

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0227

**PHASE I/II STUDY OF PRE-IRRADIATION CHEMOTHERAPY WITH METHOTREXATE,
RITUXIMAB, AND TEMOZOLOMIDE AND POST-IRRADIATION TEMOZOLOMIDE
FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA**

Study Chairs

Medical Oncology

Jon Glass, MD
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111-2497
215-923-5170
FAX# 215-923-5180
jglassmd@neuro-oncology.org

Radiation Oncology

Christopher Schultz, MD
414-805-4472
FAX# 414-805-4369
cschultz@mcw.edu

Pathology

Daniel J. Brat, MD, Ph.D.
404-712-1266
FAX# 404-727-3133
dbrat@emory.edu

Activation Date: July 22, 2003

Version Date: June 20, 2003

**RTOG Headquarters/Statistical Unit
215-574-3189
1-800-227-5463, ext. 4189**

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

INDEX

Schema

Eligibility Check

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Pathology
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Forms
- Appendix II - Performance Status Scoring
- Appendix III - Toxicity Criteria

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0227

PHASE I/II STUDY OF PRE-IRRADIATION CHEMOTHERAPY WITH METHOTREXATE, RITUXIMAB, AND TEMOZOLOMIDE AND POST-IRRADIATION TEMOZOLOMIDE FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

SCHEMA

- Pre-Irradiation Chemotherapy**
- Rituximab 375 mg/m² 3 days prior to first cycle of MTX
- R** • Methotrexate (MTX) *i.v.* 3.5 g/m² with leucovorin rescue on weeks 1, 3, 5, 7, 9 for a total of 5 cycles
- E** • Temozolomide (TMZ) daily for 5 days, weeks 4 and 8
Using the following Phase I and II schedules:
- G** ***Phase I** **Phase II**
- I** Arm 1: 100 mg/m² daily Arm 4: MTD from Phase I
- S** Arm 2: 150 mg/m² daily
- T** Arm 3: 200 mg/m² daily
- E** **Radiation Therapy**
- Whole brain radiation therapy (WBRT) 1.2 Gy b.i.d. fractions, 5 days/wk on weeks 11, 12, 13 for a total of 36 Gy
- R** **Post-RT Chemotherapy**
- Temozolomide (TMZ) 200 mg/m² per day for 5 days on weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 for a total of 10 cycles

* (See Section 13.2.2 for details)

ELIGIBILITY (See Section 3.0 for details)

- Primary CNS lymphoma based on positive biopsy, or CSF, or vitreous cytology (in association with measurable intraparenchymal tumor);
- Life expectancy of ≥ 8 weeks;
- Zubrod of 0-2;
- Absolute granulocyte count ≥ 1500/mm³; platelet count ≥ 100,000/mm³; creatinine clearance ≥ 50;
- Bilirubin, SGOT (AST), alkaline phosphatase ≤ 2 x institutional upper limits of normal
- No evidence of systemic lymphoma;
- No prior malignancy (excluding in situ carcinoma of the cervix or non-melanomatous skin cancer) unless disease free for at least 5 years;
- No prior radiotherapy to the brain or head/neck;
- No prior chemotherapy;
- No history of idiopathic sensitivity to any of the study drugs;
- No active infectious process;
- Patients who are seropositive for HIV, AIDS, or who are post organ transplant are not eligible.
- Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- Patients must sign a study-specific informed consent prior to study entry.

Required Sample Size:

Phase I:	maximum of 18 patients
Phase II:	52, including 6 from Phase I
Study Total:	52-64

RTOG Institution # _____

RTOG 0227

ELIGIBILITY CHECKLIST (7/22/03)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have evidence of primary CNS lymphoma based on positive biopsy, CSF, or vitreous cytology in association with measurable intraparenchymal tumor?
- _____(Y) 2. Does the patient have a life expectancy of ≥ 8 weeks?
- _____(Y) 3. Is the Zubrod performance 0-2?
- _____(Y) 4. Do the pretreatment laboratory values meet the criteria in Section 3.1.4 of the protocol?
- _____(N) 5. Is there evidence of systemic lymphoma?
- _____(N) 6. Does the patient have a history of prior malignancy (excluding *in situ* carcinoma of the cervix or non-melanomatous skin cancer) unless disease free for at least 5 years?
- _____(N) 7. Has the patient had prior radiotherapy to the head/neck?
- _____(N) 8. Has the patient had prior chemotherapy?
- _____(N) 9. Does the patient have a history of idiopathic sensitivity to any of the study drugs?
- _____(N) 10. Does the patient have an active infectious process?
- _____(N) 11. Is the patient seropositive for HIV/AIDS?
- _____(N) 12. Is the patient post organ transplant?
- _____(N) 13. If female, is the patient pregnant?
- _____(Y) 14. Has the patient signed a study-specific consent form?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?

(continued on next page)

RTOG Institution # _____

RTOG 0227

ELIGIBILITY CHECKLIST (7/22/03)

Case # _____

(page 2 of 2)

- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (Last, First) [Initials only effective 2/2002]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility ?
- _____ 16. Treatment Start Date
- _____ 17. Medical Oncologist
- _____ (N/Y) 18. Tissue for research in current study?
- _____ (N/Y) 19. Tissue kept for cancer research?
- _____ (N/Y) 20. Tissue kept for medical research?
- _____ (N/Y) 21. Allow contact for future research?
- _____ 22. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

- 1.1** The prognosis of primary central nervous system lymphoma (PCNSL) has improved with the use of pre-irradiation methotrexate (MTX)-based chemotherapy. Prior to the identification of the potential efficacy of MTX, whole brain irradiation (WBRT) was utilized as the initial treatment. However, outcome was unsatisfactory. Despite high objective response rates and a local control rate of 39%, the median survival of patients receiving WBRT as initial therapy was 11.6 months.¹
- 1.2** Initial clinical trials providing high dose systemic MTX prior to radiation therapy suggested improved survival. DeAngelis and colleagues initially treated 31 patients with pre-irradiation chemotherapy utilizing intravenous MTX (1 g/m²) and intrathecal MTX followed by WBRT (40 Gy plus a 1440 cGY boost). Median survival was 42 months in comparison with 21.7 months in a similar cohort receiving WBRT only as initial therapy.² Similar results were noted at the Massachusetts General Hospital. Twenty-five patients were treated with systemic MTX alone (3.5 g/m²) every 10 or 21 days followed by WBRT (30 – 46 Gy) with a resulting median survival of 33 months.³
- 1.3** However, the use of regimens not containing MTX did not provide results as encouraging as those utilizing pre-irradiation MTX. The use of pre-irradiation cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and post-irradiation Cytarabine (ARA-C) in NCCTG 86-72-52 resulted in a median survival of 9.6 months with a median survival of 20.7 months in patients completing the entire treatment regimen.^{4,5} A similar Radiation Therapy Oncology Group study (RTOG 88-06) utilized CHOD (cyclophosphamide, doxorubicin, vincristine, dexamethasone) prior to radiation therapy (with intravenous MTX for patients with meningeal disease). Median survival was 16.1 months.⁶ Observations in another clinical trial utilizing CHOP reveal that rapid responses to chemotherapy are followed by rapid recurrence.⁷
- 1.4** The addition of agents utilized in the treatment of systemic lymphoma (such as the combination of MTX and CHOD) does not appear to improve response rates or survival, while increasing toxicity.⁸
- 1.5** These initial studies strongly suggested that pre-irradiation MTX-based chemotherapy improved survival in PCSNL. The superiority of pre-irradiation high dose MTX-based chemotherapy was demonstrated in an intergroup study (*RTOG, SWOG*) in which patients received pre-irradiation chemotherapy with IV and IT MTX, procarbazine, vincristine, and post-irradiation ARA-C. During the study, the radiation dose for complete responders was changed from 45 Gy in daily fractions to 36 Gy in twice daily fractions. The 30.4 month median survival in the study was determined to be statistically superior to the 11.6 month median survival with WBRT alone, and it also was determined that this advantage was unrelated to selection bias or age.⁹ Furthermore, preliminary analysis suggests that the incidence of late neurological toxicity is less in patients receiving the twice daily WBRT fractions.¹⁰ Additionally, Blay, et al. demonstrated in a retrospective series that HDMTX-based chemotherapy provided prior to radiation therapy improves survival but not the incidence of late radiation toxicity.¹¹ Deangelis et al treated 102 patients with five cycles of methotrexate 2.5 g/m², vincristine, procarbazine, and intraventricular methotrexate (12 mg), followed by whole brain irradiation and subsequently high-dose cytarabine. Fifty-eight percent of patients with measurable disease had a complete response to preirradiation chemotherapy and 36% had a partial response. Median progression-free survival was 24.0 months and overall survival was 36.9 months.¹²
- 1.6** Despite the encouraging results in clinical trials utilizing high dose pre-irradiation MTX based chemotherapy, benefit from the addition of other chemotherapeutic agents to MTX has not been proven. However, in systemic lymphoma, multi-agent chemotherapy has been shown to be superior to single-agent chemotherapy. The lack of penetration across the blood-brain barrier is the likely explanation. Neuwelt et al. treated 17 patients with PCNSL with osmotic blood-brain barrier (BBB) disruption and combined intravenous and intra-arterial MTX based chemotherapy with deferral of WBRT until the time of recurrence.¹³ While acute toxicities were significant, the median survival was 44.5 months, suggesting that dose-intensive chemotherapy provided efficacy similar to MTX followed by WBRT.
- 1.7** Other trials have investigated the role of post-irradiation chemotherapy following initial radiation therapy. Chamberlain and coworkers treated 16 patients with PCV following a course of whole-brain irradiation with concomitant hydroxyurea.¹⁴ Median survival was similar to that achieved by other investigators, though all patients succumbed to disease. This suggests that the addition of chronic, low-dose intensity, lipophilic chemotherapy following cranial irradiation may successfully treat or suppress growth of microscopic disease that would otherwise provide a nidus for early tumor regrowth, and therefore, prolong disease-free and overall survival.
- 1.8** The following concepts would apply in the design of new clinical trials in the treatment of PCNSL:

