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Activation Date July 18, 2011

SWOG

A PHASE II TRIAL OF PET-DIRECTED THERAPY FOR LIMITED STAGE DIFFUSELARGE B-CELL LYMPHOMA (DLBCL)

NCT #01359592

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AGENTS:

Cyclophosphamide (NSC 26271)
Doxorubicin (NSC 0123127)
Prednisone (NSC 10023)
Vincristine (Oncovin) (NSC-67574)
Rituximab Chimeric Monoclonal anti-CD20 Antibody (NSC 687451)
Yttrium-90 Ibritumomab Tiuxetan (Zevalin®) (NSC-710085)

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NRG/NRG Oncology
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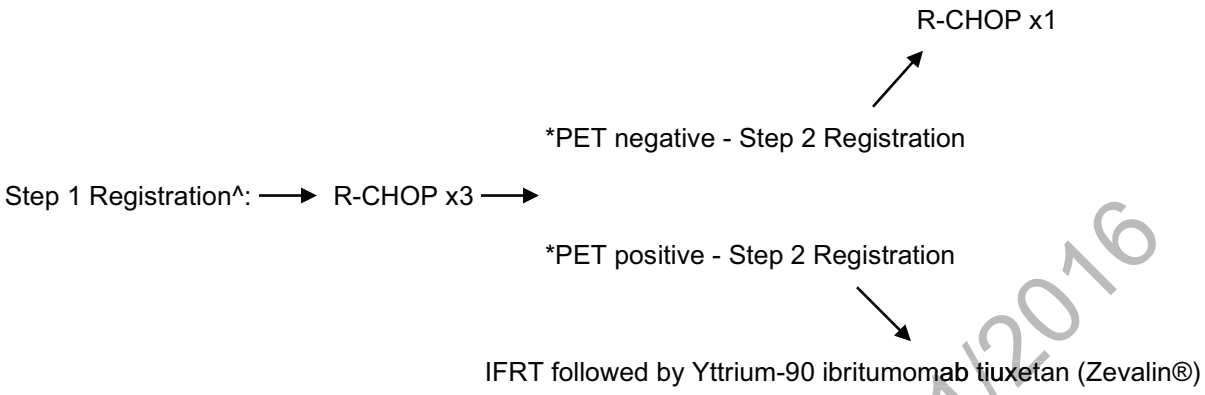
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-CTSU Fax: 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: Institutions participating through the CTSU are required to submit and amend their data electronically via Online Data Submission. Access the SWOG Workbench using your CTSU userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx. Exceptions: Data items that are not available for online submission (operative and pathology reports, patient completed forms, scan reports, etc.) may be submitted by fax at 800-892-4007. Do not submit data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: Phone: 206/652-2267; E-mail: lymph@crab.org And: For treatment or toxicity related questions contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



^ Patients who are early stage by CT but advanced stage by PET/CT will receive R-CHOP x 6 (per Section 7.6)
* These results are based on central review of the PET/CT scan after 3 cycles of R-CHOP.

1.0 OBJECTIVES

1.1 Primary objective

a. To assess the 5-year progression-free survival (PFS) rate in patients with newly diagnosed limited stage diffuse large B-cell lymphoma using PET/CT scan to direct therapy after 3 cycles of R-CHOP

1.2 Secondary objective(s)

a. To evaluate progression-free survival within the PET+ and PET- subgroups of patients with newly diagnosed limited stage diffuse large B-cell lymphoma (DLBCL).

b. To evaluate toxicity of the protocol treatments in this patient population.

c. To evaluate the response probability in this patient population.

d. To evaluate overall survival in the overall population, and within the PET+ and PET- subgroups.

e. To estimate the rate of upstaging at baseline by PET/CT among patients newly diagnosed with limited stage diffuse large B-cell lymphoma by CT imaging and describe outcomes in patients upstaged by PET/CT at baseline to advanced DLBCL.

f. To describe outcomes in the subgroup of patients upstaged by PET/CT.

g. To evaluate the association of germinal center B-cell subtype (GCB) vs. stromal-1 vs. stromal-2 gene expression signatures with PFS or overall survival (OS).

2.0 BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) and presents as limited stage disease in about 25% of the cases. The standard of care has been established by **SWOG-8736**.

SWOG-8736, "A Randomized Trial Comparing Chemotherapy Alone to Chemotherapy Followed by Radiotherapy for Localized Intermediate and High Grade Non-Hodgkin's Lymphoma", demonstrated that three cycles of CHOP chemotherapy followed by involved field radiotherapy (CHOP x 3 + IFRT) was superior to eight cycles of CHOP alone (CHOP x 8) for patients with Stage I, IE, and non-bulky Stages II, and IIE. *(1)* Five-year overall survival (OS) for CHOP x 3 + IFRT and for CHOP x 8 was 82% and 74%, respectively. Five-year progression-free survival (PFS) for CHOP x 3 + IFRT and for CHOP x 8 was 76% and 67%, respectively. Only at 7 years did the curves begin to overlap for progression-free survival and at 9 years for overall survival. *(2)*

Outcome on **SWOG-8736** also varied according to prognostic factors established for common use in the International Prognostic Index after modification for stage. *(1)* The poor risk clinical factors included Stage II disease, elevated serum LDH, WHO performance status of 2, and age greater than 60 years. Five-year OS was 94% for patients having none of the poor risk factors, 71% for one or two risk factors, and 50% for 3 risk factors ($P < 0.05$). On the basis of these results, focus for subsequent studies of intensified treatment in patients with localized aggressive NHL has been on those patients with at least one risk factor, thereby excluding those patients (25%) with none of the poor risk factors who have an outstanding probability for cure with less treatment (CHOP x 3 + IFRT).

With the goal to improve outcome for patients with one or more risk factors, SWOG has performed a series of Phase II studies testing new treatment combinations in order to identify potential regimens for comparison to standard treatment (3 cycles of CHOP followed by IFRT) in future randomized trials. An experimental arm would be selected if 3-year progression-free survival was promising for this group of patients.

S0014, the first of these pilot studies, tested the utility of adding 4 doses of rituximab to CHOP x 3 + IFRT. With the median follow-up of 5.3 years, treatment resulted in PFS of 93% at 2 years and 88% at 4 years. OS was 95% at 2 years and 92% at 4 years. These results were compared with those from a historic group of patients treated without rituximab on **SWOG-8736**, demonstrating PFS of 78% and OS of 88% at 4 years. *(3)* Addition of rituximab to CHOP prior to IFRT appeared to offer modest improvement.

S0313, the next Phase II pilot trial, examined the efficacy of CHOP x 3 + IFRT followed by consolidation with Yttrium-90 ibritumomab tiuxetan (Zevalin®). With 41 evaluable patients and median follow-up of 2 years, the 2-year PFS rate is 92% and OS is 95%, with very few relapses being observed. The treatment was very well tolerated. Grade 3 febrile neutropenia occurred only in 3/40 evaluable patients (8%), while Grade 3/4 neutropenia occurred in 30% of the patients, about half of the respective rates (15% and 65%) observed in **S0014**. Grade 3/4 thrombocytopenia in **S0313** was higher than in **S0014**, seen in 15% of the patients (vs. 3% in **S0014**), likely as a consequence of Yttrium-90 ibritumomab tiuxetan administration, but without any permanent or long-lasting effects. There was however, an 8% rate of Grade 3 radiation mucositis. *(4)*

PET/CT scan is a sensitive test for detection of lymphoma and is now included in lymphoma response assessment criteria. *(5)* It is adept at determining proliferation in residual masses. Sehn and colleagues from British Columbia Cancer Agency (BCCA) have used PET/CT scans to direct therapy in localized lymphoma. *(6)* Sixty-five patients with non-bulky Stage I and II disease, median age 67, 58% with Stage I disease, received 3 cycles of R-CHOP and were restaged with a PET/CT scan. Forty-eight (74%) patients were PET/CT -negative and received an additional cycle of R-CHOP, while 17 (26%) of patients remained PET-positive and received IFRT. At a median follow-up of 17 months, only 1 of 48 PET/CT -negative patients relapsed, with estimated 2-year PFS and OS of 97%. Of 17 patients with PET-positive disease, 3 relapsed, all outside the radiation field, and 2 died, for an estimated 2-year PFS of 83% and OS of 76%. While preliminary, this study indicates that therapy intensification can be limited to a subset of patients, and that IFRT alone is likely not sufficient to eliminate the adverse prognosis imparted by a positive PET/CT scan after 3 cycles of R-CHOP.

PET/CT scans are frequently used for initial staging as well, and may change the staging from early to advanced in about 15% of the patients. *(7)* Despite excellent outcomes with prior SWOG and BCCA studies, which utilized only CT scans for initial staging, it is possible that patients who present with limited stage DLBCL on CT but advanced stage disease on PET/CT scan may have inferior outcomes compared to patients who present with limited stage DLBCL by both CT and PET/CT staging. It would be important to study this group of patients in a safe and instructive manner, and to capture their outcomes so that historical comparison can be made to patients on prior trials where staging was performed only with CT scans. Therefore, patients who present with early stage DLBCL on CT but advanced stage disease on PET/CT scan will be enrolled in a parallel treatment arm, and will receive 6 cycles of R-CHOP chemotherapy without radiation.

Proposed design

To build both on SWOG experience with **S0014** and **S0313**, and on Phase II trial from BCCA, we propose to use PET/CT staging after three cycles of R-CHOP to direct further therapy. PET-negative patients will receive one additional cycle of R-CHOP (total of 4 cycles). PET-positive patients will receive IFRT 3-4 weeks after the third cycle of R-CHOP, followed by Yttrium-90 ibritumomab tiuxetan 3-6 weeks after completion of IFRT. **The hypothesis is that intensifying treatment in the poor-risk group with positive PET/CT will improve their outcomes, while reducing treatment in the low-risk group with negative PET/CT will decrease toxicity and thus possibly also improve outcomes.**

Relevant data from prior trials *(8)*

Shenkier and colleagues from British Columbia Cancer Agency (BCCA) confirmed the outcomes seen in the CHOP x 3 + IFRT arm of **SWOG-8736**. They reported their experience using 3 cycles of doxorubicin-based chemotherapy in Stage IA and IIA patients with non-bulky tumors. *(9)* There were 308 patients with median age of 64 and 61% had Stage I disease. Involved field radiation therapy (IFRT) was administered at 3,000 to 3,500 cGy (and 4,500 cGy in 4% of the cases) beginning 3-4 weeks after the last dose of chemotherapy. Outcomes were remarkably similar to **SWOG-8736**, with 5-year PFS of 81% and 5-year OS of 80%.

Eastern Cooperative Oncology Group (ECOG) study 1484 tested whether radiation therapy (RT) was effective as consolidation after a full course of chemotherapy. They enrolled 352 patients with bulky Stage I and II disease (31% of the patients had bulky disease) and randomized 179 patients to observation and 173 patients to consolidative radiation therapy after completion of 8 cycles of CHOP (RT was administered only if patients achieved complete (CR) or partial (PR) remission at the end of chemotherapy). *(10)* Those achieving CR received 3,000 cGy or were monitored, while those in PR all received 4,000 cGy (these PR patients were not randomized). Two hundred fifteen (61%) patients achieved CR and 98 (28%) achieved PR. Of 71 patients achieving PR who actually received RT, 22 (31%) converted to CR but this did not translate into decreased relapse rate (47% for PR vs. 46% for PR converted to CR) or in improved survival outcomes, with 6-year failure-free survival (FFS) of 63% and 6-year OS of 69%. These patients with PR following CHOP X 8 did unexpectedly well as a group, raising two issues. The first is that CR versus PR based on CT scans is not predictive of outcome prior to RT consolidation, and second, RT consolidation may have merit as an effective therapy in limited stage disease following failure of chemotherapy. Due to toxicity and further dropout, 93 patients in CR following CHOP x 8 were on observation and 79 patients in CR received RT. RT resulted in statistically borderline improvement in FFS and disease-free survival (DFS). Six-year DFS was 73% for RT and 56% for observation arms (p=0.05), while 6-year FFS was 75% vs. 56%, respectively (p=0.06). There was no statistical difference in OS at 5 years (87% for RT and 73% for observation, p=0.24), or subsequently at 10 or 15 years. It is hard to compare ECOG1484 to other studies due to lack of documentation of LDH (precluding IPI assessment), inclusion of bulky Stage II disease (33 patients), and due to tiered study design with significant dropout. The patient population appeared to be higher-risk than that of **SWOG-8736**, but the 5-year OS was comparable (82% for **SWOG-8736**), making it less likely that CHOP x 8 + RT had an advantage over CHOP x 3 + IFRT once bulky Stage II patients were excluded.

A French cooperative trial assessed chemotherapy intensification in the low-risk group. Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial LNH 93-1 randomized 329 patients to receive CHOP x 3 + IFRT (IFRT started a month after last CHOP at a dose of 4,000 cGy), and 318 patients to aggressive dose-intense chemotherapy (doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone [ACVBP]) given at 2-week intervals followed by sequential consolidation with methotrexate, etoposide, ifosfamide, and cytarabine. *(11)* Median age was 47 years, 67% of patients had Stage I disease, and 11% had bulky disease. Ninety-five percent of patients had a 0 age-adjusted IPI (aaIPI) risk score, so that the majority of patients had no risk factors using the stage-modified IPI. There was a statistically significant improvement in favor of intensive chemotherapy for both 5-year event-free survival (EFS) (82% in intensive chemotherapy group vs. 74% in CHOP x 3 + IFRT group, p<0.0001) and 5-year OS (90% in intensive chemotherapy group vs. 81% in CHOP x 3 + IFRT, p=0.001). Clinically, though, the difference in 5-year OS was relatively small, and within range of **SWOG-8736** (5-year OS of 82%), despite being tested in a low-risk group. When stage-modified IPI was assessed, 5-year OS for the intensive chemotherapy treated patients was slightly worse, and for the CHOP x 3 + IFRT treated patients was significantly worse than 5-year OS in patients with 0 risk factors treated on **SWOG-8736** with CHOP x 3 + IFRT (91% and 83% for the GELA trial vs. 95% for the SWOG trial, respectively). Intensive chemotherapy as used by GELA appeared better than CHOP x 3 + IFRT on **SWOG-8736** (85% vs. 77%), whereas, CHOP x 3 + IFRT for patients with 1 risk factor appeared comparable between groups (78% vs. 77%). ACVBP regimen has not gained traction in North American due to significant toxicity as exemplified by over 20% hospitalization rate with each of the three cycles.

