A Phase III Randomized Intergroup Trial of CHOP Chemotherapy Plus Rituximab Compared to CHOP Chemotherapy Plus ^{131}Iodine-Tositumomab for Previously Untreated Follicular Non-Hodgkin's Lymphoma (SWOG S0016)

Press, et al

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SOUTHWEST ONCOLOGY GROUP

A PHASE III TRIAL OF CHOP + RITUXIMAB VS CHOP + IODINE-131-LABELED MONOCLONAL ANTI-B1 ANTIBODY (Tositumomab) FOR TREATMENT OF NEWLY DIAGNOSED FOLLICULAR NON-HODGKIN'S LYMPHOMAS (**ARM 1, CHOP ONLY, OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02)**

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PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS; CALGB; CTSU. **Patients enrollments from institutions that are not aligned with SWOG or CALGB will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to CTSU Data Operations unless otherwise specified in the CTSU logistical appendix (see Section 19.6).**

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AGENTS:

Cyclophosphamide (Cytoxan®) (NSC-26271)
Doxorubicin (NSC-123127)
Prednisone (NSC-10023)
Vincristine (Oncovin) (NSC-67574)
Iodine-131 Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody (Tositumomab + I-131 tositumomab) (BB-IND-8283)
Rituximab Chimeric anti CD-20mab (IDEC-C2B8) (NSC-687451)

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

Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU
- Member Web site located at https://www.ctsu.org

- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.

- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.

- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888/823-5923 Fax: 215/569-0206	CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 8:00 am – 8:00 pm EST, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376. Please use the 1-888/462-3009 number for ALL other CTSU patient enrollments.]	Southwest Oncology Group Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For treatment- or toxicity-related questions contact the Study PI of the Coordinating Group.		
For eligibility questions contact the Southwest Oncology Group Data Operations Center by phone or email: Phone: 206/652-2267; Email: lymphquestion@crab.org		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 1-888/823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org **The CTSU Registered Member Web site is located at https://www.ctsu.org**		

CTSU logistical information is located in Appendix 19.6

Redacted Version of Protocol According to Instructions of Journal of Clinical Oncology Containing Only the Following Sections: Objectives, Selection of Patients including Eligibility and Ineligibility Criteria,Schema and Treatment Plan, Rules for Dose Modification, Measurement of Treatment Effect including response criteria, Reasons for early cessation, and Statistical Section.

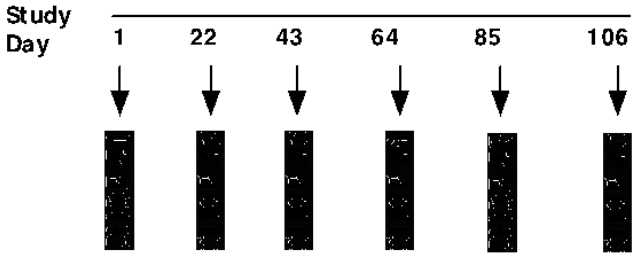
SCHEMA

REGISTRATION/RANDOMIZATION

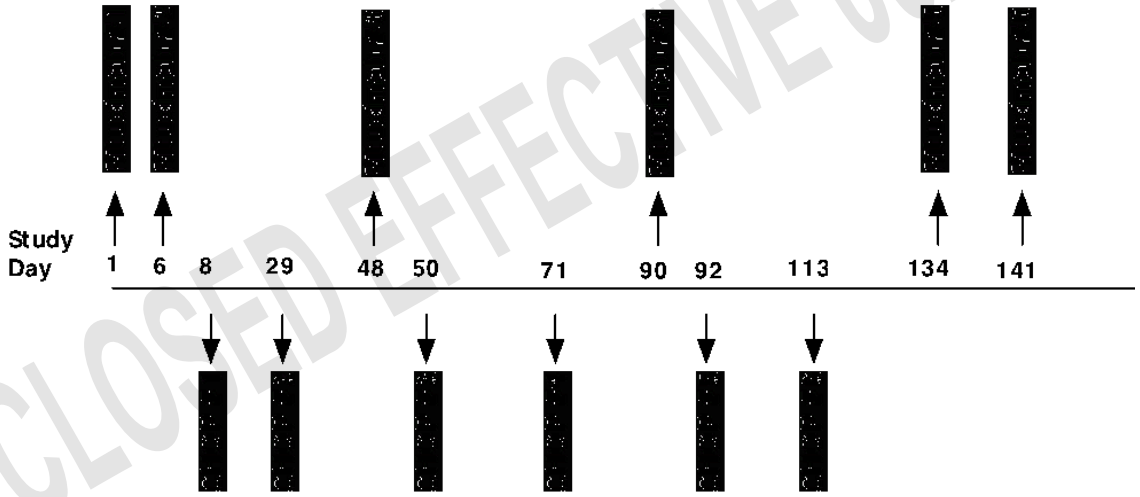
ARM 1: CHOP ONLY | **ARM 2: CHOP+RITUXIMAB** | **ARM 3: CHOP + TOSITUMOMAB + I-131 Tositumomab**

(THE CHOP ONLY ARM OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02.)