- 1.8.1 Utilization of high-dose methotrexate with leucovorin rescue;
- 1.8.2 Utilization of agents penetrating an intact blood-brain barrier;
- 1.8.3 Consideration for the utilization of novel agents that may take advantage of an open blood brain barrier prior to its reconstitution during treatment in order to enhance the treatment of bulky disease;
- 1.8.4 Use of radiation therapy regimens designed to minimize neurotoxicity;
- 1.8.5 Use of post-irradiation chemotherapy to suppress or eliminate residual tumor that would provide a nidus for recurrence.
- 1.9 A phase II clinical trial is therefore proposed to utilize these principles:
 - 1.9.1 Use of high-dose methotrexate with leucovorin rescue every two weeks;
 - 1.9.2 Addition of an agent or agents with activity against lymphoma and blood brain barrier penetration; temozolomide is an imidazotetrazine derivative that readily crosses the blood brain barrier. It undergoes rapid hydrolysis at physiologic pH to form the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA, primarily at the O-6 and N-7 positions of guanine. While approved for the treatment of anaplastic astrocytomas, reports of efficacy in CNS lymphoma have been documented.. Reni, et al. treated five patients with primary central nervous system lymphoma with temozolomide at a dose of 150 mg/m² daily for five days every four weeks. There was one patient with a durable complete response, and there was one partial response, and another with stable disease.¹⁵
 - 1.9.3 Addition of an agent active against systemic lymphoma that would be utilized to enhance treatment of bulky tumor early in the course of chemotherapy; rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. Rituximab is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma. However, there has been evidence of complete and partial responses in patients with aggressive lymphomas, including diffuse large cell lymphomas receiving rituximab monotherapy¹⁶ or in combination with standard chemotherapy, such as CHOP.¹⁷ Because rituximab is a large molecule, it does not cross the blood-brain barrier. However, the blood-brain barrier is at least partially non-functional in patients with enhancing tumor, and its use will be restricted to prior to the initiation of methotrexate, when an at least partially non-function barrier may exist. Raizer, et al. treated three patients with recurrent PCNSL with Rituximab, and noted radiographic responses in two.¹⁸
 - 1.9.4 Use of a radiation regimen intended to minimize long-term neurotoxicity;
 - 1.9.5 Continuation of chronic, low dose intensity chemotherapy following completion of radiation therapy.

2.0 OBJECTIVES

- 2.1 To assess the maximum tolerated dose (MTD) of temozolomide (TMZ) in combination with methotrexate (MTX) and rituximab (RTX) when administered prior to twice daily fractionated whole brain radiation therapy (WBRT) in patients with primary central nervous system lymphoma;
- 2.2 To compare the two-year survival rate in patients receiving pre-irradiation chemotherapy, twice-daily fractionated whole brain radiation therapy and post-irradiation temozolomide to the reported two-year survival rate of RTOG 93-10;
- 2.3 To compare the pre-irradiation chemotherapy tumor response rates to the reported rate from RTOG 93-10;
- 2.4 To report progression-free survival;
- 2.5 To assess acute and long-term neurologic toxicity, and to collect quality of life data for this patient group.

3.0 SELECTION OF PATIENTS

3.1 Conditions for Patient Eligibility

- 3.1.1 Primary CNS lymphoma (B-cell, CD20 positive) based on positive biopsy or CSF or vitreous cytology (in association with measurable intraparenchymal tumor). Cytology must demonstrate lymphoma or have an immunohistochemical diagnosis of malignant lymphocytes with a monoclonal lymphocytic population.
- 3.1.2 Life expectancy \geq 8 weeks;
- 3.1.3 Zubrod performance status of 0-2;

- 3.1.4 Absolute granulocyte count $\geq 1500/\text{mm}^3$; platelet count $\geq 100,000/\text{mm}^3$; creatinine clearance ≥ 50 , calculated with the Cockcroft-Gault Equation: $\text{Cr Clearance} = (140 - \text{age}) \times \text{wt (kg)} / (\text{Cr [mg/dl]} \times 72)$; Bilirubin, SGOT (AST), alkaline phosphatase $\leq 2 \times$ institutional upper limits of normal;
- 3.1.5 Patients must sign a study-specific informed consent prior to study entry.
- 3.2 Conditions for Patient Ineligibility**
- 3.2.1 Evidence of systemic lymphoma;
- 3.2.2 Prior malignancy (excluding in situ carcinoma of the cervix or non-melanomatous skin cancer) unless disease free for at least five years;
- 3.2.3 Prior radiotherapy to the brain or head/neck;
- 3.2.4 Prior chemotherapy;
- 3.2.5 History of idiopathic sensitivity to any of the drugs to be used;
- 3.2.6 Active infectious process;
- 3.2.7 Seropositive for HIV, AIDS, or post-organ transplant;
- 3.2.8 Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.

4.0 PRETREATMENT EVALUATIONS

All evaluations should be completed within one week prior to treatment cycle.

- 4.1 Complete, detailed medical history & physical examination;
- 4.2 MRI of the brain with and without gadolinium (See Section 11.2.3.1);
- 4.3 Laboratory studies: CBC, differential, platelets, electrolytes, LFTs, BUN, serum creatinine, urine hcG (for females of childbearing potential);
- 4.4 Slit lamp examination;
- 4.5 CSF for cytology (unless contraindicated by CNS mass effect from tumor);
- 4.6 Pulmonary function testing in patients with known pulmonary or bronchospastic disease;
- 4.7 Completion of Mini Mental Status Exam (MMSE);
- 4.8 Quality of Life assessment: Spitzer Quality of Life Questionnaire.

5.0 REGISTRATION PROCEDURES

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Radiation Dose

- 6.1.1 All patients will receive whole brain irradiation (WBRT) during weeks 11, 12, and 13, five days per week (excluding weekends). A daily dose of 2.4 Gy is to be delivered in two fractions of 1.2 Gy each with a minimum inter-fraction interval of 6 hours. The total dose to brain and meninges will be 36 Gy. All portals will be treated at each treatment.