In another GELA trial (LNH 93-4) patients older than 60 years (median age was 68 years) were randomly assigned to four cycles of CHOP (CHOP x 4, 277 patients) or CHOP x 4 + IFRT (IFRT administered at 4,000 cGy one month after last cycle of CHOP, 299 patients). (12) Ninety-five percent had a zero aaIPI risk score, and 65% had Stage I disease, so that 65% of the patients had one stage-modified IPI risk factor (older age) and 35% of them had two stage-modified IPI risk factors (older age and Stage II disease). This trial is most comparable to **SWOG-8736** by risk assessment and did not show significant differences in outcomes between the two groups. Five-year EFS was 61% in the CHOP x 4 arm and 64% in CHOP x 4 + IFRT arm (p=0.6), while 5-year OS was 72% and 68%, respectively. However, both groups did significantly worse than CHOP x 3 + IFRT in **SWOG-8736**, where 5-year OS was 82%. While patients with one stage-modified IPI risk factor fared about the same as on **SWOG-8736** (76% vs. 77%), those with two risk factors had worse outcomes (58% vs. 77%). Stage II but not bulky disease affected OS in multivariate analysis, and there was no reason to suspect under-staging. A delay in administration of radiation may have been partially responsible for worse outcome. IFRT was administered at a median of 35 days, as opposed to about 24 days in past SWOG studies. Additionally 12% did not receive radiation therapy. Therefore, failure to detect a difference in outcomes between the arms of the study may not be due to lack of efficacy of radiation therapy, but rather due to delayed application of the RT and due to failure to receive RT.

Mabthera International Trial (MInT) is a large multinational trial that enrolled 824 patients age 18-60 with bulky Stage I or Stage II-IV disease and zero to one aaIPI risk factors, and randomized them to 6 cycles of CHOP-like chemotherapy with or without rituximab. (13) Patients with bulky disease received radiation therapy, but the definition of bulky disease varied between 5, 7.5, and 10 cm. Median age was 47 years, 18% had Stage I and 55% had Stage II disease. Stage-modified IPI could not be derived from the paper, however. Based on varying definitions of bulky disease, 50% of the patients should have received 3,000-4,000 cGy of radiation therapy, and 40% did. Addition of rituximab improved CR, PFS, EFS, and OS, as expected. Bulky disease affected all outcomes measured (EFS, PFS, and OS), regardless of rituximab assignment and having presumably receiving RT. This implies that RT after full dose of rituximab-containing chemotherapy does not eliminate unfavorable risk of bulky disease. The authors further investigated the importance of bulky disease, indicating that 32% had bulky disease by conventional definition, and patients with maximal tumor diameter of 10 cm or greater had 9.1% lower 3-year EFS and 11.1% lower 3-year OS, statistically significant findings. (14) However, if the patients had Stages II-IV and bulky disease, it would only underscore that outcomes of such patients are consistent with those in advanced stage disease where the role of RT is questionable.

Translational Medicine:

Patients with germinal center B-cell (GCB) subtype of DLBCL, as defined by gene-expression profiling, have better outcomes than patients with non-GCB subtype when treated with CHOP-like therapy. (15) Most recent evidence suggests three gene expression signatures – “germinal center B-cell”, “stromal-1”, and “stromal-2.” – are of prognostic significance in DLBCL when treated with R-CHOP-like therapy. (16) Preliminary evidence suggests that limited stage DLBCL (which has better prognosis than advanced stage DLBCL) may be of GCB subtype to a greater extent than advanced stage DLBCL. (17) This could indicate a biological difference between limited stage and advanced stage DLBCL that accounts for the difference in outcomes, and which should be addressed by further studies.

Also, from SWOG’s previous work, 10 genes were found to be associated with limited stage disease, most of which are now included in the favorable stromal-1 signature. (17) Therefore, the hypothesis is that stromal-1 signature may also be more common in limited stage DLBCL, and also partially account for more favorable prognosis in limited stage DLBCL.

SWOG proposes prospective determination of gene expression signature groups as defined by Lenz et al *(16)* specifically in limited stage DLBCL, to test the hypothesis that limited stage DLBCL consists predominantly of GCB phenotype, using formalin-fixed, paraffin-embedded tissue from the diagnostic biopsy. *(18)* SWOG will also look specifically at the 10 genes from the previous work. The laboratory of Lisa Rimsza, M.D., will perform gene expression profiling using quantitative nuclease protection assay (qNPA) *(19)*, and correlate it to immunohistochemistry-based algorithms. *(20-22)*

Inclusion of Women and Minorities

This study was designed to include women and minorities. Based on recent registrations to studies involving DLBCL, it is anticipated that accrual in the race and sex subgroups will be as shown in the table below.

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	8	9	17
Not Hispanic or Latino	62	76	138
Total Ethnic	70	85	155

Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	2	2	4
Black or African American	6	8	14
Native Hawaiian or other Pacific Islander	0	0	0
White	61	74	135
Racial Category: Total of all subjects	70	85	155

3.0 DRUG INFORMATION

For information regarding Investigator Brochures, please refer to SWOG Policy 15. For this study, all drugs are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

3.1 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxidemonohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

b. TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced

cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other aklylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic

administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours.

Administration: Cyclophosphamide should be diluted in about 250 cc of normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity.

Supplier: Cyclophosphamide is commercially available and should be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information

3.2 Doxorubicin (Adriamycin) (NSC-123127)

a. DESCRIPTION

Mechanism of Action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from S. Peucetius var. caesius. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nailbeds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/M2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20 and 50 mg single-use vials, and 200 mg multidose vials as a red-orange, lyophilized powder which has a storage stability of at least two years - see expiration date on vial. Doxorubicin should be reconstituted with 5, 10, 25 and 75 ml respectively, of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/ml.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2° - 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

Supplier: This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Prednisone (NSC-10023)

a. DESCRIPTION

Prednisone is a glucocorticoid rapidly absorbed from the GI tract.

b. TOXICOLOGY

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

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

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone Cortisone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone
0.75 mg	4 mg	5 mg	20 mg 25 mg

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.4 Rituximab Chimeric Monoclonal anti-CD20 Antibody (IDEC-C2B8) (NSC-687451)

a. PHARMACOLOGY

Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and Fc domain recruits immune effector functions to mediate B cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity.

b. PHARMACOKINETICS

Pharmacokinetics: In prior studies patients treated at the 375 mg/m^2 dose levels exhibited detectable antibody concentrations throughout the treatment period and for 3-6 months after completion of treatment. B-cell recovery begins approximately 6 months following completion of treatment and median B-cell levels return to normal within 12 months of completing treatment.

1. Absorption: Immediate and results in a rapid and sustained depletion of B-cells.

2. Distribution: 3.1 L (rheumatoid arthritis), 4.5 L (Wegener's Granulomatosis/Microscopic Polyangiitis).

3. Metabolism: Uncertain excretion; may undergo phagocytosis and catabolism in the reticuloendothelial system.

4. Elimination: Median terminal half-life: Non-Hodgkin's Lymphoma 22 days (range,6-52 days), chronic lymphocytic leukemia 32 days (range, 14-62 days), rheumatoid arthritis 18 days (range, 5-78 days) Wegener's Granulomatosis/Microscopic Polyangiitis 23 days (range, 9-49 days).

c. ADVERSE EVENTS

1. Possible Side Effects of Rituximab:

The following side effects are common, occurring in more than 20%: nausea, chills, fever, infusion reaction, infection, fatigue, neuropathy.

The following side effects are less common, occurring less than 20%: Anemia, blood and lymphatic system disorders, febrile neutropenia, myocardial infarction, sinus tachycardia, supraventricular tachycardia, abdominal pain, diarrhea, vomiting, edema, pain, serum sickness, anaphylaxis, neutropenia, thrombocytopenia, lymphopenia, hyperglycemia, hypocalemia, hypokalemia, tumor lysis syndrome, arthralgia, back pain, myalgia, dizziness, headache, lethargy, progressive multifocal leukoencephalopathy, seizure, acute kidney injury, adult respiratory distress syndrome, allergic rhinitis, bronchospasm, cough, dyspnea, hypoxia, pneumonitis, sore throat, erythema multiforme, hyperhidrosis, pruritis, rash macropapular, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, flushing, hypertension, hypotension

The following are important warnings for rituximab:

Severe Infusion and Hypersensitivity Reactions: Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. An infusion-related symptom complex consisting of fever and chills/rigors has occurred in the majority of patients during the first rituximab infusion. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (including, but not limited to IV saline, diphenhydramine, and acetaminophen).

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

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections: Hepatitis B virus (HBV) reactivation in some cases resulting in fulminant hepatitis, hepatic failure, and death, has been reported in some patients treated with rituximab. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating rituximab. For patients with evidence of prior hepatitis B infection (HBsAg positive or HBsAg negative but anti-HBc positive), consult with physicians expertise in managing HBV regarding monitoring and consideration for HBV antiviral therapy. Carriers of hepatitis B

should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following rituximab therapy. In patients who develop viral hepatitis, rituximab and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming rituximab therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of rituximab and have resulted in death.

Severe Mucocutaneous Reactions: Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with rituximab. These reports included paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1-13 weeks following rituximab exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of rituximab to patients with any of these mucocutaneous reactions has not been determined.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1-77) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Cardiovascular: The incidence of serious cardiovascular events in the double-blind clinical trial for rheumatoid arthritis (RA) patients was 1.7% and 1.3% in rituximab and placebo groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies, including all rituximab regimens (3/759 = 0.4%) as compared to none in the placebo group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared to the general population, patients with RA should be monitored throughout the infusion and rituximab should be discontinued in the event of a serious or life-threatening cardiac event.

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

Renal: Rituximab administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (> 25,000/mm^3) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and rituximab is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of rituximab should be considered for those with rising serum creatinine or oliguria.

2. Pregnancy, and Lactation: Pregnancy Category C. There are no adequate and well-controlled studies of rituximab in pregnant women. Post-marketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in utero. Rituximab was detected postnatally in the serum of infants exposed in utero. Animal studies have demonstrated adverse effects including decreased (reversible) B-cells and Immunosuppression. It is recommended to use effective contraception during and for 12 months following treatment with rituximab.

   It is not known whether rituximab is secreted into human milk. Published data suggests that antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts. However, human IgG is secreted in breast milk; therefore, rituximab may also. The risks from this are unknown.

3. Drug Interactions: Formal drug interaction studies have not been performed with rituximab. Refer to the current FDA approved package insert. Concurrent use of rituximab and live vaccines may result in an increased risk of infection by the live vaccine. Immunosuppression by rituximab may diminish the therapeutic effect of both live and inactivated vaccines.

d. DOSING AND ADMINISTRATION

See Section 7.0 Treatment Plan.

e. STORAGE, PREPARATION AND STABILITY

Refer to the current FDA-approved package insert.

f. HOW SUPPLIED

Rituximab is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

3.5 Vincristine (Oncovin) (NSC-67574)

a. DESCRIPTION

Chemistry: Vincristine is one of the so-called vinca-alkaloids and is extracted from the plant cantharanthus roseus (vinca rosea).

Biochemistry: This drug appears to produce the arrest of mitosis in animal cells by interfering with microtubule function.

b. TOXICOLOGY

Human Toxicology: The primary toxic effects of vincristine are neurological with paresthesia, weakness, muscle wasting, motor difficulties including difficulty walking and slapping gait, loss of deep tendon reflexes, sensory loss, neuritic pain, paralytic ileus, bladder atony, and constipation. Rarely, it produces myelosuppression. Other side effects may include alopecia, allergic reactions, (including rare anaphylaxis, rash and edema), jaw pain, hypertension, hypotension, nausea, vomiting, diarrhea, fever, headache, oral ulceration, optic atrophy with blindness, ptosis, diplopia and photophobia. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: After IV administration, a triphasic serum decay pattern follows with half-lives of 5 minutes, 2-3 hours, and 85 hours. The range of terminal half-life is 19-155 hours. Excretion is 80% in the feces and 10-20 % in the urine.

The liver is the major excretory organ in humans and animals, and biliary obstruction causes increased toxicity in man.

Formulation: 1 mg/1 ml, 2 mg/2 ml, and 5 mg/5 ml vials containing solution.

Storage and Stability: It should be stored under refrigeration. Vincristine is available with and without preservatives so the time-frame for use once the vial has been entered varies. The intact vials have a labeled expiration date. Protect from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: Vincristine should be administered intravenously through a freely-running IV. If it extravasates, it produces a severe local reaction with skin slough. **FATAL IF GIVEN INTRATHECALLY, FOR INTRAVENOUS USE ONLY.**

Supplier: Vincristine is commercially available, and should be purchased through a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.6 Yttrium-90 ibritumomab tiuxetan (Zevalin®) (Y2B8 Radiolabeling Kit) (NC-68152-103-03)

a. DESCRIPTION

Mechanism of Action: ^{90}Y ibritumomab tiuxetan is a radiolabeled molecule composed of the murine IgG_1 kappa monoclonal antibody against CD20, ibritumomab, covalently bound to the chelator tiuxetan, which chelates the radioisotope yttrium-[90] (^{90}Y). Radiolabeled antibodies combine both biologic and radiolytic mechanisms of actions (radioimmunotherapy).

b. TOXICOLOGY

Human Toxicology: To date, all clinical experiences of ibritumomab are derived from clinical trials in patients with ≤ 25% tumor involvement in the bone marrow. The dose-limiting and most common adverse events reported to date have been hematologic toxicities, including B-cell depletion and bone marrow suppression. Nadirs of neutropenia, thrombocytopenia and anemia occur at a median of 8 - 10 weeks from baseline (range 2 - 16 weeks). Median recovery times from nadir to recovery range (ANC ≥ 1,000/mm3, Platelet ≥ 50,000/mm3 and Hb ≥ 10g/L) are 2 to 3 weeks; however, prolonged (up to 20 weeks) or irreversible bone marrow suppression has been rarely observed. Hematologic toxicities are more severe in patients with borderline platelet counts at baseline. The following table shows the incidence and duration of Grade 3 and 4 hematologic toxicity for patients with mild thrombocytopenia (100 - 149,000/mm3) at baseline who were treated at 0.3 mCi/kg (11.1 MBq/kg), and for those with normal baseline platelet count (> 150,000/mm3) treated at 0.4 mCi/kg (14.8 MBq/kg), up to the maximum dose of 32 mCi (1184 MBq).

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

*ANC < 1,000 cells/mm^3, platelets < 50,000/mm^3, and hemoglobin < 8.0 g/dL

Infectious Events: During the first 3 months after initiating ibritumomab therapy, 28.7% (100/349) of patients developed infections, of which 2.4% were Grade 3 and 2.0% were Grade 4. These Grade 3 or 4 infections included urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, osteomyelitis, upper respiratory tract infection, empyema, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ibritumomab, 6.0% (21 patients, 9 with grade 3 or 4) developed infections, which included urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, pericarditis, and intravenous drug-associated viral hepatitis and sepsis.

