

# 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

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RTOG Institution # \_\_\_\_\_

RTOG 0227

**ELIGIBILITY CHECKLIST (7/22/03)(8/18/05)**

Case # \_\_\_\_\_

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- \_\_\_\_\_(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  $\geq 8$  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?
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- \_\_\_\_\_(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?
- \_\_\_\_\_(N) 15. Does the patient have active hepatitis B?

**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 # \_\_\_\_\_

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**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.<sup>1</sup>
- 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/m<sup>2</sup>) 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.<sup>2</sup> Similar results were noted at the Massachusetts General Hospital. Twenty-five patients were treated with systemic MTX alone (3.5 g/m<sup>2</sup>) every 10 or 21 days followed by WBRT (30 – 46 Gy) with a resulting median survival of 33 months.<sup>3</sup>
- 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.<sup>4,5</sup> 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.<sup>6</sup> Observations in another clinical trial utilizing CHOP reveal that rapid responses to chemotherapy are followed by rapid recurrence.<sup>7</sup>
- 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.<sup>8</sup>
- 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.<sup>9</sup> Furthermore, preliminary analysis suggests that the incidence of late neurological toxicity is less in patients receiving the twice daily WBRT fractions.<sup>10</sup> 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.<sup>11</sup> Deangelis et al treated 102 patients with five cycles of methotrexate 2.5 g/m<sup>2</sup>, 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.<sup>12</sup>
- 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.<sup>13</sup> 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.<sup>14</sup> 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/m<sup>2</sup> 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.<sup>15</sup>
  - 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 monotherapy<sup>16</sup> or in combination with standard chemotherapy, such as CHOP.<sup>17</sup> 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.<sup>18</sup>
  - 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  $\geq 50$ , calculated with the Cockcroft-Gault Equation: 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 (8/18/05)**

- 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.
- 3.2.9 Active hepatitis B.

## **4.0 PRETREATMENT EVALUATIONS (8/18/05, 5/23/07)**

### **4.1 The following evaluations should be completed within one week prior to the first treatment cycle:**

- 4.1.1 Complete, detailed medical history & physical examination;
- 4.1.2 Laboratory studies: CBC, differential, platelets, electrolytes, LFTs, BUN, serum creatinine, urine hcG (for females of childbearing potential);
- 4.1.3 Completion of Mini Mental Status Exam (MMSE);
- 4.1.4 Quality of Life assessment: Spitzer Quality of Life Questionnaire.

### **4.2 The following evaluations should be completed within four weeks prior to first treatment cycle:**

- 4.2.1 MRI of the brain with and without gadolinium (or head CT with and without contrast; see Section 11.2.3.1);
  - 4.2.1.1 A pre-operative MRI is sufficient if there has been no debulking of the tumor
- 4.2.3 Screening for hepatitis B virus (HBV) infections and documentation of HBV vaccination history;
- 4.2.4 Slit lamp examination;
- 4.2.5 CSF for cytology (unless contraindicated by CNS mass effect from tumor);
- 4.2.6 Pulmonary function testing in patients with known pulmonary or bronchospastic disease;

## **5.0 REGISTRATION PROCEDURES**

### **5.1 Pre-Registration Requirements (8/18/05)**

Each institution must complete a Study Agent Shipment Form (Appendix V) electronically (versus handwritten for improved legibility), and fax the form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case (the shipment form is only submitted once). Allow adequate processing time (7-10 days) before calling to register the first case. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).**

### **5.2 Registration (8/18/05)**

**(12/14/04)** Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to

215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site ([www.rtog.org](http://www.rtog.org)), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

**In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191.**

## **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 (8/18/05)**

6.5.1 Radiation Toxicity Monitoring: All acute adverse events from protocol radiation therapy will be 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 ( $\leq 90$  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 Radiation Adverse Event Reporting (8/18/05)

See Section 7.8 for AdEERS Adverse Event Reporting.

## **7.0 DRUG THERAPY**

### **7.1 Pre-Irradiation Chemotherapy**

7.1.1 Patients will receive rituximab,  $375 \text{ mg/m}^2$ , intravenously three days prior to the first cycle of methotrexate (MTX).