6.2 Simulation and Target Volumes

- 6.2.1 Doses are specified as the target dose that will be representative of the dose in the center of the target volume. For two opposed coaxial equally weighted beams, the target dose will be specified on the central ray at mid-separation of beams.
- 6.2.2 Head immobilization with a thermoplastic mask or other appropriate device is encouraged. A radio opaque marker should be placed on the right and left soft tissue canthus.
- 6.2.3 A left and right lateral equally weighted, opposed field arrangement is to be used. Custom blocks or a multi-leaf collimator are to be used to shape the fields such that the meninges are included. Care should be taken in shaping the fields at the skull base to avoid inadvertent shielding of the meninges in the region of the anterior temporal lobes and the cribriform plate. The posterior one third of the orbits is to be included in the treatment volume. The anterior field edge is to be made coplanar via a gantry rotation so as to avoid contralateral ocular divergence. The anterior, posterior, and superior field borders shall include 1-2 cm of "fall off". The inferior border is the C2-3 inter-space. If ocular involvement is evident on initial slit lamp exam, a repeat slit lamp exam will be performed following induction chemotherapy pre-irradiation. If ocular involvement persists, the entirety of both eyes will be included in the

treatment volume and will receive 36 Gy. If repeat slit lamp exam shows no post-induction chemotherapy ocular involvement, only the posterior one third of the orbit is to be included.

6.2.4 Review of Simulation/Port Films

Cut-through of orbital/temporal lobes by field/block edge is a Major Deviation; however, these patients will be analyzed because of intent to treat principles.

6.3 **Technical Factors**

6.3.1 Treatment shall be delivered with megavoltage machines. Photon beams with energies of between 6 and 10 mV are to be used. Source to skin distances must be at least 80 cm.

6.4 **Treatment Planning**

6.4.1 Simulation/localization films and portal verification films are to be submitted to RTOG Headquarters for review.

6.5 **Anticipated Side Effects or Toxicity**

6.5.1 Radiation Toxicity Monitoring: All acute adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Toxicity Criteria (CTC) version 2.0. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

6.5.2 Acute Reactions: Acute (≤ 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria (CTC) version 2.0. All patients are likely to develop alopecia, erythema, and dry desquamation of the scalp within the treatment portal. Some patients may experience a headache, anorexia and or nausea. Middle ear congestion is commonly experienced following whole brain RT. Patients requiring treatment to the entire eye are likely to experience conjunctival irritation and may note dry eyes. All of the described acute effects are likely to be reversible with the exception of alopecia.

6.5.3 Late Reactions: Late (> 90 days from RT start) side effects of radiation therapy will be evaluated and graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix III). All patients are likely to have permanent partial or total alopecia corresponding to the treatment portal. Rarely, persistent middle ear effusion(s) requires myringotomy tube placement. There is a low risk of sensory neural hearing loss. All patients are at high risk of developing cataracts, which may or may not require treatment. The probability of cataract formation increases with post treatment survival time. The risk of cataract is greatest for patients who require treatment to the entire eye. All patients are at risk for developing neurocognitive dysfunction; the greatest risk is for patients > 60 years of age. There is a low risk of developing radiation necrosis of the brain, which may require surgery and/or extended use of steroids. **Instructions for grading encephalopathy late adverse events related to RT: Grade 1 NA; Grade 2 Mild signs or symptoms, not interfering with ADL; Grade 3 Signs or symptoms interfering with ADL, hospitalization indicated; Grade 4 Life-threatening, disabling; Grade 5 Death.**

6.5.4 Fatal Events

All deaths with attribution: definite, possible or probable resulting from protocol radiation therapy must be reported by telephone to the RTOG Headquarters dedicated AE line ‡(215) 717-2762 or 1-800-227-5463, ext. 4189 to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse event as required by their IRB.

All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to RTOG Headquarters Data Management AE telephone line ‡(215) 717-2762 or 1-800-227-5463, ext. 418

6.5.5 Life-threatening & Grade 4 Events

All life-threatening (an event which in view of the investigator, places the patient at immediate risk of death from the reaction) and Grade 4 events that are related, possibly related or probably related to protocol treatment using *non-standard fractionated radiation therapy must be reported by telephone to the RTOG Headquarters AE telephone line ‡(215) 717-2762 or 1-800-227-5463, ext. 4189, to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse event as specified by their IRB.

Grade 4 events from standard fractionated radiation therapy do not require telephone reporting unless specified otherwise in the protocol. This information is reported on study case report forms.

Expected grade 4 adverse events from non-standard radiotherapy may be excluded from telephone reporting if explicitly stated in the protocol

- * **Standard fractionated radiotherapy is defined as 1.8 – 2.0 Gy once daily radiation to a dose of 70.2 Gy or less, including 2D and 3D conformal radiotherapy. Non-standard fractionated radiation therapy is treatment administered using brachytherapy, radiopharmaceuticals, high LET radiation, radiosurgery, intensity modulated radiation therapy (IMRT) and conventional radiotherapy with fraction size or total dose not within the parameters specified above.**

6.5.6 Documentation

All applicable data forms and if requested, a written report from the site principal investigator must be submitted within 10 working days of the telephone report of any fatal adverse event with the attribution of **definite, possible or probable relation** to protocol radiotherapy and for grade 4 or life-threatening events as specified in (6.5.4 and 6.5.5).

7.0 DRUG THERAPY

7.1 Pre-Irradiation Chemotherapy

7.1.1 Patients will receive rituximab, 375 mg/m², intravenously three days prior to the first cycle of methotrexate (MTX).

7.1.2 Patients will receive five cycles of methotrexate at 3.5 gm/m² administered every two weeks on weeks 1, 3, 5, 7, and 9. Methotrexate is administered via intravenous infusion over four hours once per cycle. Calcium leucovorin 25 mg orally or intravenously every six hours will be initiated exactly 24 hours following the start of the MTX infusion. Methotrexate levels will be monitored daily, and calcium leucovorin will be discontinued when the MTX level is less than 10 micromolar.

7.1.3 On weeks 4 and 8, patients will receive temozolomide, 200 mg/m², by mouth per day for five days. A phase I dose escalation initially will be performed to determine the maximum tolerated dose (MTD) of temozolomide in association with methotrexate and rituximab. Three dose levels of temozolomide will be administered: 100 mg/m², 150 mg/m², and 200 mg/m². The MTD of temozolomide will be utilized as the standing dose in the phase II portion of the study (See Section 13.2).

7.1.4 Because of the lymphopenia associated with rituximab, all patients will receive the following medications as prophylaxis during pre-irradiation chemotherapy, beginning no later than five days prior to the initiation of rituximab and ending no sooner than recovery from all hematological toxicity associated with pre-irradiation chemotherapy.

- Trimethoprim/sulfamethoxazole, 160 mg/180 mg (double strength), one tablet 3x weekly (Monday, Wednesday, Friday)
- Acyclovir, 400 mg, 2x daily

7.2 Rituximab (Rituxan®)

7.2.1 Formulation

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen present on the surface of both normal and malignant B-lymphocytes. Rituximab is provided as a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (*i.v.*) administration; it is supplied at a concentration of 10 mg/ml in either 100 mg (10 ml) or 500 mg (50 ml) single-use vials. The product is formulated for *i.v.* administration in 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

7.2.2 Storage

Rituximab vials are stored at 2°–8° C (36°–46°F), should be protected from direct sunlight, and should not be used beyond expiration date stamped on the carton.

7.2.3 Adverse Effects

- **Infusion Reactions:** Mild to moderate fever and chills/rigors occur in the majority of patients during the first rituximab infusion. Other frequent infusion reaction symptoms include nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion. The incidence of infusion reactions decreases with each treatment and responds to slowing or interruption of the infusion and supportive care.

