

SOUTHWEST ONCOLOGY GROUP

A PHASE II STUDY OF IODINE-131-LABELED TOSITUMOMAB IN COMBINATION WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCERISTINE, PREDNISONE AND RITUXIMAB THERAPY FOR PATIENTS WITH ADVANCED STAGE FOLLICULAR NON-HODGKIN'S LYMPHOMA

	<u>Page</u>
SCHEMA.....	2
1.0 OBJECTIVES.....	3
2.0 BACKGROUND	3
3.0 DRUG INFORMATION	6
4.0 STAGING CRITERIA	20
5.0 ELIGIBILITY CRITERIA	21
6.0 STRATIFICATION FACTORS	23
7.0 TREATMENT PLAN.....	23
8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS	30
9.0 STUDY CALENDAR	34
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS	35
11.0 STATISTICAL CONSIDERATIONS.....	37
12.0 DISCIPLINE REVIEW.....	37
13.0 REGISTRATION GUIDELINES	38
14.0 DATA SUBMISSION SCHEDULE	40
15.0 SPECIAL INSTRUCTIONS.....	42
16.0 ETHICAL AND REGULATORY CONSIDERATIONS.....	44
17.0 BIBLIOGRAPHY	47
18.0 MASTER FORMS SET	48
19.0 APPENDIX	89

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

STUDY COORDINATORS:

Principal Investigator

Paul M. Barr, M.D. (Medical Oncology)
University of Rochester
James P. Wilmot Cancer Center
601 Elmwood Avenue, Box 704
Rochester, NY 14642
Phone: 585/273-3258
E-mail: paul_barr@urmc.rochester.edu

Jonathan W. Friedberg, M.D. (Medical Oncology)
James P. Wilmot Cancer Center
University of Rochester
601 Elmwood Avenue, Box 704
Rochester, NY 14642
Phone: 585/273-4150
Fax: 585/276-0337
E-mail: Jonathan_Friedberg@urmc.rochester.edu

Oliver W. Press, M.D. (Medical Oncology)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, D3-190
Seattle, WA 98109
Phone: 206/667-1872
Fax: 206/667-1874
Email: press@u.washington.edu

AGENTS:

Cyclophosphamide (Cytoxin®) (NSC-26271)
Doxorubicin (NSC-123127)
Iodine-131-labeled Murine Monoclonal
Tositumomab Antibody (NSC-715813)
Prednisone (NSC-10023)
Rituximab Chimeric Monoclonal anti-CD20
Antibody (IDE-C2B8) (NSC-687451)
Vincristine (Oncovin) (NSC-67574)

BIOSTATISTICIANS:

Michael LeBlanc, Ph.D. (Biostatistics)
Hongli Li, M.S. (Biostatistics)
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
Fax: 206/667-4408
Email: mleblanc@fhcrc.org
Email: hongli@fhcrc.org

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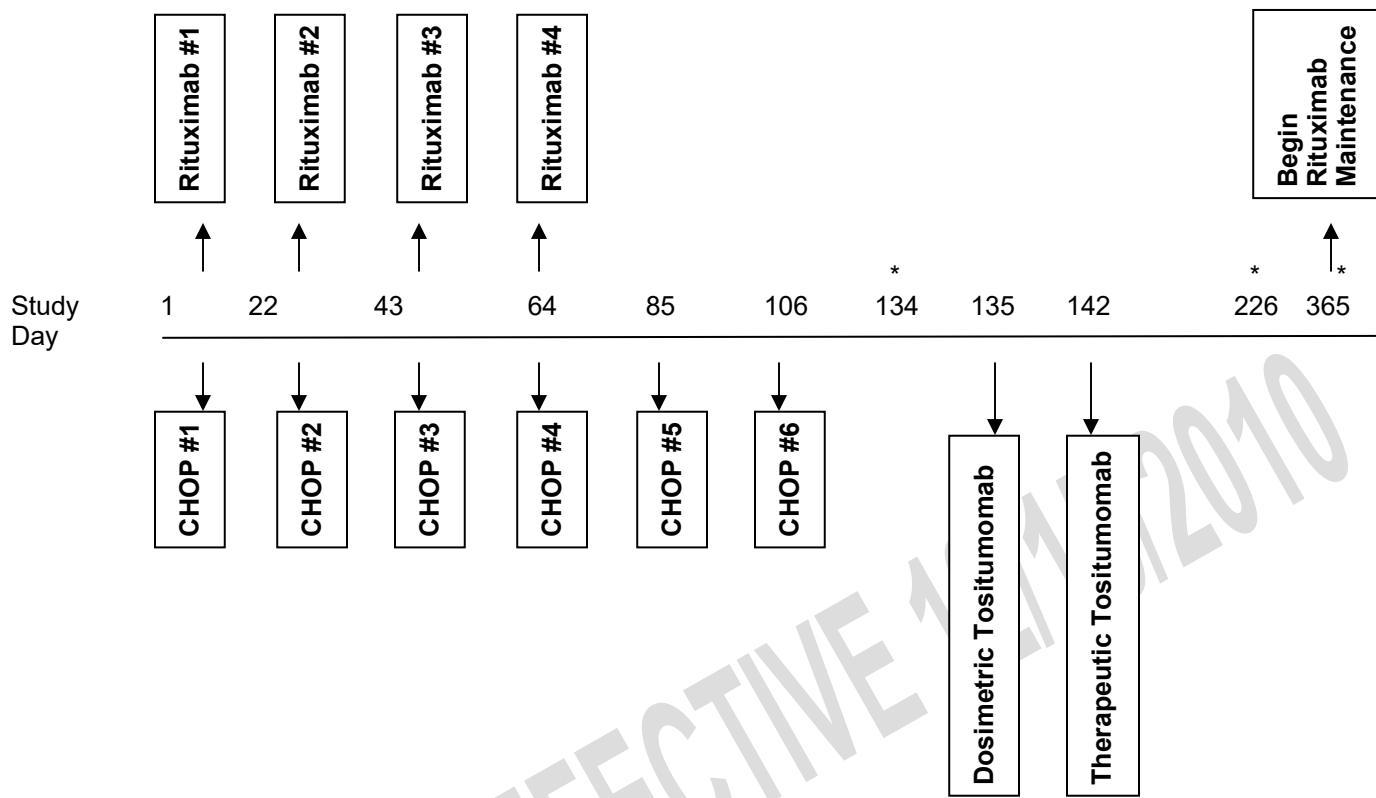


STUDY COORDINATORS (contd):

Lisa M. Rimsza, M.D. (Pathology)
Arizona Cancer Center
1501 N. Campbell Avenue, Room 5208, Box 245043
Tucson, AZ 85724-5043
Phone: 520/626-8396
Fax: 520/626-6081
E-mail: lrimsza@email.arizona.edu

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SCHEMA



* Restaging

1.0 OBJECTIVES

- 1.1 To evaluate response rate and toxicity in patients with advanced stage follicular NHL treated with R-CHOP + I-131 tositumomab with rituximab maintenance.
- 1.2 To estimate the 3-year progression-free survival rate for patients with advanced stage follicular NHL treated with R-CHOP + I-131 tositumomab with rituximab maintenance.
- 1.3 To estimate the 5-year progression-free and overall survival rate for this regimen.
- 1.4 To assess the safety profile of rituximab maintenance following the R-CHOP + I-131 tositumomab regimen.
- 1.5 To bank serum and tissue specimens for future correlative studies.

2.0 BACKGROUND

Introduction: Follicular NHL

Non-Hodgkin's lymphoma is the fifth most common cancer in the U.S., and is significantly increasing in incidence. The National Cancer Institute estimates that over 60,000 new cases of NHL will be diagnosed in the U.S. this year, and the second most common histology is follicular lymphoma. (1) More than 90% of all cases of NHL are of B-cell derivation.

Historically, advanced stage follicular lymphoma has been considered an incurable disease with standard therapeutic approaches. Significant improvements in overall survival have been reported recently when monoclonal antibodies directed against CD20 have been included in treatment programs. Sequential trials conducted since 1980 in the Southwest Oncology Group have demonstrated significant improvements in both failure-free and overall survival in the most recent therapeutic era (**S9800 and S9911**). (2) Thus, the most important advance in the treatment of follicular lymphoma over the past 30 years has been the incorporation of monoclonal antibodies into the therapeutic regimens.

Monoclonal Antibody Therapy

RITUXAN® (Rituximab, BiogenIdec, Cambridge, MA, and Genentech Inc., South San Francisco, CA) is a chimeric anti-CD20 monoclonal antibody with murine variable regions and human IgG kappa constant regions. A pivotal trial of rituximab, 375 mg/m²/week x 4 weeks, in 166 patients with relapsed or refractory follicular or low-grade lymphoma, showed overall response rate of 48%, with 6% complete responses. (3) Adverse events were brief in this trial and usually related to the initial infusion although subsequent studies have documented rare occurrences of hepatitis B reactivation with fulminant hepatitis, hepatic failure, or death. Only one patient developed an anti-chimeric antibody response. This promising response rate, along with in vitro data that suggests a chemo-sensitizing effect of the antibody, led to interest in combining rituximab with chemotherapy in indolent histologies. The majority of patients received rituximab in combination with chemotherapy in subsequent trials.

The choice of a chemotherapy regimen for such a study is controversial, since no regimen has demonstrated clear superiority over any other. Although a strong case can be made for using chlorambucil or CVP as the "standard" regimen for indolent NHL, CHOP was chosen for this trial for several compelling reasons. First, the use of a moderately aggressive regimen such as CHOP is considered most likely to produce a state of minimal tumor burden, which is considered the ideal setting for immunotherapies. (Antibody molecules are large proteins which penetrate large tumor masses poorly. Furthermore, theoretical models suggest that the maximal crossfire from radiolabeled antibodies occurs when cell clusters are less than 1 mm in diameter). Second, other adjuvant immunotherapies such as interferon-alpha have been shown to produce an

advantage in terms of progression-free or overall survival only in studies using aggressive chemotherapy regimens such as CHOP and not when combined with regimens such as chlorambucil or CVP. Finally, randomized studies suggest that combining rituximab with CHOP chemotherapy has significant benefit in follicular lymphoma. (4) The addition of rituximab to CHOP clearly provides for improved response rates and prolonged PFS compared to CHOP alone. However, in follow-up it does not appear that R-CHOP is curative, thus further improvements are needed in therapy of follicular lymphoma.

Clinical Studies with Radioimmunoconjugates

An alternative approach to enhance the efficacy of anti-CD20 antibodies involves conjugating them to cytotoxic radionuclides, which can then be selectively targeted to B lymphoid tumors. Study RIT-I-000 was the initial Phase I/II, open-label study of non-myeloablative doses of Iodine-131 tositumomab antibody for the treatment of patients with B-cell NHL of all histologic types. (5) Fifty-nine patients were enrolled. Twenty-eight patients had low-grade NHL, 14 had transformed low-grade NHL, 15 had intermediate-grade NHL, and 2 had high-grade NHL. Patients received 1 - 3 dosimetric doses followed by a therapeutic dose. The dosimetric dose(s) involved the IV administration of 5 mCi of Iodine-131 tositumomab antibody to determine the rate of whole body clearance so that a whole body radiation dose (cGy) could be calculated. Each dosimetric dose was preceded by 0, 95, or 475 mg of unlabeled antibody. Therapeutic dose-escalation was initiated at 25 cGy and adjusted in 10 cGy increments until the maximum tolerated dose (MTD) was reached. Fifty-three of the 59 patients received a therapeutic dose. The MTD was 75 cGy for patients who had not undergone BMT. A response was observed in 42/59 (71%) patients and a complete response (CR) was observed in 20/59 (34%) patients. The median duration of response was 271 days (95% confidence interval: 140 - 394 days) and median duration of CR was 566 days (95% confidence interval: 385 days to upper limit not reached). The dose-limiting toxicity was hematologic; three patients developed a platelet count < 10,000 cells/mm³ and two patients had an ANC < 100 cells/mm³. The most prevalent non-hematologic toxicities were transient, mild to moderate fever, nausea, asthenia, and chills. Nine of 59 (15%) patients developed human anti-murine antibodies (HAMA).

Study RIT-II-001 was a Phase II, multicenter, open-label study of non-myeloablative doses of Iodine-131 tositumomab antibody for the treatment of patients with low-grade B-cell lymphomas and transformed low-grade lymphomas. (6) Thirty-seven patients had low-grade NHL and 10 had transformed low-grade NHL. The median time from diagnosis was 41 months, the median number of prior therapies was 4, 91% had Stage III or IV disease, 44% had bulky disease, 44% had an elevated LDH. Patients received 1 dosimetric dose followed by a therapeutic dose. The dosimetric dose involved the IV administration of 450 mg of unlabeled antibody and 35 mg (5 mCi) of Iodine-131 tositumomab antibody to determine the rate of whole body clearance so that whole body radiation dose (cGy) could be calculated. The therapeutic dose involved IV administration of 450 mg of unlabeled antibody and 35 mg of Iodine-131 tositumomab antibody with radioactive Iodine-131 titrated to deliver 75 cGy. A response was observed in 27/47 (57%) patients and a complete response (CR) was observed in 14/47 (30%) patients. A response was observed in 6/10 (60%) patients and a CR was observed in 5/10 (50%) patients with transformed low-grade NHL. The dose-limiting toxicity was hematologic; 5 patients developed a platelet count < 10,000 cells/mm³ and, mild to moderate asthenia, nausea and fever. Only 1 of 46 (2%) patients developed HAMA following treatment as assessed by centralized validated HAMA assay.

A Phase III randomized study compared yttrium-90 ibritumomab tiuxetan radioimmunotherapy (another radioimmunoconjugate) with rituximab in 143 patients with relapsed or refractory low-grade, follicular, or transformed CD20 (+) NHL. (7) The overall response rate was 80% for the yttrium-90 ibritumomab tiuxetan group versus 56% for the rituximab group, which reached statistical significance. Complete response rates were 30% and 16% in the yttrium-90 ibritumomab tiuxetan and rituximab groups, respectively. However, there was no statistically significant benefit in response duration or survival between the two groups. This is the first randomized, controlled trial demonstrating unequivocally that a radiolabeled antibody produces

higher overall and complete response rates than the corresponding unlabeled antibody. Whether the higher response rates with radiolabeled antibodies will translate into longer overall survival will require longer follow-up.

As with rituximab, there is considerable interest in combining these radioimmunoconjugates with conventional chemotherapy as definitive treatment for de novo disease. Concurrent administration of cytotoxic chemotherapy and radioimmunoconjugates is not possible because both produce myelosuppression. **S9911** was a Phase II pilot study (n=90) in indolent lymphoma studying the feasibility and toxicity of CHOP followed by the I-131 tositumomab regimen in previously untreated patients with follicular NHL. (8) The overall response rate to the entire treatment regimen (chemotherapy + iodine-131 tositumomab) was 90%, including 67% complete remissions. Importantly, this trial demonstrated the safety of this regimen in a group of patients with a median age of patients of 50 years, and a range of 23 to 84 years. The two-year progression free survival was estimated to be 81%, which is better than observed historically with CHOP alone, or CHOP with rituximab, in patients with follicular NHL.

In **S9911**, 2% of patients were not able to receive iodine-131 tositumomab because of inadequate response to chemotherapy. Additionally, most of the responses after chemotherapy were partial responses. Since that trial was conducted, several randomized trials have demonstrated superior response rates, and improved CR rates, when rituximab is added to the chemotherapy regimen. Thus, we hypothesize that administering rituximab with CHOP chemotherapy, prior to iodine-131 tositumomab, will result in better tumor responses prior to iodine-131 tositumomab consolidation likely leading to an improved therapeutic outcome.

There is now growing experience giving CD20 targeted radioimmunotherapy after a rituximab regimen. Preliminary results of a British multicenter Phase II trial to evaluate the efficacy and safety of ⁹⁰Y ibritumomab tiuxetan in elderly pts with histologically confirmed first relapsed or primary refractory DLBCL not appropriate for autologous stem cell transplantation included 28 patients who had previously been treated with rituximab containing chemotherapy programs. Thirty-seven percent of these 28 patients were refractory to CHOP-rituximab, and the overall response rate was 19% for this group. There was no suggestion of increased toxicities despite receiving radioimmunotherapy within 6 weeks of CHOP-rituximab. (9) **S0433** is an ongoing Phase II trial in patients with diffuse large B-cell lymphoma evaluating the safety and efficacy of R-CHOP followed by Iodine-131 tositumomab. Twenty-nine patients have been enrolled thus far, without evidence of increased toxicities following Iodine-131 tositumomab therapy. Finally, preliminary results of a trial utilizing ibritumomab tiuxetan consolidation following standard chemotherapy in patients with newly diagnosed follicular lymphoma suggest a benefit to radioimmunotherapy consolidation. (10)

Several randomized studies support the role of "maintenance" rituximab (given on a schedule) in improving failure-free survival, and potentially overall survival, following chemotherapy in the de novo setting, and rituximab-chemotherapy combination treatment in the relapsed setting. **S0801** hypothesizes that rituximab maintenance will prolong failure-free survival after R-CHOP + iodine-131 tositumomab therapy. Rituximab maintenance after chemotherapy alone provides significant benefit as far as progression-free survival; and borderline overall survival benefit. There are two studies that suggest a benefit to rituximab maintenance after R-chemotherapy in the relapsed setting. Forstpointner randomized patients to rituximab maintenance vs. observation following R-FCM chemotherapy. (11) The response duration was significantly prolonged by R-maintenance after R-FCM. Van Oers and colleagues initially randomized patients with relapsed follicular lymphoma to CHOP vs. R-CHOP, and then performed a secondary randomization in responding patients to rituximab maintenance vs. observation. (12) Improved PFS was found utilizing maintenance therapy both after induction with CHOP and R-CHOP. Rituximab maintenance also improved overall survival from second randomization: 85% at 3 years versus 77% with observation. The survival benefit is only of borderline significance in patients who were treated with R-CHOP.

Current protocol

Therefore, this trial will build upon the promising results observed in **S9911**, and upon the aforementioned randomized trials, in a rational, incremental way. Treatment will be in three parts: *induction* with CHOP and rituximab therapy; *consolidation* with iodine-131 tositumomab, and *maintenance* with rituximab. It is hoped this strategy will further improve overall survival for patients with follicular NHL.

As we have demonstrated safety in our pilot study, **S9911**, and ongoing **S0433**, I-131-tositumomab will be given sequentially approximately four weeks after the last cycle of CHOP chemotherapy. We will omit rituximab from the last two cycles of CHOP chemotherapy as we have demonstrated safety of that regimen in **S0433**.

Patients known to be HIV-positive are not eligible for this study because the severely depressed immune system and poor bone marrow reserve found in HIV-infected patients, as well as the possibility of premature death, would compromise study objectives.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects.

3.0 DRUG INFORMATION

3.1 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis (2-chloroethyl) amino] tetrahydro-2H-1, 3,2-oxazaphosphorine 2-oxide monohydrate. 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 alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system. With the combination therapy the most frequent adverse event observed to date is neutropenia. Prophylactic G-CSF for subsequent cycles has been necessary. Dose reductions have been necessary for neutropenia and mucositis. For further details, refer to Section 2.0, Background.

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. 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. The occurrence of acute leukemia has

been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy. The occurrence of acute leukemia has been reported in patients treated with anthracycline/alkylator combination chemotherapy.

For prescribing information and a comprehensive list of adverse events associated with cyclophosphamide, refer to the drug package insert.

c. PHARMACOLOGY

Pharmacokinetics: 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: The drug should be diluted in about 150 cc of normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity.

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

3.2 Doxorubicin (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 nail beds 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

Pharmacokinetics: 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 150 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 the third party. This drug will not be supplied by the NCI.

3.3 Iodine-131-labeled Murine Monoclonal Tositumomab Antibody (NSC-715813)

a. DESCRIPTION

Tositumomab Antibody/Iodine-131 Tositumomab Antibody

Tositumomab Antibody is an IgG2a Kappa (murine) monoclonal antibody that binds to the CD20 antigen on the surface of the normal and malignant human B cells to induce apoptosis and mediate antibody-dependent cellular cytotoxicity. Iodine-131 tositumomab Antibody is the radionuclide-labeled monoclonal antibody that can recognize tumor-associated antigens to selectively target radioactivity to tumor cells. By using isotopes emitting beta particles to label this antibody, the radiation emitted from the radiolabeled antibody bound to a tumor cell also kills neighboring cells because the path length of beta particles can extend over several cell diameters. This crossfire of beta particles can destroy antigen-positive and -negative tumor cells, as well as untargeted antigen-positive

tumor cells within a tumor. Iodine-131 tositumomab Antibody, used in conjunction with Tositumomab Antibody, is a radioimmunotherapeutic agent being studied for the treatment of non-Hodgkin's lymphoma and other CD20-expressing B-cell malignancies.

b. TOXICOLOGY

Human Toxicology: Unlabeled tositumomab antibody and Iodine-131 tositumomab antibody infusions are approved by the FDA in non-myeloablative doses for the treatment of non-Hodgkin's lymphoma. The infusions are accompanied by few or no adverse experiences in most patients. The most frequent non-hematologic adverse experience reported was a transient mild to moderate flu-like syndrome consisting of fever (39%), and chills (19%). Other adverse experiences commonly reported include nausea (39%), asthenia (36%), headache (23%), rash (18%), anorexia (16%), infection (16%), pain (16%), myalgia (16%), arthralgia (14%), pruritus (14%), abdominal pain (13%), vomiting (13%), pharyngitis (11%), diarrhea (10%), and increased cough (10%). The concomitant administration of SSKI or other oral iodine product may contribute to the nausea and other gastrointestinal adverse experiences. Only 3% and 4% of patients experienced an adverse experience which required an adjustment to the rate of infusion during the administration of the dosimetric and therapeutic doses, respectively.