7.1.2 Patients will receive five cycles of methotrexate at  $3.5 \text{ gm/m}^2$  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. Sample orders are detailed in Appendix IV. (12/14/04)

7.1.3 On weeks 4 and 8, patients will receive temozolomide,  $200 \text{ mg/m}^2$ , 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:  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The MTD of temozolomide will be utilized as the standing dose in the phase II portion of the study (See Section 13.2). [NOTE: The phase I portion of this study established a temozolomide MTD of  $100 \text{ mg/m}^2$ ; the phase II portion of this study opened on 2/24/06, with temozolomide administered at that dose. (5/31/06)]

7.1.4 Because of the lymphopenia associated with rituximab, all patients will receive the following medications as prophylaxis during pre-irradiation chemotherapy, beginning at the time of initiation of rituximab and ending no sooner than recovery from all hematological toxicity associated with pre-irradiation chemotherapy. (5/23/07)

- Trimethoprim/sulfamethoxazole, 160 mg/800 mg (double strength), one tablet 3x weekly (Monday, Wednesday, Friday) (3/17/06)
- 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
- Hepatitis B virus (HBV) reactivation: HBV reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of the rituximab and approximately one month after the last dose. (11/23/04)
- 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 (8/18/05)

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 the package insert 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.

**7.4.5** Contraindications (12/14/04)

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

**7.4.6** Supply (12/14/04) (8/18/05)(2/14/08)

Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough has agreed to supply temozolomide free of charge for patients entered into this study. The drug will be distributed by a vendor, I.V. Solutions, Inc., under contract to RTOG. Schering-Plough has not offered financial support nor has any provision been made to share data or study results with Schering-Plough.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. Temozolomide will be distributed by I.V. Solutions, Inc. Each institution must complete a Study Agent Shipment Form (Appendix V) electronically (versus handwritten for improved legibility), and fax the form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case.

The temozolomide will not be shipped by I.V. Solutions, Inc. until the patient has been registered. I.V. Solutions, Inc. generally ships drug Mondays through Thursdays for delivery in time for the first dose. Canadian shipments may require additional time. RTOG will notify I.V. Solutions, Inc. to initiate each of these shipments. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

**Unused supplies at the sites will be returned directly to I.V. Solutions, Inc.** Additional questions about supply and delivery should be directed to:

**Angelo Corridino, RPh**  
**I.V. Solutions, Inc.**  
**162 North Main Street**  
**Old Forge, PA 18518**  
**(570) 457-9201**  
**Fax (570) 457-0465**  
[ivspublic@choiceonemail.com](mailto:ivspublic@choiceonemail.com)

## **7.5 Chemotherapy Subsequent to Radiation Therapy**

**7.5.1** Temozolomide, 200 mg/m<sup>2</sup> 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/m<sup>2</sup> 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 (5/23/07)**

**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/mm<sup>3</sup> or the platelet count is < 70,000/mm<sup>3</sup>. 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/mm<sup>3</sup> or the platelet count persistently below 70,000/mm<sup>3</sup> 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. A recurrence of the same toxicity at the lower dose will result in the discontinuation of temozolomide. (12/14/04)

**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 m<sup>2</sup> 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/mm<sup>3</sup>) 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 (or head CT 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** 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. (11/23/04)

**7.7.5** *Criteria for Treatment Discontinuation:* Rituximab should be discontinued in any patient who develops active HBV infection or hepatitis. (11/23/04)

**7.7.6** *Post-radiation chemotherapy.* Temozolomide should be administered on schedule unless the absolute neutrophil count (ANC) is < 1000/mm<sup>3</sup> or the platelet count is < 70,000/mm<sup>3</sup>. 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/mm<sup>3</sup> or the platelet count persistently below 70,000/mm<sup>3</sup> for 2 weeks, then the dose of temozolomide will be reduced by 25% to 150/mg/m<sup>2</sup>/day for the subsequent course.

## **7.8 Adverse Events (8/18/05)**

**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 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

### 7.8.2 **Adverse Events (AEs) (5/31/06)**

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient's case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also **must be reported on the SF chemotherapy flow sheet** (see Section 12.1). **NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.**

### 7.8.3 **Serious Adverse Events (SAEs) (5/31/06)**— All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

**Definition of an SAE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

SAEs reported using AdEERS also **must be reported on the SF chemotherapy flow sheet** (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

**All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers;** non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

**SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as**

“expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

**7.8.4 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or 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.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

## 7.9 AdEERS Expedited Reporting Requirements

**Phase 1 Trials Utilizing an Agent under a Non-CTEP IND and Commercially Available Agents: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Non-CTEP IND Agent [Temozolomide] and Commercially Available Agents (Rituximab, Methotrexate) in this Study**

Phase 1 Trials								
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
<p><sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a Non-CTEP IND and utilizing commercially available agents require reporting as follows:            AdEERS 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> <li>• Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>• Grade 4 unexpected events</li> <li>• Grade 5 expected events and unexpected events</li> </ul> <p><sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.</p> <p>Please see exceptions below under section entitled "Additional Instructions or Exceptions."</p> <p style="text-align: right;">March 2005</p>								

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.**

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a Non-CTEP IND and commercially available agents.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a Non-CTEP-IND and Commercially Available Agents:**  
 Not applicable.

**Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND and Commercially Available Agents: AdEERS Expedited Reporting Requirements for Adverse Events that Occur**

within 30 Days<sup>1</sup> of the Last Dose of the Non-CTEP IND Agent [Temozolomide] and Commercially Available Agents (Rituximab, Methotrexate) in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days
<p><sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a Non-CTEP IND and utilizing commercially available agents require reporting as follows:</p> <p>AdEERS 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> <li>Grade 4 and Grade 5 unexpected events</li> </ul> <p>AdEERS 10 calendar day report:</p> <ul style="list-style-type: none"> <li>Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>Grade 5 expected events</li> </ul> <p><sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.</p> <p>Please see exceptions below under section entitled "Additional Instructions or Exceptions."</p> <p style="text-align: right;">March 2005</p>									

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.**

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a Non-CTEP IND and commercially available agents.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND and Commercially Available Agents:**  
Not applicable.

## **8.0 SURGERY**

Not applicable to this study.

## **9.0 OTHER THERAPY**

Not applicable to this study.

## **10.0 PATHOLOGY (2/14/08)**

**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 Biospecimen Resource (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 Biospecimen Resource 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 Biospecimen Resource by the participating institution at same time as slides are sent for central review. Materials should be sent to the Biospecimen Resource at the address below.

### **10.3 RTOG Biospecimen Resource**

- 10.3.1** The following must be provided in order for the case to be evaluable for the Biospecimen Resource:
- 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 Biospecimen Resource. 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 Biospecimen Resource; the form must include the RTOG protocol number and patient's case number.
- 10.3.2** Submit materials to: (12/14/04) (5/31/06)(2/14/08)

**USPS mailing address** (all non-courier materials)  
RTOG Biospecimen Resource  
University of California San Francisco  
Campus Box 1800  
San Francisco, CA 94143-1800

**FedEx/Courier address** (all courier packages and all frozen samples)  
RTOG Biospecimen Resource  
University of California San Francisco  
1657 Scott Street, Room 223  
San Francisco, CA 94115

**Telephone:** 415-476-RTOG (7864)

**Fax:** 415-476-5271

[RTOG@ucsf.edu](mailto:RTOG@ucsf.edu)

### **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 Biospecimen Resource 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 Biospecimen Resource 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 (11/23/04, 12/14/04) (8/18/05) (5/31/06) (5/23/07)

Assessments	Pre-Study	Weekly During Pre-RT Chemo	Every 2 weeks <sup>†</sup> During Pre-RT Chemo	Week 10 of Tx (post-chemo pre-RT)	Week 13 (Prior to TMZ)	Weekly During TMZ	Every 4 Weeks <sup>†</sup> During TMZ	Every 2 Months During TMZ	Following Completion of Tx and at Time of Recurrence
History & Physical	X <sup>a†</sup>		X <sup>b</sup>		X				X
CBC, differential, platelets <sup>c</sup>	X <sup>†</sup>	X		X	X		X <sup>j</sup>		
Electrolytes, LFTs, BUN/Creatinine	X <sup>†</sup>		X	X	X		X		
Creatinine clearance calculation <sup>d</sup>	X <sup>†</sup>		X						
β-hCG <sup>e</sup>	X <sup>†</sup>		X		X		X		
PFTs	X <sup>†‡</sup>								
MRI brain (or head CT)	X <sup>‡</sup>			X	X			X	X
Slit-lamp examination	X <sup>‡</sup>								X <sup>h</sup>
CSF for cytology	X <sup>‡</sup>								X <sup>h</sup>
Hepatitis B screening	X <sup>‡</sup>		X <sup>i</sup>		X <sup>i</sup>			X <sup>i</sup>	
MMSE	X <sup>†</sup>			X	X			X	X
Spitzer QOL Assessment <sup>g</sup>	X <sup>†</sup>			X	X			X	X

† Within one week prior to first treatment cycle (5/23/07)

‡ Within four weeks prior to first treatment cycle (5/23/07)