- B-cell depletion with lymphopenia and risk of infection
- Grade 3 or 4 cytopenias including lymphopenia, neutropenia, thrombocytopenia, and anemia; rare instances of hemolytic anemia, aplastic anemia, and prolonged pancytopenia have been reported.
- Cardiac: Hypotension, rare cardiac failure
- Pulmonary: Serious effects include acute bronchospasm, acute pneumonitis presenting 1–4 weeks post-rituximab infusion, and bronchiolitis obliterans. More common effects include increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis.
- Immune/Autoimmune Events: uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash
- Other Less Commonly Observed Events: Agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease

7.2.4 Contraindications

Contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product.

7.2.5 Supply

Commercially available

7.3 **Methotrexate**

7.3.1 Formulation

Methotrexate (MTX) is available in 20mg, 50mg, and 1gm vials as a lyophilized preservative-free powder.

7.3.2 Storage

Once mixed, *i.v.* MTX will remain stable for 24 hours if kept refrigerated.

7.3.3 Adverse Effects

Systemic methotrexate can produce myelosuppression; GI toxicity, particularly mucositis; liver dysfunction, renal failure, and rarely, interstitial pneumonitis.

7.3.4 Contraindications

Contraindicated in patients with renal insufficiency, known hypersensitivity to methotrexate or to any component of this product.

7.3.5 Supply

Commercially available

7.4 **Temozolomide (Temodar®)**

7.4.1 Formulation

Temozolomide is supplied as a machine-filled, white opaque, preservative-free, two-piece, hard gelatin capsule available in 250 mg, 100 mg, 20 mg, and 5 mg strengths. The 250 mg and 100 mg capsules are larger in size than the 20 mg and 5 mg. Refer to Investigator Brochure for contents of the formulation. Temozolomide capsules are packaged in 30 cc, 28 mm 480 Type 1 amber glass bottles containing 30 capsules of 5 mg, 20 mg, 100 mg or 250 mg strengths.

7.4.2 Storage

Temozolomide capsules should be stored between 2°C to 30°C in amber glass bottles. Temozolomide may be dispensed to the patient in amber plastic containers.

7.4.4 Adverse Effects

Temozolomide has been well tolerated by both adults and children with the most common toxicity being mild myelosuppression. Other, less likely, potential toxicities include nausea and vomiting, constipation, headache, alopecia, rash, burning sensation of skin, esophagitis, pain, diarrhea, lethargy, and hepatotoxicity. Hypersensitivity reactions have not yet been noted with temozolomide. As is the case with many anti-cancer drugs, temozolomide may be carcinogenic. Rats given temozolomide have developed breast cancer. The significance of this finding for humans is not presently known.

7.4.4 Contraindications

Contraindicated in patients with known hypersensitivity to temozolomide or to any component of this product.

7.4.5 Supply

Commercially available

7.5 Chemotherapy Subsequent to Radiation Therapy

7.5.1 Temozolomide, 200 mg/m² per day for five days, will be administered every four weeks on weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 for a total of 10 cycles. This dosage will apply regardless of the phase I or phase II temozolomide dose provided to the patient. The initial dosage may be modified to 150 mg/m² at the treating physician's discretion based on prior toxicity. This dose will be subject to modifications as defined in section 7.7.5.

7.6 Chemotherapy At Recurrence

7.6.1 Treatment for recurrent disease will be provided at the investigator's discretion.

7.7 Dose Modification for Toxicity

7.7.1 *Pre-radiation chemotherapy*: Intravenous MTX, rituximab, and temozolomide should be administered on schedule unless the following conditions apply:

7.7.1.1 Absolute neutrophil count (ANC) is < 1000/mm³ or the platelet count is < 70,000/mm³. Drug should be withheld until the ANC returns to normal. MTX or temozolomide can then be administered at full dose if resolution occurs within two weeks.

7.7.1.2 If the ANC is persistently below 1000/mm³ or the platelet count persistently below 70,000/mm³ for over 2 weeks and the cytopenia is attributable to temozolomide and not rituximab, then the temozolomide dose will be reduced by 25% for the subsequent course. The doses of MTX will not be altered for hematological toxicity.

7.7.1.3 Any grade 3 or 4 non-hematological toxicity (other than grade 3 nausea/vomiting) will require reduction in the dose of the responsible agent by 25%. The responsible medication will be withheld until the toxicity has resolved. A recurrence of the same toxicity at the lower dose will result in the discontinuation of the responsible medication.

7.7.1.4 If a patient experiences grade 2 or higher nephrotoxicity from MTX, a repeat creatinine clearance must be obtained prior to the next dose of MTX. The creatinine clearance must be greater than 50cc/min/1.73 m² to receive further MTX.

7.7.2 G-CSF can be administered at the discretion of the individual investigator for chemotherapy-induced neutropenia (ANC < 1000/mm³) at any time during the protocol. Its use will be recorded but is not required.

7.7.3 If a patient experiences neurological deterioration that can be attributed to progressive disease during chemotherapy, the patient will proceed immediately to cranial irradiation. Progression must be documented on MR scan before chemotherapy is discontinued and RT begun. Patients with ocular involvement who have progression of their ocular disease during chemotherapy can proceed to RT even if the CNS disease is responding.

7.7.4 *Post-radiation chemotherapy*: Temozolomide should be administered on schedule unless the absolute neutrophil count (ANC) is < 1000/mm³ or the platelet count is < 70,000/mm³. If either condition applies, temozolomide should be withheld for 1 week, or less if the counts improve sooner. If the ANC is persistently below 1000/mm³ or the platelet count persistently below 70,000/mm³ for 2 weeks, then the dose of temozolomide will be reduced by 25% to 150/mg/m²/day for the subsequent course.

7.8 Adverse Drug Reaction Reporting

7.8.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for grading adverse events from chemotherapy and other systemic agents prescribed in this protocol. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0. This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.8.2 *Adverse Drug Reaction Reporting—Commercial Agent(s)*

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses a commercial anticancer agent. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery followed by an FDA Form 3500 (MedWatch) sent to the address on the form and to RTOG Data Management within ten working days. Sites are also responsible for reporting adverse events as specified by their Institutional Review Board:

7.8.2.1 Any ADR which is both serious (life-threatening [grade 4] or fatal [grade 5]) and **unexpected**;

7.8.2.2 Any increased incidence of a known ADR that has been reported in the package insert or the literature;

- 7.8.2.3 Any ADR that results in significant disability or incapacity;
- 7.8.2.4 Any infant born to a patient that was treated on this protocol and has a congenital anomaly or birth defect;
- 7.8.2.5 Any death on study if clearly related to the commercial agent(s).
- 7.8.2.6 The ADR report should be documented on FDA Form 3500 (MedWatch) and mailed or faxed to the address on the form, as well as to the RTOG Data Management Department:

RTOG Data Management
 1101 Market Street, 14th floor
 Philadelphia, PA 19107
 Phone (215) 717-2762
 Fax (215) 928-0153

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included.

- 7.8.3 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment must be telephoned to the RTOG Headquarters Data Management department within 24 hours of discovery.
- 7.8.4 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, and if available, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed/faxed within 30 days of AML/MDS diagnosis to the address on the form and to the Investigational Drug Branch (IDB) and to the RTOG Data Management Department:

Investigational Drug Branch (NCI/CTEP) P.O. Box 30012 Bethesda, MD 20824 Fax: (301) 230-0159	and	RTOG Data Management AML/MDS Report 1101 Market Street, 14 th floor Philadelphia, PA 19107 Phone (215) 717-2762 Fax (215) 928-0153
--	-----	--

All AML/MDS forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

For Patients Who Have Consented To Participate In The Tissue Component Of The Study (See Appendix IB)

10.1 Central Review — Strongly Encouraged But Not Required

- 10.1.1 The following materials should be provided to the RTOG Tissue Bank (see Section 10.3.2 for address) for central review:
 - 10.1.1.1 One H & E stained slide per positive biopsy site
 - 10.1.1.2 A Pathology Report documenting that the submitted blocks, core, or slides contain tumor; the report must include the RTOG protocol number and the patient's case number. The patient's name and/or other identifying information should be removed from the report.
 - 10.1.1.3 A Pathology Submission Form clearly stating that the tissue is being submitted for central review; the form must include the RTOG protocol number and the patient's case number.
 - 10.1.1.4 Specimens for central review will be retained until the study is terminated (See Section 10.5.2).