Bone marrow suppression is the dose-limiting toxicity and a total body dose of 75 cGy was determined to be the maximum tolerated dose for a non-myeloablative regimen in patients previously treated with chemotherapy. An absolute neutrophil count (ANC) of < 100 cells/mm³ has occurred in 3% of patients, and an ANC of < 1,000 cells/mm³ has occurred in 47% of patients. A platelet count of < 10,000 cells/mm³ has occurred in 5% of patients, and a platelet count of < 50,000 cells/mm³ has occurred in 37% of patients. A hemoglobin of < 6.5 g/dL has occurred in 4% of patients, and a hemoglobin of < 8.0 g/dL has occurred in 12% of patients. A white blood cell count of < 2,000 cells/mm³ has occurred in 41% of patients. The median nadirs were 62,000 cells/mm³ for platelet count, 1,000 cells/mm³ for ANC, and 11.1 gm/dL for hemoglobin. Blood count nadirs (which occur approximately 4 to 6 weeks after therapy) were higher and the time to recovery shorter in patients who were less heavily pretreated. The need for hematologic supportive care, which included transfusions and colony stimulating factors and were used at the discretion of the investigators, ranged from 0% in previously untreated patients to 24% in patients having received 4 or more prior therapies and was 18% overall. The frequency of HAMA-positivity was related to the extent of prior therapy; 38% in previously untreated patients versus 4% in previously treated patients (≥ 1 prior therapies). Thyroid function has been followed long-term and elevated thyroid stimulating hormone has been noted in 5 out of 106 (4%) of patients. Four of these patients have been started on oral thyroid supplementation, although clinical hypothyroidism has not been diagnosed. No significant changes in serum immunoglobulins have occurred post-treatment. Four patients developed a myelodysplastic syndrome or acute myelocytic leukemia in long-term follow-up.

c. PHARMACOLOGY

Pharmacokinetics: After IV administration, a two compartmental model best fit the data with a median terminal half-life of 70.4 hours. The mean clearance was 97.9 ± 109.2 mL/hr (mean \pm standard deviation). Dose-dependent pharmacokinetics were observed with a larger area under the curve (AUC),

slower clearance, longer terminal half-life, and smaller volume of distribution at steady state observed with increasing predose levels of tositumomab antibody. The route of excretion was renal with $65 \pm 13\%$ of the injected dose recovered in the urine over the initial 5 day time period. The mean total body effective half-lives were 65.2 ± 12.5 and 65.8 ± 12.9 hours by sodium iodide probe counts and gamma camera counts, respectively. Organ doses were modest and below normal tissue tolerances. The mean splenic dose was 399 ± 215 cGy/75 cGy total body dose (TBD). The kidney received 630 ± 201 cGy/75 cGy TBD. The cGy doses to other normal tissues from a 75 cGy whole body dose were quite modest, with the liver and the lungs receiving an average dose of 256 ± 80 cGy and 182 ± 58 cGy, respectively. The mean bladder wall dose was 202 ± 49 cGy/75 cGy TBD, the mean bone marrow dose was 103 ± 15 cGy/75 cGy TBD, and the mean blood dose was 369 ± 97 cGy/75 cGy TBD.

Formulation: Tositumomab Antibody and Iodine-131 Tositumomab Antibody:

Tositumomab antibody is a murine anti-human B-cell monoclonal antibody of the IgG_{2a} subclass. As formulated, tositumomab antibody is a sterile, clear, colorless liquid supplied in a 3 mL or 20 mL glass vial stoppered with a gray silicone-coated butyl rubber stopper and capped with an aluminum crimp seal. Each single-use 3 mL vial contains not less than 2.5 mL of solution; each single-use 20 mL vial contains not less than 16.1 mL of solution. The formulation or each single-use vial is:

Protein concentration 14.0 ± 0.7 mg/mL

Potassium phosphate: 10 mM, pH 7.2 ± 0.2

Sodium Chloride: 145 mM

Maltose: 10%

Iodine-131 Tositumomab Antibody:

The Iodine-131 tositumomab antibody is a sterile, colorless liquid in a glass vial stoppered with a gray silicone-coated butyl rubber stopper and capped with an aluminum crimp seal. Each vial is intended for single-use only.

The dosimetric vial contains not less than 1.4 mL of solution in a 10 mL vial consisting of:

Protein concentration 1.1 - 2.5 mg/mL

Calibrated activity: 8 - 12 mCi

Povidone: 5.5%

Ascorbic Acid: 0.1%

Potassium phosphate: 12.5 mM, pH 6.8 - 7.2

Sodium Chloride: 0.9%

Maltose: 1 - 2%

OR, the dosimetric vial may contain not less than 20 mL of solution in a 30 mL vial consisting of:

Protein concentration 0.10 - 0.25 mg/mL

Calibrated activity: 12 - 18 mCi

Povidone: 5.5%

Ascorbic Acid: 0.1%

Potassium phosphate: 12.5 mM, pH 6.5 - 7.2

Sodium Chloride: 0.9%

Maltose: 1 - 2%

The therapeutic vial contains not less than 20 mL solution in a 30 mL vial consisting of:

Protein concentration: 1.1 - 2.5 mg/mL

Calibrated activity: 112 - 168 mCi

Povidone: 5.5%

Ascorbic Acid: 0.1%

Potassium Phosphate: 12.5 mM, pH 6.5 - 7.5

Sodium Chloride: 0.9%

Maltose: 1 - 2%

Storage and Stability:

Tositumomab: Non-radioactive anti-tositumomab will be shipped overnight as needed to the study site. Anti-B1 must be stored at 2 - 8°C in a secure area until it is needed for use. The vials are single-use as they do not contain preservative.

I-131-Tositumomab: The lead pot containing Iodine-131 Tositumomab must be stored in a freezer until it is thawed for administration to the patient. See the section on Thawing for Administration in the User's Instructions for complete instructions on the procedure for thawing the vials. Allow approximately 20 minutes for thawing of the 10 ml dosimetric vial and approximately 60 minutes for thawing of the 30 ml dosimetric or therapeutic vial. The thawed vial may be refrigerated at 2 - 8°C for up to 6 hours. The product must be administered to the patient within 72 hours of the calibration date and time specified on the product label.

Administration: See Section 7.5c for detailed administration instructions for both unlabeled and I-131-labeled tositumomab.

Supplier: GlaxoSmithKline, will supply tositumomab antibody and I-131-tositumomab antibody free of charge for this study. Any questions regarding tositumomab antibody or Iodine-131 tositumomab antibody may be directed to the Service Center at (toll free) 877/423-9927.

Drug Ordering: Unlabeled tositumomab antibody and I-131 tositumomab antibody (dosimetric and therapeutic) will be ordered by completing one form, the Study Drug Order Form for **S0801** found on the members section of the Southwest Oncology Group website (<https://swog.org/Members/ClinicalTrials/GetSecuredFile.asp?Document=MISC2-0801.pdf>) and faxing it to GlaxoSmithKline Clinical Research Department (fax number 877/279-1512). The Study Drug Order Form must be faxed to GlaxoSmithKline by Wednesday, 4:00 p.m. Eastern Time (EST) prior to the treatment week. The product will be shipped frozen on dry ice and will be sent to the site using priority overnight delivery. Upon receipt, immediately follow the section on Procedure for Opening in the User's Instructions. For questions related to radiolabeled antibody ordering, call the Service Center at (toll free) 877/423-9927.

NOTE: Institutions must be approved by GlaxoSmithKline and receive an on-site training session prior to administering I-131 labeled tositumomab antibody. (See Section 15.1 for specific instructions.)

Drug Returns: *Unused* I-131 tositumomab antibody must be decayed at the site according to institutional policy. *Unused* non-radiolabeled tositumomab antibody must be returned. Contact the Service Center (toll free: 1-877-423-9927) for instructions. Used empty vials (from both radiolabeled and non-radiolabeled antibody) should be disposed of at the site according to institutional policies.

3.4 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

Pharmacokinetics: 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.

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.

3.5 Rituximab Chimeric Monoclonal anti-CD20 Antibody (IDE-C2B8) (NSC-687451)

a. DESCRIPTION

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

b. TOXICOLOGY

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

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 with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of rituximab. 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 ($> 25,000/\text{mm}^3$) 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.

Immunization: The safety of immunization with live viral vaccines following rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied. For patients with NHL, the benefits of primary and/or booster vaccinations should be weighed against the risks of delay in initiation of rituximab therapy.

Carcinogenesis, Impairment of Fertility, Pregnancy, and Nursing: No long-term animal studies have been performed to establish the carcinogenic potential of rituximab. Studies also have not been completed to assess mutagenic potential of rituximab, or to determine potential effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following rituximab therapy.

It is not known whether rituximab is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable.

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Rituximab (NSC 687451)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. Frequency is provided based on 986 patients. Below is the CAEPR for Rituximab.

Version 2.1, March 19, 2010¹

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		Anemia
	Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)		Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)
	Febrile neutropenia		Febrile neutropenia
CARDIAC DISORDERS			
	Myocardial infarction		Myocardial infarction
	Sinus tachycardia		Sinus tachycardia
	Supraventricular tachycardia		Supraventricular tachycardia
GASTROINTESTINAL DISORDERS			
	Abdominal pain		Abdominal pain
	Diarrhea		Diarrhea
	Nausea		Nausea
	Vomiting		Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Chills			Chills
	Edema limbs		
	Fatigue		Fatigue
Fever			Fever
Infusion related reaction			Infusion related reaction
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		Allergic reaction
		Anaphylaxis	
	Serum sickness		Serum sickness
INFECTIONS AND INFESTATIONS			
	Infection ²		Infection²
	Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus, varicella zoster, herpes simplex, West Nile virus)		Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus, varicella zoster, herpes simplex, West Nile virus)
	Infections and infestations - Other (Infection in HIV Positive Patients)		

INVESTIGATIONS		
Lymphocyte count decreased		Lymphocyte count decreased
	Neutrophil count decreased	Neutrophil count decreased
	Platelet count decreased	Platelet count decreased
	White blood cell decreased	White blood cell decreased
METABOLISM AND NUTRITION DISORDERS		
	Hyperglycemia	
	Hypocalcemia	Hypocalcemia
	Hypokalemia	
		Tumor lysis syndrome
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	Arthralgia
	Back pain	
	Myalgia	Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Tumor pain	Tumor pain
NERVOUS SYSTEM DISORDERS		
	Dizziness	Dizziness
	Headache	Headache
	Lethargy	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)
	Seizure	Seizure
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Allergic rhinitis	
	Bronchospasm	Bronchospasm
	Cough	Cough
	Dyspnea	Dyspnea
	Hypoxia	Hypoxia
	Pneumonitis	Pneumonitis
	Sore throat	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	Hyperhidrosis
	Pruritus	Pruritus
	Rash maculo-papular	Rash maculo-papular
	Skin and subcutaneous tissue disorders - Other (angioedema)	

SKIN AND SUBCUTANEOUS TISSUE DISORDERS (contd.)		
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	Urticaria
VASCULAR DISORDERS		
	Flushing	Flushing
	Hypertension	Hypertension
	Hypotension	Hypotension

¹ This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

² Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

³ Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

⁴ Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation

EYE DISORDERS - Conjunctivitis; Eye disorders - Other (ocular edema); Uveitis; Watering eyes

GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction³; Gastrointestinal perforation⁴; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture

INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hyperphosphatemia); Investigations - Other (LDH increased); Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis

NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Skin and subcutaneous tissue disorders - Other (paraneoplastic pemphigus)
VASCULAR DISORDERS - Phlebitis; Thromboembolic event; Vasculitis

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

c. **PHARMACOLOGY**

Pharmacokinetics: In prior studies patients treated at the 375 mg/m² dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the T_{1/2} following the first antibody infusion was 59.8 hours (11.1 - 104.6 hr) with a C_{max} of 271 mcg/mL. Following the fourth antibody infusion when circulating B cells had been depleted and antigenic sites coated, the T_{1/2} was 174 hr (26.4 - 442.3 hr) and C_{max} 496.7 mcg/mL.

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

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

Administration: The total amount of rituximab needed for a patient's initial four infusions (induction therapy) will be determined AT STUDY ENTRY. For subsequent maintenance rituximab, the dose should be recalculated at the beginning of each cycle.

Prepare the rituximab infusion solution as follows:

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

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

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

3.6 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

Pharmacokinetics: 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. It is also available in 1 mg/mL and 2 mg/2 mL disposable syringes.

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.

4.0 STAGING CRITERIA

- 4.1 The Ann Arbor staging criteria will be used. Stage is based on extent of disease at the time of diagnosis. Bulky disease determination is made after surgical resection, if applicable.
- 4.2 Ann Arbor Classification (AJCC Manual for Staging of Cancer, 6th ed., 2002)

STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and its associated regional lymph nodes (IIE).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE).
STAGE IV	Diffuse or disseminated involvement of one or more extra lymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement).

A = Asymptomatic

B = Unexplained fever (38°C), night sweats, unexplained weight loss > 10% of body weight over the previous six months

- 4.3 "Bulky" is defined as a mediastinal mass > 1/3 of the maximum chest diameter (i.e., internal dimension of the thoracic cavity measured at its widest point per radiograph) or any other mass ≥ 10 cm in maximum diameter.

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 **S0801** Prestudy Form (Form #62797) 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 four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

The registering institution must have submitted the **S0801** Site Contact Information Form (Appendix 19.4) and a copy of their radioactive materials license to GlaxoSmithKline and been approved by GlaxoSmithKline for this study. (The approval process is required only for the FIRST patient registered to this study by any one institution.) Institutions previously approved by GlaxoSmithKline (formerly Corixa) for the Southwest Oncology Group study **S0433** or **S0016**, need not repeat the approval process; however, they must still submit the completed form and license to GlaxoSmithKline.

SWOG Patient No. _____

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

- ____ 5.1 All patients must have previously untreated Stage III, IV, or bulky Stage II follicular B-cell non-Hodgkin's lymphoma (Grade 1, Grade 2 or Grade 3), which is positive for CD20. A pathology report providing confirmation of CD20 expression must be submitted per Section 14.4. Diffuse large cell component must be less than 25% of the biopsy.
- ____ 5.2 Pathology Review: Adequate sections and a paraffin block or at least 10 unstained sections from the original diagnostic specimen must be available for submission for review by the lymphoma pathology group as outlined in Section 12.0. An adequate biopsy requires sufficient tissue to establish the architecture and a WHO histologic subtype with certainty. Thus, core biopsies, especially multiple core biopsies MAY be adequate; whereas, needle aspirations or cytologies are not adequate. With patient's consent, any left over tissue not consumed by testing will be retained for future studies.
- ____ 5.3 All patients must have bidimensionally measurable disease (defined in Section 10.1a) documented within 28 days prior to registration. Patients with non-measurable disease (defined in Section 10.1b) in addition to measurable disease must have all non-measurable disease assessed with 42 days prior to registration.
- ____ 5.4 Patients must have a unilateral or bilateral bone marrow aspirate and biopsy performed within 42 days prior to registration. However, if the most recent biopsy was positive and was performed more than 42 days but within 6 months prior to registration, the procedure does NOT need to be repeated.
- ____ 5.5 Patients must have a CT scan of the chest and abdomen/pelvis performed within 28 days prior to registration. PET/CT is allowed if CT is of diagnostic quality and contrast enhanced.
- ____ 5.6 Patients are encouraged to participate in the central lymphoma repository tissue procurement protocol, **SWOG-8819**, and the serum procurement protocol, **SWOG-8947**, as outlined in Section 15.0. With the patient's consent, specimens should be submitted as specified in **SWOG-8819** and **SWOG-8947** and Section 9.0 of this protocol.
- ____ 5.7 Patients must be ≥ age 18.

SWOG Patient No. _____

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

- ____ 5.8 Patients must not have clinical evidence of central nervous system involvement by lymphoma. Any laboratory or radiographic tests performed to assess CNS involvement must be negative within 42 days of registration.
- ____ 5.9 Patients must not have received prior chemotherapy, radiation, or antibody therapy for lymphoma.
- ____ 5.10 All patients must have a Zubrod performance status of 0 - 2 (see Section 10.4).
- ____ 5.11 Serum LDH and hemoglobin must be measured within 28 days prior to registration.
- ____ 5.12 Patients must have a cardiac ejection fraction $\geq 45\%$ by MUGA scan or an ECHO with no significant abnormalities within 42 days prior to registration.
- ____ 5.13 Patients known to be HIV positive, or who have a history of solid organ transplantation are ineligible due to concern over immunosuppression associated with B-cell depletion. Patients at high risk of Hepatitis B virus (HBV) infection are eligible, but should be screened before initiation of rituximab (See Section 2.0 for justification).
- ____ 5.14 Patients requiring continuous supplemental oxygen therapy are ineligible.
- ____ 5.15 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- ____ 5.16 Pregnant or nursing women may not participate. Women or men of reproductive potential must have agreed to use an effective contraceptive method from the time of registration to 12 months after completion of rituximab maintenance. (For justification, see Sections 2.0 and 3.0.)
- ____ 5.17 All patients 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.
- ____ 5.18 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

SECOND REGISTRATION:

- ____ 5.19 Patients must have completed R-CHOP+ I-131 tositumomab therapy and have stable disease or better documented within 28 days prior to registering to Step 2, rituximab maintenance therapy.
- ____ 5.20 Patients must be planning to begin rituximab maintenance therapy approximately 7 months after receiving therapeutic I-131 tositumomab treatment.

6.0 STRATIFICATION FACTORS

Stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Friedberg at 585/273-4150, or Dr. Press at 206/667-1872. For dosing principles or questions, please consult the Southwest Oncology Group 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 Good Medical Practice

The following pre-study tests must be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests. If an individual test is considered to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

- a. Platelets > 100,000 cells/mcL; ANC > 1,000 cells/mcL
- b. Bilirubin ≤ 2 x ULN (unless from Gilbert's syndrome or NHL)
- c. Creatinine ≤ 2 x ULN
- d. It is suggested that Beta 2 microglobulin, urinalysis, uric acid, transaminases, and a Hepatitis B virus (HBV) screening be performed as baseline prestudy tests to assess potential treatment-related toxicities. These tests are not required for eligibility.
- e. PET scans: The role of PET imaging in follicular lymphoma is controversial, and is only required for Day 226 restaging for this study. PET/CT scans should not replace CT scans required by the protocol. There is no role for routine PET imaging during subsequent restaging procedures.

7.2 Concomitant Medications:

- a. To prevent tumor lysis syndrome in patients with bulky tumors, oral or IV fluid intake in excess of 2 L daily is encouraged during therapy. In addition, the routine administration of allopurinol (300 mg/day) is recommended prior to and during the first cycle of chemotherapy.
- b. Growth factors, including G-CSF, GM-CSF, and Neulasta are also permitted at the discretion of the treating physician (see Section 8.5).
- c. The use of routine acetaminophen 500 - 1,000 mg p.o. and diphenhydramine 25 mg p.o. or I.V. as premedications is REQUIRED prior to antibody therapy unless medically contraindicated. Diphenhydramine, epinephrine and hydrocortisone need to be available during rituximab and tositumomab infusions.
- d. Prophylactic antibiotic therapy to prevent febrile neutropenia is at the discretion of the treating physician.

7.3 R-CHOP

Treatment with CHOP will be administered every 21 days for a maximum of 6 cycles (one cycle is defined as a single 21 day course of treatment). Rituximab will be given before chemotherapy. **If circulating lymphocyte count exceeds 20,000 cells/mcL, rituximab will be omitted for the first cycle of therapy only. During the final two cycles, patients will only receive CHOP chemotherapy without rituximab.** Patients with progressive disease at restaging (after 6 cycles) will discontinue treatment. R-CHOP will be given as indicated below.

AGENT	DOSE	ROUTE	SCHEDULE	REPEAT TREATMENT INTERVAL
Cyclophosphamide	750 mg/m ²	IV over 15 minutes	Day 1	Every 21 days for 6 cycles
Doxorubicin	50 mg/m ²	Slow IV infusion	Day 1	Every 21 days for 6 cycles
Vincristine	1.4 mg/m ² (max 2.0 mg)	Slow IV infusion	Day 1	Every 21 days for 6 cycles
Prednisone	100 mg	PO	Days 1-5	Every 21 days for 6 cycles
Rituximab	375 mg/m ²	Slow IV infusion	Day 1	Every 21 days for 4 cycles

7.4 Evaluation for I-131 Tositumomab Therapy

Patients will be restaged 3-4 weeks after Day 1 dose of Cycle 6 of induction R-CHOP therapy, with CT scans of the chest, abdomen, and pelvis AND a bone marrow biopsy and aspiration, if initially involved with lymphoma (see Section 9.0). **The following conditions must be met prior to proceeding with I-131 tositumomab antibody treatment. Patients who do not qualify for I-131 tositumomab antibody treatment upon re-evaluation will be removed from protocol treatment.**

- The training session with GlaxoSmithKline must have been completed (see Section 7.5a).
- Patients must have stable disease or better.
- Patients must have no more than 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically after completion of 6 cycles of R-CHOP chemotherapy. Bilateral posterior iliac crest core biopsies are required if the percentage of intratrabecular space involved exceeds 10% on a unilateral biopsy. The mean of bilateral biopsies must be no more than 25%. The procedure for bilateral bone marrow biopsy analysis of marrow involvement is included in Appendix 19.2.
- Patients must have granulocytes $\geq 1,500/\text{mcL}$ and platelets $\geq 100,000/\text{mcL}$ within 14 days of the planned dosimetric infusion. **Patients must not have active obstructive hydronephrosis.**

7.5 Tositumomab and I-131 Tositumomab

- Institutions must have completed an on-site training session with GlaxoSmithKline representatives to review the details of drug administration and dosimetry prior to treating a patient with tositumomab and Iodine-131 tositumomab. The training session must occur prior to the dosimetric infusion of I-131 tositumomab, and the date of the training session must be noted on the

S0801 Tositumomab Treatment Form (Form #57447). For subsequent patients, the original training session date must still be noted on the **S0801** Tositumomab Treatment Form (Form #57447).