Non-hematologic toxicities that were observed in ≥ 5% of patients: **Infusional or allergic**: fever, chills, headache, flushing, dyspnea; **Body as a whole**: Asthenia, dizziness; **Cardiovascular:** hypotension; **Digestive system**: Nausea, vomiting, diarrhea, anorexia; **Skin:** rash, pruritus, edema; **Respiratory**: dyspnea, throat irritation, increased cough, rhinitis; **Pain**: Abdominal pain, arthralgia, myalgia, back pain. In addition to above, < 5% patients experienced the following Grade 3 or 4 adverse events: allergic reaction (1.1%), angioedema (0.3%), urticaria, hypoxia (0.6%), supraventricular tachycardia (0.3%), arrhythmia (0.3%)

Other reported Grade 3 or 4 adverse events: tumor pain, anemia hemolytic (0.3%); increased AKP, LDH, SGPT, SGOT, total bilirubinemia, deep thrombophlebitis (0.6%), hypochromic anemia (0.3%), anxiety (0.3%), neck pain (0.3%), pleural effusion (0.3%), arterial anomaly (0.3%), convulsion (0.3%), coronary artery disorder, (0.3%), pulmonary embolus (0.3%), encephalopathy (0.3%), granulocytosis (0.3%), (0.3%), gastrointestinal bleeding, subdural hematoma (0.3%), hepatic failure (0.3%), hyperglycemia, hypercalcemia (0.3%), hyperuricemia, (0.3%), increased prothrombin (0.3%), congestive heart failure, myocardial ischemia (0.3%), jaundice (0.3%), kidney failure (0.3%), migraine (0.3%), neuritis (0.3%), intestinal obstruction (0.3%), eye pain (0.3%), respiratory disorder (0.3%), apnea, vaginal hemorrhage (0.3%), and increased venous pressure (0.3%),

Secondary Malignancies: Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% of patients (11/211) enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to the diagnosis of MDS or AML was 1.9 years following treatment with the ibritumomab tiuxetan therapeutic regimen; however the cumulative incidence continues to increase.

The development of human anti-mouse antibodies (HAMA) has also been reported in a small number of patients.

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

c. PHARMACOLOGY

Kinetics: Pharmacokinetic and biodistribution studies were performed using ^{111}In ZEVALIN (5mCi [185 MBq] ^{111}In, 1.6 mg Ibritumomab Tiuxetan). In a study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when ^{111}In ZEVALIN was

administered without unlabeled Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg), ^{111}In ZEVALIN detected 56% and 92% of known disease sites, respectively.

In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in sustained depletion of circulating B cells. At four weeks, the median number of circulating B cells was zero (range, 0-1084 cell/mm3). B-Cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341 cells/mm3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/Dl, range 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

Formulation: Kit for the preparation of ^{90}Y ibritumomab tiuxetan. The kit consists of the following components:

- One (1) Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 mL 0.9% sodium chloride as a clear, colorless solution.
- One (1) 50 mM sodium acetate vial containing 13.6 mg sodium acetate trihydrate in 2 mL water for injection, USP as a clear, colorless solution.
- One (1) formulation buffer vial containing 750 mg albumin (human), 76 mg sodium chloride, 28 mg sodium phosphate dibasic dodecahydrate, 4 mg pentetic acid, 2 mg potassium phosphate monobasic and 2 mg potassium chloride in 10 mL water for injection, pH 7.1 as a clear yellow to amber colored solution.
- One (1) empty reaction vial.

Ibritumomab is produced in Chinese hamster ovary (CHO) cells.

Storage and Stability: The kit should be stored at 2 - 8°C (35 - 45°F).

The prepared radioisotope, ^{90}Y ibritumomab tiuxetan, if not immediately administered to the patient, should be properly shielded, stored at 2° to 8°C (36° to 46° F) and used within 8 hours of preparation.

Administration:

Preparation: Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and determination of the radiochemical purity assay of ^{90}Y Ibritumomab tiuxetan. The radiolabeling of ^{90}Y ibritumomab tiuxetan should be done according to the following directions using the radiolabeling kit described above.

1) Before radiolabeling, bring refrigerated ibritumomab tiuxetan cold kit to room temperature 25°C (77°F).

2) Clean the rubber stopper of all cold kit vials and the ^{90}Y chloride vial with a suitable alcohol swab and allow to air dry.

3) Place the ^{90}Y ibritumomab tiuxetan reaction vial in a suitable dispensing shield.

4) Using a 1 ml syringe, transfer sodium acetate to the reaction vial. The volume of sodium acetate added is equivalent to 1.2 times the volume of ^{90}Y chloride.

5) With a 1 ml syringe, aseptically transfer 40 mCi of yttrium-[90] chloride to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times, **do not shake.**

6) Using a 3 ml syringe, transfer 1.3 ml ibritumomab tiuxetan to the reaction vial. Mix completely by gently swirling and inverting the reaction vial several times. **Do not shake**.

7) Incubate the ^{90}Y ibritumomab tiuxetan reaction vial at room temperature for five minutes. Labeling more than or less than five minutes may result in inadequate radiochemical purity.

8) Using a 10 ml syringe with a large bore needle (18 - 20 G), draw formulation buffer that will result in a total volume of 10 ml when all components are added to the reaction vial. The initial volume in the reaction vial is the volumes calculated in Steps 4, 5, and 6. Ten ml minus the volumes in 4, 5, and 6, will be the volume of formulation buffer to add.

9) At the end of the five-minute incubation period, add the formulation buffer to the reaction vial. Gently add the formulation buffer down the side of the reaction vial. Do not foam, shake, or agitate the mixture.

10) Assay the ^{90}Y ibritumomab tiuxetan reaction vial in a suitably calibrated dose calibrator.

11) The percent radiochemical purity of the prepared ^{90}Y ibritumomab tiuxetan (Zevalin®) should be determined before administration to the patient.

Prior to clinical use, ^{90}Y Ibritumomab tiuxetan must be tested for radioincorporation using an instant thin-layer chromatography (ITLC) assay.

Route of Administration**:** Intravenous.

Method of Administration: ^{90}Y ibritumomab tiuxetan should be administered intravenously as a 10-minute infusion through an infusion port. A 0.22 micron filter must be used between the syringe and the infusion port. The line should be flushed with at least 10 ml of normal saline after the radiolabeled produce has been infused. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS BOLUS. Do not infuse concomitantly with another IV solution or IV medications.

Special Handling**:** The drug is a protein thus, handle gently and avoid foaming. NOTE: Do not use evacuated glass containers that require vented administration sets because this causes foaming as air bubbles pass through the solution.

Once ibritumomab tiuxetan has been radio labeled with ^{90}Y, product should be handled per institutional guidelines for radioactive material.

Supplier: Ibritumomab tiuxetan is commercially available. However, for this study the drug is being supplied by Spectrum Pharmaceuticals. The radioisotope ^{90}Y used for preparing ^{90}Y ibritumomab tiuxetan is not contained in the radiolabeling kit supplied by Spectrum. This radioisotope should be procured from suitable vendors. Radioisotope vendors should invoice Spectrum Pharmaceuticals (see Section 5.1a and Appendix 18.4 for Ordering Information).

Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

Please refer to the package insert for complete information.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

The Ann Arbor staging criteria will be used. Stage is determined based on extent of disease at the time of diagnosis. Bulk of disease is also based on extent of disease at diagnosis **(prior to surgical resection)**.

4.2 Staging Criteria

Ann Arbor Classification (AJCC Manual for Staging of Cancer, 7th ed., 2010)

STAGE I — Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

STAGE II — Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node lesions on the same side of the diaphram (IIE).

Symptoms: A = Asymptomatic

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

4.3 Bulky Disease

Bulky disease is defined as any tumor mass measuring 10.0 cm or more in diameter (greatest diameter) and/or a mediastinal mass measuring one-third or greater the maximum chest diameter. Bulky disease is measured prior to biopsy.

4.4 Stage-modified International Prognostic Index risk factors *(Ref 1)*

One point is assigned for each of the following statements that is true:

a. Age (over 60)
b. Performance status 2
c. LDH greater than institutional upper limit of normal
d. Stage II Disease

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1001** Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday two weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Initial Registration (Step 1)

_____ a. **The registering institution must submit the S1001 Site Questionnaire for yttrium-90 ibritumomab tiuxetan (Zevalin®) Administration (Appendix 18.4b) and a copy of their radioactive materials license to Spectrum Pharmaceuticals. An electronic copy of the S1001 Site Questionnaire for yttrium-90 ibritumomab tiuxetan (Zevalin®) administration can also be accessed from the SWOG website link (www.swog.org) for this study. (This process is required only for the first patient registered to this study by any one institution. The institution may not order yttrium-90 ibritumomab tiuxetan [Zevalin®] until this process is complete.)**

_____ b. Patients must have biopsy-proven de-novo Diffuse Large B-cell Lymphoma. Patients with primary mediastinal lymphoma or testicular lymphoma are not eligible. Patients with prior or simultaneous diagnosis of indolent lymphoma are not eligible. Post-transplant lymphoproliferative disorder with DLBCL morphology is ineligible.

_____ c. Patients must have non-bulky Stage I or II disease by Ann Arbor classification (see Section 4.3). This staging excludes FDG-PET evaluation. Patients who have Stage I or II non-bulky disease based on diagnostic CT scan, but are upstaged to Stage III or IV based on FDG-PET evaluation are also eligible. Stage and bulk are assigned using measurements obtained prior to biopsy.

_____ d. Patients must have a diagnostic quality contrast-enhanced CT scan of the chest, abdomen and pelvis AND baseline FDG-PET scan (see Section 7.4) performed within 28 days prior to registration. **Low resolution "localization" CT scans performed as part of a combined PET/CT scan are not adequate for enrollment or response determination on this protocol. If the patient has an allergy to CT contrast, then a non-enhanced CT will be acceptable.**

_____ e. Patients must not have clinical evidence of central nervous system involvement by lymphoma, since proposed treatment would not be able to address it adequately. Any laboratory or radiographic tests performed to assess CNS involvement must be negative and must be performed within 42 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ f. Patients may have either measurable or evaluable limited-stage DLBCL. Patients rendered free of measurable or evaluable disease by virtue of biopsy (resection) are also eligible. NOTE: If patient has measurable disease (defined in Section 10.1a) it must be documented on the Lymphoma Baseline Tumor Assessment Form. All measurable disease must be assessed within 28 days prior to registration. Patients with non-measurable disease (defined in Section 10.1b) with or without measurable disease must have all non-measurable disease assessed within 42 days prior to registration.

_____ g. Patients must have a unilateral or bilateral bone marrow biopsy performed within 42 days prior to registration.

_____ h. Pathology Review: Adequate sections or a paraffin block from the original diagnostic specimen must be submitted for review by the lymphoma pathology group as outlined in Section 12.1.

_____ i. Patients must be offered the opportunity to consent to the use of specimens for future research as outlined in Section 15.1.

_____ j. The lymphoma must express the CD20 antigen by either flow cytometry using anti-CD20 antibodies or by immunoperoxidase staining of paraffin sections. A report providing confirmation of CD20 expression must be submitted per Section 14.4c.

_____ k. Patients must have passed their 18th birthday.

_____ l. Patients must not have received prior chemotherapy, radiation, or antibody therapy for lymphoma.

_____ m. Patients must have a complete history and physical examination within 28 days prior to registration.

_____ n. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.4).

_____ o. The following tests must be performed within 42 days prior to registration either for diagnosis/staging or to obtain baseline values:

1. WBC
2. Hemoglobin
3. LDH
4. Hepatitis B-surface Ag and anti-core Ab

_____ p. Patients must have serum creatinine ≤ 2 x IULN, unless due to lymphoma, within 42 day prior to registration.

_____ q. Patients must have AST/ALT ≤ 5 x IULN, unless due to lymphoma, within 42 days prior to registration.

_____ r. Patients must have platelet count ≥ 100,000 cells/mcL and ANC ≥ 1,000 cells/mcL within 42 days prior to registration.

_____ s. Patients must have total bilirubin ≤ 2 x Institutional Upper Limit of Normal (IULN) (unless due to Gilbert's Syndrome) within 42 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ t. Patients must have a cardiac ejection fraction ≥ institutional lower limit of normal (ILLN) by MUGA scan or 2-D ECHO within 42 days prior to registration.

_____ u. Patients must not be known to be HIV-positive due to poor specificity of PET/CT scans in this population.

_____ v. No other prior malignancy is allowed except for the following: adequately treated in situ cancers (Stage 0), adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient has been in complete remission, or any other cancer from which the patient has been disease-free for at least 5 years.

_____ w. Patients must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants. Women/men of reproductive potential must have agreed to use an effective contraceptive method during the study period. A woman is considered to be "of reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ x. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ y. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 SECOND REGISTRATION (STEP 2)

_____ a. Patients must have completed 3 cycles of R-CHOP with no evidence of disease progression (see Section 10.0).

_____ b. Interim PET/CT scans must have been submitted for centralized review as outlined in Sections 7.5 and 15.2.

_____ c. If PET-negative based on the returned results from centralized review (see Section 7.5b), patients must be planning to begin further treatment within 35 days of the start of Cycle 3 of R-CHOP (see Sections 7.7-7.9). If PET-positive based on the returned results from centralized review (see Section 7.5b), it is important for patients to start IFRT as soon as possible after the end of Cycle 3 of R-CHOP. They should be planning to initiate IFRT followed by yttrium-90 ibritumomab tiuxetan within 35 days of the start of Cycle 3 of R-CHOP

6.0 STRATIFICATION FACTORS

6.1 Registration Step 1

Based on local review of the baseline PET/CT, was the patient upstaged to advanced stage DLBCL? Yes vs. No

6.2 Registration Step 2

Based on the returned results from centralized review (see Section 7.5b), is the patient PET-positive after 3 cycles of R-CHOP? Yes vs No

7.0 TREATMENT PLAN

For treatment or dose modification related questions: Please contact Dr. Daniel Persky at 520/626-8908 (dpersky@uacc.arizona.edu) or Dr. Louis S. Constine for radiation questions at 585/275-5622 (louis_constine@urmc.rochester.edu). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 General Considerations

a. Beta-2 microglobulin and Hepatitis C serology should be performed at baseline to assess potential treatment-related toxicities.

b. Patients should have a documented radiation oncology consult prior to initial registration at a Radiation Physics Center (RPC)–monitored RT facility with agreement from the consulting radiation oncologist that the patient is appropriate for this study (see Section 14.4a). All disease should be encompassable in a single radiation port (including any site of resected disease).

7.2 Pre-Medication and Supportive Care

a. Tumor lysis prophylaxis is recommended for patients with high tumor burden.

b. Use of growth factors (such as G-CSF, GM-CSF, or pegylated G-CSF) is allowed, per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196). If given, the use of growth factors MUST be recorded.

c. Use of anti-diarrheal agents such as loperamide is at the discretion of the treating physician.

d. Premedication for rituximab is mandatory and is per institutional guidelines.

e. Use of prophylactic antibiotics to prevent febrile neutropenia is at the discretion of the treating physician.