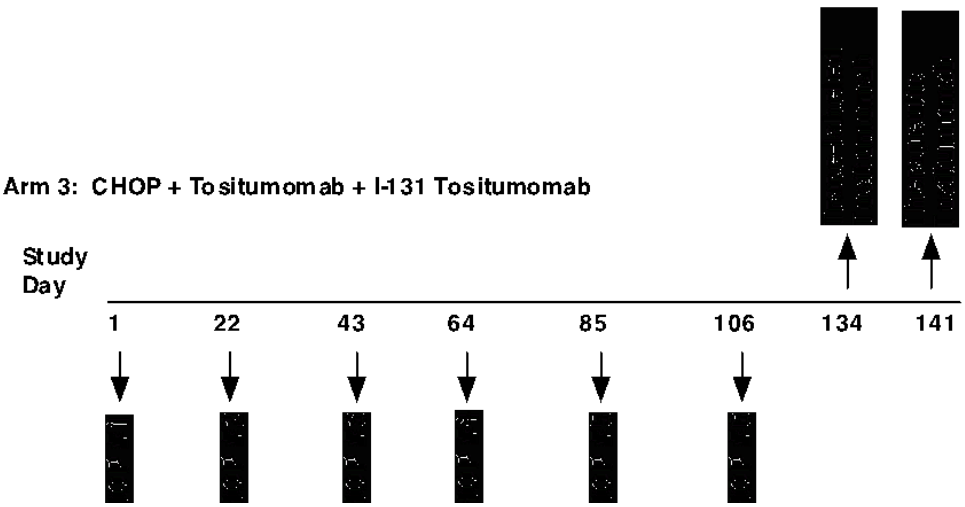
Arm 1: CHOP only



Arm 2: CHOP + Rituximab



Arm 3: CHOP + Tositumomab + I-131 Tositumomab



1.0 OBJECTIVES

1.1 To compare the progression-free survival and overall survival of patients with newly diagnosed follicular lymphoma (CD20+) treated with six cycles of CHOP chemotherapy alone, six cycles of CHOP with rituximab or six cycles of CHOP followed by Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody (tositumomab + I-131 tositumomab). **(THE CHOP ONLY ARM OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02.)**

1.2 To evaluate the response rate for patients with newly diagnosed follicular lymphoma (CD20+) treated with these regimens.

1.3 To evaluate the toxicities of CHOP with or without rituximab or Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody in patients with newly diagnosed follicular lymphomas. **(THE CHOP ONLY ARM OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02.)**

1.4 To compare the molecular remission rates by measuring clonal t(14;18)/bcl2 rearrangements in the bone marrow at baseline and at one year post-treatment.

1.5 To determine the incidence and time to development of human anti-mouse antibody (HAMA) positivity.

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 patient, this section must be photocopied, completed and submitted to the Statistical Center (see Section 14.4e).

SWOG Patient No. _____

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

_____ 5.1 **The registering institution must have submitted the S0016 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 for the Southwest Oncology Group study, S9911, need not repeat the approval process; however, they must still submit the completed form and license to GlaxoSmithKline.**

Approved (circle one) YES NO Date of Approval _____

_____ 5.2 All patients must have previously untreated follicular Non-Hodgkin's lymphoma (Grade I, II, or III).

_____ 5.3 Lymphomas must express the CD20 antigen as demonstrated by either flow cytometry or immunoperoxidase staining of paraffin sections using anti-CD20 antibodies. A report providing confirmation of CD20 expression must be submitted per Section 14.4.

_____ 5.4 Patients must have Stage III, Stage IV, or bulky Stage II extent of disease by the Ann Arbor classification (see Section 4.0).

_____ 5.5 All patients must have bidimensionally measurable disease (as defined in Section 10.1a) documented within 28 days prior to registration. Patients with non-measurable disease (as defined in Section 10.1b) in addition to measurable disease must have all non-measurable disease assessed within 42 days prior to registration.

Date measurable disease assessed _____

Date non-measurable disease assessed _____

_____ 5.6 **Pathology Review**: Adequate sections from the diagnostic specimen or core needle biopsies which are large enough to show the architecture (bone marrow biopsies and needle aspirates are insufficient) must be available for submission as outlined in Section 12.0.

Patients are also eligible to register to and submit serum for **SWOG-8947** and register to and submit tissue for **SWOG-8819**.