- 10.1.2** Daniel Brat, M.D. (404-712-1266) will perform the central review. Tissue from the pre-treatment diagnostic biopsy or surgery will be reviewed to confirm the pathology. The diagnosis of primary CNS lymphomas will follow guidelines of the WHO Classification and fulfill criteria of diffuse large B-cell lymphoma. Further studies including chromosomal analysis and immunohistochemistry for B-cell markers (CD20), T-cell markers (CD3) and pan-lymphocyte markers (lymphocyte common antigen/CD45) will be performed to further classify the tumor whenever possible.
- 10.1.3** Slides and/or cell blocks of CSF or vitreous specimens that document initial involvement (any possible specimen) also should be submitted for central review. See Section 10.1.1 for submission requirements.

10.2 Tissue Banking — Strongly Encouraged But Not Required

10.2.1 Rationale

The purpose of the RTOG Tissue Bank is to acquire and maintain high quality specimens from RTOG trials, to provide uniform access of such tissues to investigators for correlative studies, and to preserve tissue from each block through careful block storage and processing for future studies. Correlative studies using these specimens are meant to integrate new research findings into future protocol development and to provide tissue for future correlative grant applications testing important biologic questions.

RTOG has been collecting pretreatment diagnostic tissue from CNS lymphoma protocols over the last ten years. A final decision as to which tumor markers will be studied awaits the completion of this trial; it will not be ready for biomarker analysis for several years. The goal is to evaluate several biomarkers using the archived pathologic materials. The exact markers to be studied will be determined when the outcome data are mature for publication. The analyses will include patients from this trial, as well as from the previous RTOG CNS lymphoma studies, if there is tissue available.

10.2.2 Specimen Collection

Specimens will be collected from each consenting patient for the purposes of centralized review and for longer term tissue storage for correlative translational studies. Tissue specimens for banking should be taken from pre-study diagnostic biopsy or surgery. Specimens for banking will include a single H&E diagnostic slide containing primary CNS lymphoma, its corresponding paraffin block (or a punch biopsy from the block), or 15 unstained slides. Tissue blocks, punch biopsies from the block, or unstained slides should be submitted to the RTOG Tissue Bank by the participating institution at same time as slides are sent for central review. Materials should be sent to LDS hospital at the address below.

10.3 RTOG Tissue Bank

10.3.1 The following must be provided in order for the case to be evaluable for the Tissue Bank:

10.3.1.1 One H&E stained slide

10.3.1.2 A paraffin-embedded tissue block of the tumor (containing the highest grade of tumor if multiple biopsy sites contain cancer) or a 2 mm diameter core of tissue, punched from the tissue block containing tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE:** A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.3.1.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report.

10.3.1.4 A Pathology Submission Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; the form must include the RTOG protocol number and patient's case number.

10.3.2 Submit materials to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
ldhflinn@ihc.com**

10.4 Reimbursement

10.4.1 RTOG will reimburse pathologists from submitting institutions \$300 per case if fresh or flash frozen tissue is submitted, \$200 per case if a block or core of material is submitted, and \$100 per case if unstained slides are submitted. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.5 Confidentiality/Storage (See RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.html> for further details.)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 The specimens for central review and/or translational research will be retained until the study is terminated unless the patient consents to storage for additional future studies. Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Pre-Study [†]	Weekly During Pre-RT Chemo	Every 2 weeks [†] During Pre-RT Chemo	Week 10 of Tx (post-chemo pre-RT)	Week 13 (During TMZ)	Weekly During TMZ	Every 4 Weeks [†] During TMZ	Every 2 Months During TMZ	Following Completion of Tx and After ^h
History & Physical	X ^a		X ^b		X				X
CBC, differential, platelets ^c	X	X		X	X	X			
Electrolytes, LFTs, BUN/Creatinine	X		X	X	X		X		
Creatinine clearance calculation ^d	X		X						
β-hCG ^e	X		X		X		X		
PFTs	X ^f								
MRI brain	X			X	X			X	X ⁱ
Slit-lamp examination	X			X	X			X	X
CSF for cytology	X			X	X			X	X
MMSE	X			X	X			X	X ^h
Spitzer QOL Assessment ^g	X			X	X			X	X ^h

[†] Within one week prior to treatment cycle

- Baseline history and physical to consist of full history, including history of present illness, review of systems, past medical history, family history, medication, complete physical and neurological examinations, Zubrod performance status, height/weight, and BSA.
- Interval history and physical to consist of interval history, review of systems, medication, physical and neurological examinations, Zubrod performance status, weight, and BSA.
- CBC and differential may need to be performed more frequently than weekly in the setting of myelotoxicity; evaluation is at treating physician's discretion.
- Creatinine clearance may be calculated utilizing the Cockcroft-Gault Equation: Cr Clearance = $(140 - \text{age}) \times \text{wt (kg)} / (\text{Cr [mg/dl]} \times 72)$ (multiply by 0.8 for women). A 24-hour urine may also be obtained.
- For women of childbearing potential; urine hCG is acceptable.
- In patients with known pulmonary or bronchospastic disease
- Also required at regular follow-up intervals; see Section 12.1.
- Every 3 months from end of treatment for 2 years, every 6 months for years 3-5, then annually for five years
- MRI done at time of recurrence during follow-up period

11.2 Measurement of Effect

11.2.1 *Clinical and Radiographic Response*

11.2.1.1 A combination of the neurological clinical examination and gadolinium-enhanced magnetic resonance imaging (*Gd-MRI*) will be used to define overall response or progression (see Section 11.2.3). Due to improvements in neuroimaging and the fact that tumor growth in certain regions of the CNS is without immediate neurologic signs and symptoms, greater reliance is placed on neuroimaging to define response and progression.

