for effectiveness.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a randomized phase III study designed to compare the complete response rate at 6 months between Rituximab (Arm A) and Zevalin (Arm B) for treatment of asymptomatic follicular lymphoma.

16.11 Primary Endpoint: The primary endpoint of this study is the complete response rate at the 6-month disease assessment which will be compared between the two arms. A patient is considered to be a complete responder if the objective status at the 6-month disease assessment is a complete response. Any patient not meeting the definition of a complete response will be considered as a non-responder for the primary endpoint. A modified intent-to-treat approach will be employed for the primary analysis such that all randomized subjects meeting the eligibility criteria who do not cancel participation prior to treatment initiation and did not experience a major treatment violation (during the first cycle of treatment) will be included in the primary analysis. Sensitivity analysis will be conducted including all patients who did not cancel participation prior to

treatment initiation. The percentage of patients in each response category (e.g., CR, PR, STAB, Relapse/PD) will also be tabulated by arm.

16.2 Statistical Considerations:

16.21 Statistical Design:

Previous studies of treatment with four doses of single agent Rituximab in this patient population have shown CR rates of 6-33% (9 and 10). In addition, preliminary results of an additional study, the RESORT ECOG trial, show a CR rate of 15% in this same population (11). This study is designed to detect an improvement in complete response rate from 20% with Rituximab (Arm A) to 50% with Zevalin (Arm B). The proportion of patients who have a CR at 6 months will be evaluated and compared between the two treatment regimens using a two-sided α=0.05 continuity corrected Cochran–Mantel–Haenszel (CMH) test with stratification factors as defined in Section 5.0.

The primary goal of this trial is to compare the CR rate at 6 months between Rituximab and Zevalin. We will randomize 116 evaluable patients in a 1:1 ratio to Rituximab or Zevalin. This final analysis will take place after all patients have completed the disease assessment at 6 months. A sample size of 58 evaluable patients per arm (116 total evaluable) provides 90% power to detect an improvement in complete response rate from 20% to 50%, using a two-sided chi-square test at a significance level of 0.05. To ensure that 116 evaluable patients are randomized, we will enroll/randomize **128 total patients**.

The CR rate in each arm will be estimated by the number of evaluable patients who achieve a CR as the objective status on the disease assessment at 6 months divided by the total number of randomized evaluable patients in that arm. The CR rates will be compared between the two arms. If the CR rate is higher in the Zevalin arm, where the p-value is less than 0.05, this will be considered sufficient evidence that the Zevalin arm may be recommended for further testing in subsequent studies.

This study will use a dynamic allocation procedure to allocate an equal number of patients to each of the two treatment regimens.(30) This procedure will balance the marginal distributions of the stratification factors between these two treatment arms. The stratification factors that will be used are listed in Section 5.0.

This study will be based on a modified intent-to-treat approach including all randomized patients meeting the eligibility criteria who do not cancel participation prior to treatment initiation and did not experience a major treatment violation (during the first cycle of treatment) based on the randomized treatment assignment.

The study will be permitted to be published after all patients have undergone the 6-month disease assessment to establish the CR rate between each arm. This essentially fulfills the first goal of the study. See Section 16.3 for further analysis plans.

16.23 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.24 Sample Size: This study is expected to accrue a maximum of 128 patients unless undue toxicity is encountered.

16.25 Accrual Rate and Study Duration: The anticipated accrual rate is 4 patients per month. This study is expected to accrue in ~2.75 years. The total study duration is expected to be approximately ~3.25 years, or until the last patient accrued has been observed for at least 6 months.

16.3 Secondary Outcome Analyses: The secondary endpoints listed below will be evaluated in each arm independently and will also be compared between the two arms. Analysis of all endpoints will occur at the time of the primary analysis (after all patients have completed the 6-month disease assessment), after all patients have been followed for 3 years, and after all patients have been followed for 5 years. For all secondary endpoints, p-values <0.001 will be considered statistically significant at either of the first two analyses. At the 5-year analysis, p-values <0.05 will be considered as statistically significant. P-value boundaries are based on the Haybittle-Peto rule.(31, 32) A final analysis for the purpose of providing updated descriptive estimates may be undertaken after all patients have been followed for 10 years.

16.31 Progression-free survival (PFS) is defined as the time from registration to the earliest date documentation of disease progression or death due to any cause. The distribution of progression-free survival time will be estimated using the method of Kaplan-Meier within each arm and compared between the arms using a log-rank test. The progression-free survival rates at 3 years and 5 years will be estimated in each arm.