- b. GlaxoSmithKline will contact each institution (by telephone) to provide assistance and arrange for training (if required, see Section 15.1). The training session must be performed only for the FIRST patient registered to this study at any one institution. However, retraining is available upon institutional request.
- c. Tositumomab and I-131 Tositumomab will be given as indicated below:

AGENT	DOSE	ROUTE	SCHEDULE
Unlabeled Tositumomab Antibody**	450 mg	IV over 1 hour	Within 12 weeks after completion of CHOP (last dose of Cycle 6)
Dosimetric Dose ^{+f}	35 mg	IV over 20 minutes	After infusion of unlabeled tositumomab antibody
Unlabeled Tositumomab Antibody**	450 mg	IV over 1 hour	Within 7-14 days after the dosimetric dose ^v
Therapeutic Dose ^{+f}	35 mg	IV over 20 minutes	After infusion of unlabeled tositumomab antibody ^v

** Patients must receive tositumomab, 450 mg of unlabeled tositumomab antibody (to 50 mL using 0.9% sodium chloride) prior to the dosimetric dose. Seven to fourteen days later the unlabeled tositumomab dose is repeated followed by the therapeutic dose, as described in Section 7.6. Patients must be premedicated with acetaminophen 650 mg po and diphenhydramine 50 mg po prior to administration of unlabeled tositumomab antibody.

+ Patients must receive SSKI, Lugol's Solution or potassium iodide at least 24 hours prior the first infusion of the dosimetric dose. Treatment will continue daily until 14 days after the last infusion of the therapeutic dose (see Section 7.6b.3).

f Ideally, the dosimetric infusion will be given on Day 135 and the therapeutic infusion on Day 142. Due to the logistics of ordering, receiving and administering I-131-tositumomab, a 4 week period of flexibility after Day 135 will be allowed within which the radiolabeled antibody therapy may be given. However, it is recommended that institutions allow no more than 14 days between the dosimetric and therapeutic infusions of tositumomab.

^v See Section 7.6c.2.

7.6 Tositumomab administration details.

a. Preparation, Dosing, and Administration:

Patients will undergo two phases of tositumomab administration. The first phase, termed "dosimetric dose", involves the intravenous (IV) administration of a low-radioactive dose (five mCi) of iodine-131 tositumomab antibody for the purpose of determining the rate of total body clearance of radioactivity (residence time) so that a total body radiation dose can be calculated (see Appendix 19.1). The calculated total body radiation dose per mCi administered can then be used to determine how many mCi of iodine-131 conjugated with tositumomab antibody will be required to deliver the total body radiation dose in the second phase of the study, termed "therapeutic dose." Both the dosimetric dose and the therapeutic dose will be immediately preceded by an infusion of 450 mg unlabeled tositumomab antibody (see Sections 7.6b and 7.6c).

Administration of the radiolabeled tositumomab antibody will be performed by personnel authorized to deliver such doses of radioisotope to patients. Special radiation precautions will be used during and after the administration of the therapeutic dose, as required by the national and/or regional regulations for the radiopharmaceutical industry. Restrictions on patient contact with others will be set in accordance with these regulatory guidelines [Nuclear Regulatory Commission (NRC) and state laws]. The dosimetric and therapeutic doses may be given as either an outpatient or inpatient procedure depending on current NRC and state regulations.

NOTE: Unused drug must be returned as specified in Section 3.3c.

b. Dosimetric Dose:

1. Preparation of Unlabeled Tositumomab Antibody

To prepare unlabeled tositumomab antibody for administration to patients, 450 mg unlabeled tositumomab antibody is steriley-removed from the product vials and diluted to 50 mL using 0.9% sodium chloride for injection.

2. Preparation of Dosimetric Dose (i.e., Tracer Dose)

To prepare the dosimetric dose, an amount of tositumomab antibody (33 - 34 mg) is added to the trace-labeled antibody preparation (1-2 mg of tositumomab antibody radiolabeled with 5 mCi of 131-Iodine) sufficient to result in a final amount of 35 mg of tositumomab antibody. This latter preparation is then diluted to a final volume of 30 mL using 0.9% sodium chloride for injection.

3. Administration of Saturated Solution Potassium Iodide (SSKI), Lugol's Solution, or Potassium Iodide Tablets

Patients will be treated with either saturated solution of potassium iodide (SSKI) four drops by mouth, three times a day, Lugol's solution 20 drops by mouth, three times a day, or potassium iodide tablets 130 mg by mouth every day starting at least 24 hours prior to the first infusion of the Iodine-131 tositumomab Antibody (i.e., the dosimetric dose) and continuing for 14 days following the last infusion of Iodine-131 tositumomab Antibody (i.e., therapeutic dose). The SSKI or Lugol's solution may be given with juice or cola to mask taste. **In no instance should a patient receive the dosimetric dose of iodine-131 tositumomab antibody if they have not yet received at least 3 doses of SSKI, three doses of Lugol's solution, or one 130 mg potassium iodide tablet (at least 24 hours prior to the dosimetric dose).** Patients should be monitored for compliance with regard to SSKI, Lugol's solution, or potassium iodide tablets.

All concomitant medications must be recorded in the comments section of the S0801 Tositumomab Treatment Form (Form #57447).

4. Administration of Dosimetric Dose

On Day 135, patients will receive the intravenous (IV) administration of 450 mg unlabeled tositumomab antibody followed by the IV administration of the dosimetric dose (five mCi of Iodine-131 tositumomab antibody). The unlabeled antibody must be administered through an in-line filter [Abbott lab filter set with 0.22 micron filter and

injection site-15 inch option-lock (part 2679)]. The in-line filter may remain connected to or removed from the infusion line following the unlabeled antibody. A new filter should not be added for the radiolabeled infusion. Thirty to sixty minutes before the unlabeled tositumomab antibody infusion, patients will be premedicated with acetaminophen 650 mg by mouth and diphenhydramine 50 mg by mouth (unless the patient is hypersensitive to acetaminophen or diphenhydramine). Unlabeled tositumomab antibody (see Section 7.6b.1) will then be given as an intravenous (IV) infusion over 1 hour or longer depending on infusion-related adverse experiences. The dosimetric dose (see Section 7.6b.2) will be given as an intravenous infusion over 20 minutes. At the end of the infusion of the dosimetric dose, the syringe or IV bag must be refilled with 0.9% sodium chloride and the contents infused over a period of 10 minutes. Vital signs must be taken every 15 minutes during each of the tositumomab antibody infusions.

5. Whole Body Dosimetry

Whole body dosimetry will be performed separately for each patient as described in Appendix 19.1 using the worksheets provided. For all patients, whole body anterior and posterior gamma camera scans will be obtained within one hour after the completion of the administration of the dosimetric dose on Day 0 (Day 135) before any urination, and then either on Day 2, 3, or 4 (Days 137, 138 or 139) after urination and again on either Day 6 or 7 (Day 141 or 142) after urination using a gamma camera with appropriate medium- or high-energy collimator. The anterior and posterior whole body scans will be obtained at 10-30 cm/minute scan speed. Anterior and posterior whole body counts, anterior and posterior background counts, and anterior and posterior counts of a calibrated standard will be obtained and recorded. All static and whole body scan images for dosimetry will be retained electronically for submission upon request to GlaxoSmithKline or its designee.

The above-determined counts will be used to calculate the activity to be administered to deliver 75 cGy (unless adjusted for obesity and/or platelet count - see below). The mCi dose will be calculated as described in Appendix 19.1 and accompanying worksheets.

Dose Adjustments based on weight and platelet counts:

For excessively obese patients, the calculations to determine the iodine-131 tositumomab antibody activity to administer will be performed using an upper limit of mass (maximum effective mass) based upon height and gender (see Table 1, Appendix 19.1d).

The administered activity (mCi of Iodine-131 tositumomab antibody) for patients with platelet counts of 100,000 - 149,999 cells/ μ L will be adjusted to deliver 65 cGy, with additional adjustment of activity for obesity, if indicated. **Iodine I-131 antibody should not be given if platelets are less than 100,000 cells/mcL.**

The dose calibrator used for measuring the mCi of activity of Iodine-131 tositumomab antibody to be administered to the patient must be appropriately calibrated.

The dosimetry worksheets for the first three patients at each clinical site must be submitted to GlaxoSmithKline by fax to confirm that the calculations were performed correctly (Fax: 877/279-1512). A dosimetry hotline will be maintained by GlaxoSmithKline to assist in calculation of the proper therapeutic dose (Service Center, toll free 877/423-9927).

c. Therapeutic Dose:

1. Preparation

To prepare the therapeutic dose, an amount of tositumomab antibody is added to the radiolabeled preparation (tositumomab antibody labeled with enough 131 Iodine to administer the specified whole body radiation dose calculated for the patient from the dosimetric dose) sufficient to result in a final amount of 35 mg of tositumomab antibody, unless the amount of tositumomab antibody in the radiolabeled preparation is already \geq 35 mg. This latter preparation is then diluted to a final volume of 30 mL using 0.9% sodium chloride for injection. In rare cases, greater than 30 mL of Iodine-131 tositumomab antibody will be required and the dose will then be prepared in 60 mL.

2. Administration

The therapeutic dose is to be given 7 days after the administration of the dosimetric dose (may be delayed but no longer than 14 days after dosimetric dose). **Those patients who experienced an anaphylactic response or serious adverse experience felt to be related to study drug during or following trace-labeled antibody administration will be removed from protocol treatment.** Patients will be premedicated with acetaminophen and diphenhydramine as they were prior to the dosimetric dose. Patients should also still be receiving SSKI or Lugol's solution as described in Section 7.6b.3. The unlabeled antibody must be administered through an in-line filter [Abbott Lab filter set with 0.22 micron filter and injection site - 15 inch option-lock (part 2679)]. The in-line filter may remain connected to or removed from the infusion line following the unlabeled antibody. A new filter should not be added for the radiolabeled infusion. Unlabeled tositumomab antibody will then be given as an intravenous (IV) infusion over 1 hour or longer depending on infusion-related adverse experiences. The therapeutic dose will be given as an intravenous infusion over 20 minutes. At the end of the infusion of the therapeutic dose, the syringe or IV bag must be refilled with 30 mL 0.9% sodium chloride and the contents infused over a period of 10 minutes. Vital signs must be taken every 15 minutes during each of the tositumomab antibody infusions.

7.7 CNS Prophylaxis: No CNS prophylaxis is permitted.

7.8 Allopurinol: To prevent the rare event of tumor lysis syndrome in patients with bulky tumors (> 10 cm), oral or IV fluid intake in excess of 2,000 mL daily is encouraged during therapy for all patients on the study. In addition, the routine administration of allopurinol (300 mg/day) is also recommended prior to and during the first cycle of therapy. If rash occurs, allopurinol can be discontinued.

- 7.9 **Evaluation for Rituximab Maintenance Therapy:** Restaging will be repeated 12 weeks after completion of therapeutic tositumomab, with a PET scan, diagnostic CT scan of the chest, abdomen and pelvis and a bone marrow aspiration and biopsy (if initially positive). Patients showing evidence of disease progression as defined by Section 10.2f will be removed from protocol treatment (see Section 7.12).

Restaging is also requested at approximately 1 year (Day 365) after initial registration in order to determine eligibility for rituximab maintenance therapy.

- 7.10 **Rituximab Maintenance Therapy:** Rituximab maintenance therapy will begin 1 year (\pm 4 weeks) after initial registration. Treatment will be administered for 16 cycles, Cycles 7-22 (each cycle is given every 3 months).

Patients will be restaged approximately 1 year after initial registration. All patients with stable disease or better (as defined in Section 10.2) will receive rituximab maintenance therapy on the following dose/schedule. **Patients should register to rituximab maintenance therapy within 28 days after restaging (see Second Registration, Section 5.19-5.20).**

AGENT	DOSE	ROUTE	SCHEDULE	REPEAT TREATMENT INTERVAL
Rituximab	375 mg/m ²	Slow IV infusion	Day 1	q 3 months x 4 years

- 7.11 **Follow-Up Assessments:** During the rituximab maintenance phase of protocol treatment, patients will undergo follow-up assessments once every six months. After completion of rituximab maintenance, patients will undergo follow-up assessments annually thereafter for a maximum of seven years on protocol. Patients who do not complete rituximab maintenance therapy will undergo follow-up assessments every six months for two years, and then annually for a maximum of seven years on protocol.

7.12 Criteria for Removal from Protocol Treatment

- a. Progression of disease or symptomatic deterioration as defined in Section 10.2f.
- b. Unacceptable toxicity, as defined in Section 8.0. Patients who experience an anaphylactic response or serious adverse experience felt to be related to study drug during or following trace labeled antibody administration will be removed from protocol treatment (see Section 7.6c.2).
- c. Failure to meet criteria for I-131 antibody administration following completion of CHOP chemotherapy as defined in Section 7.4.
- d. Completion of protocol treatment.
- e. Delay of protocol treatment for more than 8 weeks.
- f. The patient may withdraw from the study at any time for any reason.

- 7.13 All reasons for discontinuation of treatment must be documented in the Off Treatment Notice (Form #8756).

- 7.14 All patients will be followed for a maximum of seven years or until death whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 Two different versions of the NCI Common Terminology Criteria for Averse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0

8.2 CHOP Dose Modification:

a. **Hematologic Toxicity:** The CHOP regimen should be given as described in Section 7.0 if the granulocytes are > 1,000 cells/mcL and the platelets are > 100,000 cells/mcL by the time the next cycle is due. If the blood counts have not recovered, treatment should be delayed one week and counts repeated unless low peripheral counts are due to tumor. If, after two weeks, counts have not yet recovered, the patient should be treated at 75% of the last dose received of cyclophosphamide and doxorubicin when counts have recovered to granulocytes > 1,000 cells/mcL and platelets > 100,000 cells/mcL.

Severe infection (NCI CTC Version 3.0, Grade 3 or 4) due to chemotherapy-related neutropenia requires a decrease in the doses of cyclophosphamide and doxorubicin to 75% of the last dose received. Re-escalation is at the discretion of the treating physician. Cytokines may be administered to prevent neutropenia. The NCI will not provide cytokines for this study.

b. **Impaired Hepatic Function:** All patients with bilirubin \leq 2 x the institutional upper limit of normal will receive a full initial dose of doxorubicin and vincristine. If the bilirubin rises to > 2 x the institutional upper limit of normal (but \leq 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 bilirubin is \leq 2 x the institutional upper limit of normal. If the 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 \leq 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.

Bilirubin	Doxorubicin Dose	Vincristine Dose
\leq 2 x IULN	100%	100%
> 2 - 5 x IULN	50%	50%
> 5 x IULN	0%	0%

- c. **Impaired Renal Function:** All patients with serum creatinine levels $\leq 2 \times$ the institutional upper limit of normal will receive full dose of all drugs. If creatinine rises $> 2 \times$ 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 $\leq 2 \times$ the institutional upper limit of normal.
- d. **Hemorrhagic cystitis:** 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.

CLOSED EFFECTIVE 12/15/2010

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

8.3 Rituximab Dose Antibody Modification:

- a. Patients may experience transient fever and rigors with infusion of rituximab. If Grade 3 fever (or Grade 2 fever with rigors) or Grade 2 rigors are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when fever resolves to Grade 2 or less and rigors to Grade 1 or less, the infusion should be continued, initially, at 1/2 the previous rate. Following the antibody infusion, the IV line should be kept open for medications, as needed.
- b. Hypotension, bronchospasm and angioedema have occurred as part of an infusion related symptom complex. If a Grade 3 or greater hypersensitivity/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 with bronchodilators or IV saline may be used at the physician's discretion.
- c. Precautionary hospitalization for patients experiencing severe infusion symptoms, which do not resolve after discontinuation of the cycle, is recommended.

If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during the rituximab infusion, the patient should be observed for two hours after the completion of the infusion. If a patient experiences a Grade 3 toxicity that persists until the next scheduled infusion, the patient must discontinue treatment until toxicities have resolved to Grade 2 or less. If treatment is delayed for more than three weeks, remove the patient from protocol treatment.
- d. Tumor Lysis Syndrome: Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy may be administered in conjunction with prophylactic therapy for this syndrome. Contact the Study Coordinator prior to resuming treatment in these patients.
- e. Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections: Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation. Patients with any evidence of active hepatic disease or known HBV infection should be managed as clinically appropriate and should only receive rituximab if they have control of the infection and are adequately informed of the risks. Patients who have never received vaccination for HBV, and have not had serologic testing for HBsAg, should be tested for surface antigen positivity.

In patients who develop progressive multifocal leukoencephalopathy (PML), rituximab should be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy and appropriate treatment, including antiviral therapy, should be considered. Physicians should consider PML in any patients presenting with new onset neurologic manifestations, particularly in patients with systemic lupus erythematosus (SLE) or lymphoid malignancies. Consultation with a neurologist, brain MRI, and lumbar puncture should be

considered as clinically indicated. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

- f. **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.

- g. **Cardiovascular events:** Patients with rheumatoid arthritis (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.

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, that have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and immediate post-infusion period. Patients off rituximab therapy should be closely monitored for signs and symptoms suggestive of life-threatening cardiac events and supported as clinically indicated.

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

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

8.4 Iodine-131 Tositumomab Antibody Dose Modification

Iodine-131 should be given as specified in Section 7.5 as long as counts have recovered to granulocytes \geq 1,500 cells/mcL and platelets \geq 100,000 cells/mcL.

- a. **Dose Adjustments based on weight and platelet counts:**

For excessively obese patients, the calculations to determine the Iodine-131 tositumomab antibody activity to administer will be performed using an upper limit of mass (maximum effective mass) based upon height and gender (see Table 1, Appendix 19.1d).

The administered activity (mCi of Iodine-131 tositumomab antibody) for patients with platelet counts of 100,000 - 149,999 cells/mcL will be adjusted to deliver 65 cGy, with additional adjustment of activity for obesity, if indicated. **Iodine-131 antibody should not be given if platelets are less than 100,000/mcL.**

The dose calibrator used for measuring the mCi of activity of Iodine-131 tositumomab antibody to be administered to the patient must be appropriately calibrated.

- b. **Other dose adjustments:**

During the administration of the unlabeled tositumomab antibody, tracer, and therapeutic doses, emergency support for anaphylaxis is to be readily available, including a tray for epinephrine, diphenhydramine, hydrocortisone, a laryngoscope, and an endotracheal tube. Although acute adverse experiences

occurring during the infusion or up to 24 hours after the infusion of tositumomab antibody have been infrequent, based upon past experience, symptoms of fever, nausea, vomiting, rigors, hypotension, pruritis, tachycardia, erythematous rash, urticaria, mucus membrane congestion, arthralgias, and myalgias may occur. The patient should be treated according to physician's judgment. However, it is recommended that acetaminophen 650 mg by mouth and/or diphenhydramine 50 mg by mouth or IV be given to control these symptoms if they occur. Severe rigors should also be treated at the physician's discretion but may be controlled by meperidine 25 - 50 mg IV. Experience has shown that rigors generally abate within 30 minutes without pharmaceutical intervention.

If any of these toxicities occur during antibody infusion, the rate of antibody infusion should be decreased as indicated below:

Infusion rate adjustment

Fever	Rigors	Mucosal Congestion/Edema	% Drop in Systolic BP	Infusion Rate Adjustment
Grade 1 (38.0 – 39.0°C)	Grade 1-2 (Mild to Moderate)	Grade 1-2 (Mild to Moderate)	30 – 49	Decrease by ½
Grade ≥ 2 (≥ 39°C)	Grade ≥ 3 (Severe)	Grade ≥ 3 (Severe)	≥ 50	Stop Infusion*

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

8.5 Use of Colony Stimulating Factors (CSF) and Platelet and Red Blood Cell Transfusions

Colony Stimulating Factors (CSF) should be administered only in accordance with published ASCO guidelines. Use of CSF under these conditions will be at the discretion of the treating investigator, but must be recorded on the **S0801** Induction R-CHOP Treatment Form (Form #23097).

Platelet transfusions should be administered only in patients with Grade 3 or 4 thrombocytopenia with obvious bleeding. The use of platelet and red cell transfusions under these conditions will be at the discretion of the treating investigator, but must be recorded on the corresponding **S0801** Treatment Summary Form(s) (Form #23097, 57447, or 14046).

- 8.6 For treatment or dose modification related questions, please contact Dr. Friedberg at 585-273-4150 or Dr. Press at 206/667-1872.
- 8.7 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR **S0801**, "A Phase II Study of Iodine-131-Labeled Tositumomab in Combination With Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, and Rituximab Therapy for Patients with Advanced Stage Follicular Non-Hodgkin's Lymphoma"

REQUIRED STUDIES	Induction Therapy						Evaluation for I-131 Tositumomab	Antibody Treatment		Ω				Rituxan	Follow Up				
	PRE Day		Cycle 1 Day		Cycle 2 Day			Cycle 3 Day		Cycle 4 Day		Cycle 5 Day		Cycle 6 Day		Day	Day	Day	Maintenance Cycles 7-22
	STUDY	1	22	43	64	85	106	134	135	142	226	365							
PHYSICAL																			
History & Physical Exam	X		X	X	X	X	X	X					X	X	X	Δ		X	
Weight & Performance Status	X												X	X	X	Δ		X	
Tumor Assessment	X												X	X	X	Δ		X	
Toxicity Notation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Δ		X	
LABORATORY																			
CBC, Platelets & Differential	X	B		X	X	X	X	X	X				X	X	X	Δ		X	
Hemoglobin	X																		
Serum Creatinine	X	B		X	X	X	X	X	X				X	X	X	Δ		X	
Bilirubin	X	B		X	X	X	X	X	X				X	X	X	Δ		X	
SGOT/SGPT and/or Alk Phosphatase	X	B											X	X	X	Δ		X	
LDH	X												X	X	X	Δ		X	
Thyroid Stimulating Hormone (TSH)	X												X	X	X	Δ		X	
Beta 2 Microglobulin	X	B																	
Uric acid	X	B											X						
Urinalysis	X	B											X						
HBV screening	X	B															X		
Immunophenotyping (CD20)	X																		
Materials for pathology review #	X																		
Bone marrow aspir/biopsy	X												X*		X*	X*			
GlaxoSmithKline approval	X																		
GlaxoSmithKline training session													X						
RESEARCH SPECIMENS ↗																			
Serum for SWOG-8947	X																		
Tissue for SWOG-8819	X																		
X-RAYS AND SCANS																			
Diagnostic CT scan: Chest, Abdomen, Pelvis	X												X	X	X	Δ		X	
PET/CT	X	f											X						
MUGA or 2-d ECHO	X																		
TREATMENT (See Section 7.3) π																			
Induction Therapy																			
Rituximab		X†	X	X	X	X													
Cyclophosphamide		X	X	X	X	X	X	X	X	X									
Doxorubicin		X	X	X	X	X	X	X	X	X									
Vincristine		X	X	X	X	X	X	X	X	X									
Prednisone		X	X	X	X	X	X	X	X	X									
Consolidation																			
SSKI, Lugol's, Potassium Iodide §													X	§	X	§	X	§	
Unlabeled anti-tositumomab antibody													X	X					
I-131 anti-tositumomab dosimetric infusion													X						
Whole Body Dosimetry ¶													X	¶	X	¶			
I-131 anti-tositumomab therapeutic infusion ¥													X	¥					
Maintenance Therapy																			
Rituximab (375 mg/m² q 3 months x 4yrs)																		X	

NOTE: Data submission forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

f PET/CT is optional at baseline but required at Day 226 restaging. There is no role for routine PET imaging during subsequent restaging procedures.