11.2.2 *Clinical Neurological Examination*

- 11.2.2.1 Neurological performance will be monitored by grading both symptoms and signs. A comprehensive neurological examination will be performed at each study visit. Evaluation will be based on any changes in the neurological clinical exam from the previous examination. Changes should be unrelated to post-ictal state or other unrelated events such as infection.
- 11.2.3 Neuroimaging
- 11.2.3.1 Patients will be evaluated for objective tumor assessments by Gd-MRI. MRI scans will be performed on mid- and high-field magnets (1.0-1.5 T). The following are suggested MRI protocols: **Sagittal T1W, T2 FSE sequence, and pre- and post-gadolinium axial T1W and post-gadolinium coronal T1W images will be acquired.** The axial scans should be acquired in a plane that images both the anterior and posterior commissures (*along the AC-PC line*) and should cover the entire brain. The coronal scans must cover the tumor. The post-gadolinium series will be acquired immediately after intravenous infusion of 0.1 mmol/kg gadolinium. The axial scans should be comprised of 12 or more scans to encompass the intracranial contents from the cranial base to the convexity. A technique that utilizes 5 mm cuts with a 1 mm gap is preferred on the axial images.
- 11.2.3.2 MRI scans with and without contrast will be obtained in patients pre- and post-operatively (pre-study entry). Scans will be done:
- Post-chemotherapy and pre-radiotherapy
 - Post-radiotherapy and immediately prior to the initiation of post-RT TMZ
 - Every 2 months during post-RT TMZ
- 11.2.3.3 MRIs required for submission:
- Pretreatment evaluation
 - Post-chemotherapy (pre-RT)
 - Post completion of all therapy
 - At progression during therapy and at the time of recurrence during follow-up period
- 11.2.3.4 MRIs will be submitted to RTOG Headquarters for review by neuroradiologists.
- 11.2.4 Criteria for Response
- 11.2.4.1 Therapeutic response will be measured by the following:
- Response (Sections 11.2.4.2.1-7)
 - Disease-free survival, as determined by enhanced MR scan, and lumbar puncture and ophthalmological examination, if indicated.
 - Survival
- 11.2.4.2 Response: All tumor measurements must be recorded in millimeters and must have the longest diameter and its perpendicular applied at the widest portion of the tumor recorded. For those with multifocal disease the sum of the products of the two greatest diameters of all measurable lesions will be used to determine response. Cranial MR scans will be the primary means of assessing tumor size. **The duration of the response and the time to progression will be recorded.**
- 11.2.4.2.1 **Complete Response (CR)**: Disappearance of all enhancing tumor; the patient must be off steroid therapy and neurologically stable or improved. For those patients with a positive cytology, a response will constitute the disappearance of malignant cells from the CSF on both ventricular and lumbar specimens.
- 11.2.4.2.2 **Major Partial Response (PR-1)**: Greater than or equal to a 90% reduction in enhancing tumor, stable or reduced steroid dose, and the patient must be neurologically stable or improved.
- 11.2.4.2.3 **Partial Response (PR-2)**: Less than 90% decrease in enhancing tumor; no simultaneous increase in size of any lesion or the appearance of new lesions may occur. Patient must be on a stable or decreasing dose of steroids and be neurologically stable or improved.
- 11.2.4.2.4 **Progressive Disease (PD)**: Greater than 25% increase in enhancing tumor or the appearance of new lesions in the brain, eye, or the appearance of a new positive CSF cytology. The patient may be neurologically stable or worse and on stable or increasing doses of corticosteroid.
- 11.2.4.2.5 **Stable Disease (SD)**: All other situations.
- 11.3 Ineligible and Inevaluable Patients
- 11.3.1 Patients that are registered and retrospectively found to be ineligible for this trial may discontinue forms submission upon notification of ineligibility from HQ. Data until that point, however, must be submitted to RTOG. These patients will be excluded from all analyses.

11.3.2 Patients that are registered and receive no protocol drug will be excluded from all analyses. Institutions should notify HQ of this situation in writing. No further data will be required by RTOG.

11.4 Long-term Neurotoxicity/Quality of Life Assessments

11.4.1 Quality of life will be assessed using the Spitzer Quality of Life Questionnaire. The Spitzer QL Index is an objective quality-of-life index utilized to measure quality of life in patients with cancer. Developed to assess progression of disease in patients with terminal cancer, it has been shown to correlate with the level of health in patients with cancer with adequate internal consistency and interrater reliability.

11.4.2 Neurocognitive status will be assessed using the Mini Mental Status Exam (MMSE). The MMSE is a commonly used method for assessing cognitive mental status. It has demonstrated utility in detecting impairment and following the course of an illness including assessment of response to treatment. The MMSE is also a commonly utilized research tool to screen for cognitive disorders in epidemiological studies and follow cognitive changes in clinical trials. While the MMSE has limited specificity with respect to individual clinical syndromes, it represents a brief, standardized method by which to grade cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. Furthermore, it provides a total score that places the individual on a scale of cognitive function.

11.4.3 The Mini Mental Status Examination was utilized in the prior CNS lymphoma protocol (RTOG 93-10), and limited comparisons can be made. This is the first trial for primary central nervous system lymphoma that has utilized the Spitzer tool. The purpose of the utilization of this tool is to provide an overview of the tolerability of treatment and/or changes in quality of life occurring during therapy. It is not certain how the information derived will be utilized in the current protocol, but it may be utilized as a baseline for future trials.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

NOTE: Prompt data submission is required for Phase I statistical analysis.

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Slides/Blocks (P2) Mini Mental Status Exam (MS) Pretreatment Spitzer QOL (PQ)	Within 2 weeks of study entry
<u>Final Dosimetry Information:</u> Pretreatment MRI Scan/Report (MR) (ME) Post-Chemo, pre-RT MRI Scan/Report (MR) (ME) Post Completion of all Therapy MRI Scan/Report (MR) (ME) Films (Simulation and Portal) (TP) Radiotherapy Form (T1) Mini Mental Status Exam (MS) Spitzer QOL (PF)	Within 1 week of RT end
Mini Mental Status Exam (MS) Spitzer QOL (PF) Initial Follow-up Form (FS)	Week 10 and Week 13

Follow-up Form (F1) Mini Mental Status Exam (MS) Spitzer QOL (PF)	Every 3 months from end of treatment for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.
Study Specific Flowsheets (SF)	Every 4 weeks during chemotherapy
Mini Mental Status Exam (MS) Spitzer QOL (PF)	Every 2 months during TMZ
MRI Scan/Report (MR) (ME)	At progression during therapy; at recurrence during follow up
Autopsy Report (D3)	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Rate of toxicities

13.1.2 Two-year overall survival rate

13.1.3 Pre-irradiation chemotherapy tumor response rates.

13.1.4 Progression free survival

13.2 Phase I Component

13.2.1 Evaluation of Pre-Irradiation Chemotherapy Toxicity

The primary objective of this phase of the study is to determine the maximum tolerated dose (MTD) of induction temozolomide combined with methotrexate and rituximab. A dose limiting toxicity (DLT) is defined as any grade 3 or 4 non-hematological toxicity (other than grade 3 nausea/vomiting). Toxicity evaluation for this dose escalation will include all toxicities occurring prior to the start of radiation therapy. If the patient does not receive radiation therapy, then toxicity evaluation will include all toxicities occurring through week 15. If at any time a grade 5 toxicity is observed, accrual will be suspended, and the Study Chair will review the event. Furthermore, if the cumulative incidence (obtained by time to event analysis), at any time, of combined acute/late DLTs estimates the toxicity rate to be greater than 30% at any dose level, then the Executive Committee will be notified, and the committee will determine whether to stop accrual.

13.2.2 Dose Escalation

This study consists of two possible induction temozolomide dose escalations of 50 mg from the starting dose of 100 mg/m² (5 days on weeks 4 and 8). Dose escalation will follow the standard 3+3 design, although up to six patients may be accrued per dose level before suspending accrual for toxicity evaluation. If none of the first three patients (0/3), or one of the first three and none of the second three (1/3 and 0/3), experience a DLT (as defined in Section 13.2.1), then the current dose level will be considered acceptable, and the next dose will be opened. Otherwise, the current dose level will be considered too toxic. The highest dose achieved with an acceptable level of toxicity will be considered the Maximum Tolerable Dose (MTD). All patients starting temozolomide will be evaluable for toxicity. Note that the patients finally determined to be at the MTD will be included in the phase II component. **Maximum size for the phase I component of the study will be 18 patients.**

13.3 Phase II Component

13.3.1 Primary Endpoint

The primary endpoint of the phase II component is two-year survival. This trial builds upon the experience of RTOG 93-10, which reported a median survival time of 37.0 months and two-year survival of 64% measured from the time of study registration. With a sample size of 47 evaluable patients, a one-group χ^2 test with a 0.20 one-sided significance level will have 87% power to detect the difference between the null hypothesis two-year survival rate of 64% and the alternative rate of 77% (a 20% increase). Assuming a 5% inevaluability rate (See Section 11.3 for definition of ineligible and unevaluable patients), **the total required sample size is 52 patients** (including 6 patients from the MTD of the phase I component).

13.3.2 Secondary Endpoint

The secondary endpoint of pre-irradiation chemotherapy tumor response rate will also be evaluated, RTOG 93-10 reported a pre-irradiation chemotherapy response rate of 59%. Using a one-group χ^2 test with a 0.20 one-sided significance level will have 81% power to detect the difference between a null hypothesis complete response rate of 59% and the alternative rate of 71% (a 20% increase).

13.4 Patient Accrual

Based on RTOG 93-10, patient accrual is expected to be 2.75 cases per month. At this rate, it will take 19 months to accrue the required 52 cases. If the average monthly accrual rate is less than 1 patient, the study will be re-evaluated with respect to feasibility.