16.32 Time to any therapy (TTNT) is defined as the time from registration to the date of initiation of any treatment for follicular lymphoma. The distribution of time to any therapy will be estimated using the method of Kaplan-Meier within each arm and compared between the arms using a log-rank test. The percentage of patients free of any therapy at 3 years and 5 years will be estimated in each arm.

16.33 Time to chemotherapy (TTC) is defined as the time from registration to the date of initiation of chemotherapy for follicular lymphoma. The distribution of time to chemotherapy will be estimated using the method of Kaplan-Meier within each arm and compared between the arms using a log-rank test. The percentage of patients free of chemotherapy at 3 years and 5 years will be estimated in each arm.

16.34 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables

will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Rates of individual adverse events (grade 3 and higher) will be compared between arms using a Fisher's exact test.

16.4 Correlative Research: The correlative endpoints listed below will be evaluated in each arm independently and may also be compared between the two arms. For each measure, values may be investigated with respect to response (CR vs. less than CR) using two-sample t-tests (continuous measures) or chi-square tests (categorical measures). Relationship with time to event measures (PFS, TTNT, TTC) will be evaluated using Kaplan-Meier methods and log-rank statistics (categorical measures) or Cox proportional hazards models (continuous measures). For values collected at more than one time point, changes over time will be evaluated using paired-t-tests (continuous measures) or McNemar's or Bhapkar's tests (categoical measures). Endpoints and additional analyses are described below. Analysis involving quality of life are described in Section 16.47.

16.41 The incidence of exon 2 bcl2 mutations will evaluated at baseline.

16.42 Tissue Tregs and tissue monoctyes will be quantified for the on study tumor biopsies. These values will be reported as percentages.

16.43 Serum cytokines will be analyzed for each time point (pre-treatment and 6 months). Each cytokine will be evaluated in reference to normal controls and levels will be categorized as normal, elevated, or suppressed.

16.44 Vitamin D levels will be evaluated at on study. At each time point, Vitamin D level will be categorized as normal (sufficient) vs. abnormal (insufficient). Vitamin D insuffiency will be defined as a 25 hydroxy-vitamin D (D2 + D3) level <25 ng/mL in the central (Mayo) laboratory.

16.45 Beta-2 microglobulin (B2m) plus LDH score will be evaluted in relation to the institutional upper limit of normal (IULN). Patients will be categorized at baseline as low risk (both factors ≤ 150% ULN), intermediate risk (one factor ≤ 150% IULN and the other factor > 150% ULN), or high risk (both factors > 150% IULN). The prognostic value of B2m plus LDH score in relation to PFS will be evaluated using Kaplan-Meier methods and log-rank statistics. Use of B2m plus LDH was previously reported. (18)

16.46 ALC, AMC, and ALC/AMC ratio will be measured at baseline and after treatment. Both the absolute and relative change will be summarized for each measure.

16.47 Quality of life will be assessed prior to review of treatment response and discussions of patient's general health since last treatment evaluation. QOL will be measured using the FACT-Lym. The FACT-Lym consists of the FACT-

General (FACT-G) with 27 items and a lymphoma-specific concerns scale with 15 items, each item measured on a 0-4 scale (0=not at all; 4=very much). The FACT-G is a general measure of quality of life of cancer patients containing four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. It is widely used in cancer clinical trials and is reliable and valid for general research purposes (33) The additional items of the lymphoma-specific concerns scale were developed to capture items relevant to the QOL of lymphoma patients. The FACT-Lym has been shown in a cohort of non-Hodgkin's lymphoma patients to be easy to administer, reliable, valid, and sensitive to change.(34) The recall period for the FACT-Lym is 7 days. The FACT-Lym will be administered to all willing patients via a paper booklet in clinic at baseline and at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months while the patient remains in the active monitoring phase of the study (on treatment or in observation). The FACT-Lym will be scored according to the published scoring algorithm with the following scale scores computed at each time point: physical well-being (PWB, 7 items, score range 0-28), social/family well-being (SWB, 7 items, score range 0-28), emotional well-being (EWB, 6 items, score range 0-24), functional well-being (FWB, 7 items, score range 0-28), FACT-G total score (PWB+ SWB+ EWB+ FWB, score range 0-108), FACT-LymS score (lymphoma-specific concerns, 15 items, score range 0-60), FACT-Lym total score (FACT-G+ FACT-LymS, score range 0-168), and the Trial Outcome Index (PWB+ FWB+ FACT-LymS, score range 0-116). A clinically meaningful change is defined as 2-3 points in the PWB and FWB (35) 3-7 points in the FACT-G total (35) and 3-5 points in the FACT-LymS (36).