- a. 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.
- b. Interval history and physical to consist of interval history, review of systems, medication, physical and neurological examinations, Zubrod performance status, weight, and BSA.
- c. CBC and differential may need to be performed more frequently than weekly in the setting of myelotoxicity; evaluation is at treating physician's discretion.
- d. Creatinine clearance may be calculated utilizing the Cockcroft-Gault Equation: Cr Clearance = (140-age) x wt (kg)/(Cr[mg/dl] x 72) (multiply by 0.8 for women). A 24-hour urine may also be obtained.
- e. For women of childbearing potential; urine hCG is acceptable.
- f. In patients with known pulmonary or bronchospastic disease.
- g. Also required at regular follow-up intervals; see Section 12.1.
- h. Slit-lamp examination and lumbar puncture performed at time of recurrence. (12/14/04) (5/31/06)
- i. Any patient with a previous history of hepatitis B or abnormalities on screening in the absence of previous vaccination will need to have re-screening done at the 4-week mark, pre- and post-RT, and every 2 months for a total of 1 year from receiving rituximab. (11/23/04) (8/18/05) (5/31/06)
- j. A CBC is to be performed at weeks 3 and 4. If there are no toxicities in the first cycle, then the CBC may be performed once monthly at the investigator's discretion. (5/23/07)
- k. Head CT with and without contrast may be utilized for patients unable to obtain an MRI, However, one imaging modality (MRI or CT) must be utilized during the course of the trial. (5/23/07)

## **11.2 Measurement of Effect (5/23/07)**

### **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). Head CT scanning with and without contrast may be substituted if MRI scanning is not feasible (for example, is contraindicated due to implant hardware). 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. Patients who are unable to undergo brain MRIs will undergo CT scans with and without intravenous contrast. Axial CT scans will be performed with and without contrast and 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 CT scan 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 (or head CT scans) with and without contrast will be obtained in patients pre- and post-operatively (pre-study entry) if there has been tumor debulking or if there has been a greater than 4-week interval between the first scan and the date of enrollment. 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** Neuroimaging 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** Neuroimaging 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 (or head CT 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. Brain MR scans (or head CT 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 (12/14/04)**  
**(RTOG, 1818 Market Street, Philadelphia, PA 19103, 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 <b>(A5)</b>	Within 2 weeks of study entry	
Initial Evaluation Form <b>(I1)</b>		
Pathology Report <b>(P1)</b>		
Slides/Blocks <b>(P2)</b>		
Mini Mental Status Exam <b>(MS)</b>		
Pretreatment Spitzer QOL <b>(PQ)</b>		
<u>Final Dosimetry Information:</u>	Within 1 week of RT end	
Pretreatment MRI Scan/Report <b>(MR) (ME)</b>		
Post-Chemo, pre-RT MRI Scan/Report <b>(MR) (ME)</b>		
Post Completion of all Therapy MRI Scan/Report <b>(MR) (ME)</b>		
Films (Simulation and Portal) <b>(TP)</b>		
Radiotherapy Form <b>(T1)</b>		
Mini Mental Status Exam <b>(MS)</b>		
Spitzer QOL <b>(PF)</b>		
Mini Mental Status Exam <b>(MS)</b>		Week 10 and Week 13
Spitzer QOL <b>(PF)</b>		
Initial Follow-up Form <b>(FS)</b>		
Follow-up Form <b>(F1)</b>	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.	
Mini Mental Status Exam <b>(MS)</b>		
Spitzer QOL <b>(PF)</b>		
Study Specific Flowsheets <b>(SF)</b>	Every 4 weeks during chemotherapy	
Mini Mental Status Exam <b>(MS)</b>	Every 2 months during TMZ	
Spitzer QOL <b>(PF)</b>		
MRI Scan/Report <b>(MR) (ME)</b>	At progression during therapy; at recurrence during follow up	
Autopsy Report <b>(D3)</b>	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) or any hematological toxicity resulting in the discontinuation of temozolomide as defined in Section 7.7.1.2. 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. (12/14/04)

#### **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/m<sup>2</sup> (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  $\chi^2$  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  $\chi^2$  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 accrual to 93-10, patient accrual is expected to be 1.8 cases per month. At this rate, it will take 29 months to accrue the required 52 cases. If the average monthly accrual rate is consistently less than 1 patient, the study will be re-evaluated with respect to feasibility. (12/14/04)

### **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: (12/14/04)

<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	1	1	2
Not Hispanic or Latino	28	34	62
<b>Ethnic Category: Total</b>	29	35	<b>64</b>
<b>Racial Category</b>			
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
<b>Racial Category: Total</b>	29	35	<b>64</b>

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**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.