See Section 12.0.

Ω Restaging must occur 12 weeks after completion of therapeutic tositumomab (approximately Day 226), as well as on Day 365 after initiation of CHOP. The same assessments that were used at baseline should be used for restaging.

✓ Patients removed from protocol treatment for any reason will be evaluated at that time by repeating CBC with platelets, LDH, creatinine, liver enzymes, CT of chest, abdomen and pelvis, and all pre-treatment scans to evaluate disease. Follow-up evaluations will include all restaging tests and will occur every six months for two years then annually for a maximum of seven years on protocol.

£ Evaluation for I-131 tositumomab therapy: Re-evaluation will occur 4-12 weeks after Day 1 dose of Cycle 6 of CHOP (see Section 7.5b).

π Patients with progressive disease at any time will discontinue protocol treatment (see Section 10.2f).

§ These tests are required prestudy for Good Medical Practice (see Section 7.1 for guidance on timing and interpretation of these results).

* Repeat if initially abnormal.

¤ SSKI, Lugol's or Potassium Iodide will be administered at least 24 hours prior to the dosimetric dose and will continue for 14 days following the last infusion of radiolabeled tositumomab antibody.

¶ Three whole body scans will be done: the first on Day 1 after the dosimetric infusion (projected to be Day 134 of the protocol treatment), the second on either Day 3, 4, or 5 after the dosimetric infusion and the third on either Day 7 or 8 after the dosimetric infusion (see Section 7.6b.5).

¥ The therapeutic dose is to be given 7 days after the administration of the dosimetric dose (may be delayed but no longer than 14 days after the dosimetric dose).

CBC/platelets/differential should be checked weekly after the therapeutic infusion until the patient experiences a nadir and recovers from the nadir (6-8 weeks).

¤ See Section 15.0.

† If circulating lymphocyte count exceeds 20,000 cells/ml, rituximab will be omitted for the first cycle.

Δ Rituxan maintenance should be administered once every 3 months for 4 years beginning approximately 1 year after initiation of induction therapy. History, physical exam, weight, performance status, and toxicity notation as well as restaging labs should be performed every 6 months throughout Rituxan maintenance. CT scans should be performed every 6 months for 2 years, then annually throughout Rituxan maintenance.

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. **Note:** PET 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 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. (13) 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 no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. If the PET 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 lesions visible on PET 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), 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. 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 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 no pretreatment PET scan or when the PET scan was positive before therapy, PET should be positive in at least one previously involved site. Tumor measurements must be obtained by an imaging modality other than PET. 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 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. 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 $\geq 50\%$ increase in the GTD of any node > 1 cm in shortest axis, or $\geq 50\%$ 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 $\geq 50\%$ increase in GTD of any previously involved node with a diameter ≤ 1.0 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 the both the long and short axes are > 1 cm. In patients with no pretreatment PET scan or when the PET scan was positive before therapy, lesions should be PET positive. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline. **Note:** Appearance of any new lesion on PET 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.
- b. **CRU**: One objective status of CRU documented before relapse but not qualifying as a CR.
- c. **PR**: One objective status of PR documented before progression but not qualifying as a CR or CRU.
- d. **Stable**: At least one objective status of stable 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:

<u>GRADE</u>	<u>SCALE</u>
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 10.2f), or death due to any cause. Patients last known to be alive and progression-free 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 and are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

- 11.1 We estimate the accrual rate to this protocol to be approximately 9-10 patients per month. SWOG protocol **S9911** used a similar combination of CHOP chemotherapy with iodine-131 tositumomab in patients with follicular NHL, and accrued at a rate of over 10 patients per month. The most recent SWOG protocol in follicular lymphoma (**S0016**), a randomized study, accrued on average 9 patients per month.
- 11.2 This is the primary objective of the study: Eighty eligible patients accrued over 12 months with 36 months of additional follow-up will be sufficient to estimate the true 3-year PFS within this group to within +/- 0.11. A true 3-year PFS of 85% would be of interest, while further testing would not be pursued if the true 3-year PFS probability is 70% or lower. An estimated 3-year PFS rate of 79% or greater will be considered evidence warranting further study of the regimen. This design has a significance level of 5.3% and power of 95%.
- 11.3 Secondary endpoints include 5-year PFS, 5-year overall survival, and response. The probability of response or a particular toxicity can be estimated to within at worst ± 0.11 with 80 patients (95% confidence interval). Any adverse event with at least a 5% probability will be seen at least once (98% chance).
- 11.4 **Data and Safety Monitoring:** There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Coordinator, Study Statistician, and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Coordinator. 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, and Executive Officer 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 of follicular non-Hodgkin's lymphoma.

- 12.2 All pathology submissions for patients registered on this study by Southwest Oncology Group institutions and affiliates must be entered and tracked using the SWOG Online Specimen Tracking System. Southwest Oncology Group members may log on to the Specimen Tracking System via the CRA Workbench (<http://gill.crab.org/txwb/logon.asp>) using their SWOG roster ID numbers and passwords.

In the online Specimen Tracking System, laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory ID number for this study may be found listed next to the laboratory name in Section 12.3 below.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM. THERE ARE NO EXCEPTIONS. For any questions or problems regarding the Specimen Tracking System, please send an email to technicalquestion@crab.org

- 12.3 The following materials are to be submitted for review:
- a. One representative H&E section from each block of the original diagnostic specimen. (Note: Needle aspirates are not adequate for this submission. Consult with Dr. Rimsza's laboratory if adequacy of specimen is in question.)
 - b. Either 12 unstained slides or a paraffin block from the representative diagnostic specimen. If a block is sent, then the tissue will be conserved (no more than 12 additional cuts will be made). **Send paraffin block on cool packs to keep the paraffin from melting.**
 - c. One copy of the pathology report.
- 12.4 Failure to submit a registered patient's pathology materials for pathology will make the patient ineligible.
- 12.5 Pathology materials are to be submitted within 28 days of registration to:
- Lab #2: SWOG Lymphoma Repository – University of Arizona
Arizona Health Science Center
Department of Pathology, Room 5211, Box 245043
1501 North Campbell Avenue
Tucson, AZ 85724-5043
- Contact: Yvette Frutiger/Lisa M. Rimsza, M.D.
Phone: 520/626-7477
FAX: 520/626-6081
Email: frutiger@email.arizona.edu

The materials must be identified with a "SWOG Pathology Materials" label on the outside of each package. If this label is missing, the materials will not be reviewed, rendering the patient ineligible. These labels will be provided by the Data Operations Center in Seattle. To obtain additional labels, please call 206/652-2267 and ask for the Pathology/RT Coordinator.

- 12.6 With patient's consent any left over tissue not consumed by testing will be retained for future studies.

13.0 REGISTRATION GUIDELINES

- 13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment). Second registration must also take place no more than 5 working days prior to planned start of rituximab maintenance therapy.
- 13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

- a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (<http://swog.org>) and click on the *Logon* link to go to the SWOG Members Area logon page (<https://swog.org/visitors/logon.asp>). This Web program is available at any time except for periods listed **under Down Times**. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at <https://swog.org/visitors/logonhelp.asp>. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page**.

To register a patient 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 to the institution where a registration is occurring, and
3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

- b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group 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 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 are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).
- 14.3 Data Submission Procedures.
- a. Southwest Oncology Group 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 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

14.4 WITHIN 7 DAYS OF INITIAL REGISTRATION:

Submit a copy of the following:

- a. **S0801** Prestudy Form (Form #62797)
- b. Lymphoma Baseline Tumor Assessment Form (Form #39601). CT reports are required for the baseline CT scan.
- c. Pathology report confirming histology and CD20+ antigen expression.

14.5 WITHIN 28 DAYS OF INITIAL REGISTRATION:

Submit histopathologic materials (H&E stained section, and paraffin block or 12 unstained slides) along with a copy of the pathology report to the Southwest Oncology Group Lymphoma Repository - University of Arizona (see Section 12.0).

14.6 AT PRESTUDY (PRIOR TO INITIATION OF TREATMENT):

(Optional) Submit tissue (for **SWOG-8819**) and/or serum for (**SWOG-8947**).

14.7 AT THE END OF EACH CYCLE OF INDUCTION R-CHOP TREATMENT:

Submit the **S0801** Induction R-CHOP Treatment Form (Form #23097) and the **S0801** Induction Therapy Adverse Event Form (Form #33275).

14.8 WITHIN 4 – 12 WEEKS AFTER THE COMPLETION OF R-CHOP TREATMENT:

Submit the **S0801** Patient Re-Evaluation Form (Form #19777).

14.9 AFTER COMPLETION OF TOSITUMOMAB TREATMENT:

Submit the **S0801** Tositumomab Treatment Form (Form #57447) and the **S0801** Induction Therapy Adverse Event Form (Form #33275).

14.10 EVERY 3 MONTHS AFTER EACH DOSE OF RITUXIMAB MAINTENANCE THERAPY:

Submit the **S0801** Maintenance Therapy Form (Form #14046) and the **S0801** Maintenance Therapy Adverse Event Form (Form #57656)

14.11 WITHIN 14 DAYS OF DISCONTINUATION OF R-CHOP + I-131 TOSITUMOMAB THERAPY OR RITUXIMAB MAINTENANCE THERAPY:

Submit the Off Treatment Notice (Form #28829).

14.12 THREE MONTHS AFTER OFF TREATMENT:

Submit the **S0801** Induction Therapy Adverse Event Form (Form #33275) (if the patient was on R-CHOP induction therapy) or the **S0801** Maintenance Therapy Adverse Event Form (Form #57656) (if the patient was on rituximab maintenance therapy).

14.13 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of the **S0801** Induction or Maintenance Therapy Adverse Event Form (Form #33275 or Form #57656) and the **S0801** Treatment Form(s) (Form #23097, 57447, or 14046) (if the patient was still on protocol treatment) and the Follow-Up Form (Form #64587) documenting date, site, and method for determining progression/relapse.

14.14 WITHIN 14 DAYS OF EACH DISEASE ASSESSMENT UNTIL PROGRESSION:

Submit the Lymphoma Follow-Up Tumor Assessment Form (Form #27780). CT reports are required for the follow-up CT scans.

14.15 AFTER PROTOCOL TREATMENT: EVERY SIX MONTHS FOR 2 YEARS AND ANNUALLY THEREAFTER UNTIL 7 YEARS AFTER REGISTRATION:

Submit the Follow-Up Form (Form #64587).

14.16 WITHIN FOUR WEEKS OF KNOWLEDGE OF SUBSEQUENT MALIGNANCY:

Submit the Notice of Second Malignancy (Form #27456) documenting date, site, and method for determining malignancy.

14.17 WITHIN FOUR WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death (Form #49467) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Instructions for obtaining institutional approval and training prior to registration and I-131 treatment of patients:

Prior to registration of any patient the registering institution must be approved by GlaxoSmithKline for the delivery of iodine-131 tositumomab antibody therapy. The Site Contact Information Form (Appendix 19.4) and radioactive materials license must be faxed to GlaxoSmithKline at the number listed on the bottom of the form. If approved, GlaxoSmithKline will send the institution an approval notice.

GlaxoSmithKline will contact the institution to provide assistance and to arrange for an on-site training session for iodine-131 tositumomab antibody therapy (if required or requested). Training may occur at any time after initial patient registration, but it must be completed before the patient can receive the iodine-131 tositumomab antibody therapy.

NOTE: GlaxoSmithKline approval and training must be performed prior to I-131 treatment only for the first patient registered to and treated on this study at any one institution. Institutions that have previously completed on-site training for the Southwest Oncology Group studies, S0016 or S0433, or as Expanded Access Program sites (EAP) need not repeat the training. However, retraining is available upon institutional request.

15.2 Institutions are encouraged to submit serum and tissue for banking for future correlative studies (see Section 5.4) by registering to SWOG-8819 and SWOG-8947.

15.3 General Specimen Submission Instructions

a. All submitted specimens must be labeled with the protocol number (**S0801**), SWOG patient number, patient's initials, and date of specimen collection.

b. The Federal Guidelines for Shipment are as follows:

1. The specimen must be wrapped in an absorbable material;
2. The specimen must then be placed in an AIRTIGHT container (like a resealable bag);
3. Pack the resealable bag and specimen in a styrofoam shipping container;
4. Pack the styrofoam shipping container in a cardboard box.
5. The cardboard box must be marked as "BIOHAZARD".

15.4 Specimen Tracking System

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on to the Specimen Tracking system via the CRA Workbench (<https://gill.crab.org/twbt/logon.aspx>) using their SWOG roster ID numbers and passwords. First-time non-SWOG users must refer to start-up instructions located at <https://gill.crab.org/SpecTrack/>.

In the online Specimen Tracking system laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory number for specimen submission is outlined in Section 15.5c.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (<https://gill.crab.org/SpecTrack/Documents/Instructions.pdf>); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

A copy of the Shipment Packing List produced by the Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

15.5 Directions for collecting and shipping serum and tissue samples for banking

a. Serum collection

1. For serum sample collections, institutions should register patients to **SWOG-8947** (Central Lymphoma Serum Repository Protocol).
2. Timing of collection: Serum for **S0801** should be obtained prior to treatment on Day 1 of Cycle 1.
3. Refer to **SWOG-8947** for specimen processing and shipping instructions. **SWOG-8947** provides guidelines on whether to spin/separate sample and when to use cool packs or dry ice depending on the day of the week the specimen is shipped.

b. Tissue collection

1. For tissue sample collection, institutions should register patients to **SWOG-8819** (Central Lymphoma Repository Tissue Procurement Protocol).
2. Timing of collection: Snap-frozen tissue (> 5 mm³, "pea size" to "almond size") from the pre-treatment diagnostic biopsy should be obtained.
3. Refer to **SWOG-8819** for specimen processing and shipping instructions regarding regulations for packaging and use of dry ice.

c. All specimens above should be shipped to the following address:

Lab #2: SWOG Lymphoma Repository – University of Arizona
Arizona Health Science Center
Department of Pathology, Room 5211, Box 245043
1501 North Campbell Avenue
Tucson, AZ 85724-5043

Contact: Yvette Frutiger/Lisa M. Rimsza, M.D.
Phone: 520/626-7477
FAX: 520/626-6081
Email: frutiger@email.arizona.edu

NOTE: DO NOT SEND SPECIMENS ON FRIDAY. SEND MONDAY – THURSDAY ONLY!

15.5 Serum and tissue specimens will be collected and stored at the SWOG Lymphoma Repository until funding is obtained to perform future correlative studies.

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.

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 more timely monitoring of patient safety and care. The following guidelines

prescribe expedited adverse event reporting for this protocol. See also Appendix 19.5 for general and background information about expedited reporting.

b. Reporting methods

- This study requires that expedited adverse event reporting use 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 Southwest Oncology Group Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to CTEP by telephone at 301/897-7497. Once Internet connectivity is restored, a 24-hour notification phoned in, must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1, as applicable.

d. Other recipients of adverse event reports

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

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

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, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received the commercial drug(s).

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 secondary AML/MDS/ALL**

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in CTEP-AERS.
 - i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:
 - Leukemia secondary to oncology chemotherapy
 - Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify, ____)" and insert MDS as the specify term.
 - Treatment related secondary malignancy
 - ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as "Secondary malignancy-Other (specify, ____)". Report MDS as "Myelodysplasia," in the BLOOD/BONE MARROW category.
 - iii. Secondary malignancies other than AML/ALL/MDS that are related to protocol treatment must also be reported in CTEP-AERS.
 - iv. Non-treatment related cases of AML/ALL/MDS must be reported as follows:

In protocols using CTCAE Version 4.0 for SAE reporting, report as "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify"

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as "Myelodysplasia" and Leukemias as "Blood/Bone Marrow - Other (Specify, __)"

For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

2. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

Submit the Report and documentation to:

Investigational Drug Branch **and**
by fax at 301-230-0159

Southwest Oncology Group
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

CLOSED EFFECTIVE MAY 2010

17.0 BIBLIOGRAPHY

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18.0 **MASTER FORMS SET**

- 18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.
- 18.2 This section includes copies of all data forms which must be completed for this study.
- a. **S0801** Registration Worksheet, Registration Step 1 (Form #45592) (12/15/08)
 - b. **S0801** Registration Worksheet, Registration Step 2 (Form #14379) (12/15/08)
 - c. **S0801** Prestudy Form (Form # 62797) (12/1/08)
 - d. **S0801** Induction R-CHOP Treatment Form (Form #23097) (12/1/08)
 - e. **S0801** Tositumomab Treatment Form (Form #57447)
 - f. **S0801** Maintenance Therapy Treatment Form (Form #14046) (12/1/08)
 - g. **S0801** Induction Therapy Adverse Event Form (Form #33275) (12/1/08)
 - h. **S0801** Maintenance Therapy Adverse Event Form (Form # 57656) (12/1/08)
 - i. **S0801** Patient Re-Evaluation Form (Form #19777) (12/1/08)
 - j. Lymphoma Baseline Tumor Assessment Form (Form #39601) (12/15/08)
 - k. Lymphoma Follow-Up Tumor Assessment Form (Form #27780) (12/15/08)
 - l. Off Treatment Notice (Form #28829) (6/15/06)
 - m. Notice of Death (Form #49467) (9/1/03)
 - n. Follow-up Form (Form #64587) (9/15/03)
 - o. Notice of Second Malignancy (Form #27456) (10/15/00)

Informed Consent Model for S0801

*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 Southwest Oncology Group 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 Southwest Oncology Group Operations Office.

Readability Statistics:

Flesch Reading Ease	52.4 (targeted above 55)
Flesch-Kincaid Grade Level	10.2 (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 <http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- 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 <http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035> or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- 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.

S0801, "A Phase II Study of Iodine-131-Labeled Tositumomab in Combination With Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab Therapy for Patients With Advanced Stage Follicular Non-Hodgkin's Lymphoma"

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 follicular B-cell lymphoma. This is a cancer of the lymph nodes, which is rarely cured with current treatments.

Why is this study being done?

Treatment of follicular lymphoma uses a combination of drugs (called CHOP) with an antibody (rituximab). The rituximab antibody is a protein that is partly of mouse origin and partly of human origin. Rituximab attaches to white blood cells (B cells) in your blood and tumor. This leads to death of lymphoma cells using your immune system. These treatments are usually given once every 3 weeks for 6 times.

The Iodine-131 tositumomab antibody is a mouse antibody attached to radioactive Iodine (radiolabeled). These antibodies also attach to white blood cells (B cells) in your blood and tumor. The combination of CHOP chemotherapy and this antibody have been used to treat patients with lymphoma and have been shown to be active against lymphoma. We are doing this experimental study to see if patients treated with CHOP chemotherapy and rituximab followed by I-131 tositumomab followed by long-term rituximab therapy alone may have longer lasting tumor shrinkage, than patients treated with CHOP chemotherapy and rituximab alone.

There are numerous therapeutic options currently utilized for patients with follicular lymphoma. The best responses have been observed when monoclonal antibodies like rituximab and iodine-131 tositumomab are combined with chemotherapy. With these combinations, the length of response may exceed 5 years. The current research study hopes to further improve on these response durations by adding rituximab maintenance therapy to a standard approach, which in other trials has been shown to be safe and well-tolerated.

Researchers would also like to do laboratory testing on tissue samples in order to find out as much as possible about non-Hodgkin's lymphoma and how this treatment might affect the disease. Some of your tissue must be submitted for this

study for testing in order to confirm your type of non-Hodgkin's lymphoma, and evaluate for proteins on the surface of the lymphoma cells. In addition, your bone marrow will be evaluated to determine if the treatment affects normal blood cells over time. If any tissue is left over, you may choose to allow this tissue to be kept for research purposes. Also, you may choose to allow additional tissue and serum to be sent to a lab and used for research purposes.

How many people will take part in the study?

About 80 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 CT scan or PET/CT scan.
- Routine blood and urine tests (to measure your kidney, liver, and thyroid function).
- Hepatitis B virus (HBV) screening (recommended for patients at high risk of infection)
- A MUGA scan or echocardiogram to monitor your heart function.
- You will also have your bone marrow examined (called "bone marrow aspiration and biopsy") at the start of this study. (1/11/10) A bone marrow biopsy will also be taken at the end of treatment with chemotherapy, and at one year after completion of treatment if the first bone marrow biopsy is abnormal. (1/11/10) 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. These are regular tests for many patients with lymphoma. 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. With your consent, bone marrow samples will be sent to a lab and stored for future laboratory studies.
- Your initial biopsy sample will be sent to our pathology laboratory to confirm your diagnosis. Extra tests may be done on your tissue sample to classify your tumor type and to see if a certain protein (CD20) that is targeted with this therapy is present on your tumor cells.