13.5 Analyses Plans

13.5.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) compliance rate of treatment delivery with respect to protocol prescription;
- c) the frequency and severity of the toxicities.

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study and, if necessary, the Executive Committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

Analysis of the phase II study component will be undertaken when documentation of at least two years of follow up or death prior to two years has been received for each patient. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables by treatment arm;
- d) observed results with respect to the endpoints described in Section 13.3.

The analysis will be carried out on the intent-to-treat basis. This is defined as all patients who at least start chemotherapy. A significant result, per Section 13.3,1 will indicate this regimen as promising and will provide support for pursuing a phase III trial. Subgroup analyses will be undertaken depending upon the size of the subsamples.

13.6 Inclusion of Women and Minorities

No publications have reported a survival difference between genders or races in this patient population. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, a statistical analysis will be performed to examine such possible differences, if accrual across classes of race and gender permits. The projected gender and minority accruals are shown below:

Ethnic Category	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	28	24	62
Ethnic Category: Total	29	25	64
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	0	1	1
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	28	33	61
Racial Category: Total	29	35	64

REFERENCES

1. Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma. *J Neurooncol.* 43:241-247, 1999.
2. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. *J Clin Oncol.* 10:635-643, 1992.
3. Glass J, Gruber ML, Cher L, Hochberg F. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. *J Neurosurg.* 8:188-195, 1994.
4. O'Neill BP, O'Fallon JR, Earle JD, Colgan JP, Brown LD, Krigel RL. Primary central nervous system non-Hodgkin's lymphoma: Survival advantages with combined initial therapy? *Int J Radiat Oncol Biol Phys.* 33:663-673, 1995.
5. O'Neill BP, Wang CH, O'Fallon JR, et al. Primary central nervous system non-Hodgkin's lymphoma (PCNSL): Survival advantages with combined initial therapy? A final report of the North Central Cancer Treatment Group (NCCTG) Study 86-72-52. *Int J Radiat Oncol Biol Phys.* 43:559-563, 1995.
6. Schultz C, Scott C, Sherman W et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: Initial report of Radiation Therapy Oncology Group protocol 88-06. *J Clin Oncol.* 14: 556-64, 1996.
7. Lachance DH, Brizel DM, Gockerman JP et al. Cyclophosphamide, doxorubicin, vincristine, and prednisone for primary central nervous system lymphoma: Short-duration response and multifocal intracerebral recurrence preceding radiotherapy. *Neurology.* 44:1721-1727, 1994.
8. Glass J, Shustik C, Hochberg FH, Cher L, Gruber ML. Therapy of primary central nervous system lymphoma with pre-irradiation methotrexate, cyclophosphamide, doxorubicin, vincristine, and dexamethasone (MCHOD). *J Neurooncol.* 30:257-265, 1996.
9. Schultz C, Scott C, DeAngelis L et al. Radiation therapy (RT) alone vs. pre-RT chemotherapy (CTX) for the treatment of primary CNS lymphoma (PCNSL): Age matched survival analysis of RTOG 83-15 and 93-10. *J Clin Oncol.* 19:159a, 2000.
10. Fisher B, Seiferheld W, Schultz C, DeAngelis L, Nelsen D, Schold S, Curran W: Secondary analysis of RTOG 9310: An intergroup phase II combined modality treatment of primary central nervous system lymphoma with chemotherapy and hyperfractionated radiotherapy. *Int J Radiat Oncol Biol Phys.* 3(Suppl 1):166, 2001.
11. Blay JY, Conroy T, Chevreau C, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: Analysis of survival and late neurological toxicity in a retrospective series. *J Clin Oncol.* 16:864-871, 1998.
12. DeAngelis L, Seiferheld W et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol.* 20(24):4643-4648, 2002.
13. Neuwelt EA, Goldman DL, Dahlborg SA et al. Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: Prolonged survival and preservation of cognitive function. *J Clin Oncol.* 9:1580-1590, 1991.
14. Chamberlain MC, Levin VA. Primary central nervous system lymphoma: A role for adjuvant chemotherapy. *J Neurooncol.* 14:271-275, 1992.
15. Reni M, Ferreri AJM, Candela M, Abbadessa A, Villa E. Salvage therapy with temozolomide in immunocompetent patients with primary brain lymphoma (PBL). ASCO 2001.
16. Coiffier B, Haioun C, Ketterer N, Et Al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. *Blood.* 92:1927-32, 1998.
17. Vose JM, Link BK, Grossbard M et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive Non-Hodgkin's lymphoma. *J Clin Oncol.* 19: 389-397, 2001.
18. Raizer J, DeAngelis L, Zelenetz A, Abrey L. Activity of Rituximab in Primary Central Nervous System Lymphoma PCNSL. ASCO Proceedings 2000, Abstract 242.

APPENDIX IA

RTOG 0227

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

PHASE I/II STUDY OF PRE-IRRADIATION CHEMOTHERAPY WITH METHOTREXATE, RITUXIMAB, AND TEMOZOLOMIDE AND POST-IRRADIATION TEMOZOLOMIDE FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have central nervous system lymphoma.

This study has two parts. In part one, the first six patients treated on this study will receive 100 mg of temozolomide by mouth per day for 5 days during weeks 4 and 8 of pre-irradiation chemotherapy. If no more than 1 of these patients experience severe side effects, then the dose of temozolomide will be increased to 150 mg per day for 5 days during weeks 4 and 8 of pre-irradiation chemotherapy for the next six patients. If no more than 1 of these patients experience severe side effects, then the dose of temozolomide will be increased to 200 mg per day for 5 days during weeks 4 and 8 of pre-irradiation chemotherapy for the next 6 patients. In part two of the study, all patients will begin treatment at 200 mg of temozolomide for 5 days during weeks 4 and 8 of pre-irradiation chemotherapy, or the dose that has been determined to be safe in part one of the study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the use of pre-irradiation chemotherapy (rituximab, temozolomide, and methotrexate), whole brain radiation, and post-irradiation chemotherapy (temozolomide) has on you and your cancer.

This research is being done because we are seeking to improve the survival of patients with this disease by adding additional medications (rituximab and temozolomide) to methotrexate and irradiation, which are the standard of care for central nervous system lymphoma.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 52-64 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

As part of this treatment, you will receive five treatments with methotrexate by vein. Methotrexate is given every two weeks, and requires hospitalization. Three days prior to the first treatment with methotrexate, you will receive another form of chemotherapy, rituximab, by vein. This will be given as an outpatient. You will also receive a third chemotherapy drug, temozolomide, for five days the week after the second and fourth treatments with methotrexate. This can be taken orally (by mouth) at home.

The dose of temozolomide you receive depends upon when you join the study. If you are among the first six patients, you will receive 100 mg of temozolomide per day. If this dose is found to be safe and you are among the next 6 patients on the study, you will receive 150 mg of temozolomide per day. If this dose is found to be safe and you are among the next 6 patients on the study, you will receive 200 mg of temozolomide. If this dose is found to be safe, all other patients that join the study will receive this dose.

Following completion of the fifth methotrexate treatment, whole brain radiation therapy will be started. You will be treated twice daily, Monday through Friday, for three weeks.

After completion of radiation therapy, you will receive an additional ten treatments with temozolomide. You will take temozolomide orally at home every four weeks for five days in a row.

If you take part in this study, you will have the following tests and procedures:

Before starting any treatment, you will have

- A history and physical examination
- Blood tests (including a pregnancy test for women who can have children)
- A brain MRI (if not already performed after surgery)
- An examination of the eyes called a slit lamp examination to evaluate for any tumor within the eyes. This involves close examination of the inside of the eyes by an ophthalmologist.
- A lumbar puncture (spinal tap) to evaluate for any spread of the tumor to the linings of the brain and spinal cord. This involves placement of a small needle into the back to remove spinal fluid for laboratory examination. This is performed as an outpatient and uses local anesthesia.
- Lung function (breathing) tests if you have a history of lung disease

- You will be asked to collect your urine for 24 hours to evaluate kidney function.