_____ 5.7 Patients must have a bilateral or unilateral bone marrow aspirate and biopsy performed within 42 days prior to registration.

Date of bone marrow biopsy/aspirate _____ Positive/Negative (circle one, prior to data submission as outlined in Section 14.4)

_____ 5.8 **Pretreatment specimens of heparinized marrow (2 - 3cc) for t(14;18)/bcl2 assessment must be submitted to Dr. Rita Braziel per Section 15.2**

Date specimen submitted _____

SWOG Patient No. _____

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

_____ 5.9 Patients must agree to the serum sample submission schedule for HAMA testing as outlined in Section 15.5.

_____ 5.10 Patients must have a chest x-ray or CT scan of the chest and a CT scan of the abdomen and pelvis within 28 days prior to registration.

Chest x-ray or CT Scan Date _____ Positive/Negative (circle one, prior to data submission as outlined in Section 14.4)

Abdomen and Pelvis CT Scan Date _____ Positive/Negative (circle one, prior to data submission as outlined in Section 14.4)

_____ 5.11 Patients must have a $ß_2$ microglobulin performed within 28 days prior to registration, and the value must be known at the time of registration for stratification purposes.

$ß_2$ microglobulin value _____ IULN _____

Date _____

_____ 5.12 Patients must not have clinical evidence of central nervous system involvement by lymphoma. Any laboratory tests that are performed to assess clinical signs of central nervous system involvement must have been performed within 42 days prior to registration, and the results must be negative.

Date tests performed (if needed) _____

_____ 5.13 Patients must not have received prior chemotherapy for lymphoma. Patients must not have received prior monoclonal antibodies for malignant disease. (Prior treatment with prednisone for non-lymphoma related illness(es) is allowed.)

_____ 5.14 Patients must not have received prior radiation therapy for lymphoma.

_____ 5.15 Patients must not have a history of hypersensitivity to iodine.

_____ 5.16 All patients must have a Zubrod performance status of 0, 1 or 2 (see Section 10.4).

_____ 5.17 Patients must have passed their 18th birthday.

_____ 5.18 Patients must have granulocytes >1,500 /μl and platelets > 100,000/μl within 28 days prior to registration.

Granulocytes _____ Date _____

Platelets _____ Date _____

_____ 5.19 Patients must have fewer than 5000 circulating lymphoid cells per μl on a white blood cell differential count within 28 days prior to registration.

Circulating lymphoid cells/μl _____ Date _____

_____ 5.20 Patients with a history of impaired cardiac status (including history of severe coronary artery disease, cardiomyopathy, congestive heart failure or serious arrhythmia) are not eligible. If the patient's cardiac history is questionable, a MUGA Scan or 2-d ECHO must be obtained within 42 days prior to registration (patients with ejection fractions < institutional lower limit of normal will not be eligible).

MUGA scan or 2-d ECHO (if performed) _____

ILLN _____ Date MUGA or 2-d ECHO obtained _____

SWOG Patient No. _____

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

_____ 5.21 Patients known to be HIV-positive are not eligible. (For justification of this exclusion, see Section 2.0.) Patients at high risk of Hepatitis B virus infection should be screened before initiation of rituximab.

_____ 5.22 Pregnant or nursing women may not participate. Women or men of reproductive potential must agree to use an effective contraceptive method from the time of registration to 6 months after receiving the Iodine-I31 Anti-B1 Antibody. (For justification of this exclusion, see Section 2.0 - 3.0)

_____ 5.23 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for five years.

5.24 If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day. **In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.**

_____ 5.25 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and federal guidelines.

_____ 5.26 At the time of patient registration, the treating institution's name and ID number must be provided 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.

6.0 STRATIFICATION FACTORS

A dynamic allocation scheme will be used to randomize patients to the two remaining arms at registration. Arm 1: CHOP chemotherapy with concurrent rituximab antibody **[ARM 1, CHOP ONLY, WAS PERMANENTLY CLOSED EFFECTIVE 12/15/02]**, Arm 2: CHOP followed by I-131 antiB-1-antibody (tositumomab). Patients will be balanced with respect to the following stratification factor:

$ß_2$ microglobulin > IULN: yes vs. no

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Press at 206/667-1872 or Dr. Maloney at 206/667-5616.