7.3 R-CHOP

See Section 7.6 for treatment of patients who were upstaged to advanced stage DLBCL based on local review of the baseline PET/CT

Agent	Dose	Route	Day	Schedule [a]
Rituximab [b]	375 mg/m^2	IV infusion	Day 1	Every 21 days for 3 cycles
Cyclophosphamide [b]	750 mg/m^2	IV infusion over 30-60 minutes	Day 1	Every 21 days for 3 cycles
Doxorubicin [b]	50 mg/m^2	IV push	Day 1	Every 21 days for 3 cycles
Vincristine [b]	1.4 mg/m^2 (max 2 mg)	IV push or infusion	Day 1	Every 21 days for 3 cycles
Prednisone [b]	100 mg	PO once daily	Days 1-5	Every 21 days for 3 cycles

[a] One cycle = 21 days. Patients who are defined as early stage by CT but advanced by prestudy PET/CT will receive 6 cycles of R-CHOP. For these patients an interim PET/CT will not determine further treatment.

[b] Rituximab and CHOP can be given in any order. If both rituximab and CHOP cannot fit in one day, either rituximab or CHOP can be given on Day 2. Day 1 prednisone may be substituted by a bioequivalent dose of a different corticosteroid.

7.4 FDG-PET/CT Imaging

a. This study requires FDG-PET/CT imaging at diagnosis, after three cycles of R-CHOP chemotherapy, and 12 weeks after last treatment (see Section 7.9a.4). FDG-PET imaging will be used to assess the adequacy of R-CHOP x 3 for each individual patient and to determine whether treatment should be changed due to a suboptimal response to three cycles of R-CHOP. Patients who discontinue treatment early will also be required to have a PET/CT scan 12 weeks after the last treatment.

b. Combined PET/CT scans are required for this study and older "stand-alone" FDG-PET scans are not adequate for entry to this study. **However, it should be noted that low resolution "localization" CT scans performed as part of combined PET/CT scans are NOT adequate for tumor measurements or response determinations and that high resolution, diagnostic quality CT scans must also be performed at study entry and at completion of therapy for all patients.**

7.5 Centralized Review of PET/CT scans at the Imaging and Radiation Oncology Core Rhode Island (IROC RI)

a. To ensure the highest standards and consistency between different centers, **interim** FDG-PET/CT scans must be submitted to IROC RI for centralized review (see Section 15.2). **Response determinations and treatment decisions (e.g. continuation of R-CHOP or switch to IFRT+ Yttrium-90 ibritumomab tiuxetan (Zevalin®)) must be based on the centralized review of the FDG-**

PET scan and NOT on scan assessments by local physicians. The crucial FDG-PET scan conducted after the 3rd cycle of R-CHOP should be performed on Day 15-18 of Cycle 3 (i.e. 14-17 days after Day 1 dose of R-CHOP during Cycle 3).

b. **Centralized review will be performed by a member of a team of PET/CT readers. If an immediate review is needed, please call IROC RI directly at 401/753-7600 and ask for the S1001 Study Manager. All scans will be submitted to IROC RI via AG Mednet (see Section 15.2). IROC RI will assign the scans to the expert reviewers for response determination and then will transmit the results to the SWOG Statistical Center and to the site's primary contact with 72 hours of image receipt (not including weekends).**

The central PET/CT expert review will focus only on the assessment of lymphoma disease sites. This central expert review will NOT provide a comprehensive assessment of the entire PET/CT study and will thus NOT record incidental findings and abnormalities unrelated to lymphoma. Centralized PET/CT is done for the purpose of this trial; it does NOT relieve local PET/CT readers of their responsibility to issue a comprehensive PET/CT report.

c. Further treatment must not be administered until the results of the central review of the interim PET/CT scan are available. Determination of FDG-PET positivity or negativity will be performed using a 5 point scoring system. According to these guidelines, scans will be judged to be positive if lesions are more hypermetabolic than the liver by visual, qualitative inspection.

d. **Absolute and relative standard uptake values (SUVs) will be recorded for research purposes but MUST NOT be used to determine scan positivity because of inter-institution variations in scan performance and the acknowledged lack of standardization for SUV values.** Details of submission of PET/CT scans to IROC RI for centralized review and on the performance and interpretation of PET/CT scans are listed in Section 15.2.

7.6 Patients Upstaged by Baseline FDG-PET scan

Patients found to have advanced stage DLBCL based on local review of the baseline PET scan will receive 6 cycles of R-CHOP. These patients will follow the PET/CT imaging schedule in Section 7.4a, although the interim scan after 3 cycles of R-CHOP will NOT determine subsequent protocol therapy.

The Second Registration and the treatment schedules described below in Sections 7.7 and 7.8 do not apply to these patients.

7.7 Continued R-CHOP Regimen (for PET negative patients only)

After the initial 3 cycles of R-CHOP, if FDG-PET imaging indicates that patient disease is PET negative, then patients will continue treatment with one additional cycle of R-CHOP chemotherapy (a total of 4 cycles). Patients must be planning to begin the fourth cycle of R-CHOP within 35 days of starting Cycle 3 of R-CHOP. R-CHOP will be administered according to the standard dosing regimen as summarized in Section 7.3.

7.8 IFRT Plus Yttrium-90 ibritumomab tiuxetan (Zevalin®) (only for patients who are PET positive)

a. **Radiation Therapy:** Patients should start IFRT as soon as possible after the Day 15-18 PET/CT scan that follows Cycle 3 of R-CHOP, but no later than Day 35 after initiation of Cycle 3 of R-CHOP. Zevalin® treatment should begin 3-6 weeks after Radiation Therapy is completed.

1. General Concepts of Treatment:

Multi-agent chemotherapy is to be relied on to treat potential microscopic disease. Therefore, an involved field approach with irradiation is to be used. Lymph node regions or organs known to have been involved by overt disease prior to initiation of therapy are to be treated. It is therefore **recommended** that the radiation oncologist evaluate the patient prior to the start of chemotherapy, and **required** that the attending radiation oncologist examine the patient prior to initiation of radiation therapy. The radiation oncologist and medical oncologist should then jointly agree on the necessary treatment volume to treat clinically involved lymph node groups or regions. Clinical examination, radiographic evaluation and use of other imaging modalities (i.e., magnetic resonance imaging) are all suitable techniques for assessment of overt disease.

CT-based planning is required on this study. Standard, 3D conformal, or intensity modulated radiation treatment planning may all be used. The choice of treatment technique should depend on the tandem goal of encompassing the involved disease, and the adjacent nodes or tissues that might harbor microscopic disease, while minimizing exposure to critical normal tissues such as lung, heart, kidney, bowel, and spinal cord, and breast in females. **Proton therapy is not allowed on this study.**

A copy of the written radiation therapy consultation note describing the proposed treatment plan (sites of involvement, doses, radiation portals and technical factors) is to be submitted per Section 14.4a.

Since all patients are PET positive, by definition they will be considered to have achieved a partial (PET/CT) response to R-CHOP. A minimum dose of 3,600 cGy should be delivered to the tumor region, and a boost up to 900 cGy is recommended to a maximum dose of 4,500 cGy to residual disease by CT, or positive by PET/CT. Simultaneous boosts are not allowed. The dose fractionation will be 180 cGy per day.

2. Credentialing

Centers participating in this protocol using 3D-CRT are required to complete the 3D Benchmark. Those using IMRT must complete the IMRT Questionnaire and either the IMRT Benchmark or RPC head and neck phantom. Benchmark materials may be obtained from the Imaging and Radiation Oncology Core Rhode Island (IROC RI) (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. Contact the Radiological Physics Center (RPC) at http://rpc.mdanderson.org/rpc for information regarding their IMRT phantoms.

3. Technical Factors:

Beam Energy: Megavoltage equipment is required. Minimal acceptable energy will be 4 MV or greater x-rays. If treatment of lymph node sites located close to the surface of the skin is necessary (i.e., supraclavicular fossa) and beam energies of greater than 8 - 10 MV are to be used, care must be taken (i.e., by use of bolus) so that superficial structures are not under-dosed. For certain sites, electron beams of adequate energy may be appropriate (i.e., pre-auricular region). Electron doses should be calculated at the 90% isodose line.

Treatment Distance: The minimal treatment distance should be 80 cm for either SSD or SAD technique.

4. Target. Volumes

The **Gross Tumor Volume (GTV)** is defined as the initial volume occupied by radiographic or palpable disease. This will include extended nodal volumes within a traditional lymph node compartment.

The **Clinical Target Volume (CTV1)** is the anatomical location of the initially involved lymph nodes or areas of extranodal extension.
The **Clinical Target Volume (CTV2)** is the anatomical location of residual disease by CT, or positive by PET/CT. Areas of concern to the site investigator may be included in this volume.

The **Planning Target Volume (PTV1)** is defined as the margin around the CTV1 to account for patient motion and set-up variability.

The **Planning Target Volume (PTV2)** is defined as the margin around the CTV2 to account for patient motion and set-up variability.

Examples of Target Volumes for Common Sites:

Cervical/Supraclavicular Region
The entire ipsilateral cervical/supraclavicular regions should be treated if disease was present in any part of this region. If the disease extended to the midline, the bilateral cervical/supraclavicular regions should be treated.

Mediastinum/Hilar region
The mediastinal field should encompass the cephalad-caudad extent of disease at diagnosis, but only the lateral extent of residual disease present after the completion of chemotherapy, and should be a shaped field encompassing the mediastinum, with a 1.5 cm margin laterally and extending inferiorly to at least 5 cm below the lower extent of disease atpresentation, and include the bilateral hilar regions. In the event of involvement of the anterior-superior mediastinum, the portal should include the bilateral supraclavicular regions, even if uninvolved, with a superior margin at the level of the superior border of the larynx (if supraclavicular adenopathy was present) or the inferior border of the larynx (if there was no supraclavicular adenopathy). Intrathoracic sites of extralymphatic extension (e.g. lungs, pleura, chest wall, pericardium) should be included as well if these extralymphatic sites of extension were considered to be part of the patient's initial disease. Only the prechemotherapy involved portion of the extralymphatic extension should be treated, using a 1.5 cm margin.

Axillary Region
The ipsilateral axillary, infraclavicular and supraclavicular areas will be treated. The superior border should be at the superior border of the larynx (if supraclavicular adenopathy was present) or the inferior border of the larynx (if there was no supraclavicular adenopathy).

Para-aortic Region
The width of the para-aortic field should conform to the volume necessary to treat residual disease after chemotherapy with 1.0 - 1.5 cm margins. The superior margin will extend to the top of T10. The inferior margin should be at the L4 - L5 interspace.

Pelvis/Groin
When treating groin nodes both femoral and external iliac nodes should be included in the radiation field. Depth of treatment should be tailored to depth of involved nodes as documented on treatment planning CT.

Unusual Sites
Contact Louis Constine, M.D. (louis_constine@urmc.rochester.edu) or at 585/275-5622.

5. Prescribed Dose

The prescribed dose to PTV1 should be 3,600 cGy, delivered with a fractionation of 180 cGy per day. PTV2 will receive an additional dose up to 900 cGy at 180 cGy per day to achieve a total dose to PTV2 of 4140-4,500 cGy. The additional dose to PTV2 may not be delivered as a simultaneous boost.

6. Dose Uniformity

For all treatments, 95% of the protocol dose must cover 100% of the PTV and no more than 10% of the CTV or PTV should receive more than 110% of the protocol dose. Appropriate compensating filters, wedges or boosting/blocking can be performed in order to achieve suggested dose uniformity. For instance, a common situation of dose inhomogeneity is an APPA field arrangement encompassing the neck and mediastinum. Lightly weighted concurrent boost fields (e.g. making use of the independent primary collimators on modern linear accelerators) directed at the inferior portion of the mediastinum may efficiently improve dose homogeneity. With 3D CRT, wedges, compensators, and other methods of generating more uniform dose distributions are encouraged.

7. Heterogeneity Corrections

Calculations that take into account tissue heterogeneities shall be used and the algorithms used for these corrections must be IROC RI-approved. For questions about these approved algorithms, please contact IROC RI (www.QARC.org).

8. Treatment Techniques

Patient Position: Supine throughout is preferable. Generally treat with arms akimbo (hands on hips) or arms at sides. If axillary lymph nodes are involved, positioning with the arms up is also acceptable. Appropriate immobilization devices are highly recommended.
Field Shaping: Use custom shielding with divergent and individually cut blocks or multileaf collimators.

9. Motion Management

Accounting for the effects of respiratory motion is particularly important when IMRT is used. In such cases an assessment should be made to determine the extent of motion present. If the degree of motion is greater than the PTV margin, some form of motion management should be applied.

When IMRT is used, the Motion Management Reporting Form shall be submitted with the Quality Assurance Documentation materials to describe the methods used and evidence of the remaining tumor motion (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT).

10. In-Room Verification of Spatial Positioning

Portal imaging is the most common system used to verify patient position in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal pair (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging.

Treatment position will be verified at least weekly by one of these techniques.

11. Organs at Risk

Spinal Cord: Spinal cord dose is not to exceed 4,500 cGy at 180 cGy per day. Where possible, exclusion of the spinal cord after it has received 4,000 cGy is desirable.

Heart: Maximum dose to the heart is not to exceed 4,000 cGy. When a substantial (> 50%) portion of the heart must be encompassed by treatment fields, the total dose to this volume should be kept less than 3,000 cGy.

Lungs: It is permissible to treat lung volumes proximate to known tumor sites with full radiation doses (i.e., margin of 1 - 2 cm). The volume of lung receiving over 2000 cGy (V20) should be kept to less than 35%.

Small Bowel: Significant volumes of small bowel should not be irradiated to more than 4,000 cGy. Small volumes may be treated to a maximum of 4,500 cGy.

Kidney: It is desirable to maintain renal doses to less than 1,800 cGy where possible. When both kidneys are to be treated, maximum renal dose to one normal kidney is 1,500 cGy.

12. Therapy Interruptions

Should skin or mucosal irritation, myelosuppression, bowel symptoms (i.e., diarrhea) or similar normal tissue difficulty develop, short interruptions in treatment may take place. When possible, these should be limited to less than 1 week; should interruptions of more than 2 weeks be necessary, the patient must be removed from the protocol.

13. Dose Calculation and Reporting

IMRT Dose Verification: If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry.

Critical Organs and DVH's: The maximum dose to the spinal cord shall be calculated and reported on the RT-2 form. Dose volume histograms for all target volumes and organs at risk shall be submitted. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

Digital Data**:** Submission of the treatment plan in digital format is required. Please refer to www.QARC.org under "Digital Data" for guidelines regarding digital submission.

Supportive data and Forms may be submitted in digital format via sFTP along with the Treatment Planning System Output.

b. Yttrium-90 ibritumomab tiuxetan (Zevalin®) Regimen (Zevalin® treatment should begin 3-6 weeks after Radiation Therapy is completed.)