**[NOTE:** Part one of this study was completed on 2/24/06 and determined that the safe dose of temozolomide is 100 mg for 5 days during weeks 4 and 8 of pre-irradiation chemotherapy. You are enrolling in part two of this study, which has the dose of 100 mg. (5/31/06)]

**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? (8/18/05) (5/31/06) (5/23/07)**

As part of this treatment, you will receive five treatments with methotrexate by vein. Methotrexate is given every two weeks; hospitalization is strongly suggested but not mandatory. 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. **[NOTE: Part one of this study was completed on 2/24/06 and determined that the safe dose of temozolomide is 100 mg. You are enrolling in part two of this study, which has the dose of 100 mg. (5/31/06)]** 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 (or CT scan of your head) (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 (or CT scan of your head)
- 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 (or CT scan of your head) will be performed every two months. A slit lamp examination and a lumbar puncture may also be performed if the tumor begins to grow again. 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 (or CT scan of your head).

### **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 Whole Brain Radiation**

##### Very Likely

- Scalp redness or soreness
- Hair loss
- Fatigue or sleepiness

##### Less Likely

- Upset stomach, nausea, and possible vomiting
- Loss of appetite
- General weakness
- Dry mouth or altered taste

- Cataract formation, typically several years after radiation treatment
- Dry and/or itchy eyes
- Middle ear congestion

Less Likely But Serious

- Permanent hair loss
- Hearing loss
- Eye injury resulting in blindness
- Behavioral changes, diminished memory, and/or mental slowing
- Local brain swelling requiring long-term steroid use and/or 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)

### Additional Risk Information

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor immediately. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

## **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? (8/18/05)**

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.

The drug temozolomide will be provided without cost to you by Integrated Therapeutics, Inc., a subsidiary of Schering-Plough. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug.

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

**Participant statement:**

I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

\_\_\_\_\_

Patient's Name

\_\_\_\_\_

Signature

\_\_\_\_\_

Date

**Witness statement:**

I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

\_\_\_\_\_

Name of Person Obtaining Consent

\_\_\_\_\_

Signature

\_\_\_\_\_

Date

## 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> ).

## APPENDIX IV (12/14/04)

### **SAMPLE METHOTREXATE ORDERS**

#### **Hydration:**

D5 ½ NS or ½ NS at 100 ml/hour with 100 mEq/liter of sodium bicarbonate and 20 mEq/liter of KCl.

#### **Methotrexate orders:**

Start methotrexate only if urine output is greater than 100 ml/hour and urine pH is greater than 7.0

Methotrexate 3.5 gm/m<sup>2</sup> in 500 ml ½ NS with 100 mEq of sodium bicarbonate over 4 hours.

#### **Leucovorin orders:**

Leucovorin 25 mg every 6 hours to begin exactly 24 hours after start of methotrexate.

#### **Input/output monitoring:**

Check urine pH and output every 2 hours.

If output is less than or equal to 100 ml/hour, increase IV fluid rate by 25 ml/hour and encourage PO hydration.

If pH is less than or equal to 7.0, give sodium bicarbonate 100 mEq IV or 1300 mg PO.

#### **Laboratory studies:**

Daily CBC, creatinine.

Methotrexate level daily beginning 24 hours after start of methotrexate infusion.

**APPENDIX V (2/1/05, 4/13/05)(8/18/05)**

**RTOG 0227**

**TEMOZOLOMIDE SHIPMENT FORM**

Each institution must complete a Study Agent Shipment Form (SASF) electronically (versus handwritten for improved legibility) and fax the form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Canadian institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case.

**NOTE:** This form must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) for form processing before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment.

**NOTE:** The Study Agent Shipment Form for this study (for electronic completion) is available on the RTOG web site, [www.rtog.org](http://www.rtog.org), next to the protocol. Use the form below **only** if the RTOG web site is unavailable (**please write legibly**), and fax it as instructed above.

**SHIP TO:**

Name: \_\_\_\_\_

Address: \_\_\_\_\_

(No P.O. addresses)

\_\_\_\_\_

\_\_\_\_\_

Telephone: \_\_\_\_\_

Email: \_\_\_\_\_

Fax#: \_\_\_\_\_

RTOG Institution#: \_\_\_\_\_

Institution Name: \_\_\_\_\_

IRB Approval Date: \_\_\_\_\_

Investigator (PI) Signature \_\_\_\_\_ Date: \_\_\_\_\_

Investigator Name (Print) \_\_\_\_\_

Investigator NCI # \_\_\_\_\_

<b>U.S. Sites</b>	<b>Canadian Sites</b>
Fax completed forms to: <b>CTSU Regulatory Office</b> Fax 215-569-0206	Fax completed forms to: <b>RTOG Headquarters</b> Fax 215-574-0300

**RTOG HEADQUARTERS APPROVAL**

**DATE:**