The primary QOL analysis will be conducted at the time of the primary clinical analysis and will include the baseline, month 3 and month 6 QOL data. Additional analyses will be conducted after patients have been followed for 3 years and for 5 years. The primary analysis will compare the FACT-TOI between arms at the 3 month and the 6 month time points using analysis of covariance adjusting for the baseline FACT-TOI score. Mean FACT-TOI will be graphically presented by arm using a mean plot with standard deviation error bars including all available data with pateints according to the randomized treatment assignment. Baseline characteristics will be comapred between arms within the subject of patients who provide QOL data at one or more time points using t-tests for continuous variables and chi-squared tests for categorical variables. To assess for selection bias, baseline characteristics for patients who provide QOL data at one or more time points will be compared to patients who do not provide any QOL data using t-tests for continuous variables and chi-squared tests for categorical variables. Subseqent analysis will include comarison of FACT-TOI area-under-the-curve from baseline to 6 months between arms using analysis of covariance adjusting for the baseline FACT-TOI score. Responder-type analysis will also be performed in which the percentage of patients who report a 6-point worsening from baseline at either 3 or 6 months will be compared between arms using a chi-square test . The "responder" definition will be investigated using cumulative distribution curves. Lastly, a

linear mixed-effects model will be used to compare the FACT-TOI over time between arms with the post-baseline FACT-TOI score as the modeled outcome and predictors are baseline FACT-TOI, arm, time (treated as a continuous variable and measured at the planned month of assessment), and treatment-by-time interaction. Similar analyses described for the FACT-TOI will be repeated for the other scale scores, and for all scales after 3 and 5 years of follow-up.

Missing data will be handled in several ways. All analyses will first be completed using all available data, followed by analyses completed using imputed data using the arm minimum followed by the arm maximum. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be compared to assess the degree to which missing data impacts study results.

For all statistical analyses, p-values <0.05 will be considered statistically significant. For interpreting the clinical significance of effects will be evaluted using the FACT cut-offs described above as well as using Cohen's cut-offs (37): <0.20=trivial; 0.20-<0.50=small; 0.50-<0.80=moderate; and >/=0.80=large.

16.5 Data & Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules (these rules apply to Arm A and Arm B independently): Both Arms A (rituximab) and B (Zevalin) are commercial agents used at the FDA-approved dose with standard CBC and bone marrow criteria. Since the doses are the same, we do not expect any difference in the toxicity profile as described in the label. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

In our previous study of single-agent rituximab for untreated FL(10), we observed 14% grade 3,4 AEs. In previous Zevalin studies for untreated FL (14) there was, as expected, 15% grade 3 and 17% grade 4 (total 32% grades 3,4) neutropenia that was reversible. There was no grades 3,4 non-hematologic toxicity. These toxicities, if they occur, do so within 12 weeks for both Arms A and B. Accrual will be temporarily suspended to <u>both arms</u> if at any time we observe events considered at least possibly related to study treatment (i.e., an

adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

- if 3 or more patients in the first 12 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 12 patients have been treated, 25% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting

16.61 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.25 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.62 Publications: This study includes endpoints that require various amounts of follow-up. Due to this, primary endpoint results will be reported after all patients have completed the 6-month response assessment (6-12 months after completion of accrual). Time to event endpoints including PFS, TTNT, and TTC will require additional follow-up. These measures may be reported in the initial report with the CR rate, as well as after 3 years, 5 years, and 10 years after the completion of accrual.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.83 The geographical region served by MCCC has a population which includes approximately 5% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 5% of patients will be classified as minorities by race and about 45% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race for All Phase 2 and 3 Studies

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	57	69	0	126
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	58	70	0	**128**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	56	68	0	124
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	58	70	0	**128**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	**Mandatory or Optional**	**Type of Tissue to Collect**	**Block, Slides, Core, etc. (# of each to submit)**	**Visit 1 (Screening)**	**Process at site? (Yes or No)**	**Temperature Conditions for Storage /Shipping**
Central Path review	Mandatory	H&E stained slides	H&E stained diagnostic slides	X	No	Ambient air
Tregs, Monocytes (Section 17.31)	Optional	Paraffin embedded	1 paraffin-embedded block; if block not available then 1 H&E slide and 20 (4µ) unstained slides	X	No	Ambient air
Bcl-2 mutations (Section 17.31)	Optional	Paraffin embedded		X	No	Ambient air
Research Fresh Tissue	Optional for patients enrolled at Mayo only	Fresh	Excisional or core needle (3-6 cores) biopsy	X	No	

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Central pathology review will be conducted for confirmation of diagnosis by [redacted] nd colleagues at Mayo Clinic Rochester.