AGENT	DOSE	ROUTE	DAYS
Rituximab	250 mg/m^2	Slow IV	1 then 7, 8, or 9
^{90}Y ibritumomab tiuxetan	See below	10 min IV infusion	7, 8 or 9

1. Yttrium-90 ibritumomab tiuxetan (Zevalin®) should be dosed at 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with platelets counts ≥ 150,000/mm3 and at 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet counts of 100,000 - 149,000/mm3. **The prescribed, measured and administered dose of Yttrium-90 ibritumomab tiuxetan (Zevalin®) must not exceed the absolute maximum allowable dose of 32.0 mCi (1,184 MBq), regardless of the patient's body weight. Do not give Yttrium-90 ibritumomab tiuxetan (Zevalin®) to patients with a platelet count < 100,000/mm3.**

2. Radiation Safety Precautions are minimal: No isolation required, patients should wash their hands thoroughly after urination, and use of a condom is recommended during sexual intercourse to avoid transfer of body fluids.

7.9 Disease Evaluation Off Treatment

a. 12 weeks after the last treatment:

1. Physical examination

2. Laboratory tests: CBC, LDH, and beta-2 microglobulin.

3. Contrast enhanced CT scan of chest, abdomen and pelvis (+ neck, if performed at baseline).

4. FDG-PET/CT scan: Patients that are removed from protocol treatment must receive a PET/CT scan before starting subsequent therapy.

b. Follow Up – see Calendar (Sections 9.2 or 9.3)

1. Clinical trial conduct during COVID-19 pandemic

In order to provide participating sites flexibility in ongoing patient treatment in the current COVID-19 pandemic healthcare environment, utilization of offsite / local healthcare resources for conduct of participant's annual history and physical exam is allowable with appropriate oversight by the Responsible Investigator, and this utilization of local healthcare providers does not need to be documented as being done due to COVID-19 pandemic or other extenuating circumstances. In addition, the following extended window for the annual follow-up visit is allowable per protocol.

The allowable window for the **S1001** annual follow-up visit, including annual laboratory tests and CT scans, is being extended to ± 60 days, where the Responsible Investigator determines that the delayed assessment helps to assure the safety of the patient, with consideration for the COVID-19 and related extenuating circumstances.

The Responsible Investigator's rationale for using the extended window must be documented in the patient chart as resulting from the COVID-19 pandemic or extenuating circumstance. Please note that in the absence of a COVID-19 pandemic-related extenuating circumstance, the allowable best practice window of ± 14 days remains in effect.

7.10 Criteria for Removal from Protocol Treatment

a. Documented progression of disease as defined in Section 10.2d.

b. Development of unacceptable toxicity, as defined in Section 8.0.

c. Treatment delay of over 2 weeks.

d. Completion of protocol treatment.

e. The patient may withdraw from the study at any time for any reason.

7.11 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.12 Follow-Up Period

All patients will be followed for a maximum of seven years from registration or until death whichever occurs first

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 CHOP Dose Modification

a. Blood/Bone Marrow Toxicities: The R-CHOP regimen should be given as described in Section 7.3 if the ANC is > 1,000 cells/mcL and the platelets are > 100,000 cells/mcL by the time the next cycle is due. Re-escalation is at the discretion of the treating physician.

b. Impaired Hepatic Function: All patients with total bilirubin ≤ 2 x the institutional upper limit of normal (IULN) will receive a full initial dose of doxorubicin and vincristine. If the total bilirubin rises to > 2 x the institutional upper limit of normal (but ≤ 5 x IULN), the doxorubicin and vincristine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the total bilirubin is ≤ 2 x the institutional upper limit of normal. If the total bilirubin rises to > 5 x the institutional upper limits of normal, doxorubicin and vincristine should be discontinued for that cycle. If hepatic function has not recovered to ≤ 2 x the institutional upper limits of normal by the time the next cycle is due, then remove patient from protocol treatment. In cases of obstruction of biliary duct by tumor mass, a biliary drainage shunt should be placed prior to chemotherapy.

Total bilirubin	Doxorubicin Dose	Vincristine Dose
≤ 2 x IULN	100%	100%
> 2 - 5 x IULN	50% (of last dose received)	50% (of last dose received)
> 5 x IULN	Discontinue	Discontinue

c. Impaired Renal Function: All patients with serum creatinine levels ≤ 2 x the institutional upper limit of normal will receive full dose of all drugs. If creatinine rises to > 2 x the institutional upper limit of normal, the dose of cyclophosphamide must be reduced by 25% from last dose. Re-escalation is at the discretion of the treating physician if the serum creatinine level drops to ≤ 2 x the institutional upper limit of normal.

d. Cystitis Noninfective: Cyclophosphamide will be discontinued and the patient removed from protocol treatment if Grade 3 or 4 hemorrhagic cystitis resulting from this drug occurs. Adequate fluid intake is recommended during therapy.

e. Peripheral Motor Neuropathy: Patients experiencing Grade 3 vincristine-related neuropathy (e.g., obstipation, weakness) will have the dose of vincristine reduced by 50% for all further cycles of R-CHOP. Patients experiencing Grade 4 vincristine- related neuropathy will have vincristine omitted from all future cycles of R-CHOP.

8.3 Rituximab Dose Modification

a. Infusion reactions: Patients may experience transient fever and chills with infusion of rituximab. If Grade 2 chills (or Grade 2 fever with chills) are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when fever resolves to Grade 2 or less and chills to Grade 1 or less, the infusion should be continued, initially, at half the previous rate. If a Grade 3 or greater allergic reaction occurs, antibody infusion should be interrupted and may be resumed at a 50% reduction in rate when symptoms have completely resolved. Treatment with diphenhydramine and acetaminophen is recommended; additional treatment may be used at the physician's discretion. If a patient experiences a Grade 3 toxicity that persists until the next scheduled infusion, the patient must discontinue treatment until toxicities have resolved to Grade 2 or less.

b. Hepatitis B Reactivation with Related and Other Viral Infections: Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with rituximab. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during rituximab treatment. In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy, and institute appropriate treatment.

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

d. Cardiovascular: Rituximab should be discontinued in the event of a serious or life-threatening cardiac arrhythmia.

e. Renal: Discontinuation of rituximab should be considered for those with rising serum creatinine or oliguria.

8.4 Yttrium-90 ibritumomab tiuxetan (Zevalin®) Dose Modification

a. Serious Infusion Reactions: Rituximab, alone or as a component of the yttrium-90 ibritumomab tiuxetan therapeutic regimen, can cause severe, including fatal, infusion reactions (see Section 8.3a).

b. Prolonged and Severe Cytopenias: Do not give yttrium-90 ibritumomab tiuxetan to patients with a platelet count < 100,000/mm^3. Monitor complete blood counts (CBC) and platelet counts following the yttrium-90 ibritumomab tiuxetan therapeutic regimen weekly until levels recover or as clinically indicated. Do not administer the yttrium-90 ibritumomab tiuxetan therapeutic regimen to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Monitor patients for cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the yttrium-90 ibritumomab tiuxetan therapeutic regimen.

c. Severe Cutaneous and Mucocutaneous Reactions: Discontinue the yttrium-90 ibritumomab tiuxetan therapeutic regimen in patients experiencing a severe cutaneous or mucocutaneous reaction.

8.5 Dose Modification Contacts

For treatment or dose modification-related questions, please contact Dr. Daniel Persky (dpersky@uacc.arizona.edu) at 520/626-8908 or Dr. Louis Constine (louis_constine@urmc.rochester.edu) at 585/275-5622 (for RT related questions).

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI Via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 STEP 1: Cycles 1-3 of R-CHOP and Interim PET/CT

		Cycle 1			Cycle 2			Cycle 3 £		
REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9
PHYSICAL										
History and Physical Exam	X				X			X		
Weight and Performance Status	X				X			X		
Disease Assessment	X									
Toxicity Notation					X			X		
Radiation Oncology Consult (recommended)	X									
LABORATORY										
CBC/Differential/Platelet	X				X			X		
Serum creatinine	X				X			X		
Bilirubin, total	X				X			X		
ALT and AST	X				X			X		
LDH	X									
HBV screening	X									
HCV screening Δ										
Bone marrow asp/biopsy	X									
Materials for pathology review	X									
X-RAYS AND SCANS										
CT chest/abdomen/pelvis	X									
PET/CT	X									X¶
MUGA or 2-d ECHO	X									

Calendar 9.1 continued on next page. (Corresponding footnotes are continued on next page.)

		Cycle 1			Cycle 2			Cycle 3 £		
REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9
SPECIMENS-PATH REVIEW (See Section 12.0)										
Paraffin Block	X									
RESEARCH SPECIMENS (See Section 15.0)										
Paraffin Block ß	X									
Serum ß	X									
TREATMENT (See Section 7.3)^										
Rituximab (Day 1)		X			X			X		
Cyclophosphamide (Day 1)		X			X			X		
Doxorubicin (Day 1)		X			X			X		
Vincristine (Day 1)		X			X			X		
Prednisone (Days 1-5)		X			X			X		

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

Δ Recommended for patients at high risk of HCV infection.

¶ Interim PET/CT must be conducted on Day 15-18 of Cycle 3 (see Section 7.5a). Patients that are NOT upstaged by PET/CT at baseline will register to Step 2.

^ If patient does not continue treatment, then follow up is required (see Section 7.9a).

ß If patient consents to banking specimens, the serum and paraffin block are required.

£ For patients upstaged by PET/CT at baseline, treatment and tests will continue at these intervals until the patient has received 6 cycles of R-CHOP.

9.2 Step 2: Cycle 4 of R-CHOP (Patients that are PET negative.)

Required Studies	Cycle 4				√ Follow-Up	
	Wk 1	Wk 2	Wk 3	12 Weeks Post R-CHOP	Pre-Progression	Post-Progression
PHYSICAL						
History and Physical	X			X	X	X
Weight and Performance Status	X			X	X	X
Disease Assessment				X	X	
Toxicity	X			X		
LABORATORY						
CBC/Differential/Platelets	X			X	X	X
LDH	X			X	X	X
X-RAYS AND SCANS						
CT chest/abdomen/pelvis				X	X	
PET/CT				X		
TREATMENT						
Rituximab (Day 1)	X					
Cyclophosphamide (Day 1)	X					
Doxorubicin (Day 1)	X					
Vincristine (Day 1)	X					
Prednisone (Day 1-5)	X					

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

√ After off-treatment, follow-up exams and tests will be repeated once every 6 months for two years and then annually (±14 days) thereafter for seven years. See also Section 7.9b.1 for extended allowable windows for assessments in the event of a COVID-19 extenuating circumstance.

9.3 STUDY CALENDAR

Step 2: IFRT + Yttrium-90 ibritumomab tiuxetan (Zevalin®) (Patients that are PET positive.)

Required Studies	RT π	Day	Day	Day	12 Weeks Post Ibritumomab Tiuxetan	√ Follow-Up	
		1	4,5,6	7, 8, or 9		Pre-Progression	Post-Progression
PHYSICAL							
History and Physical					X	X	X
Weight and Performance Status					X	X	X
Disease Assessment					X	X	
Toxicity		X		X	X		
LABORATORY							
CBC/Differential/Platelets	X				X	X	X
LDH	X				X	X	X
X-RAYS AND SCANS							
CT chest/abdomen/pelvis					X	X	
PET-CT					X		
TREATMENT							
Radiation Therapy	X						
Yttrium-90 Ibritumomab Tiuxetan				X			
Rituximab		X		X			

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

√ After off-treatment, follow-up exams and tests will be repeated once every 6 months for two years and then annually (±14 days) thereafter for seven years. See also Section 7.9b.1 for extended allowable windows for assessments in the event of a COVID-19 extenuating circumstance.

π Zevalin® treatment should begin 3-6 weeks after Radiation Therapy is completed.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of Lesions

a. **Measurable Disease**: Lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray, or other conventional technique and have a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease. **Note:** PET/CT scans are insufficient for evaluation of measurable disease.

b. **Non-measurable Disease**: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by CT or disease documented only by PET/CT imaging or indirect evidence (e.g., lab values).

10.2 Objective Disease Status

Objective status is to be recorded at each evaluation according to the 2007 revised Cheson et al. criteria. *(5)* All measurable lesions up to a maximum of 6 lesions (largest) should be identified as target lesions at baseline. If there are more than 6 measurable lesions the remaining will be identified as non-target lesions and included as non-measurable disease. The 6 lesions should be selected according to the following features: they should be from disparate regions of the body as possible and they should include mediastinal and retroperitoneal areas of disease if these sites have measurable lesions. Measurements must be provided for target lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease with the exception of the following. In patients with a positive PET/CT scan before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. If the PET/CT scan was negative before therapy, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses > 1 cm and ≤ 1.5 cm in GTD and > 1 cm in their short axis before treatment must have regressed to ≤ 1 cm in their short axis. No new lymphoma lesions should be visible on PET/CT scan or by any other imaging studies. The spleen and/or liver, if considered enlarged at baseline based on physical examination or imaging study (other than PET/CT), must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at same site. Normalization of markers (e.g., LDH) definitely assignable to NHL. Tumor measurements must be obtained by an imaging modality other than PET/CT. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies to patients with at least one lesion that does not qualify for a CR. For patients with measurable disease, ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to six dominant lesions identified at baseline. No new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by ≥ 50% in SPD. In patients with a positive PET/CT scan before therapy, PET/CT should be positive in at least one previously involved site. Tumor measurements must be obtained by an imaging modality other than PET/CT. All disease must be assessed using the same technique as baseline. **Note:** Patients who meet all other criteria, but have new lesions observed on PET/CT scan only (i.e., not confirmed on CT or other imaging studies), are considered partial responders.

c. **Stable Disease (SD)**: Does not qualify for CR, PR, or Relapsed/Progressive Disease. Tumor measurements must be obtained by an imaging modality other than PET/CT. Persistent abnormalities seen on CT scans must be FDG-avid on PET/CT scans. All disease must be assessed using the same technique as baseline.

d. **Relapsed Disease (after CR)/Progressive Disease (after PR, SD)**: At least 50% increase in the SPD of target measurable nodal lesions over the smallest sum observed (over baseline if no decrease during therapy), or ≥ 50% increase in the GTD of any node > 1 cm in shortest axis, or ≥ 50% increase in the SPD of other target measurable lesions (e.g., splenic or hepatic nodules) over the smallest sum observed. Appearance of any new bone marrow involvement. Appearance of any new lesion > 1.5 cm in longest axis, or ≥ 50% increase in GTD of any previously involved node with a diameter ≤ 1 cm in the short axis such that its longest axis is now > 1.5 cm. Lymph nodes should be considered abnormal for relapse or progressive disease only if the long axis is > 1.5 cm, or if both the long and short axes are > 1 cm. In patients with a positive PET/CT scan before therapy, lesions should be PET positive. Tumor measurements must be obtained by an imaging modality other than PET/CT. All disease must be assessed using the same technique as baseline. **Note:** Appearance of any new lesion on PET/CT alone (not confirmed by CT or other imaging modality) is NOT considered relapse/progression.