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 laboratory blood tests (to measure your kidney, liver, and thyroid function): Tests will be done on Day of each treatment cycle (every 21 days), 12 weeks after tositumomab treatment is completed, one year after starting treatment, and at follow-up.
- You will receive the drugs cyclophosphamide, doxorubicin, and vincristine and rituximab through a needle in your vein on the first day of each treatment "cycle". Each "cycle" lasts 21 days. You will also receive the drugs acetaminophen and diphenhydramine by mouth before the rituximab to help control pain and prevent possible allergic reaction. You will also take the drug prednisone by mouth (pills) for the first five days of the cycle. This combination of drugs is known as CHOP and rituximab. It will take about 15 - 45 minutes to receive the cyclophosphamide, 5 - 20 minutes for the doxorubicin, and 5 - 15 minutes for the vincristine, and up to 6 hours to receive the rituximab. This treatment will be repeated every 21 days for 6 cycles as long as your disease is getting better. The rituximab will not be given during the last two cycles. If your disease or symptoms get worse, you will stop treatment on this study and be offered other options by your doctor.
- Standard medications will be used to help prevent side effects, such as nausea, fevers, and allergic reactions. Stool softeners will be given to prevent constipation. These medications do not require a prescription, and are commonly used during CHOP and rituximab therapy. In certain cases, your physician may recommend a medication to help prevent kidney problems from death of lymphoma cells ("tumor lysis"). Finally, in certain cases, your physician may suggest a medication to help your body produce red blood cells or white blood cells. In all cases, your physician will provide detailed instructions and information regarding these treatments.
- In addition, about four weeks after you finish the sixth cycle of the rituximab-CHOP chemotherapy, you will receive a test dose of iodine-131 tositumomab (called the "dosimetric" dose). It will take about 1 1/2 hours to receive your test dose. You will first receive the "cold" non-radioactive antibody through your vein over 60 minutes, followed by the "hot" radioactive antibody through your vein over 20 - 30 minutes. Following this test dose, your whole body will be scanned three times with a special machine (called gamma scans) over the period of a week as an outpatient to determine the correct treatment dose of the antibody. One to two weeks after the test dose, you will receive a treatment dose (called the "therapeutic" dose) of the Iodine-131 tositumomab antibody over about 1/2 to 1 hour. You will again receive the "cold" and then the "hot" antibody through your vein as described above. Each time you receive the antibody you will receive the drugs acetaminophen and diphenhydramine before your antibody dose to help control pain and prevent allergic reaction. You will also be given either a potassium iodide solution or potassium iodide tablets to protect your thyroid gland from damage at least 24 hours before you receive the first dose of the iodine -131 tositumomab antibody (dosimetric dose). You will continue to receive the potassium iodide for at least 14 days after you receive the second dose of the antibody (therapeutic dose). You may also receive the drug meperidine if you have trouble with muscle stiffening (rigors) during or

after your infusions. Patients who have bad side effects with the test dose will not receive the treatment dose of the antibody.

- Four or five visits to a nuclear medicine physician will be required during this period of time in order to receive the test dose of I-131-tositumomab, have three gamma scans performed and then receive the treatment dose of I-131 tositumomab. As mentioned above, you will need to take potassium iodide beginning the day before and continuing for several weeks after I-131-tositumomab to prevent damage to your thyroid gland from the radioactive iodine. Depending on the regulations in your state, you may have to stay in "radiation isolation" in the hospital for two to four days following the radiolabeled antibody treatment. If your state permits outpatient therapy with I-131 tositumomab, you will be given special instructions by the nuclear medicine physician on how to limit exposure of other family members to the radioactivity which has been given to you. If your disease or symptoms get worse, you will stop treatment on this study and be offered other treatment by your doctor.
- Beginning approximately 1 year after entering the study, you will receive a single dose of rituximab through a needle in your vein once every 3 months for 4 years. Each single dose will take about 3-4 hours to complete.

How long will I be in the study?

We think it will take you about 5 months to finish the initial CHOP-rituximab + I-131 tositumomab treatments. You will return to your doctor about 3 months after you complete your initial treatment for tests and scans. You will then return for a follow-up visit to your doctor every 3 months for 4 years for rituximab maintenance treatment. During the rituximab maintenance phase of protocol treatment, follow-up visits to your doctor will occur every 6 months.

After completion of rituximab maintenance treatment, you will return to your doctor once a year for a maximum of 7 years (from the time you first entered the study). Your doctor may wish to see you more often.

If you do not complete the rituximab maintenance treatment, you will return to your doctor every 6 months for 2 years, and then once a year for maximum of 7 years (from the time you first entered the study).

Your doctor 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 drug combination can be evaluated by your doctor. (12/15/08) (1/11/10) 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 drug combination. (1/11/10) 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 CHOP chemotherapy treatment (cyclophosphamide, doxorubicin, vincristine, prednisone) include the following:

Likely

- Nausea/vomiting
- Hair loss
- Less appetite
- Blood cell counts go down
- Swelling/puffy appearance (face/stomach area)

Less Likely

- Allergic reaction (like rash, itching, swelling, cough, lowered blood pressure)
- Inflammation of the blood vessels in the skin where the drugs are given
- Sores in the mouth
- Skin and nails change color
- Fingernails and toenails become loose
- Flushing
- Itching of skin
- Headache
- Stomach pain
- Jaw pain
- Weak bones

- **Diarrhea/constipation**
- **Fever**
- **Infection**
- **Chills**
- **Tiredness**
- **Lower or higher blood pressure**
- **Muscle weakness**
- **Tingling in the arms and legs**
- **Itchy, swollen eyes**
- **Watery eyes**
- **Changes in eyesight**
- **Changes in the test to measure heart functions**
- **Bladder irritation (avoided by drinking 8-10 glasses of water a day)**
- **Change in color of urine**
- **Dizziness**
- **Mood swings/depression**
- **Changes in personality**
- **Menstrual changes**

Rare, but Serious

- **Scarring of lungs/shortness of breath**
- **Shaking**
- **Heart failure**
- **Chance of blood cancer**
- **Dehydration requiring intravenous fluids**
- **Pneumonia which may require antibiotics**
- **Your blood counts may become very low from drug. You may be given GCSF to help prevent this risk. If you get fever during the time your blood counts are low, you may require antibiotic therapy, or admission to the hospital. Severe, life-threatening infections may occur under these circumstances. Your physician will provide detailed instructions on what to do if you get fever.**

Risks and side effects related to the antibody rituximab include the following:

Likely

- **Fever**
- **Chills**
- **(deleted 6/3/10)**
- **(updated and moved to Less Likely 6/3/10)**
- **(updated and moved to Less Likely 6/3/10)**
- **Decreased number of a type of white blood cell (lymphocyte) (updated 6/3/10)**
- **Reaction that can occur during or following the infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.**
(updated and added from Rare but Serious 6/3/10)

Less Likely

- **Vomiting**
- **Diarrhea**
- **Headache or head pain (updated 6/3/10)**
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump) (updated 6/3/10)**
- **Hives (updated 6/3/10)**
- **Swelling of body tissue underneath the skin (updated 6/3/10)**
- **Sudden reddening of the face and/or neck (updated 6/3/10)**
- **Cough (updated 6/3/10)**
- **Sore throat (updated 6/3/10)**
- **(deleted 6/3/10)**
- **Joint pain (updated 6/3/10)**
- **Back pain (updated 6/3/10)**
- **Muscle pain (updated 6/3/10)**
- **Belly pain (updated 6/3/10)**
- **Pain in the area of the tumor (updated 6/3/10)**
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness) (updated 6/3/10)**
- **(deleted 6/3/10)**
- **(deleted 6/3/10)**
- **(deleted 6/3/10)**
- **(deleted 6/3/10)**
- **Excess sweating (updated 6/3/10)**
- **Lack of enough red blood cells (anemia) (updated 6/3/10)**
- **Decreased number of a type of red blood cell that help to clot blood (platelet) (updated 6/3/10)**
- **(deleted 6/3/10)**
- **High blood pressure (updated 6/3/10)**
- **Low blood pressure (updated 6/3/10)**
- **(deleted 6/3/10)**
- **Swelling of the arms and/or legs (updated 6/3/10)**
- **Stuffy or runny nose, sneezing (updated 6/3/10)**
- **Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath (updated 6/3/10)**
- **(deleted 6/3/10)**
- **Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. (updated 6/3/10)**
- **Thickening of blood/serum as found in Waldenstrom's macroglobulinemia (a cancer of certain blood cells) (added 6/3/10)**
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils) (added 6/3/10)**

- **Heart attack caused by a blockage of a blood vessel supplying part of the heart** (*added 6/3/10*)
- **Fast heartbeat; regular rhythm** (*added 6/3/10*)
- **Fast heartbeat usually originating in an area located above the ventricles** (*added 6/3/10*)
- **Nausea or the urge to vomit** (*updated and moved from Likely*)
- **Fatigue or tiredness** (*updated and moved from Likely*)
- **Pain** (*added 6/3/10*)
- **Allergic reaction to certain medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance)** (*added 6/3/10*)
- **Infection** (*added 6/3/10*)
- **Awakening of viruses which have been latent/dormant** (*added 6/3/10*)
- **Infection in HIV positive patients** (*added 6/3/10*)
- **Decreased number of a type of white blood cell (neutrophil/granulocyte)** (*added 6/3/10*)
- **Decrease in the total number of white blood cells (leukocytes)** (*added 6/3/10*)
- **Increased blood sugar level** (*added 6/3/10*)
- **Decreased blood level of calcium** (*added 6/3/10*)
- **Decreased blood level of potassium** (*added 6/3/10*)
- **Abnormal drowsiness or sluggishness, an unusual lack of energy** (*added 6/3/10*)
- **Convulsion or seizures** (*updated and added from Rare but Serious 6/3/10*)
- **Sudden or traumatic injury to the kidney** (*updated and added from Rare but Serious 6/3/10*)
- **Shortness of breath** (*added 6/3/10*)
- **Decrease in the oxygen supply to a tissue** (*added 6/3/10*)
- **Inflammation of the lungs that may cause difficulty breathing and can be life-threatening** (*added 6/3/10*)
- **Itching** (*added 6/3/10*)

Rare, but serious

- (*deleted 6/3/10*)
- (*updated and moved to Less Likely 6/3/10*)
- (*updated and moved to Less Likely 6/3/10*)
- (*deleted 6/3/10*)
- **Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure.** (*updated 6/3/10*)
- (*updated and moved to Likely 6/3/10*)
- (*deleted 6/3/10*)

- *(deleted 6/3/10)*
- *(deleted 6/3/10)*
- **Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.** *(added 6/3/10)*
- **Disease affecting brain tissue, caused by the JC virus.** *(added 6/3/10) (9/24/10)*
- **Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs** *(added 6/3/10)*
- **Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue** *(added 6/3/10)*
- **Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)** *(added 6/3/10)*
- **Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)** *(added 6/3/10)*

CLOSED EFFECTIVE 12/15/2010

Immunizations: The safety of immunization with any vaccine, particularly live viral vaccines, following rituximab therapy has not been studied. It is recommended that you consult with your doctor before receiving immunizations following rituximab therapy.

Risks and side effects related to the antibody tositumomab include the following:

Likely

- Fever
- Weakness
- Chills
- Loss of appetite
- Nausea/vomiting
- Diarrhea
- Rash
- Tumor site pain
- Decrease in blood counts

Less Likely

- Lowered blood pressure causing lightheadedness/dizziness
- Allergic reaction including rash, hives, itching, shortness of breath
- Development of "human anti-mouse antibodies" (limiting ability for further treatment with antibodies)
- Infection
- Joint pain
- Muscle pain
- Abdominal pain
- Headache
- Nose inflammation
- Throat inflammation
- Cough
- Diarrhea
- Reduced thyroid gland activity (fatigue, feeling cold, dry skin, constipation)
- Rapid heartbeat at time of injection
- Flushing
- Numbness
- Infrequent urination
- Bronchitis

Rare, but Serious

- Severe allergic reaction
- Bone marrow damage

- Chance of developing acute leukemia or other cancers
- Increased calcium and/or potassium
- Increased uric acid
- Kidney failure
- Blood clot in the lung

Reproductive risks: You should not become 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 this experimental technique will be more useful against 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 non-Hodgkin's lymphoma 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;
- The Southwest Oncology Group
- GlaxoSmithKline (the manufacturer of tositumomab)

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 drug will be (*provided free of charge/charged in the usual way*). The parts of the research consisting of keeping research records 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 cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab are commercially available. Iodine-131 tositumomab is also commercially available, but will be supplied for this study by GlaxoSmithKline at no cost to you.

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/understanding/insurance-coverage>. 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.

Occasionally, researchers working with the Southwest Oncology Group (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.

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 for use of excess diagnostic tissue for research purposes.

Preserved tissue from your tumor must be submitted for this study in order to confirm your type of non-Hodgkin's lymphoma. There may be some tissue remaining once your diagnosis has been confirmed. If you are willing to allow this excess tissue to be used for research purposes, please specify your consent below.

Also, if you are willing to submit additional frozen and preserved tissue and blood for research purposes, you will be registered to the Central Lymphoma Repository Tissue Procurement Protocol, **SWOG-8819** and/or the Central Lymphoma Serum Repository Protocol, **SWOG-8947**. Your responses will also apply to any specimens sent for these studies.

CLOSED EFFECTIVE 12/15/2010



SWOG Lymphoma Repository
c/o Lisa M. Rimsza, M.D.
Arizona Health Science Center
Department of Pathology, Room 5211, Box 245043
1501 North Campbell Avenue
Tucson, AZ 85724-5043
Phone: 520/626-7477

Consent Form for Use of Specimens for Research

About Using Specimens for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some tissue and blood to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

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 is 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 the Southwest Oncology Group 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.

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 may be kept for use in research to learn about, prevent, treat, or cure cancer. (1/11/10)**

Yes No

- 2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease). (1/11/10)**

Yes No

- 3. Someone may contact me in the future to ask me to allow other uses of my specimen. (1/11/10)**

Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group 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 _____

Date _____

CLOSED EFFECTIVE 12/15/2010

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 the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, 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 the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group 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 the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group 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 to the researcher. The researcher will not know who you are.

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

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group 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).

CLOSED EFFECTIVE 12/15/2010

SOUTHWEST ONCOLOGY GROUP S0801 REGISTRATION WORKSHEET

Page 1 of 2

A Phase II Study of Iodine-131-Labeled Tositumomab in Combination with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab Therapy for Patients with Advanced Stage Follicular Non-Hodgkin's Lymphoma

Activation Date: December 1, 2008

Last Amended Date:

Registration Step: **1**

INSTRUCTIONS: All of the information on this Registration Worksheet and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Worksheet must be entirely filled out and referred to during the registration. **Do NOT submit this worksheet as part of the patient data.**

Registrar's SWOG Roster ID Number:

SWOG Investigator Number:

SWOG Patient ID Status: New Patient Previous Patient:

SWOG Patient ID:

If the patient has a SWOG Patient ID assigned by a prior registration or Specimen Tracking, choose "Previous Patient" and use that number.

SWOG Treating Institution Number:

Check that IRB approval is current for this institution prior to registering. Registrations are not allowed if the IRB approval is expired.

Date Informed Consent Signed: / /

Date HIPAA Authorization signed: / / (Not required if Country of Residence is not USA)

Projected Start Date of Treatment: / /

Patient's Name: _____ (Full names preferred, initials OK)

Patient's Date of Birth: / /

Country of Residence: US (USA) CA (Canada) Other: _____

If USA, Patient Social Security Number: - - ZIP Code:

If Canada, Social Insurance Number: - - Postal Code: -

Both Social Security Number and Social Insurance Number are desired, but optional. Do not enter invalid numbers in either field.

Patient's Race (select all that apply):

- White Native Hawaiian or Other Pacific Islander American Indian or Alaska Native
 Black or African American Asian Unknown

Patient's Ethnicity:

- No (not Spanish) Yes, Mexican Yes, Puerto Rican Yes, Cuban Yes, Central American
 Yes, South American Yes, NOS Yes, Other: _____ Unknown

Method of Payment:

- Private insurance Veterans-sponsored Military or Veterans-sponsored, NOS Medicare
 Medicare and Private insurance Medicaid Medicaid and Medicare Self Pay (no insurance)
 No means of payment (no insurance) Unknown Other: _____

Patient Gender: Female Male

continued on next page

45592

12/1/2008



**SOUTHWEST ONCOLOGY GROUP
S0801 REGISTRATION WORKSHEET**

Page 2 of 2

Indicate how the patient answered the following questions on the consent form

If this is not the EXACT WORDING on the consent form, phone in the registration and tell the registrar how the wording was changed.

- My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer. Yes No
- My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease). Yes No
- Someone may contact me in the future to ask me to allow other uses of my specimens. Yes No
- 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

Has the Southwest Oncology Group Registration Worksheet been completed entirely and is the patient eligible according to the current version of protocol section 5.0?

Yes No

Comments (notes from Confirmation of Registration):

SWOG Patient ID:

Assigned Treatment Arm:

Treatment Name: _____

Expectations Notes:

Other Notes:

45592

12/1/2008



**SOUTHWEST ONCOLOGY GROUP
S0801 REGISTRATION WORKSHEET**

Page 1 of 1

A Phase II Study of Iodine-131-Labeled Tositumomab in Combination with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab Therapy for Patients with Advanced Stage Follicular Non-Hodgkin's Lymphoma

Activation Date: December 1, 2008
Last Amended Date:
Registration Step: **2**

INSTRUCTIONS: All of the information on this Registration Worksheet and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Worksheet must be entirely filled out and referred to during the registration. **Do NOT submit this worksheet as part of the patient data.**

Registrar's SWOG Roster ID Number:

SWOG Investigator Number:

SWOG Patient ID Status: New Patient Previous Patient:

SWOG Patient ID:

SWOG Treating Institution Number:

Projected Start Date of Treatment: / /

Method of Payment:

- Private insurance Veterans-sponsored Military or Veterans-sponsored, NOS Medicare
 Medicare and Private insurance Medicaid Medicaid and Medicare Self Pay (no insurance)
 No means of payment (no insurance) Unknown Other: _____

Has the Southwest Oncology Group Registration Worksheet been completed entirely and is the patient eligible according to the current version of protocol section 5.0?

Yes No

Comments (notes from Confirmation of Registration):

Assigned Treatment Arm: Treatment Name: _____

Other Notes:

14379

12/1/2008



SOUTHWEST ONCOLOGY GROUP
S0801 PRESTUDY FORM

Page 1 of 3

SWOG Patient ID

SWOG Study No. S 0 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Instructions: Submit this form within 14 days of registration. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ELIGIBILITY VERIFICATION:

Each of the fields below corresponds to a criterion in Section 5 and must be completed for patient to be eligible.

PATIENT AND DISEASE DESCRIPTION

Performance status:

Date of first pathologic diagnosis: / / /

Stage of disease at diagnosis: I II III IV

Does the patient have bulky disease (any mass ≥ 10 cm in diameter or a mediastinal mass $> 1/3$ chest diameter)? No Yes

Symptoms: A (No Symptoms) B (Fever, Weight Loss, and/or Night Sweats)

Has the patient received any prior chemotherapy, radiation, or antibody treatment for lymphoma? No Yes

Date of unilateral or bilateral bone marrow biopsy and aspirate: / / /

Result: Positive Negative

Date of chest CT scan: / / /

Date of abdomen/pelvis CT scan: / / /

(Note: CT scans may have been performed at the same time or separately)

Were any laboratory or radiographic tests performed to assess CNS involvement? No Yes

Date of tests to assess CNS involvement: / / /

Result: Positive Negative

LABORATORY VALUES Document values in units listed

Hematologic:

ANC , / mcL

Platelets , / mcL

WBC . $\times 10^3$ / mcL

Lymphocytopenia (% of total WBC)

Hemoglobin . g/dL

Serum Beta2 Microglobulin . $\mu\text{g}/\text{mL}$

Collection date:

/ / /

/ / /

/ / /

/ / /

/ / /

12/1/2008

62797



SOUTHWEST ONCOLOGY GROUP
S0801 PRESTUDY FORM

Page 2 of 3

SWOG Patient ID

SWOG Study No. S 0 1

Registration Step 1

Patient Initials _____ (L, F M)

LABORATORY VALUES, continued

Hepatic:

Collection date:

Total bilirubin . mg/dL ULN . mg/dL / /

Please record the appropriate transaminase lab value:

SGOT U/L ULN U/L / /

OR

SGPT U/L ULN U/L / /

Renal:

Collection date:

Serum creatinine . mg/dL ULN . mg/dL / /

LDH:

U/L ULN U/L / /

Cardiac:

Collection date:

Ejection fraction (select one) MUGA ECHO
 % / /

ADDITIONAL PRESTUDY DATA:

CURRENT LYMPHATIC TISSUE INVOLVEMENT

Is there current nodal involvement above the diaphragm? No Yes

If Yes, number of sites involved above the diaphragm*:

Is there current nodal involvement below the diaphragm? No Yes

If Yes, number of sites involved below the diaphragm*:

Is there current splenic involvement? No Yes

* Instructions for counting the number of involved nodal sites are on page 3 of this form.