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to initial 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 judgement of the treating physician. The Study Coordinator must be contacted if there are significant deviations, in the opinion of the treating investigator, in the values of these tests.

a. A pretreatment serum bilirubin < 2 x the institutional upper limit of normal and a serum creatinine < 2 x the institutional upper limit of normal.

b. A serum level of LDH (lactose dehydrogenase) should be obtained.

c. An EKG should be performed within 42 days prior to registration and it should be free of any arrhythmias (excluding sinus arrhythmia or infrequent premature ventricular contractions).

d. Urinalysis, uric acid, and SGOT and/or Alkaline Phosphatase be should performed in order to assess potential treatment-related toxicities.

e. TSH

f. Hepatitis B Virus (HBV) screening

7.2 At the time of registration, patients will be randomized to one of the three treatment arms described below.

NOTE: Institutions with patients randomized to Arm 3 will be contacted by GlaxoSmithKline (by telephone) to provide assistance, discuss the drug order process, obtain current drug shipping address information and arrange for on-site training in the administration of the I-131 Anti-B1 antibody, if needed, (see Sections 7.5 and 15.1). A protocol specific training is required for all institutions with patients randomized to Arm 3. In addition, members of the treatment team are required to participate in the general Bexxar training program. Drug orders cannot be processed without this requirement being met.

7.3 **Arm 1 - CHOP Chemotherapy: (THE CHOP ONLY ARM OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02.) Treatment with CHOP as described below will be administered every 21 days for a maximum of 6 cycles. Patients with progressive disease at any time while receiving treatment will be removed from protocol treatment (see Section 7.9a). All patients will receive identical starting doses regardless of marrow status.**

TABLE 1 - CHOP CHEMOTHERAPY:

DRUG	DOSE	ROUTE	DAYS	RE-TX Interval
Cyclophosphamide	750 mg/m^2	IV infusion over 15 minutes	1	q 21 days for up to 6 cycles
Doxorubicin	50 mg/m^2	Slow IV injection	1	q 21 days for up to 6 cycles
Vincristine	1.4 mg/m^2 (max 2.0 mg)	Slow IV injection	1	q 21 days for up to 6 cycles
Prednisone*	100 mg	PO	1 - 5	q 21 days for up to 6 cycles

***Prednisone should be omitted if the patient has a history of recent active peptic ulcer disease or if peptic ulcer symptoms occur during treatment. The reason for omitting this drug must be noted on flow sheet.**

Patients randomized to Arm 1 (CHOP only) should not receive any further treatment after completion of the six cycles of CHOP until progression.

See Section 8.2 for CHOP treatment dose modifications.

7.4 **Arm 2 - CHOP + concurrent rituximab**:

a. CHOP Chemotherapy: Patients randomized to Arm 2 will be treated with six cycles of CHOP + six doses of rituximab according to the schedule described by Czuczman et al. *(20)* The CHOP chemotherapy will be administered at three week intervals as described below for a maximum of six cycles.

b. Rituximab Infusions: The six rituximab infusions will be administered concurrently with the CHOP chemotherapy as described below.

TABLE 2 - CHOP CHEMOTHERAPY PLUS RITUXIMAB INFUSIONS:

DRUG	DOSE	ROUTE	DAYS	NOTES
Cyclophosphamide	750 mg/m^2	IV infusion over 15 minutes	8, 29, 50, 71, 92, 113	
Doxorubicin	50 mg/m^2	Slow IV injection	8, 29, 50, 71 92, 113	
Vincristine	1.4 mg/m^2 (max 2.0 mg)	Slow IV injection	8, 29, 50, 71 92, 113	
Prednisone*	100 mg	PO	First 5 days of each CHOP cycle	
Rituximab Infusions #1, #2	375 mg/m^2	Slow IV (see Section 7.4c for dose rate)	1, 6	CHOP Cycle 1 only
Rituximab Infusions #3, #4	375 mg/m^2	slow IV (see Section 7.4c for dose rate)	48, 90 (48 hours before beginning CHOP cycle)	CHOP Cycles 3 and 5 ONLY
Rituximab Infusions #5, #6	375 mg/m^2	slow IV (see Section 7.4c for dose rate)	134,141 3 and 4 weeks	FOLLOWING CHOP Cycle 6

*Prednisone should be omitted if the patient has a history of recent active peptic ulcer disease or if peptic ulcer symptoms occur during treatment.

Rituximab infusions #1 and #2 will be administered on Days 1 and 6 before the first CHOP cycle, with CHOP chemotherapy being administered on Day 8.

Rituximab infusions #3 and #4 will be administered on Days 48 and 90 (two days before the third and fifth cycles of CHOP).

Rituximab infusions #5 and #6 will be given after Cycle 6 of CHOP on Days 134 and 141, respectively (three and four weeks, respectively after Cycle 6 of CHOP).

c. Although patients with non-Hodgkin's lymphoma that are eligible for this study should not have markedly elevated numbers of circulating malignant cells, the following should be noted. For some patients, tumor lysis syndrome has been reported to occur within 12 - 24 hours after the first rituximab infusion. Prophylaxis to prevent the rare event of tumor lysis syndrome in patients with bulky tumors (> 10 cm) or with markedly elevated numbers of circulating malignant cells is recommended.