10.3 Best Response

a. CR: One objective status of CR documented before relapse.

c. PR: One objective status of PR documented before progression but not qualifying as a CR.

d. Stable: At least one objective status of stable disease documented at least 6 weeks after registration, not qualifying as anything else above.

e. Increasing Disease: Objective status of progression within 12 weeks of registration not qualifying as anything else above.

f. Inadequate assessment, response unknown: Progression greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod performance status scale:

GRADE

0	Fully active; able to carry on all pre-disease activities without restriction.
1	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	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From date of registration to date of first observation of progressive disease (as defined in 10.2d), or death due to any cause. Patients last known to be alive without report of progression or relapse are censored at date of last contact.

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Eligibility Rate

Assuming an ineligibility rate of 10%, there is anticipation to accrue a total of 155 patients in order to obtain 140 eligible patients. Assuming that 15% of eligible patients will have been upstaged at baseline by PET/CT, approximately 120 patients will receive therapy directed by the results of PET/CT imaging after 3 cycles of R-CHOP. Thirty of these patients are anticipated to be PET-positive, assuming a PET-positive rate of 25%. If the actual rate of PET-positivity is less than 25%, accrual will continue until 30 PET-positive patients have been accrued. Accrual to SWOG's most recent first line limited stage DLBCL trial **S0014** was approximately 4 patients per month. Thus, accrual is anticipated to take approximately 39 months. Based on interest from the leadership of the ECOG-ACRIN and Alliance lymphoma committees, there is the potential for intergroup participation, which could reduce accrual time to approximately 2 years.

11.2 Accrual Goals

We plan to accrue 140 eligible patients, which is sufficient to estimate the 5-year PFS rate (given complete follow-up) to within 6% (95% confidence interval). Historical 5-year PFS estimate of 85% in this patient population against an alternative hypothesis of 93% will be tested. Consideration of an observed 5-year PFS estimate of 90% or greater to indicate further investigation of this PET-directed therapy is warranted. Using an exact binomial test, this design has a Type I error of .057 and 93% power. Note that this nonparametric binomial test is preferred, since such a low event rate means that even minor deviations from an exponential survival distribution can have a large effect on Type I and Type II error rates.

Since all patients with limited stage disease based on CT imaging (including those upstaged by PET/CT imaging) will be included in this study, it is expected that the distribution of stage-modified IPI risk factors in this population will be consistent with that observed in previous studies. The historical rate and target for 5-year PFS are based upon the assumption that the breakdown in stage-modified IPI will be according to the table below.

To address any differences between the distribution of stage-modified IPI risk factors observed in this study and the historical data, the test against the hypothesized historical rate will be adjusted based on the observed stage-modified IPI frequency in the study population.

Stage-Modified IPI Risk Factors	Percentage of Study Population	Estimated 5-Year PFS
0	30%	95%
1-2	65%	82%
3-4	5%	60%

11.3 PFS Estimation

Estimation of PFS within the PET-positive and PET-negative subgroups will be done. With 35 patients in the PET-positive subgroup, an estimation of the 5-year PFS rate (given complete follow-up) to within 17% (95% confidence interval) will be possible. With 105 patients in the PET-negative subgroup, the estimation of the 5-year PFS rate (given complete follow-up) to within at worst 5% (95% confidence interval), given the true PFS rate is greater than 90%, although when binomial probabilities are this extreme, the confidence intervals about them are highly asymmetric. Due to the lack of adequate historical data among PET-positive and PET-negative patients, no formal hypothesis testing will be conducted within either of these subgroups.

11.4 Upstaged patients

The subgroup of patients who are upstaged by PET/CT imaging at baseline will be described. Both the fraction of patients in this study population who are upstaged and clinical outcomes within this subgroup will be of interest, although if the fraction is approximately 10-15% as expected, then these analyses will be largely descriptive in nature due to limited numbers.

11.5 Feasibility

The feasibility of registering patients to PET-directed therapy will be monitored at the statistical center. If, among the first 40 patients registered to this study, fewer than 80% complete 3 cycles of R-CHOP and then continue on PET-directed therapy per Section 7.0, then protocol accrual will be held and consideration will be given to protocol modifications.

11.6 Analysis of early progression in PET-negative patients

Data on early progressions among PET-negative patients will be analyzed at the statistical center. If the 1-year PFS rate among the first 20 eligible PET-negative patients is less than 85% (17/20), then protocol accrual will be held and consideration will be given to protocol modifications. Similar steps will be taken if the 1-year PFS rate among the first 30 eligible PET-negative patients is less than 87% (26 /30), or if among the first 40 it is less than 88% (35/40). Monitoring will continue beyond this point, although assuming a monthly accrual rate of 4 patients, accrual is expected to be nearly completed by the time the first 40 eligible patients are analyzed. Simulation studies show that this procedure does not appreciably affect the overall power of the study.

11.7 Gene expression analysis

If adequate tissue is received from 80% of patients, then gene expression signatures (GCB vs stromal-1 vs stromal-2) on 112 eligible patients would be available for analysis. If, for example, 70% of patients show the GCB phenotype, then, assuming 5-year PFS of 85% and 3.3 years of accrual, the power for a one-sided 0.10 level logrank test is approximately 90% to detect a hazard ratio of 3.0 with respect to PFS between GCB and

non-GCB patients, corresponding to 90% and 73% 5-year PFS in GCB and non-GCB patients, respectively. If 50% of patients show the GCB phenotype, then the power of this test is approximately 84%. If outcomes are better than this, then power will be more limited.

11.8 Data and Safety Monitoring Committee

There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

All patients registered to this study will undergo pathology review. The purpose of this review is to verify the histologic diagnosis.

a. Pathology materials collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/members/clinicaltrials/specimens/lymphpath.asp).

b. Failure to submit a registered patient's pathology materials for pathology will make the patient ineligible.

12.2 Radiation Therapy Review

Rapid Review: It is recommended that cases be submitted for review before the start of treatment. Submission within 7 days of the onset of radiotherapy is acceptable if pre-treatment review is not possible.
Submit the following data for rapid review:

Treatment Planning System Output

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. When using IMRT, orthogonal isocenter images are sufficient.
- Isodose distributions (in absolute dose preferred) for the composite treatment plan in the axial, sagittal and coronal planes at the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method (if normalized isodoses are sent) must be clearly indicated.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Beams-eye-view (BEV) of portals showing collimator, beam aperture, target volume and critical structures.

Digital Data:

- Submission of the treatment plan in digital format is required. Please refer to www.QARC.org under "Digital Data" for guidelines regarding digital submission.
- Supportive data and Forms may be submitted in digital format via sFTP along with the Treatment Planning System Output.

Supportive Data:

- Copies and reports of CT scans, PET/CT scans, and other diagnostic determinations used for the planning target volumes. This includes the studies done prior to treatment (pre-chemotherapy) and those done prior to radiotherapy (post-chemotherapy).
- Copies of verification images for each field.
- Documentation of an independent check of the calculated dose when IMRT is used.

Forms:

- RT-1/IMRT Dosimetry Summary Form.
- Motion Management Reporting Form, if IMRT is used for tumors of the thorax.

Within 1 week of the completion of radiotherapy, the following data shall be submitted for all patients :

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

Electronic submission via sFTP for all data is preferred. Alternatively the supportive data and forms may be sent to:

Imaging and Radiation Oncology Core Rhode Island
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: 401/753-7600
Fax: 401/753-7601

Dosimetry and Physics Question should be directed to:
IROC RI Protocol Dosimetrist
Imaging and Radiation Oncology Core Rhode Island
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: 401/753-7600
Fax: 401/753-7601

Questions regarding the radiotherapy section of this protocol should be directed to:

Louis S. Constine, M.D.
Phone: 585/275-5622
E-Mail: louis_constine@urmc.rochester.edu

12.3 Definitions of Deviations in Protocol Performance

Prescription Dose

Minor Deviation: The prescribed dose differs from that in the protocol by between 6% and 10%.
Major Deviation: The prescribed dose differs from that in the protocol by more than 10%.

Dose Uniformity

Minor Deviation: More than 10% of PTV1 (or PTV2, if used) receives more than 120% of the protocol-specified dose or 95% of the protocol-specified dose covers less than 95% but more than 90% of the respective PTV.
Major Deviation: More than 25% of PTV1 (or PTV2, if used) receives more than 120% of the protocol-specified dose or 95% of the protocol-specified dose covers less than 90% of the respective PTV.

Critical Organ

Minor Deviation: The maximum dose to any point on the spinal cord is > 45 Gy but <50 Gy. The lung V20 is > 35 Gy.
Major Deviation: The maximum dose to any point on the spinal cord is > 50 Gy. The lung V20 > 40%.

Volume

Tight Volumes
Minor Deviation: Field margins are less than the protocol-specified margin.
Major Deviation: Field margins shield, miss, or transect target volumes.
Excessive Volumes
Minor Deviation: Field margins are 1-3 cm beyond protocol-specified margins.
Major Deviation: Field margins are >3 cm beyond protocol-specified margins.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigational/Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data includes the SWOG patient number, study ID, and patient initials.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF INITIAL REGISTRATION:

Submit a copy of the following:

S1001 Prestudy Form

Lymphoma Baseline Tumor Assessment Form

Pathology report confirming histology and documentation of CD20 expression.

Radiation Oncology Consult (if already performed)

Radiology reports for both diagnostic CT and PET/CT (submit by FAX per Section 14.3b)

Baseline PET/CT scan submission per Section 15.2

b. WITHIN 28 DAYS OF REGISTRATION:

Submit histopathologic materials along with a copy of the pathology report to the SWOG Lymphoma Repository (see Section 12.1).

Submit materials as outlined in Section 15.1.

c. WITHIN 7 DAYS AFTER THE END OF EACH CYCLE OF R-CHOP TREATMENT:

Submit the **S1001** Chemotherapy Treatment Form and the **S1001** Adverse Event Form.

d. AFTER INTERIM FDG-PET SCANNING:

See Sections 15.2 and 18.1 for instructions on submission of PET/CT data to IROC RI. Also fax the FDG-PET scan reports as outlined in Section 14.3b.

e. WITHIN 7 DAYS AFTER REGISTRATION TO STEP 2 (PET POSITIVE PATIENTS ONLY):

Submit Radiation Oncology Consult, if not already submitted after initial registration.

f. WITHIN SEVEN DAYS OF COMPLETION OF RADIATION THERAPY:

Submit a copy of the following:

1. Materials as specified in Section 12.2 directly to IROC RI at the address in Section 12.2.

2. **S1001** Checklist for Submission of Radiation Oncology Assurance Materials. This is available on the IROC RI website at www.qarc.org.

g. AFTER IFRT + YTTRIUM-90 IBRITUMOMAB TIUXETAN (ZEVALIN®) TREATMENT:

Submit **S1001** Radioimmunotherapy Treatment Form and the **S1001** Adverse Event Form.

h. WITHIN 14 DAYS OF REMOVAL FROM PROTOCOL TREATMENT:

Submit the Off Treatment Notice.

i. THREE MONTHS AFTER OFF TREATMENT:

Submit the **S1001** Adverse Event Form.

j. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of the **S1001** Adverse Event Form, the **S1001** Chemotherapy Treatment Form (if the patient was still on R-CHOP treatment), the S1001 Radioimmunotherapy Treatment Form (if the patient was still on IFRT + Yttrium-90 ibritumomab tiuxetan (Zevalin®) and the Follow-Up Form documenting date, site, and method for determining progression/relapse

k. WITHIN 14 DAYS OF EACH DISEASE ASSESSMENT UNTIL PROGRESSION:

Submit the following:

1. Lymphoma Follow-Up Tumor Assessment Form.

2. Radiology reports from all scans performed to assess disease.

m. AFTER PROTOCOL TREATMENT: EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL 7 YEARS AFTER REGISTRATION:

Submit the Follow-Up Form.

n. WITHIN FOUR WEEKS OF KNOWLEDGE OF SUBSEQUENT MALIGNANCY:

Submit the Notice of Second Malignancy documenting date, site, and method for determining malignancy.

o. WITHIN FOUR WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Correlative Studies and Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) within 28 days after registration:

a. Submission of specimens is required, if the patient consents to the submission of specimens, at the following times (see Section 9.1)
   - Paraffin block or slides at baseline
   - Serum at baseline

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/LymSpecimens.asp), or via the link on the **S1001** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.2 Instructions for Electronic Submission of Digital PET/CT Image Scans via AG Mednet

FDG-PET/CT scans must be submitted electronically via the AG Mednet service provided by SWOG as described below and in Appendices 18.1-18.3. (Please note that while AG Mednet service is provided by SWOG, SWOG will not be responsible for the cost. Specific information about the imaging workflow and instructions can be found at http://www.agmednet.

a. Electronic Submission Set-Up

Upon IRB approval, you can begin the process to use the AG Mednet Desktop Agent. To request access, email agmednetadmin@swog.org and provide the following information:

- Contact Name
- Email Address
- Phone Number
- Site Name
- Site Number (optional)
- Address
- Trial Name
- Trial ID
- Date

b. **Registration via the AG Mednet Portal**

1. If your site is qualified to participate in the trial, the SWOG Trial Administrator will invite you to the trial via the AG Mednet Portal. When you are added, you will receive a welcome email notification prompting you to register in the portal:

   https://portal.agmednet.net

2. Complete the 3 pages of registration information. This includes creating your own username and password and a challenge question and answer.

3. When you are finished with registration, the portal will display a "Registration Complete" page. At this point you now have access to the trial. After you download the Desktop Agent, you will be able to login with your new username and password. You will also receive a registration confirmation email notification.

c. **Download the Desktop Agent and Login**

All participating sites need to download the AG Mednet Desktop Agent. The AG Mednet Desktop Agent can be accessed from a networked PC with *Java 6 plug-in* installed. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 6 installed. If you do not have Java 6 installed, downloading the Desktop Agent automatically downloads Java 6.

1. Launch your web browser and type in the following URL. This will download the AG Mednet Desktop Agent to your system:

   https://portal.agmednet.net/Desktop-Agent

2. Type in your user name and password.

3. Click "Launch"

   NOTE: This will place an icon on your desktop so, for future submissions, you can click on the "AG Mednet" icon, and it will automatically launch and request your user name and password when clicked.

d. **Submission (DICOM Exam)**

1. Click on the tab "DICOM Import" (top of screen)

2. For CD/DVD, load a disc into your machine

3. A normal directory tree will be visible (close any DICOM viewers that may pop-up). Select the location of your DICOM files (i.e., the CD/DVD drive) or your PACS server. (NOTE: if sending from a PACS or Modality, use the DICOM Query or DICOM Receive Tab. Further details are available in the user guide on the Welcome Tab)

4. Find the time-point you wish to submit and select the "DICOMDIR" file and click "Import Exam." Click "Close" when complete*

5. Click the "Exam List" tab (top of screen)

6. Select the exam you want to submit from "Available Exams" by clicking on a row within the table. In the image preview, you will see a picture of the data selected. Please check this is what you intend to submit. If not, select a different exam or go back to step A or E and select a different exam from the exam list.