CURRENT EXTRANODAL INVOLVEMENT

Is there current extranodal involvement? No Yes

If Yes, select all that apply: Bone Marrow Lung Liver CNS/Brain
 GI Tract Other: _____

12/1/2008

continued on next page

62797



**SOUTHWEST ONCOLOGY GROUP
S0801 PRESTUDY FORM**

Page 3 of 3

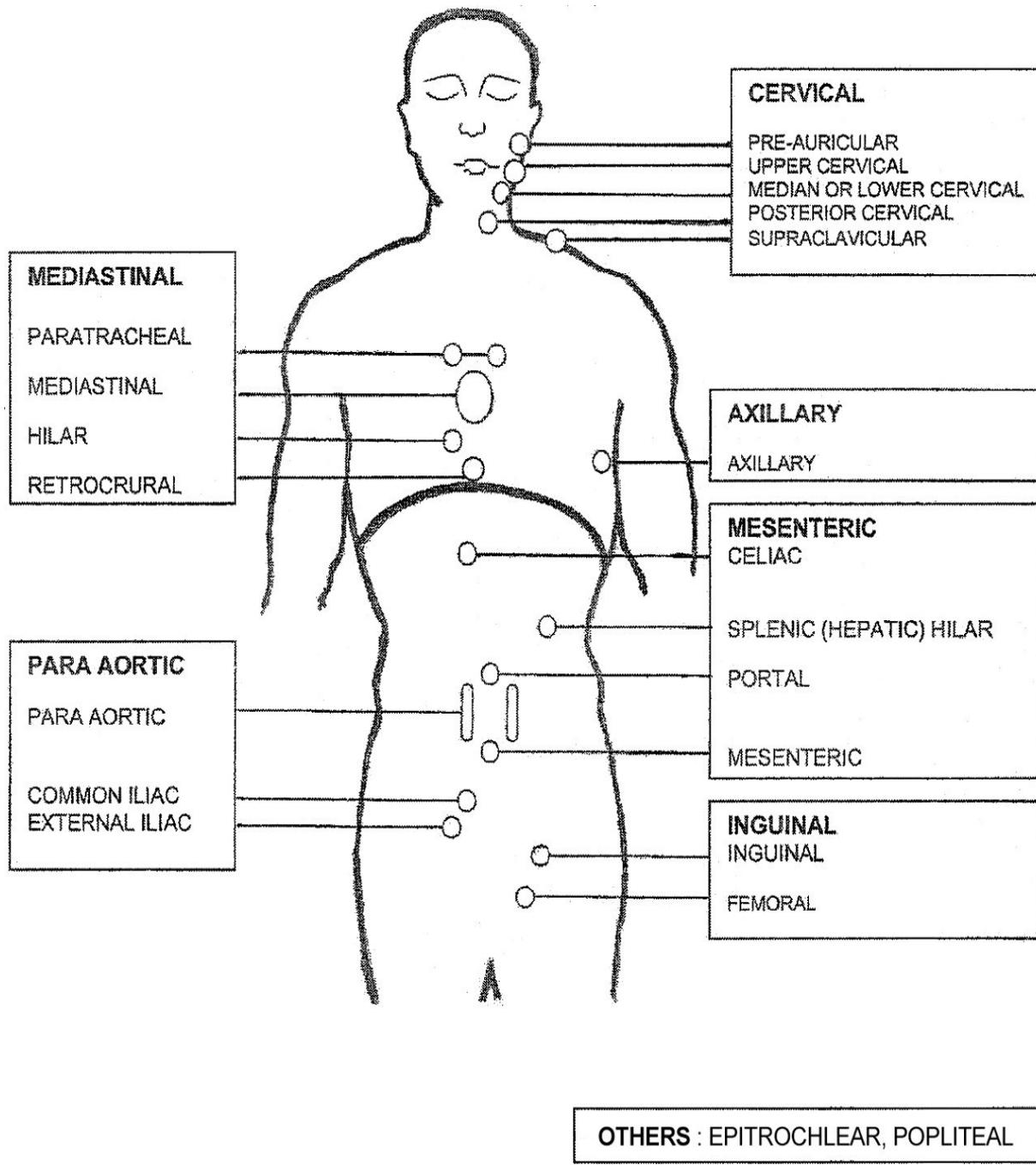
SWOG Patient ID

SWOG Study No. S 0 8 0 1

Registration Step 1

Patient Initials _____ (L, F M)

Instructions: The figure below indicates how to count the number of involved nodal sites according to Solal-Celigny et al., *Blood*, 2004. Each box represents a nodal area. Multiple involved nodes within a single nodal area (or box) are counted as 1 nodal site. Bilateral disease is counted as 2 nodal sites. Bilateral nodal areas include axillary, cervical, inguinal, epitrochlear, and popliteal. The mediastinal, mesenteric, and para aortic nodal areas are not considered to be bilateral; in these cases multiple involved nodes from each are counted as at most only 1 nodal site. Iliac nodes are a component of the para aortic nodal area and are also NOT considered to be bilateral. (Note: Other non-bilateral sites include preaortic and subcarinal; these are counted as 1 nodal site.)



Comments:

12/1/2008

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SOUTHWEST ONCOLOGY GROUP
S0801 INDUCTION R-CHOP TREATMENT FORM

SWOG Patient ID

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SWOG Study No. S 0 8 0 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after each cycle (*1 cycle = 21 days*) of induction R-CHOP therapy. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in a **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

STATUSDate of Last Contact or Death:

--	--	--

 /

--	--	--

 /

--	--	--	--	--

Vital Status: Alive Dead

(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? No Yes

(submit Follow-up Form)

TREATMENT FOR THIS CYCLECurrent Cycle Number

--	--

(see instructions)

Cycle start date:

--	--	--

 /

--	--	--

 /

--	--	--	--	--

Weight (first day this cycle):

--	--	--

.

--	--

 kgDate of last treatment for this cycle:

--	--	--

 /

--	--	--

 /

--	--	--	--	--

BSA (first day this cycle):

--	--

.

--	--

 m²

Were there any dose modifications or additions/omissions to protocol treatment?

 No Yes, planned (per protocol guidelines), specify in comments Yes, unplanned (not per protocol guidelines), specify in comments

Report total dose/number of days for reporting period

Agent	Total Dose	Number of Days						
Cyclophosphamide	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td><td> </td></tr></table> mg					<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td></tr></table>		
Doxorubicin	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table> mg				<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td></tr></table>			
Vincristine	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td>.</td><td> </td></tr></table> mg		.		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td></tr></table>			
	.							
Prednisone	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table> mg				<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td></tr></table>			
Rituximab	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td><td> </td></tr></table> mg					<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td></tr></table>		

Comments:

23097

(TX0801I)

12/1/2008



SOUTHWEST ONCOLOGY GROUP
S0801 TOSITUMOMAB TREATMENT FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S | 0 | 8 | 0 | 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form at the end of I-131 treatment. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in a **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

STATUS

Date of Last Contact or Death: / /

Vital Status: Alive Dead

(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? No

Yes

(submit Follow-up Form)

TOSITUMOMAB TREATMENT

Start date: / /

Weight (first day this cycle): . kg

Date of last treatment: / /

BSA (first day this cycle): . m²

Were there any dose modifications or additions/omissions to protocol treatment?

No

Yes, planned (per protocol guidelines), specify in comments

Yes, unplanned (not per protocol guidelines), specify in comments

Report total dose for reporting period

Agent	Dose
Dosimetric: Unlabeled Tositumomab	 mg
Dosimetric: I-131 labeled Tositumomab	 mg
Dosimetric: Iodine-131 dose	 mCi
Therapeutic: Unlabeled Tositumomab	 mg
Therapeutic: I-131 labeled Tositumomab	 mg
Therapeutic: Iodine-131 dose	 mCi

Comments:



SOUTHWEST ONCOLOGY GROUP
S0801 MAINTENANCE THERAPY TREATMENT FORM

SWOG Patient ID

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SWOG Study No. S 0 8 0 1

Registration Step

2

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after each cycle (*1 cycle = 3 months*) of rituximab maintenance therapy. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in a **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

STATUSDate of Last Contact or Death:

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Vital Status: Alive Dead

(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? No Yes

(submit Follow-up Form)

TREATMENT FOR THIS CYCLECurrent Cycle Number

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Cycle start date:

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Weight (first day this cycle):

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 kgDate of last treatment for this cycle:

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BSA (first day this cycle):

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 m²

Were there any dose modifications or additions/omissions to protocol treatment?

- No
- Yes, planned (per protocol guidelines), specify in comments
- Yes, unplanned (not per protocol guidelines), specify in comments

Total dose of Rituximab for this reporting period:

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 mg**Comments:**

SOUTHWEST ONCOLOGY GROUP
S0801 INDUCTION THERAPY ADVERSE EVENT FORM

SWOG Patient ID SWOG Study No. **S 0 8 0 1**Registration Step **1**

Patient Initials _____ (L, F M) Institution/Affiliate _____ Physician _____

Cycle submission: R-CHOP cycle 1 R-CHOP cycle 4 R-CHOP cycle 6
 R-CHOP cycle 2 R-CHOP cycle 5 Post I-131 tx
 R-CHOP cycle 3

Instructions: Please complete this form at the end of every cycle of R-CHOP (cycles 1-6) and 2 weeks after completion of I-131 therapy. Report adverse events occurring up until the next cycle of treatment begins. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

ADVERSE EVENTS Reporting period start date: / / (Day 1 of this Cycle)
 Reporting period end date: / / (Day one of next cycle. If final cycle, date of first visit or contact after resolution of acute adverse events.)

Were adverse events assessed during this time period?

- No Yes, but no reportable adverse events occurred
 Yes, and reportable adverse events occurred (report below)

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
IM00	Allergic reaction	<input type="checkbox"/>	<input type="checkbox"/>	SK11	Rash	<input type="checkbox"/>
HE20	Hemoglobin	<input type="checkbox"/>	<input type="checkbox"/>	GI01	Anorexia	<input type="checkbox"/>
HE00	Leukocytes	<input type="checkbox"/>	<input type="checkbox"/>	GI23	Dehydration	<input type="checkbox"/>
HE40	Lymphopenia	<input type="checkbox"/>	<input type="checkbox"/>	GI20	Diarrhea	<input type="checkbox"/>
HE30	Neutrophils	<input type="checkbox"/>	<input type="checkbox"/>	GI00	Nausea	<input type="checkbox"/>
HE10	Platelets	<input type="checkbox"/>	<input type="checkbox"/>	GI10	Vomiting	<input type="checkbox"/>
CA50	Hypertension	<input type="checkbox"/>	<input type="checkbox"/>	IN30	Febrile neutropenia	<input type="checkbox"/>
CA51	Hypotension	<input type="checkbox"/>	<input type="checkbox"/>		Infection with Grade 0-2 ANC	
CA06	Left ventricular diastolic dysfunction	<input type="checkbox"/>	<input type="checkbox"/>	INL05	Lung	<input type="checkbox"/>
CA07	Left ventricular systolic dysfunction	<input type="checkbox"/>	<input type="checkbox"/>		Infection with Grade 3-4 ANC	
CL20	PTT	<input type="checkbox"/>	<input type="checkbox"/>	ICL05	Lung	<input type="checkbox"/>
FL40	Fatigue	<input type="checkbox"/>	<input type="checkbox"/>		Infection with unknown ANC	
FL01	Fever	<input type="checkbox"/>	<input type="checkbox"/>	IUL05	Lung	<input type="checkbox"/>
FL20	Insomnia	<input type="checkbox"/>	<input type="checkbox"/>	LY01	Edema: head and neck	<input type="checkbox"/>
FL10	Rigors/chills	<input type="checkbox"/>	<input type="checkbox"/>	LY02	Edema: limb	<input type="checkbox"/>
FL30	Sweating	<input type="checkbox"/>	<input type="checkbox"/>	LY03	Edema: trunk/genital	<input type="checkbox"/>
SK90	Alopecia	<input type="checkbox"/>	<input type="checkbox"/>	LY04	Edema: visceral	<input type="checkbox"/>

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

continued on next page

33275

12/1/2008



SOUTHWEST ONCOLOGY GROUP
S0801 INDUCTION THERAPY ADVERSE EVENT FORM

SWOG Patient ID SWOG Study No. S 0 8 0 1Registration Step 1

Patient Initials _____ (L, F M)

Cycle submission: R-CHOP cycle 1 R-CHOP cycle 4 R-CHOP cycle 6
 R-CHOP cycle 2 R-CHOP cycle 5 Post I-131 tx
 R-CHOP cycle 3

ADVERSE EVENTS, continued

	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*		CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
				CTC Adverse Event Term	CTC Adverse Event Term
LY05	Lymphedema - related fibrosis	<input type="checkbox"/>	<input type="checkbox"/>	PAM14	Muscle
ME04	AST	<input type="checkbox"/>	<input type="checkbox"/>	LU00	Dyspnea
ME05	Bilirubin	<input type="checkbox"/>	<input type="checkbox"/>	LU10	Hypoxia
ME06	Creatinine	<input type="checkbox"/>	<input type="checkbox"/>	GU53	Renal failure
ME31	Hyperglycemia	<input type="checkbox"/>	<input type="checkbox"/>	GU03	Urinary frequency
ME30	Hypoglycemia	<input type="checkbox"/>	<input type="checkbox"/>	SY10	Tumor lysis syndrome
ME90	Hypophosphatemia	<input type="checkbox"/>	<input type="checkbox"/>		
NR50	Neuropathy-motor	<input type="checkbox"/>	<input type="checkbox"/>		
NR60	Neuropathy-sensory	<input type="checkbox"/>	<input type="checkbox"/>		
	Pain			CTC Adverse Event Term, Other <i>(specify using CTCAE 3.0 terminology)</i>	
PAM02	Bone	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>
PAN37	Headache	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>
PAM11	Joint	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments: (Please explain any "other" adverse events reported above)

33275

12/1/2008



SOUTHWEST ONCOLOGY GROUP
S0801 MAINTENANCE THERAPY ADVERSE EVENT FORM

SWOG Patient ID

SWOG Study No. S 0 8 0 1

Registration Step 2Patient Initials (L, F M)Current Cycle Number:

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form at the end of every cycle (*1 cycle = 3 months*) of rituximab maintenance therapy. Report adverse events occurring up until the next cycle of treatment begins. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

ADVERSE EVENTS		Reporting period start date: <input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> (Day 1 of this Cycle)		
		Reporting period end date: <input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> (Day one of next cycle. If final cycle, date of first visit or contact after resolution of acute adverse events.)		
Were adverse events assessed during this time period?				
<input type="checkbox"/> No <input type="checkbox"/> Yes, but no reportable adverse events occurred <input type="checkbox"/> Yes, and reportable adverse events occurred (report below)				
CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
IM00	<input type="checkbox"/>	<input type="checkbox"/>	SK11	<input type="checkbox"/>
HE20	<input type="checkbox"/>	<input type="checkbox"/>	GI01	<input type="checkbox"/>
HE00	<input type="checkbox"/>	<input type="checkbox"/>	GI23	<input type="checkbox"/>
HE40	<input type="checkbox"/>	<input type="checkbox"/>	GI20	<input type="checkbox"/>
HE30	<input type="checkbox"/>	<input type="checkbox"/>	GI00	<input type="checkbox"/>
HE10	<input type="checkbox"/>	<input type="checkbox"/>	GI10	<input type="checkbox"/>
CA50	<input type="checkbox"/>	<input type="checkbox"/>	IN30	<input type="checkbox"/>
CA51	<input type="checkbox"/>	<input type="checkbox"/>	Infection with Grade 0-2 ANC	
CA06	<input type="checkbox"/>	<input type="checkbox"/>	INL05	<input type="checkbox"/>
CA07	<input type="checkbox"/>	<input type="checkbox"/>	Infection with Grade 3-4 ANC	
CL20	<input type="checkbox"/>	<input type="checkbox"/>	ICL05	<input type="checkbox"/>
FL40	<input type="checkbox"/>	<input type="checkbox"/>	Infection with unknown ANC	
FL01	<input type="checkbox"/>	<input type="checkbox"/>	IUL05	<input type="checkbox"/>
FL20	<input type="checkbox"/>	<input type="checkbox"/>	LY01	<input type="checkbox"/>
FL10	<input type="checkbox"/>	<input type="checkbox"/>	LY02	<input type="checkbox"/>
FL30	<input type="checkbox"/>	<input type="checkbox"/>	LY03	<input type="checkbox"/>
SK90	<input type="checkbox"/>	<input type="checkbox"/>	LY04	<input type="checkbox"/>

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

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12/1/2008



57656

SOUTHWEST ONCOLOGY GROUP
S0801 MAINTENANCE THERAPY ADVERSE EVENT FORM

SWOG Patient ID SWOG Study No. S 0 8 0 1Registration Step 2Patient Initials (L, F M)Current Cycle Number: **ADVERSE EVENTS, continued**

	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*		CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*	
LY05	Lymphedema - related fibrosis	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	PAM14	Muscle	<input type="checkbox"/> <input type="checkbox"/>
ME04	AST	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	LU00	Dyspnea	<input type="checkbox"/> <input type="checkbox"/>
ME05	Bilirubin	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	LU10	Hypoxia	<input type="checkbox"/> <input type="checkbox"/>
ME06	Creatinine	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	GU53	Renal failure	<input type="checkbox"/> <input type="checkbox"/>
ME31	Hyperglycemia	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	GU03	Urinary frequency	<input type="checkbox"/> <input type="checkbox"/>
ME30	Hypoglycemia	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	SY10	Tumor lysis syndrome	<input type="checkbox"/> <input type="checkbox"/>
ME90	Hypophosphatemia	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>			
NR50	Neuropathy-motor	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>			
NR60	Neuropathy-sensory	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>			
	Pain				CTC Adverse Event Term, Other (specify using CTCAE 3.0 terminology)	
PAM02	Bone	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
PAN37	Headache	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
PAM11	Joint	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>

* Attribution codes: 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments: (Please explain any "other" adverse events reported above)

57656

12/1/2008



**SOUTHWEST ONCOLOGY GROUP
S0801 PATIENT RE-EVALUATION FORM**

Page 1 of 1

SWOG Patient ID

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SWOG Study No. S

0	8	0	1
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Registration Step

1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Instructions: Please complete this form after patient re-evaluation 4-8 weeks after the completion of R-CHOP chemotherapy. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

BONE MARROW INVOLVEMENT

Date of bone marrow biopsies to assess lymphoma involvement after 6 cycles of R-CHOP:

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Mean intrabecular marrow space involvement after 6 cycles of R-CHOP:

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LABORATORY VALUES *Note: Lab values must be collected within 14 days of the planned dosimetric infusion.*

Hematologic:

Collection date:

AGC

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 / mcL

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Peripheral platelet count

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 / mcL

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TOSITUMOMAB TREATMENT SCHEDULE

Will patient receive Tositumomab therapy? Yes No

If Yes, planned date of dosimetric infusion:

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Comments:

(S0801EVAL)

12/1/2008

19777


SOUTHWEST ONCOLOGY GROUP
LYMPHOMA BASELINE TUMOR ASSESSMENT FORM

Page 1 of 2

SWOG Patient ID

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SWOG Study No. S

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Registration Step

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Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Record the requested information for all measurable lesions and all sites of non-measurable disease, including sites visualized only by PET scan. Please refer to Section 10.1 of the protocol for definitions. If an organ or site has too many measurable lesions to measure at each evaluation, choose three to follow as measurable disease and record the rest as evaluable disease. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

SITES OF MEASURABLE LESIONS

Sites	Tumor Measurement (cm)		Assessment Code*	Date of Assessment	PET Status **
L1		.	x		
L2		.	x		
L3		.	x		
L4		.	x		
L5		.	x		
L6		.	x		

SITES OF NON-MEASURABLE DISEASE

Other Sites of Disease	Extent	Assessment Code*	Date of Assessment	PET Status **
S1				
S2				
S3				
S4				
S5				

Sites Visualized Only by PET Scan

P1	P2	P3	P4	P5	Date of Assessment	

* Assessment Codes:	05-Endoscopy	14-Radioisotope scan	99-Other (specify below and indicate lesion number)
01-Palpation	10-Plain film/X-ray without contrast	15-Ultrasound	
02-Visualization	11-Plain film/X-ray with contrast	17-Spiral CT scan	
03-Colposcopy	12-CT scan	20-Histologic confirmation	
04-CA-125 assay	13-MRI scan	21-Cytologic confirmation	

**** PET Status:** 0-Negative 1-Positive 8-Not applicable 9-Not imaged by PET

continued on next page

39601

(CORETB_BTA)

12/15/2008



SOUTHWEST ONCOLOGY GROUP
LYMPHOMA BASELINE TUMOR ASSESSMENT FORM

Page 2 of 2

SWOG Patient ID

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SWOG Study No. S

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Registration Step

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Patient Initials _____ (L, F M)

List all **negative** diagnostic tests/studies used to evaluate patient for malignancy.

Tests/studies

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Tests/studies

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Comments:

39601

12/15/2008



SOUTHWEST ONCOLOGY GROUP

Page 1 of 2

LYMPHOMA FOLLOW-UP TUMOR ASSESSMENT FORM

SWOG Patient ID SWOG Study No. S Registration Step

Patient Initials _____ (L, F M)

Reporting Period Start Date: / /

Institution / Affiliate _____

Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Record the requested information for all measurable lesions and all sites of non-measurable disease, including sites visualized only by PET scan. Please refer to Section 10.1 of the protocol for definitions. If an organ or site has too many measurable lesions to measure at each evaluation, choose three to follow as measurable disease and record the rest as evaluable disease. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

SITES OF MEASURABLE LESIONS

Sites	Tumor Measurement (cm)			Assessment Code*	Date of Assessment	PET Status **												
	<input type="text"/>	.	<input type="text"/>		<input type="text"/>													
L1	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
L2	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
L3	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
L4	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
L5	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
L6	<input type="text"/>	.	<input checked="" type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>

SITES OF NON-MEASURABLE DISEASE

Other Sites of Disease	Extent	Assessment Code*	Date of Assessment	PET Status **					
			<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>
S1		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>
S2		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>
S3		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>
S4		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>
S5		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	.	<input type="text"/>

Sites Visualized Only by PET Scan

P1	P2	P3	P4	P5	Date of Assessment													
					<input type="text"/>	/	<input type="text"/>	.		<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
					<input type="text"/>	/	<input type="text"/>	.		<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
					<input type="text"/>	/	<input type="text"/>	.		<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
					<input type="text"/>	/	<input type="text"/>	.		<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>
					<input type="text"/>	/	<input type="text"/>	.		<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>	/	<input type="text"/>	.	<input type="text"/>

* Assessment Codes:	05-Endoscopy	14-Radioisotope scan	99-Other (specify below and indicate lesion number)
01-Palpation	10-Plain film/X-ray without contrast	15-Ultrasound	
02-Visualization	11-Plain film/X-ray with contrast	17-Spiral CT scan	
03-Colposcopy	12-CT scan	20-Histologic confirmation	
04-CA-125 assay	13-MRI scan	21-Cytologic confirmation	

**** PET Status:** 0-Negative 1-Positive 8-Not applicable 9-Not imaged by PET

(CORETB_FUTA)

12/15/2008



27780

LYMPHOMA FOLLOW-UP TUMOR ASSESSMENT FORM

SWOG Patient ID SWOG Study No. S Registration Step

Patient Initials _____ (L, F M)

Reporting Period Start Date: / /

List all **negative** diagnostic tests/studies used to evaluate patient for malignancy.