Oral premedication (2 tablets [350 mg]) of acetaminophen and 50 to 100 mg oral diphenhydramine hydrochloride) may be administered 30 - 60 minutes prior to starting each infusion of rituximab. A peripheral or central intravenous (IV) line will be established. During the rituximab infusion, the patients vital signs (blood pressure, pulse, respiration, temperature) should be monitored every 15 minutes x 4 until stable and then hourly until the infusion is discontinued. Available at bedside prior to rituximab administration will be ephinephrine for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. The initial dose rate at the time of the first rituximab infusion should be 50 mg/hr for the first hour. If no toxicity is seen, the dose rate may be escalated

gradually (50 mg/hr increments at 30-minute intervals) to a maximum of 300 mg/hr. If the first dose of rituximab is well tolerated, the starting flow rate for the administration of subsequent doses will be 100 mg/hr, then increased gradually (100 mg/hr increments at 30-minute intervals) not to exceed 400 mg/hr.

Precautionary hospitalization for patients experiencing severe symptoms or infusion reactions which do not resolve after discontinuation or completion of the cycle is recommended.

See Section 8.2 for CHOP treatment dose modifications.

See Section 8.3 for rituximab dose modifications.

7.5 Arm 3 - CHOP followed by 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 S0016 Tositumomab Treatment Form (Form #57993). For subsequent patients, the original training session date must still be noted on the S0016 Tositumomab Treatment Form (Form #57993).

GlaxoSmithKline will contact each institution (by telephone) to provide assistance and arrange for training (if required) shortly after randomization of the first patient to Arm 3 (see Section 15.1). (The training session must be performed only for the FIRST patient randomized to ARM 3 of this study at any one institution.) However, retraining is available upon institutional request.

a. CHOP chemotherapy: Patients randomized to Arm 3 will receive six cycles of CHOP chemotherapy at three week intervals as described in Table 3 of Section 7.5c.

b. Re-evaluation: Patients on Arm 3 will be re-evaluated no earlier than 4 weeks but no later than 8 weeks after the completion of CHOP chemotherapy (see Section 9.3). **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.**

1. The training session with GlaxoSmithKline must have been completed.

2. 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 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.

3. Patients must have granulocytes ≥ 1,500/μl and platelets ≥ 100,000/μl within 14 days of the planned dosimetric infusion.

Patients must not have active obstructive hydronephrosis.

c. **TABLE 3** - CHOP CHEMOTHERAPY PLUS TOSITUMOMAB INFUSIONS:

Administration of I-131-Tositumomab: Tositumomab will be administered after the completion of CHOP chemotherapy and re-evaluation as described below.

DRUG	DOSE	ROUTE	DAYS	RE-TX Interval
Cyclophosphamide	750 mg/m^2	IV infusion over 15 minutes	1	q 21 days for up to 6 cycles
Doxorubicin	50 mg/m^2	Slow IV injection	1	q 21 days for up to 6 cycles
Vincristine	1.4 mg/m^2 (max 2.0 mg)	Slow IV injection	1	q 21 days for up to 6 cycles
Prednisone*	100 mg	PO	1 - 5	q 21 days for up to 6 cycles
Unlabeled Anti-B1 Antibody **	450 mg	IV over 1 hour	Day 134^{ƒ}	
Dosimetric Dose^{+}	35 mg	IV over 20 minutes	Day 134	
Unlabeled Anti-B1 Antibody**	450 mg	IV over 1 hour	Day141$^{√}$	
Therapeutic Dose^{+}	35 mg 20 minutes	IV over	Day141$^{√}$	

* Prednisone should be omitted if the patient has a history of recent active peptic ulcer disease or if peptic ulcer symptoms occur during treatment.

** Patients must receive 450 mg of unlabeled Anti-B1 Antibody (to 50 mL using 0.9% sodium chloride) prior to both the dosimetric and therapeutic dose. Patients must be premedicated with acetaminophen 650 mg po and diphenhydramine 50 mg po prior to administration of unlabeled anti-B1 antibody (see Sections 7.5c.2ii and 7.5c.3ii).

+ 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 until 14 days after the last infusion of the therapeutic dose (see Section 7.5c.2iii).

ƒ Ideally, the dosimetric infusion will be given on Day 134 and the therapeutic infusion on Day 141. Due to the logistics of ordering, receiving and administering I-131-tositumomab, a 4 week period of flexibility after Day 134 will be allowed within which the radiolabeled antibody therapy may be given. However, no more than 14 days are allowed between the dosimetric and therapeutic infusions of tositumomab.

√ See Section 7.5c.3ii.

1. 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 anti-B1 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 anti-B1 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 anti-B1 antibody (see Sections 7.5c2.iv and 7.5c.3ii).