7. In "Available Tasks for Selected Exam" (bottom left of screen), click "Assign Exam to Trial." In pop-up box, select **S1001** from drop-down list and click "Assign Trial."

8. In "Available Tasks for Selected Exam" (bottom left of screen), click "De-identification" and click "Do Task."

9. In the pop-up box, click into the first blank cell under “De-identified Value.” Follow the on screen guidance and enter required data. Then click the next blank cell below the first and repeat until all blank cells are populated. As you complete these cells, the red cross will turn into blue checks. If a red cross remains after data has been entered, please check that the data is correct and change if applicable.

10. Click out of the cells and click “De-identify” (bottom of pop-up). AG Mednet will then remove any personal patient information from the DICOM metadata fields and replace this information with the study-specific data you entered in the table. Click close when complete.

11. In “Available Tasks for Selected Exam” (bottom left of screen), click “Transmittal Form” and click “Do Task.” The Data Transmittal Form will open. Complete all mandatory fields according to the study protocol. If you attempt to save the form without completing all mandatory fields, an alert will appear, prompting you to complete the remaining fields. If you want to print the form, click the “Print” button prior to saving. When the form is complete, click the “Save” button.

12. In “Available Tasks for Selected Exam” (bottom left of screen), click “Upload Exam” and click “Do Task.”

13. Data will now be transmitted. Upload time is variable (depending on network connection and the size and number of images), but AG Mednet can be left running in the background and the computer used for other work. Once the data has been transmitted, a message will pop-up and AG Mednet can be closed.

14. You can import new exams and process them during the upload.

15. After 15 minutes of inactivity, the Desktop Agent will lock out. However, this does not interfere with the upload. You only need to log back in if you want to import another exam.

*In most cases, a DICOMDIR file will be generated by scanners. However, if this is not the case, please select “All Files” from the drop-down box at the bottom of the “DICOM Import” screen. Data can then be selected manually from the directory tree and “Import Exam” clicked. The process is then the same as where a DICOMDIR file exists.

Note: The person responsible for activating the desktop agent should be involved in submitting the exams as the Desktop Agent requires specific log-in verification. All questions regarding AG Mednet use should be directed to 888-9AGMEDNET, and hit 2 for the support option.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.5 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at: http://ctepcancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must also be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if online CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog, before preparing the report.

Table 16.1: Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210/614-0006.

f. Reporting Pregnancy, Fetal Death, and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions SOC.**

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 FDG-PET Imaging Methods

18.2 Imaging Site Personnel Form

18.3 Acquisition Data for FDG-PET/CT Scan

18.4 Drug Ordering Forms

a. Zevalin and Radioisotope Ordering Instructions for Zevalin Clinical Trials

b. Site Questionnaire for Zevalin Administration

18.5 Determination of Expedited Adverse Event Reporting Requirements

18.1 FDG-PET Imaging Methods

FDG-PET/CT scans with ^{18}Fluorine- fluorodeoxyglucose (FDG) will be performed at baseline, after 3 cycles of R-CHOP chemotherapy, and at completion of chemotherapy.

Response determinations and treatment decisions for this protocol will be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians.

Baseline PET/CT scan:
All patients should have a pre-treatment FDG-PET/CT scan as a baseline to compare with subsequent scans to assess response. This should be performed no more than 28 days before registration. The baseline scan must be submitted within 24 hours upon image acquisition to IROC RI at study entry to assure that the submitted scan is of adequate quality for review before treatment decisions are required. IROC RI will confirm the receipt of the baseline scan data to the site within 24 hours and send a Quality Check Report within 1-3 business days. If the baseline scan data is non-compliant, as determined by one of the PET/CT expert readers, the submitting site will be notified of this decision and will be asked to rectify all non-compliant issues when the interim response scan is obtained. Non-compliant baseline scans will not disqualify patient participation in this trial, because it is only the interim scan that determines patient management. However, compliance with study requirements is strongly encouraged for the baseline scan. IROC RI will notify the SWOG Statistical Center and the sites primary contact of this decision, point out the specific issues of non-compliance, and advise the participating site regarding how to rectify this when the interim scan is obtained.

Interim Response PET/CT scan:
To assess the response to the first three cycles of R-CHOP chemotherapy, an interim PET/CT scan will be performed on Day 15-18 of Cycle 3 of R-CHOP chemotherapy (i.e. 14-17 days after the Day 1 administration of the R-CHOP drugs). Scan data must be submitted within 24 hours upon image acquisition to IROC RI for real-time centralized review to determine next treatment. This second PET/CT scan should have been scheduled at the time of starting Cycle 3 of R-CHOP treatment, to ensure appropriate timing and availability of response scans. The PET/CT images need to be electronically uploaded to IROC RI on the day of examination (no later than 24 hours after scanning) via AG Mednet service (see Section 15.2 for submission instructions). IROC RI will assign the scans to the expert reviewers for response determination and then will transmit the results to the SWOG statistical center and to the sites primary contact via an email from the S1001@QARC.org email address within 72 hours of image receipt (not including weekends or holidays).

Please see the table below delineating the acceptable days in which the Cycle 3 PET/CT scan can be scheduled. Depending on what day of the week the **third** cycle of R-CHOP was started, the table indicates the days in which the post-cycle 3 PET/CT has to be completed. The days in which scans can be completed appear shaded. Scans must be scheduled according to this table in order to provide IROC RI the PET/CT images to perform a central review and return findings in sufficient time to begin Day 1 of the determined treatment. This table is based on a 72-hour turnaround from the time of image receipt at IROC RI.

		SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	*SU*	*M*	*TU*	*W*	*TH*	*F*	*SA*
Cycle 3 start	**Sunday**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*	*7*
	Monday		1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*
	Tuesday			1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*
	Wednesday				1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*
	Thursday					1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*
	Friday						1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*	*2*
	Saturday							1	2	3	4	5	6	7	8	9	10	11	12	13	14	**15**	**16**	**17**	**18**	19	20	21	22	23	24	25	26	27	28	*1*

Final Response Assessment scan:
To assess the final response after completion of all therapy, patients should have repeat whole body PET/CT scans and diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (and neck, if done at baseline), 12 weeks after completion of the last treatment. The final response scan must be submitted within 72 hours upon image acquisition to IROC RI. IROC RI will transmit the scan data to the SWOG Statistical Center.

Scanning Facilities

- Only full-ring dedicated PET/CT scanners are acceptable. The CT of the PET/CT is used for attenuation correction of PET/CT data and anatomic localization. CT settings should follow institutional guidelines (usually 120-140kV, at least 60mA).

- A documented daily quality control procedure must be in place and records kept.

- Scans must be sent by electronic data transfer via AG Mednet service to IROC RI. For further information on transfer of imaging data to IROC RI, see Section 15.2.

Scanning Protocol

Patient preparation
Non-diabetic patients should fast for at least 4 hours prior to the scan. Plain (unflavored water) should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetic patients should ideally be given a morning appointment. They should take their usual antidiabetic medication (oral or insulin) and eat a light meal (lighter than they normally would) on that morning. The time interval between that morning meal and PET/CT scan should be approximately 3-4 hours.

Blood glucose of all patients should be measured on arrival and consideration given to rescheduling when the blood glucose level is higher than 200 mg/dl. Insulin should not be administered to reduce glucose level when the blood glucose is > 200 mg/dl at the time of arrival in the PET/CT clinic.

Oral diazepam may be given if desired to reduce brown fat uptake one hour prior to tracer injection.

Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) may be administered, according to institutional guidelines. Intravenous contrast may also be administered, provided this is done in a technique that avoids deterioration of the CT images by streak artifacts from high-concentration iv. contrast bolus.

Detailed scanning protocol

1. Administer 260 - 555 MBq (7-15mCi) ^{18}F- FDG
2. Emission part of the scan should start no earlier than 60 and no later than 80 minutes after injection.
3. The exact same period of uptake must be used for staging and response scans – within 15 minutes.
4. Perform attenuation corrected 'half-body' PET-CT scan to cover the area from the base of the skull to mid-thigh. This should be done with the arms above the head.
5. Perform a separate head and neck scan, with arms down, ONLY IF this is the only site of disease.
6. Attenuation correction of PET/CT emission data will be based on the low dose CT from the PET/CT.
7. It is critical that follow-up PET/CT scans be performed in an identical way to the baseline scan, with the same PET/CT scanner, same scan direction (skull to thighs or thighs the skull), and consistent arm positioning (arms up or arms down).

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed.

Information to be recorded and transferred for each patient:
For each patient, study data acquisition information and patient information must be recorded on the **Acquisition Data for FDG-PET/CT Scan** form (see Appendix 18.2) and submitted to IROC RI. Image data must be transferred to IROC RI at the same time as the completed **Acquisition Data for FDG-PET/CT Scan** form. For further information on transfer of imaging data to IROC RI, see Section 15.2.

The following image files are required:
- Attenuation corrected half body images (skull base to mid thigh)
- Non-attenuation corrected half body images
- Half body CT scan
- Attenuation corrected view of head and neck (if performed)
- Non-attenuation corrected view of head and neck (if performed)
- Head and neck CT scan (if performed)
  Projection images (MIPs) are not required

See Section 15.2 image submission instructions for central review.

Reporting
PET/CT scans will be reviewed and scored by a member of a team of expert PET/CT readers who are blinded to the patient's clinical status. Visual interpretation will be used. A local report may also be issued but it is the score from the central review that will be used to determine subsequent treatment for trial purposes.

The PET/CT response scans will be scored with reference to sites of presumed lymphomatous involvement on the PET/CT staging scan

Negative
1 no uptake
2 uptake ≤ mediastinum
3 uptake > mediastinum but ≤ liver
Positive

4 uptake > liver in some sites even if uptake ≤ liver or mediastinum at other sites
5 uptake > liver in over 90% of sites or development of new uptake consistent with progressive disease

For the purpose of this study, Scores 1, 2, 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as 'negative' for disease and scores 4, 5 with uptake greater than liver will be regarded as 'positive' for disease. A separate analysis will be performed on patients with a score of 3 whose scan findings are analogous to the concept of 'minimal residual disease' (MRD) referred to in earlier published data on the use of PET/CT in lymphoma. However for the purposes of treatment, patients with a score of 3 on the interim PET/CT scan will be regarded as negative for disease.

Standard uptake values (SUVs) will be used to quantify tracer uptake, and response to therapy will be determined by the change in SUV for scans acquired before and after therapy. The change in SUV will be correlated with actual prognosis to test the possibility of defining "quantitative response categories" which may have prognostic value. SUV numbers will be used in a post hoc analysis and the most appropriate measure to be used will be determined. The use of SUVmax and variations of SUVmax will be used in this analysis.

SUVs will be measured either by using a volumetric region of interest (ROI) that clearly encompasses a given lesion (carefully avoiding areas of higher normal activity in the vicinity, such as kidneys or bladder), or with a circular ROI. If a circular ROI is used, this needs to be done in several slices to assure that the recorded SUV is indeed the highest SUV within a given lesion. SUV max will be reported, normalized to body weight. A total of 6 lesions will be measured in this protocol.

Radiation Dosimetry

The whole body dose for FDG is about 0.10 rad/mCi, and the effective dose equivalent about 0.10 rem/mCi (0.03 mSv/MBq). For the suggested activity range of 7-15 mCi, the effective dose equivalent will be 0.7-1.5 rem (7.8 – 16.6 mSv). (ARSAC Notes for Guidance 2006). The target organ is the urinary bladder wall, which will receive 0.22 rad/mCi with a realistic one hour voiding interval (ICRP Publication 53). The dose from a low dose (140 kV, 80mA) CT as part of a PET/CT is about 0.9 rad (rem) or 9 mSv (Wu et al. Eur J Nucl Med Mol Imaging 31:38-43, 2004).

SUV Analysis

The study will rely on visual interpretation only. However data will be collected for post hoc analysis to determine whether visual interpretation can be refined and semi-quantitative measures used to subgroup patients further into 'tighter' quantitative response categories which may have prognostic value. A scheme for analysis of semi-quantitative data is suggested below.

The 'hottest' lesions at staging will be chosen for SUV analysis but if subsequently the response scan shows residual activity at sites different from the 'hottest' lesions at staging, these sites will be used as the index lesions instead. Uptake in up to 6 lesions will be documented. The maximum SUV within the lesion will be calculated using decay corrected administered dose and body weight. The maximum SUV will be selected using a region of interest placed on the axial PET/CT slice with the highest uptake. The maximum CT diameter of the mass will be recorded on the axial slice with the greatest CT diameter. Note the PET/CT and CT axial slices may not match as the maximum SUV may occur within the lesion in a different axial plane to the maximum size on CT. If this occurs and the entire lesion shows at least some degree of FDG uptake, the maximum CT diameter in transaxial dimension should be recorded. However, if only a section of a large residual mass shows residual FDG uptake on the interim scan, then the CT diameter should be measured on the slice where that residual FDG uptake occurs.

18.2 Imaging Site Personnel Form

Responsible CRA Contact Complete Address E-mail Phone Number Fax Number	**Diagnostic Imaging Department Contact** Complete Address E-mail Phone Number Fax Number

Please provide the information requested above. Provide the middle initial for individuals who commonly use them. Also, please add or correct the degree/title as necessary. This information will be retained by IROC RI.

Once completed, you may **fax or e-mail this form to:**

Imaging and Radiation Oncology Core Rhode Island
ATTN: **S1001**
FAX: 401/753-7601
E-MAIL: S1001@QARC.org

Call the IROC RI **S1001** Study Manager at 401/753-7600 with any questions.

Thank you for your assistance.

18.3 Acquisition Data for FDG-PET/CT Scan

ACQUISITION DATA FOR FDG-PET/CT SCAN
(to be completed by PET/CT scanning facility)

PET-CT Scan acquired at ……

Patient's initials: ……

Patient's SWOG number: ……

Referring Consultant: ……

Consultant telephone number: ……

Consultant fax number: ……

Hospital name and address: ……

Date of PET/CT scan: ……

Time of administration of activity (hour:min) ……

Activity at time of administration (MBq) ……

Site of tracer administration and state left or right ……

Patient height (cm) ……

Patient weight (kg) ……

Patient fasting state (time last ate) ……

Patient blood glucose ……

Daily quality control result for the day of the scan……..

Any deviations from the previously forwarded protocol?.....