Tests/studies

Date
 / /
 / /

Tests/studies

Date
 / /
 / /

Comments:



SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

Page 1 of 1

SWOG Patient ID

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SWOG Study No. S

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Registration Step

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Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment.
 List protocol-directed treatments that the patient received.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately;
 end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section.

Place an **[X]** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** at the top of the form.

Treatment Start Date

Treatment End Date

Regimen or Procedure or Site(s)

(If more room is needed, please continue on a separate page)

Off Treatment Reason (select one):

- Treatment completed per protocol criteria
 Adverse event/side effects/complications, specify: _____
 Patient withdrawal/refusal after beginning protocol therapy, specify: _____
 Patient withdrawal/refusal prior to beginning protocol therapy, specify: _____
 Disease progression, relapse during active treatment; Sites: _____
 Death on study (submit Notice of Death form)
 Other, specify: _____

For any adverse event, was treatment termination medically required?

- No Yes, specify: _____

For any patient refusal, was reason due to adverse event/side effects/complications?

- Yes, specify: _____
 No, specify other reason for refusal: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy:

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Will patient receive further treatment?

- No Yes, specify: _____ Unknown

Date of Last Contact or Death:

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Vital Status: Alive Dead (submit Notice of Death form)

Comments:

6/15/2006

28829



SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

Page 1 of 1

SWOG Patient ID

Most Recent SWOG Study No. S

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.

Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: / / (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

No Primary Cause Contributory Possible Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

Cancer of most recent SWOG study, specify cancer: _____

Cancer of other SWOG study, specify cancer: _____

Other cancer, specify: _____

Toxicity from disease related treatment (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? No Yes Unknown

Source(s) of death information:

- Autopsy report
- Medical record / Death certificate
- Physician
- Relative or friend
- Other, specify: _____

Comments:

49467

9/1/2003



SOUTHWEST ONCOLOGY GROUP

FOLLOW UP FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S

Registration Step

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until relapse or progression, at time of relapse or progression, and at protocol-specified intervals after relapse or progression. Also submit at time of diagnosis of second primary. All dates are MONTH, DAY, YEAR. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: Alive Dead Date of last contact or death: / /

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer (since submission of the previous follow-up form)?

No Yes If Yes, Date of Last Clinical Assessment: / /

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

No Yes If Yes, Date of Relapse or Progression: / /

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or MDS (myelodysplastic syndrome) been diagnosed that has not been previously reported?

No Yes If Yes, Date of Diagnosis: / /

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

No Yes If Yes, Date of First Non-Protocol Therapy: / /

Agent Name(s): _____

LONG TERM ADVERSE EVENT

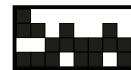
Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

No Yes If Yes, Adverse Events and Grades: _____

Comments:

64587

9/15/2003



**SOUTHWEST ONCOLOGY GROUP
NOTICE OF SECOND MALIGNANCY**

Page 1 of 1

SWOG Patient No.

SWOG Study No. S

Protocol Step

Patient Initials _____ (L, F, M)

Institution/Member _____ Physician _____

Groups Other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

Instructions: Report any malignancy of a new histologic type or any malignancy of a previous type which is judged to be a new primary. Do not report recurrences on this form. **Note:** If available, submit pathology report documenting the second malignancy along with this form. Refer to the protocol regarding sample submission instructions for second malignancies. All dates are **MONTH, DAY, YEAR**. Circle **AMENDED** items in red.

Type (site, histology) of second malignancy:

Date of First Pathologic Diagnosis:
 / /

Notes:

(PRIM2)

10/15/2000

27456



19.0 **APPENDIX**

- 19.1 Dosimetry Instructions and Worksheets
 - a. Dosimetry Instructions
 - b. Worksheet #1 - Gamma Camera Daily Quality Control
 - c. Worksheet #2 - Gamma Camera Whole Body Dosimetry
 - d. Table 1 - Maximum Effective Mass
 - e. Table 2 - Activity Hours
 - f. Graph 1 - Total Body Residence Time Estimation
- 19.2 Assessment of Bone Marrow Involvement
- 19.3 Drug Ordering Instructions for Tositumomab and Iodine I-131 Tositumomab
- 19.4 SWOG **S0801** Site Contact Information Form
- 19.5 Determination of Expedited Adverse Event Reporting Requirements

CLOSED EFFECTIVE 12/15/2010

19.1a Dosimetry Instructions

Dosimetry Instructions for Iodine I-131 Tositumomab Therapeutic Regimen Anterior and Posterior Counts

- a. **INTRODUCTION:** Dosimetry is required to determine the necessary administered therapeutic activity (mCi dose of Iodine I-131) for each subject to receive a specified total body absorbed radiation dose. The administered activity of Iodine I-131 is subject specific and affected by body mass and how rapidly the body eliminates the Iodine I-131 (clearance). On average, clearance is more rapid for subjects with enlarged spleen, high tumor burden or bone marrow involvement. The intersubject variability can be accounted for by adjusting the administered activity based on the subject measured total body clearance.

A pre-therapy dosimetric dose is administered to determine the subject's total body clearance, or residence time. Whole body gamma camera counts are done at three time points after the dosimetric infusion. These counts are then used to calculate the total body residence time for each subject. Subject weight is used to determine the activity hours. The Iodine I-131 therapeutic activity needed to deliver a fixed total body radiation dose can then be calculated using the residence time and activity hours. The following sections describe the techniques, schedules and procedures for quality control, whole body gamma camera scans, background determination, gamma camera sensitivity measurement, and the calculation of the Iodine-131 therapeutic dose. Worksheets are provided to capture the data and calculations. These worksheets will be monitored to ensure compliance and accurate calculations.

- b. **SCANNING SCHEDULE:** Following administration of the dosimetric dose, three anterior and posterior whole body scans are performed. The first scan is on Day 0 (within 1 hour of the dosimetric infusion prior to voiding); the second is on Day 2, 3 or 4; and the third is on Day 6 or 7. The second and third scans occur after voiding. The dosing and administration schedule is diagrammed below.

Time Points	Procedure
Day 0 – within 1 hour after the dosimetric infusion	Gamma camera quality control, I-131 source scan, background scan Whole body anterior and posterior camera scan (before voiding)
Day 2, 3, or 4	Gamma camera quality control, I-131 source scan, background scan Whole body anterior and posterior camera scan after voiding
Day 6 or 7	Gamma camera quality control, I-131 source scan, background scan Whole body anterior and posterior camera scan after voiding Complete Iodine 131 activity calculation

- c. **GAMMA CAMERA:** Manufacturer-specific quality control procedures should be followed for the gamma camera/computer system, the collimator, and the dose calibrator. Less than 20% variance between maximum and minimum pixel count values in the useful field of view is acceptable on Iodine-131 intrinsic flood fields and variability < 10% is preferable. Iodine-131-specific camera uniformity corrections are strongly recommended, rather than applying lower energy correction to the Iodine-131 window. Camera extrinsic uniformity should be assessed at least monthly using ^{99m}Tc or ^{57}Co as a source with imaging at the appropriate window.

Additional (non-routine) quality control procedures are required. To assure the accuracy and precision of the subject total body counts, the gamma camera must undergo validation and daily quality control on each day it is used to collect subject images.

Use the same setup and region of interest (ROI) for calibration, determination of background, and whole body subject studies.

The gamma camera must have a large or extra large field of view with a digital interface. It must be equipped with a parallel-hole medium or high energy collimator.

Set up computer and camera as follows:

- Parallel hole medium or high energy collimator
- Symmetric window (20-25%) centered on the 364 keV photo peak of Iodine-131 (314 - 414 keV)
- Matrix Size: appropriate whole body matrix
- Scanning speed: 10-30 cm/minute

All whole body scans must be stored electronically and made available to GSK, its designee, and/or the FDA, if requested.

The same equipment and parameters (computer and camera setup, collimator, and scanning speed) must be used for the source, background and subject scans at each of the three time points.

- d. **QUALITY CONTROL:** Prior to scanning the subject, a quality control check must be done on the equipment to be used. Institution- and/or manufacturer-specific quality control procedures for the gamma camera, computer, collimator(s), and dose calibrator should be followed each day the camera is used. The performance of the dose calibrator and the gamma camera must be within performance guidelines. Steps must be taken to ascertain reasons for variation and corrective measures must be taken before infusing or scanning the subject.

1. **Iodine I-131 Calibration Source:** Camera sensitivity for Iodine-131 must be determined each day. Determination of the gamma camera's sensitivity is obtained by scanning a calibrated activity of Iodine-131 (e.g., 200–250 μCi in at least 20 mL of saline within a sealed pharmaceutical vial). The radioactivity of the Iodine-131 source is first determined using a NIST-traceable-calibrated clinical dose calibrator at the Iodine-131 setting.

Record the activity ($\mu\text{Ci}_{\text{I}-131}$).

Using the computer and camera setup described above, obtain an anterior and posterior whole body scan with the Iodine-131 source positioned on the center of the imaging table near where the subject's navel would be located. The camera should be at distance of 30cm above the table to simulate subject imaging parameters and should be of the same length as the subject scans.

Draw regions of interest (ROIs) around the entire fields of view of the anterior image and posterior image to obtain the anterior source counts and posterior source counts (ROI is not necessary if the camera displays the total counts after each acquisition). Record the source anterior counts (C_{SA}) and source posterior counts (C_{SP}). The same ROIs should be used for source, background, and whole body subject counts for each scan.

2. **Background Count:** The background in the imaging room must be determined within one hour of each subject scan.

Maintain the same camera and computer setup, collimator, and scanning speed used for scanning the Iodine-131 source. Scan the table with the camera at a distance of 30cm above the table to simulate subject imaging parameters and should be of the same length as the subject scans.

Draw ROIs around the entire fields of view to obtain the anterior background counts and posterior background counts (ROI is not necessary if the camera displays the total counts after each acquisition). These ROIs should be the same as the ones used for the Iodine-131 source. Record the anterior background counts (C_{BA}) and posterior background counts (C_{BP}).

3. **Gamma Camera Sensitivity Measurement:** For each time point, calculate the background-corrected source count (defined as the geometric mean). The following equation is used:

Background-corrected source

$$\text{Count} = C_{\text{BCS}} = \sqrt{(C_{\text{SA}} - C_{\text{BA}})(C_{\text{SP}} - C_{\text{BP}})}$$

Next, divide the background-corrected source count (C_{BCS}) by the calibrated Iodine-131 source activity ($\mu\text{Ci}_{\text{I}-131}$) measured that day near the time of the scanning of the source, to obtain the calibration factor in counts per μCi ,

$$\text{Counts per } \mu\text{Ci} = C_{\text{BCS}} / \mu\text{Ci}_{\text{I}-131}.$$

The calibration factor is a measure of camera sensitivity and should be relatively constant. When values vary by more than 10%, the reason for the discrepancy should be determined. For example, this may be due to abnormally high or low background counts or inaccurate dose calibrator measurement. In this case, verify that the same camera, acquisition parameters, and ROIs have been used and also that there is no contamination present; if appropriate, the subject should be rescanned or the calibrated source activity should be measured again.

- e. WHOLE BODY SUBJECT SCANS: Once the proper quality control steps have been taken and confirmed, the whole body subject scans can then be performed.

Maintain the camera and computer setup from the source and background scans. For any particular subject, the same gamma camera, collimator(s), scan speed and field of view or length must be used for all scans. The camera head(s) should be as close as possible to the subject, and the scans should be centered on the midline of the subject. Extremities should be included in the field of view of the scans, and the arms should not cross over the body. Record the start time (t). Scan the whole length of the subject. Acquire the anterior and posterior whole body images for gamma camera counts.

Draw ROIs around the entire fields of view to obtain the anterior subject counts and posterior subject counts (ROI is not necessary if the camera displays the total counts after each acquisition). The same ROIs should be used as the ones used for the Iodine-131 source and background. Record the subject anterior counts (C_A) and subject posterior counts (C_P).

1. Subject Whole Body Counts

The same background counts (C_{BA} and C_{BP}) obtained for the quality control step can be used to determine the background-corrected subject count. For each time point, calculate the background corrected total body count (defined as the geometric mean). The following equation is used:

Background-corrected subject

$$\text{count} = C = \sqrt{(C_A - C_{BA})(C_P - C_{BP})}$$

The background corrected subject counts at each of the three timepoints are referred to as C_1 , C_2 , and C_3 .

- f. CALCULATION OF IODINE-131 ACTIVITY (THERAPEUTIC DOSE): The data obtained from the three whole body scans will be used to calculate the subject specific Iodine-131 activity needed to administer the fixed total body dose of radiation.

For a physician that has not completed the Bexxar certification process, that individual must send the dosimetry calculations for the first 3 subjects for review to Bexxar Service Center prior to the administration of the Iodine I-131 Tositumomab.

To calculate the subject specific Iodine-131 activity, the activity hours (mCi h) and residence time (h) need to be determined.

1. Activity Hours (mCi h)

Gender, height, and weight determine the activity hours (mCi h). For obese subjects (subjects weighing more than 137% of their lean body mass), the maximum effective mass will be used to determine the activity hours rather than their actual body weight. Table 1, Maximum Effective Mass, will confirm which mass to use.

Table 1 is separated by gender. Look up the subject's height under the appropriate gender column. Record the maximum effective mass (kg) given for that particular height. For heights not included in the table, convert the height into centimeters (inches x 2.54) and use the following formula:

Males: Maximum Effective Mass (kg) = 65.76 + (1.452) (Ht. in cm – 152)

Females: Maximum Effective Mass (kg) = 62.34 + (1.247) (Ht. in cm – 152)

Compare the subject's actual weight in kilograms (pounds x 0.454) to the maximum effective mass (kg), whichever value is less will be the mass (kg) used to determine the activity hours (mCi h) in Table 2.

Look up the appropriate mass in Table 2, Activity Hours. Record the activity hours (mCi h) given for that particular mass. If necessary, round the mass (eg, 59.2 kg should be rounded to 59 kg). For mass between 140kg and 160kg, use the following formula:

Activity hours (mCi hr) = 14287 + (88.74) (Wt. in kg – 140)

2. Residence Time (h)

Residence time (h) is determined by using the Graphical Estimate of The Total Body Residence Time graph, labeled Graph 1. By plotting percent-injected activity (%IA) versus the time from dosimetric dose (hours) for all three scans, the residence time can be estimated.

To calculate the percent-injected activity (%IA), use the background-corrected subject counts (C_1 , C_2 , and C_3) for each scan. Since the first scan is done the day of the infusion, the percent-injected activity for scan 1 (%IA₁) will always be 100%. For scans 2 and 3, the percent-injected activity remaining is calculated by dividing $C_{(2 \text{ or } 3)}$ by C_1 multiplied by 100:

$$\%IA_1 = 100\%$$

$$\%IA_2 = \frac{C_2}{C_1} \times 100\%$$

$$\%IA_3 = \frac{C_3}{C_1} \times 100\%$$

Next, determine the amount of time (T in hours) elapsed since the start of the Iodine .131 Tositumomab dosimetric dose infusion to the start of each subject count.

Plot each point (%IA, T) on the graph; there will be three points representing each scan. Draw a best-fit line from 100% (the pre-plotted Day 0 value) through the 2 plotted points (if the line does not intersect the two plotted points, one point must lie above the best-fit line and one point must lie below the best-fit line). Determine the x-axis value of the graph at the point where the best-fit line intersects the horizontal 37% injected activity line; this is the total body residence time (h).

3. Iodine I-131 Activity

Using the activity hours, residence time, and the prescribed total body dose, the Iodine I-131 activity can now be calculated:

$$\text{I-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi h)} \times \text{Prescribed Total Body Dose (cGy)}}{\text{Residence Time (h)} \quad 75 \text{ (cGy)}}$$

4. Sample Calculation

R-H is a 63-year-old, 5'6" male who weighs 90 kg. His baseline platelet count is 121,000 cells/mm³ and his percent injected activities at 1 h, 72 h, and 168 h were 100%, 50%, and 20%, respectively. From Table 1, his maximum effective mass is determined to be 88.5 kg. Because his maximum effective mass is less than his actual weight, the maximum effective mass is used to look up the value for activity hours in Table 2; the activity hours are 9490 mCi h. By plotting the time and percent injected activity values for the last 2 time points on Graph 1, the residence time is determined to be 103 hours. The equation for the Iodine-131 therapeutic activity required is then solved as follows:

$$\text{Iodine-131 Activity (mCi)} = \frac{9490 \text{ mCi h} \times 65 \text{ cGy}}{103 \text{ h} \quad 75 \text{ cGy}} = 80 \text{ mCi}$$



Site Number (*GSK will complete*): _____
 Patient Identification Number: _____
 Patient Initials (LFM): _____

DOSIMETRY CALCULATION WORKSHEETS FOR SWOG S0801 PROTOCOL

Instructions for completing worksheets:

- Enter all dates as MM/DD/YYYY and times as HH:MM based on a 24-hour clock (i.e. 13:30)
- Gamma Camera and settings should be consistent for all scans done (i.e. I-131 source, background, and patient counts)
- A preliminary dose estimate must be done after the second scan. The estimated dose must be communicated to the Bexxar Service Center to determine if an additional vial may be required for the therapeutic dose.
- When patient dose calculation is complete, fax all Worksheets to GSK at (877) 279-1512 or via email to BEXXARServiceCenter@GSK.com for confirmation of calculations (for the first 3 patients enrolled at the study site or until GSK determines it is no longer necessary).
- If using a commercial radiopharmacy, fax Worksheet #2 to radiopharmacy, *after receiving confirmation of calculations*.

Worksheet #1 — Equipment and Settings Evaluation

STUDY DAY	Day 0	Day 2, 3, or 4	Day 6 or 7
DATE			
DOSE CALIBRATOR ACTIVITY			
Time Measured			
I-131 source activity (A_s) in μCi			
GAMMA CAMERA SETTINGS			
Camera Name			
Energy Window Setting (20%-25%)	__ %	__ %	__ %
Collimator:	<input type="checkbox"/> Medium Energy <input type="checkbox"/> High Energy		
Total Body Scan Speed (10 – 30 cm/min)			
Scan Length (cm)			
Camera anterior height above table (cm)			
IODINE-131 SOURCE COUNTS (Anterior and Posterior)			
Time started (t)			
Total Anterior Count (C_{SA})			
Total Posterior Count (C_{SP})			
BACKGROUND COUNTS (Anterior and Posterior)			
Time started			
Total Anterior Count (C_{BA})			
Total Posterior Count (C_{BP})			
CALCULATIONS			
Background Corrected Source Count			
$C_S = \sqrt{(C_{SA} - C_{BA})(C_{SP} - C_{BP})}$			
Calibration Factor (counts per μCi)			
$CF = C_S / AS (\mu\text{Ci})$			

Date Recorded/Initials _____

Reference: 1. Wahl RL, Kroll S, Zasadny KR, Patient specific whole-body dosimetry: principles and a simplified method for clinical implementation. J Nucl Med. 1998;39(suppl): 145-205.