Administration of the radiolabeled anti-B1 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 3.5c.

2. Dosimetric Dose:

i. Preparation of Unlabeled Anti-B1 Antibody

To prepare unlabeled anti-B1 antibody for administration to patients, 450 mg unlabeled anti-B1 antibody is sterilely-removed from the product vials and diluted to 50 mL using 0.9% sodium chloride for injection.

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

To prepare the dosimetric dose, an amount of anti-B1 antibody (33 - 34 mg) is added to the trace-labeled antibody preparation (1-2 mg of anti-B1 antibody radiolabeled with 5 mCi of 131-Iodine) sufficient to result in a final amount of 35 mg of anti-B1 antibody. This latter preparation is then diluted to a final volume of 30 mL using 0.9% sodium chloride for injection.

iii. 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 po tid, Lugol's solution 20 drops po tid, or potassium iodide tablets 130 mg po qd starting at least 24 hours prior to the first infusion of the Iodine-131 Anti-B1 Antibody (i.e., the dosimetric dose) and continuing for 14 days following the last infusion of Iodine-131 Anti-B1 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 Anti-B1 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 given in conjunction with the administration of tositumomab treatment must be recorded in the comments section of the S0016 Tositumomab Treatment Form (Form #57993).

iv. Administration of Dosimetric Dose

On Day 1, patients will receive the intravenous (IV) administration of 450 mg unlabeled anti-B1 antibody followed by the IV administration of the dosimetric dose (five mCi of Iodine-131 anti-B1 antibody). The unlabeled antibody must be administered through a 0.22 micron in-line filter. 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 anti-B1 antibody infusion, patients will be premedicated with acetaminophen 650 mg po and diphenhydramine 50 mg po (unless the patient is hypersensitive to acetaminophen or diphenhydramine). Unlabeled anti-B1 antibody (see Section 7.5c.2i) 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 7.5c2ii) 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 anti-B1 antibody infusions.

v. Whole Body Dosimetry

Whole body dosimetry will be performed separately for each patient as described in Appendix 19.1d, using the worksheets provided. For all patients, whole body anterior gamma camera scans will be obtained within one hour after the completion of the administration of the dosimetric dose on Day 1 (Day 134 of Arm 3 treatment) before any urination, and then either on Day 3, 4, or 5 (Days 136, 137 or 138) after urination and again on either Day 7 or 8 (Day 140 or 141) after urination using a gamma camera with appropriate medium- or high-energy collimator. The anterior whole body scans will be obtained at 30 -100 cm/minute scan speed. Anterior whole body counts, anterior background counts, and anterior 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 anti-B1 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 anti-B1 antibody) for patients with platelet counts of 100,000 - 149,999 cells/mm^3 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/mm^3.**

The dose calibrator used for measuring the mCi of activity of Iodine-131 anti-B1 antibody to be administered to the patient must be appropriately calibrated.

The dosimetry worksheets for the first 3 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).

3. Therapeutic Dose:

i. Preparation

To prepare the therapeutic dose, an amount of anti-B1 antibody is added to the radiolabeled preparation [anti-B1 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 anti-B1 antibody, unless the amount of anti-B1 antibody in the radiolabeled preparation is already ≥ 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 anti-B1 antibody will be required and the dose will then be prepared in 60 ml.

ii. 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 7.5c.2iii. The unlabeled antibody must be administered through a 0.22 micron in-line filter. 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 anti-B1 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 anti-B1 antibody infusions.

7.6 CNS Prophylaxis: There will be no CNS prophylaxis on any of the three treatment arms of this protocol.

7.7 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/d) is also recommended prior to and during the first cycle of therapy on all three arms of the study. If rash occurs, allopurinol can be discontinued.

7.8 Restaging: All patients will be assessed for response 200 and 365 days after initiation of therapy and then every six months as specified on the study calendars (see Section 9.0). Day 200 was chosen for restaging because this uniform assessment timepoint should allow evaluation of patients on all three arms of the protocol at least four weeks after completion of therapy.

Restaging will include history, physical examination, complete blood cell counts with differential, chest X-ray or Chest CT scan (depending on which was done prestudy), abdominal and pelvic CT scans, and bone marrow aspiration and biopsy (only required at Day 200 if marrow was initially involved with lymphoma). For all patients who do not progress, a bone marrow aspirate and biopsy is required at Day 365 for routine bone marrow testing and t(14;18) studies (see Section 15.4).

7.9 Criteria for Removal from Protocol Treatment

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

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

c. Failure to meet criteria for I-131 antibody administration following completion of CHOP chemotherapy (for Arm 3 patients only, see Section 7.5b).

d. Completion of protocol treatment.