If yes, please specify ……

	START TIME	NO OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
Skull Base - Thighs				
HEAD & NECK SCAN (if acquired)				

RESULT OF INTERIM PET-CT SCAN **(AFTER CYCLE 3) according to 5 point scale:**

1: no uptake
2: uptake ≤ mediastinum
3: uptake > mediastinum but ≤ liver
4: uptake > liver at some sites even if uptake ≤ liver or mediastinum at other sites
5: uptake > liver in > 90% of initial sites or development of new sites consistent with progressive disease

Local Report

Score 1 2 3 4 5 (please circle)

List sites of residual uptake (score 4 and 5):……

……

Comments e.g. positive sites elsewhere in the body:……

Name:……
Date:……

Signature:……..

WHEN COMPLETED, SEND BOTH SHEETS WITH IMAGE DATA FILES (SEE PROTOCOL) TO IROC RI AND RETAIN FIRST COPY FOR FDG-PET/CT CENTER RECORDS

Imaging and Radiation Oncology Core Rhode Island
Attn: **S1001**
FAX: 401/753-7601
E-mail: S1001@QARC.org

18.4 Drug Ordering Forms

a. Zevalin and Radioisotope Ordering Instructions for Zevalin Clinical Trials

ZEVALIN & RADIOISOTOPE ORDERING INSTRUCTIONS FOR ZEVALIN CLINICAL TRIALS

I. Radioactive Materials License

Prior to initiating the study at your site the supplier must be in possession of the study site's radioactive materials license (RML) and tax ID number. If your site has previously enrolled patients in a Zevalin study, the RML and tax ID information for your institution has already been submitted to the isotope suppliers.

II. Placing Orders

Step 1. SITE

- When a patient is scheduled for treatment, the study site will complete the Site Questionnaire form and send to Spectrum Pharmaceuticals by e-mail (zevalinsupport@sppirx.com) or fax (877-264-8483).
- Spectrum will contact site to confirm appropriate training and ordering procedures.
- Spectrum will provide each site with a Zevalin Order Worksheet.
- Site will complete the Zevalin Order Worksheet for each patient treatment, and fax form to their radiolabeling pharmacy.
- The order should be placed no later than the Thursday prior to the week of ^{111}In scheduled therapy date.

Step 2. Radiolabeling Pharmacy

- The radiolabeling pharmacy will fax or e-mail the Zevalin Order Worksheet to Spectrum Pharmaceuticals (E-mail: zevalinsupport@sppirx.com or fax (877-264-8483).

Step 3. Zevalin Support Services

- Spectrum will process the ^{111}In, ^{90}Y and Zevalin Kit orders and ship to the radiolabeling pharmacy.
- The radiolabeling pharmacy will compound the product and deliver to the nuclear medicine department of the study site.
- Spectrum will fax or e-mail shipment confirmation to the radiolabeling pharmacy and the site requestor.

III. Radiopharmacy/Customer Service –

The Radiopharmacy and the Customer Service group will then coordinate getting the Zevalin kits and radioisotopes to the radiopharmacy and then to the sites for patient administration.

18.4b. Site Questionnaire for Zevalin Administration

This questionnaire is meant to establish which SWOG sites are set up to administer Zevalin and what specific training each site needs from Spectrum. It will also confirm to Spectrum where and to whom antibody and isotope will be sent when patient is scheduled.

SITE NAME: _____

ADDRESS (street, city, state, zip): _____

1. Is your site licensed (radioactive materials license), trained and able to administer Zevalin? YES ☐ NO ☐
2. Has your site administered Zevalin? YES ☐ NO ☐ If yes, date _____
3. Does your site need initial/refresher training on Zevalin administration? YES ☐ NO ☐
4. Name of physician who will administer Zevalin: _____

   FAX: _____ Phone: _____ E-mail: _____

   Nuclear Medicine ☐ Radiation Oncologist ☐
5. Name of the nuclear medicine department contact person (i.e., Manager, Lead Technologist, etc.):

   _____

   Address: _____ Fax: _____ Phone: _____
6. Name of the commercial Nuclear Pharmacy: _____
7. Name of commercial Nuclear Pharmacy Contact Person: _____ E-mail: _____

   Address: _____ Fax: _____ Phone: _____
8. Name of Site Study Coordinator Contact Person :_____ E-mail: _____

Please complete the Site Questionnaire and send to Spectrum Pharmaceuticals by e-mail (zevalinsupport@sppirx.com) or Fax (877-264-8483). A Spectrum representative will be in touch with you to confirm order procedures and assure all relevant staff have been appropriately trained in administration of Zevalin.

18.5 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

Informed Consent Model for S1001

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

- This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

  Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	___ (targeted above 55)
Flesch-Kincaid Grade Level	___ (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the Principal Investigator of a cancer treatment trial is a physician. If this model is used for a trial in which the Principal Investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://pubs.cancer.gov/ncipl/details.aspx?prodid= P105* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy. *(3/12/14)*
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

  *NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://pubs.cancer.gov/ncipl/details.aspx?prodid= P105* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy. *(3/12/14)*
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S1001, "A Phase II Trial of PET-Directed Therapy for Limited Stage Diffuse Large B-Cell Lymphoma (DLBCL)"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a kind of cancer called non-Hodgkin lymphoma called Diffuse Large B Cell Lymphoma (DLBCL) that is considered limited.

Why is this study being done?

Limited (or early) Stage Diffuse Large B-cell Lymphoma is curable in many people, but some still relapse, and some develop side-effects after this treatment. *(sentence added 9/30/11)* **This study uses a radiologic test called PET/CT scan to determine treatment after initial doses of a standard chemotherapy called "R-CHOP" (the drugs doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab). Although all of the agents used in this study are FDA approved, the purpose of the study is to give more intensive treatment to patients whose PET/CT scan shows that they are at a greater chance of still having active lymphoma, and to give less intensive treatment to patients whose PET/CT scan shows that they have a smaller chance of still having active lymphoma. In this way, we hope to improve the cure rate for all patients while decreasing the side effects of the treatment.**

Researchers would also like to request the leftover tissue from your original biopsy to study the biology of stage I/II Diffuse Large B-cell lymphoma. You will also have the option to submit blood samples for research purposes only. This will be explained later in this consent form.

How many people will take part in the study?

About 155 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment including a PET/CT scan and a CT scan of the chest, abdomen, and pelvis.
- Routine laboratory blood tests (to measure your kidney and liver function and to test for hepatitis B virus [HBV]) *(updated 3/12/14)*
- You will get an ECHO and/or a MUGA scan to test your heart function. *(added 3/12/14)*
- You will also have your bone marrow examined (called "bone marrow aspiration and biopsy") at the start of this study. Your skin over your hipbone will be numbed by a shot of local anesthetic (lidocaine) given just under your skin. A needle will be inserted through the numbed skin and into the hipbone. The bone marrow will be removed by using suction and a twisting motion of the needle. You may have minor discomfort, and minor infection is also possible. Sometimes allergic reactions to the anesthetic may occur. The bone marrow will be looked at to find out if any lymphoma cells are present, and to determine the status of normal blood cells.
- Your initial biopsy sample will be sent to our pathology laboratory to confirm your diagnosis.

During the study…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine blood tests (or any tests your doctor thinks are needed to ensure your safety): Before each cycle of treatment, at follow up visits, and at your doctor's discretion.
- Disease Assessment (including full body PET/CT scans, CT scans of the chest, abdomen and pelvis: After Cycle 3 of R-CHOP chemotherapy (PET/CT scan only) AND 12 weeks after the last cycle of chemotherapy (both PET/CT and CT scans).

- Once you are registered to the study, you will begin treatment with a standard combination of chemotherapy drugs called "R-CHOP." The drug combination includes: doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab. The doxorubicin, cyclophosphamide, vincristine, and rituximab will be given to you through a needle in your vein on Day 1 of a 21 day cycle. The first cycle would take about 8 hours, but the other cycles could be given as fast as 4 hours. You will initially be given 3 cycles of this drug combination. You will also take the drug prednisone by mouth (pills) on Days 1-5, of the cycle.

- Standard medications will be used to help prevent side effects, such as nausea, fevers, and allergic reactions. Some of these medications do not require a prescription, and are commonly used during R-CHOP therapy. In all cases, your physician will provide detailed instructions and information regarding these treatments.

After completing three cycles of R-CHOP chemotherapy, you will have a full body PET/CT scan to determine if your lymphoma is still active. If the review of your PET/CT scan shows that your disease is likely inactive, then you will receive an additional cycle of R-CHOP for consolidation. If the review of your PET/CT scan shows that your disease may still be active, then you will receive radiation therapy to areas of your body involved by lymphoma, followed by a drug regimen called Yttrium-90 ibritumomab tiuxetan (Zevalin®).

How long will I be in the study?

Following the completion of this experimental study, your doctor will continue to follow your health status every 6 months for 2 years, and then every year for a maximum of 7 years from the time you entered the study. The follow-up evaluation tests that are standard to cancer care will include a medical history, physical examination, and performance status.

The researcher may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the experimental treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the completion of this experimental treatment. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the R-CHOP combination chemotherapy (doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab) include: *(section updated 3/12/14)*

.

COMMON, SOME MAY BE SERIOUS In 100 people receiving R-CHOP, more than 20 and up to 100 may have:
• Nausea/vomiting, loss of appetite, constipation • Chills, fever • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Numbness and tingling of the arms and legs • Tiredness, weakness and difficulty walking • Hair loss • Sores in the mouth • Absence of menstrual period which may decrease the ability to have children • Blood in urine and/or red colored urine, saliva or sweat • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Headache, jaw pain and/or muscle pain and/or belly pain • Increased appetite and weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving R-CHOP, from 4 to 20 may have:
• Anemia which may require blood transfusions and cause tiredness • Bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in the eye, throat or stomach • A tear or hole in the stomach that may require surgery • Diarrhea, heartburn • Hepatitis which may cause yellow eyes and skin • Dizziness • Cough, stuffy nose, hoarseness • Increased sweating • Organ damage which may cause infection, bleeding, may require transfusions, joint pain and loss of motion, dialysis • Scarring of the lungs • Blockage of internal organs which may cause shortness of breath, wheezing and vomiting • Itching, rash, blisters on skin

OCCASIONAL, SOME MAY BE SERIOUS (contd.) In 100 people receiving R-CHOP, from 4 to 20 may have:
• **Low blood pressure which may cause feeling faint** • **Loss or absence of sperm which may lead to an inability to father children** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Fluid around the heart** • **Cancer of the bone marrow (leukemia) caused by chemotherapy** • **Loss of nails, darkening of the nail beds or skin or hands and feet** • **Cloudiness of the eye, visual disturbances, drooping eyelids** • **Non-healing wound** • **Diabetes, kidney stones**

RARE, AND SERIOUS In 100 people receiving R-CHOP, 3 or fewer may have:
• **Heart stops beating** • **Seizure**

Risks and side effects related to involved field radiation therapy are standard and should be discussed with your physician. *(9/30/11)*

Risks and side effects related to the Yttrium-90 ibritumomab tiuxetan include: *(section updated 3/12/14)*

COMMON, SOME MAY BE SERIOUS In 100 people receiving Yttrium-90 ibritumomab tiuxetan, more than 20 and up to 100 may have:
• **Fatigue** • **Chills** • **Nausea** • **Bone marrow suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, cells that line the mouth, stomach and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells) and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to anemia, an increased risk of bleeding and infection. Should these effects occur, they can be treated with blood products (transfusions), growth factors (drugs that stimulate the bone marrow) and antibiotics.**

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Yttrium-90, from 4 to 20 may have:

- **Fever**
- **Infections**
- **Flushing and/or sweating**
- **Abdominal pain or enlargement**
- **Diarrhea and/or constipation**
- **Swelling of soft tissues due to allergic reaction**
- **Runny nose**
- **Fast heart rate**
- **Low blood pressure**
- **Shortness of breath, coughing, wheezing**
- **Insomnia (inability to or difficulty in falling asleep)**
- **Dizziness**
- **Headache**
- **Nose bleeds, or bleeding from the stomach or intestines**
- **Soreness/ulcers in mouth and throat: Temporary irritation to the mouth and the lining of the gastrointestinal track may lead to mouth ulcers (similar to canker sores). Anesthetic medications may ease the mouth discomfort.**
- **Skin rash/redness/itching**
- **Weight gain**
- **Bruising or bleeding into the skin**
- **Loss of appetite**
- **Dehydration/dry mouth**
- **Heartburn and/or vomiting**
- **Swelling of the extremities (feet, legs, hands, arms, etc.)**
- **Anxiety and depression**
- **Numbness or tingling in the fingers or toes**
- **Muscle aches or joint aches**
- **Pain such as in back, bladder, bone, chest, neck or tumor pain**

RARE, AND SERIOUS
In 100 people receiving Yttrium-90, 3 or fewer may have:

- **Severe rash involving mucous membranes and skin. Rarely, these reactions could be fatal**

<u>Reproductive risks</u>: You should not get pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that using PET/CT scans to tailor treatment after 3 cycles of R-CHOP will be more effective at treating the cancer compared to the usual treatment, there is no proof of this yet. We hope the information learned from this study will benefit other patients with DLBCL in the future. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Your local Institutional Review Board (IRB)
- The National Cancer Institute (NCI);
- The Food and Drug Administration (FDA), involved in keeping research safe for people;
- Imaging and Radiation Oncology Core Rhode Island (IROC RI): a central review center helping to review the PET/CT scan results to confirm your response to treatment. *(Revised 3/12/14)*
- A qualified representative of AG Mednet (the company providing image transfer of PET/CT scans)
- SWOG
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials.
- Spectrum Pharmaceuticals

(following 2 paragraphs added 3/12/14)
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drugs will be *(provided free of charge/charged in the usual way).* The parts of the research consisting of keeping research records and collecting and storing research specimens for both current and future studies will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

The doxorubicin, rituximab, vincristine, cyclophosphamide, and prednisone are commercially available. Spectrum Pharmaceuticals, Inc., will provide you with the yttrium-90 ibritumomab tiuxetan (Zevalin®) free of charge for this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide. *(updated 3/12/14)* You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This following section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

1. Future Contact

Occasionally, researchers working with SWOG may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact.

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

Consent Form for Use of Specimens for Research

About Using Specimens for Research

Note to sites: This section refers to the tissue and serum submission described in Section 15.1 of the protocol. Sites are required to offer patients the opportunity to consent to this.

If you agree below, part of your original tumor biopsy and a small amount of your blood (a couple of teaspoonfuls) will be sent to a central lab to be used for testing as described below.

We would like to keep some of the specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens are not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens and will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While SWOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

(following two paragraphs added 3/12/14)

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, the Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens (leftover tissue or blood) may be kept for use in research to learn about, prevent, treat, or cure cancer.**

   Yes No

2. **My specimens (leftover tissue or blood) may be kept for use in research to learn about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant (or legally authorized representative) _____
(updated 3/12/14)

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, the Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).