Then periodically during treatment, you will have

- A history and physical examination
- Blood tests (including a pregnancy test for women who can have children)
- A brain MRI
- An examination of the eyes called a slit lamp examination to evaluate for any tumor within the eyes.
- A lumbar puncture (spinal tap) to evaluate for any spread of the tumor to the linings of the brain and spinal cord.
- You will be asked to collect your urine for 24 hours to evaluate kidney function.

These are considered standard procedures that would be performed in any person undergoing chemotherapy for primary central nervous system lymphoma, regardless of whether they are enrolled in a clinical trial.

Also, you will be asked to complete a written and verbal test to evaluate your memory and thinking skills, and a questionnaire asking about your quality of life before starting therapy, at the end of radiation therapy, and in follow-up visits. This test and questionnaire are not necessarily required in people receiving treatment for this disease but not enrolled in a clinical trial, but will help the investigators gain knowledge about how well treatment is tolerated and how it affects brain function. It is anticipated that it will take 15 minutes to complete the written testing and 10 minutes to complete the verbal test.

During pre-radiation chemotherapy, blood tests will be performed every week, including (if appropriate) a pregnancy test every two weeks. A history and physical and a 24-hour urine collection to test kidney function also will be performed every two weeks during pre-radiation chemotherapy.

After radiation therapy, during treatment with temozolomide, some blood tests will be performed weekly; other blood tests will be performed every 4 weeks. A brain MRI, a slit lamp examination, and a lumbar puncture will be performed every two months. These tests would be required for any person undergoing chemotherapy with temozolomide.

At the completion of all treatment, you will be seen for follow up. The following tests will be required every three months from the end of treatment for 2 years, every six months for years 3-5, then annually for five years: A history and physical examination, a brain MRI, a slit-lamp examination, and a lumbar puncture.

HOW LONG WILL I BE IN THE STUDY?

You will receive treatment in this study for approximately fifty weeks. Additionally, follow up after completion of treatment will be required every three months from the end of treatment for 2 years, every six months for years 3-5, then annually for five years.

The researcher may decide to take you off this study if your tumor begins to grow again or if there are side effects that prevent safe administration of additional chemotherapy. Unforeseen circumstances, such as a loss of drug supply, loss of funding, unacceptable toxicity, or new information regarding the treatment of primary central nervous system lymphoma may cause the study to stop early.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first. If you do decide to withdraw from the study, you will be provided with treatment that is considered standard of care for your circumstances.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long lasting or permanent.

Risks Associated With Brain Irradiation

Very Likely

- Scalp redness or soreness
- Hair loss
- Dry mouth or altered taste
- Fatigue or sleepiness
- Headaches
- Weakness
- Seizure

Less Likely

- Fever, chills, or heavy sweating
- Upset stomach, nausea, and/or vomiting
- Loss of appetite

Less Likely But Serious

- Permanent hair loss

- Hearing loss
- Eye injury resulting in blindness
- Mental slowness
- Behavioral changes
- Blood clots
- Severe damage to normal brain tissue that may require additional surgery

Risks Associated with Rituximab

Very Likely

- Mild to moderate fever and chills/rigidity
- Other symptoms may occur, usually within 30 to 120 minutes of beginning the first infusion, and include nausea, vomiting, itching, hives, swelling of the lips or throat, lowered blood pressure, increased blood pressure, headache, difficulty breathing, throat irritation, running nose, rash, decreased appetite, muscle aches, or dizziness. These symptoms generally improve with each treatment and respond to slowing or interrupting the therapy and treating the symptoms.
- Lowering of the number of B-lymphocytes in the blood, which help fight off infection

Less Likely

- Lowered blood counts with risk of bleeding, bruising, or infection
- Serious blood disorders (hemolytic anemia, aplastic anemia, and prolonged pancytopenia) resulting in prolonged lowering of blood cell counts with resulting prolonged risk of bleeding, bruising, or infection
- Nausea and/or vomiting
- Decreased appetite and/or weight loss
- Itching
- Rash
- Hives
- Weakness
- Sleepiness
- Headache
- Runny nose
- Throat irritation
- Cough
- Heartburn
- Swelling of the throat
- Inflammation of the sinuses
- Temporary contraction of muscles and narrowing of the tubes that carry air in the lungs and/or shortness of breath
- Uncontrolled movements of arms or legs
- Dizziness and/or vertigo
- Muscle pain and/or joint pain
- Changes in behavior, such as agitation, depression, or uneasiness
- Abnormal sensation, such as tingling
- Decreased sensation; numbness
- High blood pressure
- Low blood pressure
- Injection site pain
- Inability to sleep
- Low blood sugar

Less Likely But Serious

- Inflammation of the contents of the eye, resulting in visual problems
- Inflammation of the optic nerve which may result in visual loss in one eye
- Acute inflammation of the lungs with resulting chest pain and shortness of breath 1-4 weeks after infusion

- Cardiac failure (rare)

Risks Associated With Temozolomide

Very Likely

- Lowered blood counts with risk of bleeding, bruising, or infection
- Nausea and/or vomiting

Less Likely

- Headache
- Loss of appetite
- Constipation
- Diarrhea
- Fatigue
- Sores in the mouth
- Inflammation of the esophagus, which may result in difficulty swallowing
- Skin rash; burning sensation of skin
- Mild hair loss

Less Likely But Serious

- Irritation of skin and mucous membranes if exposed to content of capsules
- Temporary rise in liver enzymes. This is a laboratory result that may be an indicator of a mild toxic effect on the liver that usually does not affect any bodily functions. Blood tests monitoring liver enzymes are performed every two weeks during chemotherapy before radiation therapy and every four weeks during chemotherapy after radiation therapy.

Risks Associated With Methotrexate

Very Likely

- Mouth sores, which may result in difficulty eating
- Diarrhea

Less Likely

- Seizures
- Decreased coordination
- Periods of deep and lasting unconsciousness
- Liver not functioning properly
- Lung problems

Less Likely But Serious

- Lowered blood counts with risk of bleeding, bruising, or infection
- Kidney failure

This study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your

doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

Treatment may result in a temporary or permanent loss of the ability of a man or woman to bear children.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with central nervous system lymphoma in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Committee, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

_____ Name

_____ Telephone Number

For information about this study, you may contact:

_____ Name

_____ Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Visit the NCI's Web sites for comprehensive clinical trials information at
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
(Physician Data Query) visit <http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

Patient's Name

Signature

Date

Name of Person Obtaining Consent

Signature

Date

APPENDIX IB

RTOG 0227

SAMPLE CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

PHASE I/II STUDY OF PRE-IRRADIATION CHEMOTHERAPY WITH METHOTREXATE, RITUXIMAB, AND TEMOZOLOMIDE AND POST-IRRADIATION TEMOZOLOMIDE FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue 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 tissue that remains for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Your tissue may be helpful for research whether you do or do not have cancer.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue before it is given to a researcher. Reports about research done with your tissue 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 tissue for future research is up to you. **No matter what you decide to do, it will not affect your care or your participation in this study.**

If you decide now that your tissue 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 and then any tissue that remains will no longer be used for research; or, you may request that your tissue be returned to you or your designee.

In the future, people who do research may need to know more about your health. While your doctor/institution 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 tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

BENEFITS

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

RISKS

Physical Risks

Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and rarely, creation of an abnormal opening or passage.

Social-Economic Risks

There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _____ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

MAKING YOUR CHOICE

If you have any questions about the research involving your tissue or about this form, please talk to your doctor or nurse, or call the institution's research review board at _____ (IRB's phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". **No matter what you decide to do, it will not affect your care or your participation in this study.**

1. **My tissue may be used for the research in the current study.**

Yes No

2. **My tissue may be kept for use in research to learn about, prevent, or treat cancer.**

Yes No

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

Yes No

4. **Someone from my doctor's office/institution may contact me in the future to ask me to take part in more research.**

Yes No

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (<i>Karnofsky 90-100</i>).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<i>Karnofsky 70-80</i>).
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 (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).