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

7.10 All reasons for discontinuation of treatment must be documented on the Off Treatment Notice (Form #22204).

7.11 All patients will be followed until death.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 This study will utilize the CTC (NCI Common Toxicity Criteria) Version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). **All appropriate treatment areas should have access to a copy of the CTC Version 2.0.**

8.2 CHOP Dose Modification (for Arms 1 - 3): In the case of multiple toxicities, dose modifications should be based on the most severe dose-limiting toxicity. **(THE CHOP ONLY ARM OF THIS STUDY WAS PERMANENTLY CLOSED, EFFECTIVE 12/15/02.)**

a. Hematologic Toxicity: The CHOP regimen should be given as described in Section 7.0 if the granulocytes are > 1,500 cells/μl and the platelets are > 100,000 cells/μl 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.

Grade 3 or 4 infection (NCI Common Toxicity Criteria Version 2.0) 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. In this study, growth factors will not be administered to prevent neutropenia.

For patients who experience Grade 3 or 4 neutropenia or develop neutropenic fever between cycles of chemotherapy, growth factors may be added to all subsequent cycles of chemotherapy. Dose of CHOP may be re-escalated on future cycles at the discretion of the investigator.

Pegfilgrastim (pegylated G-CSF), filgrastim (G-CSF), and sargramostim (GM-CSF) are acceptable growth factors. These growth factors are commercially available and should be purchased through third party mechanisms. The Southwest Oncology Group will not provide growth factors for this study.

b. Impaired Hepatic Function: All patients with bilirubin ≤ 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 ≤ 5 x IULN), the doxorubicin and vincristine doses must be reduced by 50% to avoid undue hepatic toxicity. Full doses should be given once the bilirubin is ≤ 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 ≤ 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 the biliary duct by tumor mass, a biliary drainage shunt should be placed prior to chemotherapy.

Bilirubin	Doxorubicin Dose	Vincristine Dose
≤ 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 ≤ 2 x the institutional upper limit of normal will receive full doses of all drugs. If the creatinine rises > 2 x the institutional upper limit of normal, the dose of cyclophosphamide must be reduced by 25%. Re-escalation to full dose is at the discretion of the treating physician if the serum creatinine level drops to ≤ 2 x 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 and allopurinol are recommended during therapy.

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 Antibody Dose Modification and Cycle Delay (for Arm 2):

a. Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. If Grade 3 fever (or Grade 2 fever with rigors) or Grade 2 rigors are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and the severity of the side effects should be evaluated.

The patient should be treated according to the best available local practices and procedures. Following observation, when fever resolves to Grade 2 or less and rigors to Grade 1 or less, the infusion should be continued, initially, at 1/2 the previous rate. Following the antibody infusion , the IV line should be kept open for medications, as needed.

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, the rituximab infusion should be interrupted and may be resumed at a 50% reduction in rate when symptoms have completely resolved. Treatment with diphenhydramine and acetaminophen is recommended; additional treatment with broncodialators or IV saline may be used at the physician's discretion. Precautionary hospitalization for patients experiencing severe infusion symptoms which do not resolve after discontinuation of the cycle is recommended.

If there are no complications during the rituximab infusion, the IV line may be discontinued one hour after completion of the infusion. 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.

c. 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.

d. 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 onsent 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.

e. 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.

f. 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.

g. 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.

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

8.4 Iodine-131 Anti-B1 Antibody Dose Modification and Cycle Delay (form Arm 3):

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

a. Dose Adjustments based on weight and platelet counts:

For excessively obese patients, the calculations to determine the Iodine-131 anti-B1 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 anti-B1 antibody) for patients with platelet counts of 100,000 - 149,999 cells/mm^3 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/mm^3.**

The dose calibrator used for measuring the mCi of activity of Iodine-131 anti-B1 antibody to be administered to the patient must be appropriately calibrated.

b. Other dose adjustments:

During the administration of the unlabeled anti-B1 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 anti-B1 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 po and/or diphenhydramine 50 mg

po 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 1/2
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.

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

Colony Stimulating Factors (CSF), such as pegfilgrastim (pegylated G-CSF), filgrastim (G-CSF) and sargramostim (GM-CSF), should be administered only in accordance with published ASCO guidelines. *(36)* Use of CSF under these conditions will be at the discretion of the treating investigator, but must be recorded in the comments section of the appropriate treatment form.

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 in the comments section of the appropriate treatment form.

8.5 For treatment or dose modification related questions, please contact Dr. Press at 206/667-1872 or Dr. Maloney at 206/667-5616.

8.6 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.

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, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. **Note**: CT scans remain the standard for evaluation of nodal 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 imaging techniques or disease documented by indirect evidence only (e.g., lab values).