For more information, visit our Web site at www.BEXXAR.com or call the Bexxar Service Center at 1-877-4-BEXXAR (877-423-9927)





Site Number (*GSK will complete*): _____

Patient Identification Number: _____

Patient Initials (LFM): _____

Worksheet #2a — Determination of Iodine-131 Activity for the Therapeutic Dose of *BEXXAR* (Continued)

A. Dosimetric Dose Infusion		B. Determination of Activity Hours			
Date of Infusion: _____		Patient gender: <input type="checkbox"/> Male <input type="checkbox"/> Female			
Start Time (t_{INF}): _____		Patient height: _____ cm Patient weight: _____ kg			
End Time: _____ (not including flush)		Patient maximum effective mass (Table 1) _____ kg			
Residual after infusion: _____ mCi _____ time		Is patient weight above maximum effective mass?			
Net activity to patient: _____ mCi		<input type="checkbox"/> Yes - Use maximum effective mass (from Table 1) to determine Activity Hours			
		<input type="checkbox"/> No - Use patient's actual weight to determine Activity Hours			
		Activity Hours (Table 2): _____ mCi-hour			
C. Determination of Total Body Dose (cGy)					
Baseline platelet count: _____ cells/ mm ³					
Date: _____					
Prescribed Total Body Dose:					
<input type="checkbox"/> 65 cGy (for PLT count of 100,000 to <150,000 cells/mm ³) <input type="checkbox"/> 75 cGy (for PLT count of \geq 150,000 cells/mm ³)					
D. Calculation of Actual Administered Activity for Dosimetric Dose					
Measured Activity (Act_D) of Dose Prior to Administration		Activity (mCi)	Initials	Date	Time
Measured Residual Activity (Act_{DR}) After Administration		Activity (mCi)	Initials	Date	Time
Actual Administered Activity (Act_{DA})		Act_D	- Act_{DR}	= Act_{DA}	

(Worksheet #2a continued on next page)



Site Number (*GSK will complete*): _____
 Patient Identification Number: _____
 Patient Initials (LFM): _____

**Worksheet #2a — Determination of Iodine-131 Activity for the Therapeutic Dose of *BEXXAR*
(Continued)**

E. Determination of Residence Time (h) Using Whole Body Gamma Camera Counts		
STUDY DAY	Day 0	Day 2, 3, or 4
Day 6 or 7		
DATE		
SAME CAMERA AND ACQUISITION PARAMETERS AS WORKSHEET #1	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes
GAMMA CAMERA COUNTS		
PATIENT TOTAL BODY COUNTS (Anterior AND Posterior)		
Time Started (t_s)		
Total Anterior Count (C_A)		
Total Posterior Count (C_P)		
BACKGROUND COUNTS (Anterior and Posterior)		
Time		
Total Anterior Count (C_{BA})		
Total Posterior Count (C_{BP})		
Calculations		
Background Corrected Patient Counts		
$C = \sqrt{(C_A - C_{BA})(C_P - C_{BP})}$	$C_1 =$	$C_2 =$
		$C_3 =$
Time from start of ^{131}I Tositumomab Infusion to start of Patient Counts (t) = $t_s - t_{\text{INF}}$	$t_1 =$	$T_2 =$
		$T_3 =$
Percent Injected Activity $\%IA = C_2 \text{ or } C_3 / C_1 \times 100$	$\%IA_1 = 100\%$	$\%IA_2 =$
Date Recorded/Initials		$\%IA_3 =$
F. Determination of Residence Time From Graph 1		
TOTAL BODY RESIDENCE TIME (TBRT est)	hours*	
=		
TOTAL BODY RESIDENCE TIME (TBRT)	hours^	
=		

*After Day 2, 3, or 4, complete section G (Worksheet 2B)

^After Day 6 or 7, complete section H (Worksheet 2B)

Reference: 1. Wahl RL, Kroll S, Zasadny KR, Patient specific whole-body dosimetry: principles and a simplified method for clinical implementation. J Nucl Med. 1998;39(suppl): 145-205.

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Site Number (*GSK will complete*): _____
 Patient Identification Number: _____
 Patient Initials (LFM): _____

Worksheet #2b — Determination of Iodine-131 Activity for the therapeutic dose of BEXXAR

G. Estimated Iodine-131 Activity From Day 0 and Day 2, 3, or 4 Date Calculated/Initials: _____

$$\text{Estimated } {}^{131}\text{Iodine Activity (mCi)} = \frac{\text{Activity Hours (mCi h)}}{\text{TBRT (est)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

$$\text{Estimated } {}^{131}\text{Iodine Activity (mCi)} = \frac{\text{_____}}{\text{_____}} \times \frac{\text{_____}}{75 \text{ cGy}} = \boxed{\text{_____}} \text{ mCi}$$

DATE AND TIME OF PLANNED ADMINISTRATION: _____
 Date _____ Time _____

Physician's Signature _____

H. Prescribed Iodine-131 Activity From Day 0 and Day 2, 3, or 4 Date Calculated/Initials: _____

$${}^{131}\text{Iodine Activity (mCi)} = \frac{\text{Activity Hours (mCi h)}}{\text{TBRT (h)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

$${}^{131}\text{Iodine Activity (mCi)} = \frac{\text{_____}}{\text{_____}} \times \frac{\text{_____}}{75 \text{ cGy}} = \boxed{\text{_____}} \text{ mCi}$$

DATE AND TIME OF PLANNED ADMINISTRATION: _____
 Date _____ Time _____

Physician's Signature _____

After completing this section, fax worksheets 1, 2A, and 2B to the BEXXAR Service Center at (877) 279-1512

I. Calculation of Actual Administered Activity for Therapeutic Dose

Measured Activity (Act_T) of Dose Prior to Administration

	Activity (mCi)	Initials	Date	Time
--	----------------	----------	------	------

Measured Residual Activity (Act_{TR}) After Administration

	Activity (mCi)	Initials	Date	Time
--	----------------	----------	------	------

Actual Administered Activity (Act_{TA})

	Activity (mCi)	Initials	Date	Time
--	----------------	----------	------	------

Act_T	Act_{TR}	=	Act_{TA}
----------------	-------------------	---	-------------------

Reference: 1. Wahl RL, Kroll S, Zasadny KR, Patient specific whole-body dosimetry: principles and a simplified method for clinical implementation. J Nucl Med. 1998;39(suppl): 145-205.

For more information, visit our Web site at www.BEXXAR.com or call the Bexxar Service Center at 1-877-4-BEXXAR (877-423-9927)



Site Number (*GSK will complete*): _____
 Patient Identification Number: _____
 Patient Initials (LFM): _____

Table 1
 Maximum Effective Mass

MEN			WOMEN		
Height (ft—inches)	Height (cm)	Maximum Effective Mass (kg)	Height (ft—inches)	Height (cm)	Maximum Effective Mass (kg)
4'-5"	134.5	40.5	4'-5"	134.5	40.7
4'-6"	137.0	44.2	4'-6"	137.0	43.8
4'-7"	140.0	47.9	4'-7"	140.0	47.0
4'-8"	142.0	51.6	4'-8"	142.0	50.2
4'-9"	145.0	55.3	4'-9"	145.0	53.3
4'-10"	147.5	59.0	4'-10"	147.5	56.5
4'-11"	150.0	62.7	4'-11"	150.0	59.7
5'-0"	152.5	66.3	5'-0"	152.5	62.8
5'-1"	155.0	70.0	5'-1"	155.0	66.0
5'-2"	157.5	73.7	5'-2"	157.5	69.2
5'-3"	160.0	77.4	5'-3"	160.0	72.3
5'-4"	162.5	81.1	5'-4"	162.5	75.5
5'-5"	165.0	84.8	5'-5"	165.0	78.7
5'-6"	167.5	88.5	5'-6"	167.5	81.8
5'-7"	170.0	92.2	5'-7"	170.0	85.0
5'-8"	172.5	95.8	5'-8"	172.5	88.2
5'-9"	175.5	99.5	5'-9"	175.5	91.3
5'-10"	178.0	103.2	5'-10"	178.0	94.5
5'-11"	180.5	106.9	5'-11"	180.5	97.7
6'-0"	183.0	110.6	6'-0"	183.0	100.8
6'-1"	185.5	114.3	6'-1"	185.5	104.0
6'-2"	188.0	118.0	6'-2"	188.0	107.2
6'-3"	190.5	121.7	6'-3"	190.5	110.3
6'-4"	193.0	125.4	6'-4"	193.0	113.5
6'-5"	195.5	129.0	6'-5"	195.5	116.7
6'-6"	198.0	132.7	6'-6"	198.0	119.8
6'-7"	200.5	136.4	6'-7"	200.5	123.0
6'-8"	203.0	140.0	6'-8"	203.0	126.2
6'-9"	205.5	143.8	6'-9"	205.5	129.3
6'-10"	208.5	147.5	6'-10"	208.5	132.5
6'-11"	211.0	151.2	6'-11"	211.0	135.7
7'-0"	213.5	154.9	7'-0"	213.5	138.8

Multiply pounds by 0.454 to obtain kilograms. Multiply inches by 2.54 to obtain centimeters. To calculate the maximum effective mass for patient heights not included in above table, use the following formulas:

Males: **Maximum Effective Mass (kg) = 65.76 + 1.452 (Ht. in cm - 152)**
 Females: **Maximum Effective Mass (kg) = 62.34 + 1.247 (Ht. in cm - 152)**



Site Number (GSK will complete): _____
 Patient Identification Number: _____
 Patient Initials (LFM): _____

Adapted from (K. Zasadny, R. Wahl, et al., J Nuc Med 1995; 36(5):214. "Total Body Mass Lean").

Table 2
 Activity Hours

Mass ¹ (kg)	Activity Hours (mCi h)								
40.0	4638	60.0	6686	80.0	8670	100.0	10595	120.0	12463
40.5	4690	60.5	6737	80.5	8718	100.5	10643	120.5	12509
41.0	4743	61.0	6787	81.0	8767	101.0	10690	121.0	12556
41.5	4796	61.5	6838	81.5	8816	101.5	10738	121.5	12602
42.0	4848	62.0	6888	82.0	8864	102.0	10785	122.0	12648
42.5	4901	62.5	6938	82.5	8913	102.5	10833	122.5	12694
43.0	4953	63.0	6989	83.0	8961	103.0	10880	123.0	12741
43.5	5005	63.5	7039	83.5	9010	103.5	10927	123.5	12787
44.0	5057	64.0	7089	84.0	9058	104.0	10975	124.0	12833
44.5	5109	64.5	7139	84.5	9106	104.5	11022	124.5	12879
45.0	5160	65.0	7189	85.0	9154	105.0	11069	125.0	12925
45.5	5212	65.5	7238	85.5	9202	105.5	11116	125.5	12971
46.0	5264	66.0	7288	86.0	9251	106.0	11163	126.0	13017
46.5	5315	66.5	7338	86.5	9299	106.5	11210	126.5	13063
47.0	5366	67.0	7387	87.0	9347	107.0	11257	127.0	13109
47.5	5418	67.5	7437	87.5	9394	107.5	11304	127.5	13155
48.0	5469	68.0	7486	88.0	9442	108.0	11351	128.0	13200
48.5	5520	68.5	7536	88.5	9490	108.5	11398	128.5	13246
49.0	5571	69.0	7585	89.0	9538	109.0	11445	129.0	13292
49.5	5621	69.5	7634	89.5	9585	109.5	11492	129.5	13337
50.0	5672	70.0	7683	90.0	9633	110.0	11538	130.0	13383
50.5	5724	70.5	7733	90.5	9682	110.5	11585	130.5	13429
51.0	5775	71.0	7783	91.0	9730	111.0	11632	131.0	13474
51.5	5826	71.5	7833	91.5	9779	111.5	11678	131.5	13520
52.0	5878	72.0	7883	92.0	9827	112.0	11725	132.0	13565
52.5	5929	72.5	7932	92.5	9875	112.5	11771	132.5	13611
53.0	5980	73.0	7982	93.0	9924	113.0	11818	133.0	13656
53.5	6031	73.5	8031	93.5	9972	113.5	11864	133.5	13701
54.0	6082	74.0	8081	94.0	10020	114.0	11910	134.0	13747
54.5	6133	74.5	8130	94.5	10068	114.5	11957	134.5	13792
55.0	6184	75.0	8180	95.0	10117	115.0	12003	135.0	13837
55.5	6234	75.5	8229	95.5	10165	115.5	12049	135.5	13882
56.0	6285	76.0	8278	96.0	10213	116.0	12095	136.0	13928
56.5	6335	76.5	8327	96.5	10261	116.5	12141	136.5	13973
57.0	6386	77.0	8376	97.0	10309	117.0	12187	137.0	14018
57.5	6436	77.5	8425	97.5	10357	117.5	12233	137.5	14063
58.0	6486	78.0	8474	98.0	10404	118.0	12279	138.0	14108
58.5	6536	78.5	8523	98.5	10452	118.5	12325	138.5	14153
59.0	6586	79.0	8572	99.0	10500	119.0	12371	139.0	14198
59.5	6636	79.5	8621	99.5	10548	119.5	12417	139.5	14242

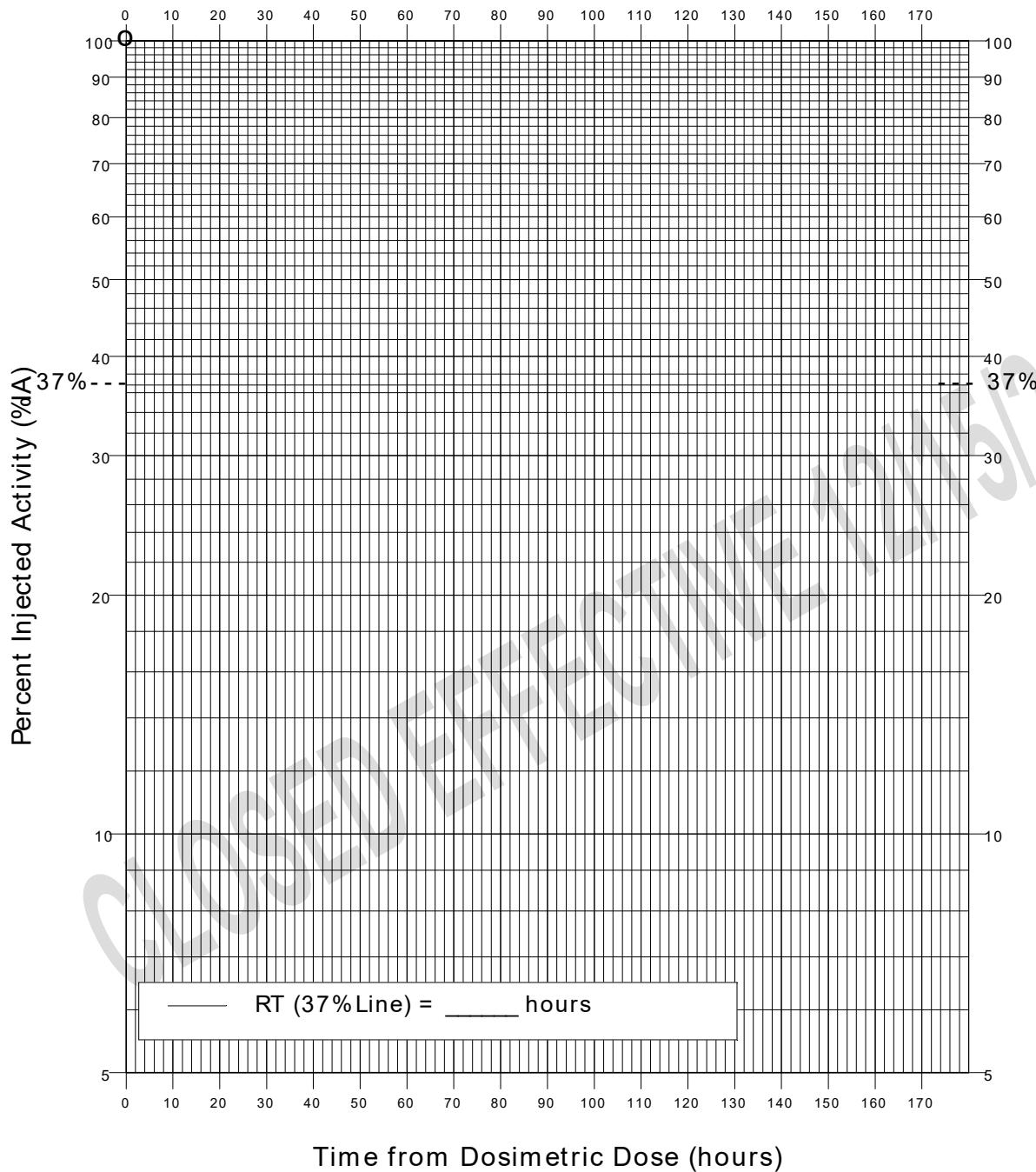
¹ The minimum of the patient's actual weight (kg) or maximum effective mass (kg) from Table 1. For values between 140 kg and 160 kg, use the following formula:

$$\text{Activity Hours (mCi h)} = 14287 + (88.74) (\text{Wt in kg} - 140)$$



Site Number (*GSK will complete*): _____
Patient Identification Number: _____
Patient Initials (LFM): _____

Graph 1 Total Body Residence Time Estimation



19.2 ASSESSMENT OF BONE MARROW INVOLVEMENT

Pathology procedure for determining percentage of bone marrow involvement with lymphoma by bilateral biopsy.

1. Bone marrow core biopsies are collected bilaterally. Results of a unilateral biopsy are acceptable if that result indicates that less than 10% of the intratrabecular space is lymphoma. The results of reading the two biopsies are averaged and extrapolated to the entire bone marrow. The core biopsy specimens are sectioned longitudinally if they are longer than 0.5 cm in length. Three or 4 of these sections for each biopsy specimen can be positioned on a slide, stained, and read. One slide is prepared per biopsy sample. If a biopsy specimen is 0.5 cm or less in length, then it is sectioned sagittally and about 10 to 12 sections of each biopsy are positioned on a slide, stained, and read. Again one slide is prepared from each specimen.
2. The sections for each patient are generally fixed, embedded, and stained using hematoxylin and eosin. Where the histopathology of the specimen is not clear with H & E, sections of the specimen will be analyzed for cell surface markers by immunohistopathology using antibodies, such as L26, which binds to the CD20 antigen. The monoclonal nature of lymphoma cells cannot be established on fixed specimens, as the kappa and lambda antigens are denatured by fixation.
3. The lymphoma disease of almost all patients occurs as foci of disease cells within the bone marrow. The percentage of the total field areas that are composed of these foci are estimated visually over each section. A few patients have diffuse disease which is more difficult to quantitate, but again the percentage of bone marrow area on sections which is involved with lymphoma is visually estimated. The mean percentage of the total fields consisting of lymphoma cells is calculated for the two biopsy specimens. It is assumed that all bone marrow has a similar level of infiltration with disease as the core biopsies.

CLOSED EFFECTIVE 12/31/2010

DRUG ORDERING INSTRUCTIONS FOR TOSITUMOMAB AND IODINE I-131 TOSITUMOMAB

Step 1: Determining scheduling dates for treatment

- Availability of study drug varies according to the manufacturing schedule. Please contact the Service Center at 1/877-423-9927 as far in advance as possible to confirm drug availability on the potential treatment dates.
 - The Dosimetric and Therapeutic doses are administered 7 to 14 days apart.
 - **Alternate** dates for the Dosimetric and Therapeutic doses should also be considered.

Step 2: Ordering Product

After the treatment dates have been scheduled, the Study/Site Coordinator completes the first section of the Study Drug Order Form and faxes it to **GlaxoSmithKline (Fax #: 877/279-1512) no later than Wednesday 4pm EST the week prior to scheduled Dosimetric dose.**

- GlaxoSmithKline will fax the Study Drug order form back to the Study/Site Coordinator to confirm initiation of the order.
- The Study/Site Coordinator then faxes the returned Study Drug order form, along with the written physician order, to the radiopharmacy.
- GlaxoSmithKline will forward radiopharmacy contact information to the Service Center. The Service Center will contact the radiopharmacy to complete the order.
- - When completing an order, a Service Center Consultant will ask the radiopharmacy for the information provided on the Study Drug Order Form.
 - The order must be completed by Thursday 4pm the week prior to the Dosimetric dose.
 - The Service Center is open 5 days per week (Monday-Friday) from 8am and 6pm (EST). A recording will provide you with alternatives if you contact the Service Center outside of these hours.

Radiopharmacy is the department that will be preparing the radioactive doses for administration. This may be an in-house radiopharmacy, commercial radiopharmacy or someone in the nuclear medicine department.

Step 3: Shipment of Prepared Doses

The nonradiolabeled and radiolabeled components of Study Drug are supplied from 2 distinct locations.

- All study drug (both nonradiolabeled and radiolabeled) is shipped to the radiopharmacy.
- The radiopharmacy prepares the Dosimetric and Therapeutic doses and delivers the doses to the nuclear medicine facility within the treatment center.
- The radiopharmacy also delivers the nonradiolabeled components of the study drug to the pharmacy at the treatment center.

Step 4 — Treating the Patient

The patient should be treated with the Dosimetric and Therapeutic doses of Study Drug according to the scheduled treatment dates.

- The estimated mCi requirements for the Therapeutic dose should be calculated based on results of the **first and second** gamma-camera whole-body counts.

The radiopharmacy or Study/Site Coordinator must contact Service Center with the estimated mCi requirements to determine if a second vial of Study Drug may be necessary.

- The actual mCi requirements for the Therapeutic dose should be calculated based on results of **all three** gamma-camera whole-body counts and forwarded to the radiopharmacy, along with the written physician order, so that the dose may be prepared.
- Check Pharmacy Insert, provided with the drug shipment, for expiration date. **DO NOT USE STUDY DRUG AFTER EXPIRATION DATE.**

For answers to any questions, please contact the Service Center at 1-877-423-9927.

19.3b

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CLOSED EFFECTIVE 12/15/2010

SWOG S0801 SITE CONTACT INFORMATION FORM**Medical Oncology Investigator Information**

Name:	Degree:	
Institution:		
CCOP affiliate if applicable:		
Address:		
Address:		
City:	State:	Zip:
Telephone:	Fax:	
Email:		

Research Nurse/Study Coordinator (for this study): _____

Tel: _____ Fax: _____ E-mail: _____

Nuclear Medicine/Radiation Oncology/Radiopharmacy Information

1) Which department will administer the radiolabeled component of Bexxar™?

Nuclear Medicine Radiation Oncology

(Provide name of appropriate contact person in Nuclear Medicine or Radiation Oncology)

Contact Name: _____
 Phone: _____ Fax: _____
 E-mail: _____

2) Does your current radioactive materials license allow you to have up to 300mCi of Liquid Iodine¹³¹ (not capsules)?

Yes No

If no, please explain _____

3) Who will prepare the Bexxar™ dose?

Commercial Radiopharmacy _____ Onsite Radiopharmacy
Name of Radiopharmacy

(Provide name of appropriate contact person in Commercial or Onsite Radiopharmacy)

Contact Name: _____
 Phone: _____ Fax: _____
 E-mail: _____

4) Does the Gamma Camera(s) have whole body scanning capability?

Yes No

Collimator: High Energy Medium Energy

5) Has your institution implemented the new Nuclear Regulatory Commission (NRC) guidelines release of patients administered radioactive materials?

Yes No Would like to implement, need assistance

PLEASE FAX THIS FORM, THE RADIOACTIVE MATERIALS LICENSE FOR YOUR INSTITUTION, AND FOR THE COMMERCIAL RADIOPHARMACY (IF APPLICABLE) TO GLAXOSMITHKLINE AT (610/917-6119).

19.5 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 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

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, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *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. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.* Expected events are those that have been previously identified as resulting from administration of the agent. 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

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.

CLOSED EFFECTIVE 12/15/2010