The appropriate representative tumor tissue samples will be forwarded to the Lymphoma SPORE Biospecimens Core for central diagnostic review and classification to confirm the diagnosis. This is a retrospective review to determine the evaluability of the patient's data for analysis. The results of the review are the purposes of the trial only and will not be returned to the site.

Required materials [redacted]):

- Lymphoma Pathology Reporting Form (Complete Section I only)
- Bone marrow biopsy report
- Tumor tissue pathology report
- Tumor tissue diagnostic H&E stained slide
- Tumor tissue immunochemistry or immunophenotyping by flow cytometry report (if available)

17.3 Correlative Tissue Collection

17.31 Paraffin Embedded Tissue

17.311 Representative diagnostic FFPE tumor tissue block. If block cannot be sent then please send one (1) H&E slide, and twenty (20) 4µm unstained air-dried slides. Do not coverslip the unstained slides. If questions please [redacted]

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤14 days after registration
Adverse Event– Baseline	
Measurement – Baseline	
Tumor Tissue Biopsy Pathology Report	
CT/PET/MRI Scan Report	
Research Paraffin Embedded Submission – Baseline (All Patients)	≤30 days after registration
Research Fresh Tissue Submission – Baseline (Mayo Patients only)	
Research Blood Submission	≤ 21 days after registration
End of Active Treatment/Cancel Notification	Submit ≤14 days after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet	≤14 days after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Booklet Compliance	≤14 days after registration - This form **must** be completed only if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.

Central Pathology Review Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Pathology Materials (this is for central review, eligibility, etc.)	Submit ≤30 days after registration (see Section 17.0)

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment	X[2]	X	

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Observation			X[1]
Nadir/Adverse Event (Cycles 1 & 2 Only)	X	X	X[3]
Measurement	X	X	X
Research Blood Submission			X (see Section 14.0)
Patient Questionnaire Booklet [4]	X	X	X
Booklet Compliance [5]	X	X	X
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		At each occurrence (see Section 10.0)[3]
CT/PET/MRI Scan Report	X[6]		X[6]

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. AE form and expedited reports needed for Cycle 1 (treatment – months 0-3) and Cycle 2 (first cycle of observation – months 3-6) only.
4. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
5. This form must be completed **only** if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.
6. Submit copy of documentation of response or progression to the Lymphoma SPORE Operations Office, Attention: QAS for LS138D.

Follow-up Material(s)

CRF	**Event Monitoring Phase[1]**				
	q. 12 months until PD[2]	At PD[2]	After PD q. 12 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 10 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for LS138D.

19.0 Budget

19.1 Costs charged to patient: rituximab and Zevalin are standard of care and will be commercial

19.2 Tests to be research funded: Lymphoma SPORE will cover the research translational costs and kits and mailing. This will involve the clinical trials core B and the Biospecimens Core.

19.3 Other budget concerns: Protocol administration, study coordinator time, data management, and statistical analysis efforts will be funded by Acrotech Biopharma.

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Appendix I ECOG Performance Status Scale

Appendix I **ECOG Performance Status Scale**	
Grade	***Descriptions***
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II Patient Information Sheet

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains one set of questions:
   - FACT-Lym (42 questions)

2. Directions on how to complete the set of questions are written on the top of the set.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Appendix III Lymphoma Blood Collection Kit –
Specimen Checklist and Shipping Instructions

Hematology Malignancies Program/Predolin Biobank
The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study of Immunotherapy Versus Zevalin For Patients with New, Untreated Follicular Lymphoma Who are Candidates for Observation

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- 8.5ml ACD (yellow top) collection tubes
- 10ml EDTA (purple top) collection tube
- 10ml Red Top collection tube
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following Peripheral blood specimens:
    - 17ml into two (2) ACD tubes
    - 10ml in one (1) EDTA tube
    - 10ml in one (1) Red Top tube
2. All specimens are to be clearly labeled with the protocol number LS138D, the patient's initials (last, first, middle) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Patient Information Form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please e-mail [redacted] to notify the laboratory when samples are being shipped. Indicate the protocol number, the Fed Ex tracking number, name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