10.2 **Objective Disease Status:** Objective status is to be recorded at each evaluation. 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 nodes for which the following must be true: for patients with at least one measurable lesion and 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 GTD must have regressed to < 1.0 cm in GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biospy and aspirate at same site. Normalization of markers. (e.g., LDH definitely assignable to NHL). All disease must be assessed using the same technique as baseline.

b. **Complete Response Unconfirmed (CRU):** For patients who do not qualify for CR. Complete disappearance of all measurable and non-measurable disease, regressed, non-palpable spleen and other previously enlarged organs, except with one or more of the following features: 1) all residual nodal masses > 1.5cm in GTD at baseline reduced by 75% in SPD or 2) bone marrow indeterminate. No new lesions. All disease must be assessed using the same technique as baseline.

c. **Partial Response (PR):** Applies to patients with at least one measurable lesion that do not quality for a CR or CRU. A 50% decrease in the SPD for up to six identified dominant lesions identified at baseline. No new lesions and no increase in the size of liver or spleen or other nodes. Spleenic and hepatic nodules must have regressed in size by at least 50% in SPD. All disease must be assessed using the same technique as baseline.

d. **Stable:** Does not qualify for CR, CRU, PR, Relapsed/Progressive Disease. All disease must be assessed using the same technique as baseline.

e. **Relapsed Disease:** If a (CR,CRU) was achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) or 50% increase in the GTD of any node greater than 1cm in shortest axis using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of a new lesion/site. Death due to disease without prior documentation of progression.

f. **Progressive Disease:** If a (CR,CRU) was not achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Appearance of a new lesion/site. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Death due to disease without prior documentation of progression.

g. **Assessment inadequate, objective status unknown**: Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

Notes: Bone marrow status is evaluated as follows:

Positive: Unequivocal cytological or architectural evidence of malignancy.

Negative: No aggregates or only a few well-circumscribed lymphoid aggregates.

Indeterminate: Does not qualify for either positive or negative status. Note this typically consists of increased number or size of aggregates without cytological or architectural atypia.

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.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance 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 self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of 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 Section 10.2f) or death due to any cause.

10.6 **Time to Death:** From date of registration to date of death due to any cause.

11.0 STATISTICAL CONSIDERATIONS (NOTE: DUE TO PERMANENT CLOSURE OF CHOP ONLY, ARM 1, THE STATISTICAL CONSIDERATIONS HAVE BEEN RE-WRITTEN, EFFECTIVE 12/15/02)

11.1 Based on **S9800** and S9911 the anticipated accrual rate to the two arm study is 9-10 patients per month.

11.2 The primary objective of this trial is to compare CHOP/rituximab versus CHOP/tositumomab in terms of progression-free survival. Based on S9800 pilot data we assume that the hazard rate for CHOP/rituximab is approximately .175 (approximately 2 year progression-free survival rate of 70%). Approximately 500 eligible patients randomized over 4.5 years with 2 additional years of follow-up will be required to have power of .86 to detect a hazard ratio of conventional therapy to experimental therapy arm of 1.50 based on a one-sided .025 level stratified logrank test and assuming exponential progression-free survival distributions. Analysis of treatment differences will be adjusted (stratified) for the design specified stratification factor (serum beta 2 microglobulin) used in the patient randomization (see Section 6.0). A sample size of 250 per arm is sufficient to estimate the response rate or any given toxicity to within 6% for each regimen.

11.3 The proportion of patients testing HAMA positive will estimated at Days 133, 200, 365, and 596. Assuming samples are available on 100 patients, and given historical data showing HAMA rates are generally less than 20% at 18 months, then the fraction of patients that are HAMA positive can be estimated to at least ± .08 (95% confidence interval).

11.4 This study will be monitored throughout accrual and follow-up periods by the Southwest Oncology Group Data and Safety Monitoring Committee (DSMC). In addition to monitoring by the DSMC, formal interim analyses will be done after 50% of eligible patients have been randomized and again after 75% of the eligible patients have been randomized. Evidence to suggest early termination of the study at the time of an interim analysis would be if the null hypothesis of no difference, or the alternative of a hazard ratio of conventional therapy to experimental therapy of 1.50 progression-free survival were rejected at the .0025 level. The actual decision to terminate the study early will be made by the DSMC, and will take into consideration overall survival, progression-free survival and other factors such as toxicities and complications. If the study is not terminated early, reporting of results at the time closure will be considered if the null hypothesis of no difference, or the alternative of a hazard ratio of conventional therapy to experimental therapy of 1.5 for progression-free survival were rejected at the .0025 level. If the study is not terminated early or not reported early due to not rejecting the hypothesis tests at the time closure, the final analysis on progression-free survival using a one-sided .021 level stratified logrank test will be completed approximately 2 years after study closure.