[redacted]

Patient Information Form

Specimen Date: / /

Institution/Affiliate:

Physician:

Patient Initials (last name, first name):

Protocol #: LS138D

Lymphoma SPORE Subject ID #:

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

Please indicate which samples are being shipped at this time:

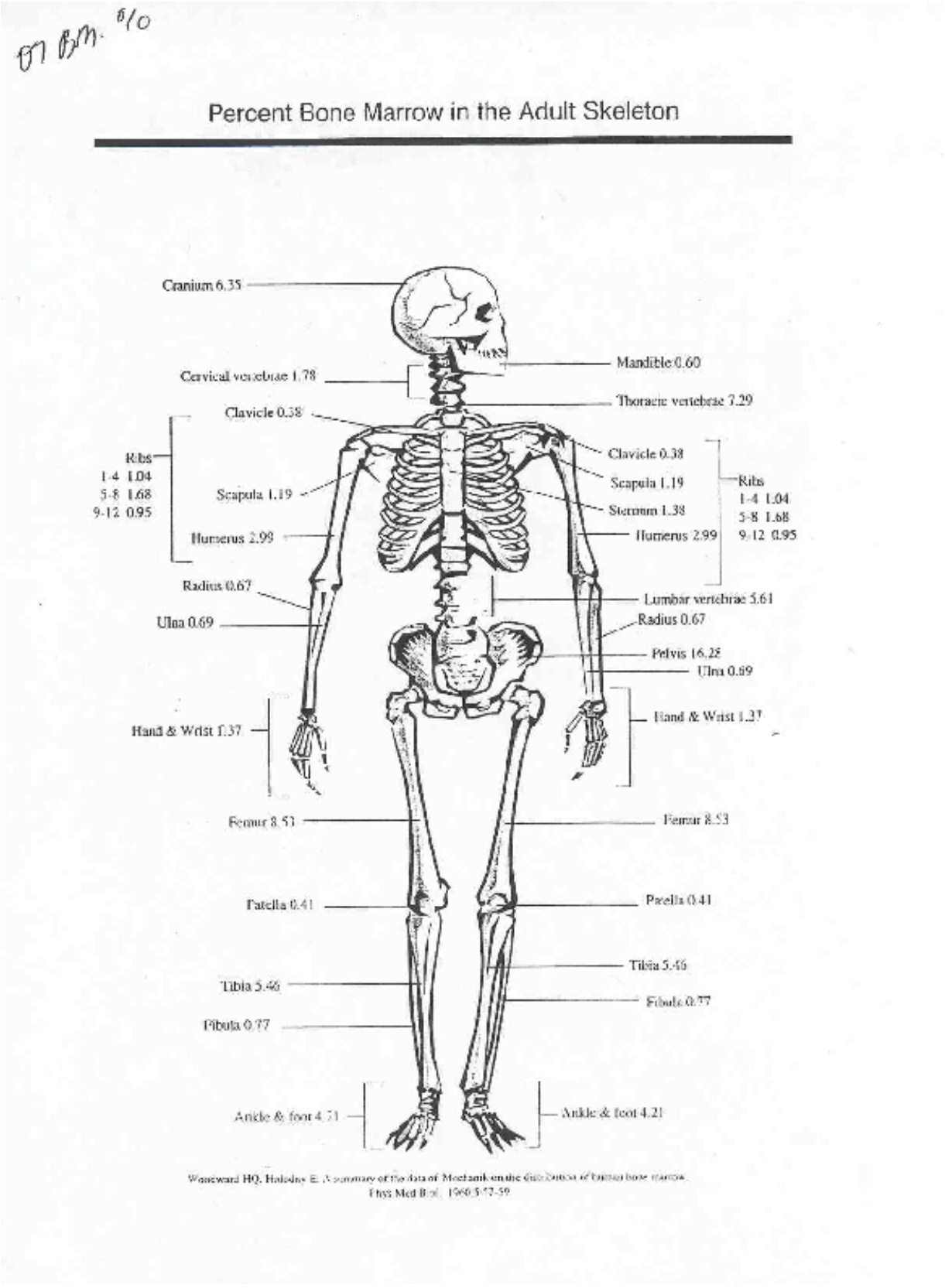
1. Visit 1 (Screening /Baseline)
2. Visit 2 (End of 6 months/End of Cycle 2)

Any questions concerning sample collection for the LS138D study please contact:

[redacted]

Affiliates who anticipate participating in this study should please call in advance for kits.

Appendix IV Bone Marrow



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