

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0420

### A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME

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**Activation Date: 11/11/2004**

**Version Date: 10/27/2004**

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#### SCHEMA

- R**    **Radiation Therapy**  
2.0 Gy x 30 fractions, 5 days a week x 6 weeks for a total dose of 60 Gy
- E**
- G**    **Concurrent Chemotherapy**  
Temozolomide for 6 weeks during radiation beginning the night before the first dose of radiation
- I**
- S**    **Post-Radiation Chemotherapy**  
Temozolomide and irinotecan for 1 year or until progression or unacceptable toxicity, beginning 4 to 6 weeks after completion of radiation therapy
- T**
- E**
- R**

**Patient Population:** (See Section 3.0 for Eligibility)

Histopathologically confirmed, newly diagnosed glioblastoma multiforme

Diagnosis made by surgical biopsy or excision

The tumor must be supratentorial in location.

Patient must have recovered from surgery or any post-operative infection or complication prior to study entry, and therapy must begin  $\leq$  5 weeks after surgery.

**Required Sample Size: 99 patients**

RTOG Institution # \_\_\_\_\_  
RTOG 0420  
Case # \_\_\_\_\_

**ELIGIBILITY CHECKLIST (11/11/2004)**  
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- \_\_\_\_\_ (Y) 1. Does the patient have histopathologically confirmed newly diagnosed glioblastoma multiforme?
- \_\_\_\_\_ (Y) 2. Diagnosis made by surgical biopsy or excision?
- \_\_\_\_\_ (Y) 3. Is the tumor supratentorial?
- \_\_\_\_\_ (Y) 4. Has the patient recovered from the effects of surgery, post-operative infection, or other complications?
- \_\_\_\_\_ (Y) 5. Will therapy begin  $\leq$  5 weeks after surgery?
- \_\_\_\_\_ (Y) 6. Does the patient have an estimated survival of at least 8 weeks?
- \_\_\_\_\_ (Y) 7. Zubrod performance 0-1?
- \_\_\_\_\_ (Y) 8. Age  $\geq$  18 years?
- \_\_\_\_\_ (Y) 9. Has a diagnostic contrast-enhanced MRI or CT scan been performed preoperatively prior to study entry?
- \_\_\_\_\_ (Y,N) 10. Has a diagnostic contrast-enhanced MRI or CT scan been performed postoperatively prior to study entry?  
\_\_\_\_\_ (Y) If no, was diagnosis by stereotactic biopsy?
- \_\_\_\_\_ (Y) 11. Do the patient's laboratory values meet the criteria specified in Section 3.1.12?
- \_\_\_\_\_ (Y,N) 12. Does the patient require anti-seizure medications?  
(Y) If yes, is the patient on stable or decreasing doses for at least 2 weeks prior to study entry?
- \_\_\_\_\_ (Y,N) 13. Is the patient receiving an enzyme inducing antiepileptic drug?  
(Y) If yes, will the patient be switched to an NEIAED per Section 3.1.10?
- \_\_\_\_\_ (N) 14. Is the patient pregnant or lactating?
- \_\_\_\_\_ (N) 15. Is the patient's histology grade less than glioblastoma multiforme?
- \_\_\_\_\_ (N) 16. Does the patient have *recurrent* malignant glioma?
- \_\_\_\_\_ (N) 17. Does the patient have any detected tumor foci below the tentorium or beyond the cranial vault?
- \_\_\_\_\_ (N) 18. Does the patient have any major medical or psychiatric illness, which in the investigator's opinion will prevent administration or completion of the protocol therapy?
- \_\_\_\_\_ (N) 19. Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma *in situ* of uterus, cervix or bladder, unless disease free for  $\geq$  5 years?
- \_\_\_\_\_ (N) 20. Has the patient received any prior radiation to the head or neck (except for T1 glottic cancer) resulting in overlap of radiation fields?
- \_\_\_\_\_ (Y) 21. Can the patient be regularly followed by the investigator?

(continued on next page)

\_\_\_\_\_ (N) 22. Is the patient known to have Acquired Immune Deficiency Syndrome (AIDS)?

\_\_\_\_\_ (Y) 23. Have all the pre-treatment evaluations been done as specified in Section 3.1?

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

RTOG 0420

**ELIGIBILITY CHECKLIST (11/11/2004)**

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

(page 2 of 3)

**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?

\_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

\_\_\_\_\_ 5. Patient's Initials (First Middle Last) (if no middle initial, use hyphen)

\_\_\_\_\_ 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 (U.S. Residents)

\_\_\_\_\_ 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

\_\_\_\_\_ (Y/N) 18. Tissue used for research in current study?

\_\_\_\_\_ (Y/N) 19. Tissue kept for cancer research?

\_\_\_\_\_ (Y/N) 20. Tissue kept for medical research?

\_\_\_\_\_ (Y/N) 21. Allow contact for future research?

**(continued on next page)**

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

RTOG 0420

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

**ELIGIBILITY CHECKLIST (11/11/2004)**

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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 Background**

Glioblastomas are rapidly growing primary brain tumors associated with a high degree of morbidity and mortality. Current management is based on cytoreduction through a combination of surgery, radiotherapy, and chemotherapy. Despite this multi-disciplinary approach to treatment, glioblastoma remains a life-threatening disease.

Overall median survival for patients with newly diagnosed glioblastomas and Karnofsky performance status (KPS) > 60 treated with radiation and chemotherapy after surgery reported in several randomized trials ranges from 42 to 95 weeks.<sup>1</sup> Fine et al. reported the results of meta-analysis of 16 randomized trials evaluating the use of various chemotherapeutic regimens in patients with newly diagnosed malignant gliomas.<sup>2</sup> These data suggest that patients with newly diagnosed malignant gliomas, including glioblastoma multiforme (GBM), may benefit from adjuvant chemotherapy in terms of survival. The most commonly used agent or regimen in these studies included a nitrosourea.

The nitrosoureas, BCNU and CCNU, are chemotherapeutic agents approved for the treatment of patients with malignant glioma at first relapse. Response rate (defined as responders plus stable disease) for single agent BCNU in the treatment of patients with GBM at recurrence has been reported at 29% with a median time to progression of 22 weeks.<sup>3</sup> The median time to progression for recurrent malignant gliomas following treatment with various other chemotherapeutic agents ranges from 16-50 weeks.<sup>3</sup> Response rates (defined as responders plus stable disease) in these same studies have ranged from 0-55% in patients with GBM. A single chemotherapeutic agent has not emerged as a standard in the treatment of patients with malignant glioma or GBM at relapse.

### **1.2 Temozolomide**

Temozolomide is a cytotoxic alkylating agent that has demonstrated clinical antitumor activity, been relatively well-tolerated, and has an acceptable safety profile in phase I and II trials in patients with various advanced cancers, including malignant gliomas.<sup>4-9</sup> Temozolomide has an uncomplicated and well-defined pharmacokinetic profile.<sup>10</sup> Temozolomide was shown to be effective in prolonging progression-free survival (PFS) and maintaining or improving health-related quality of life (HRQL) in adult patients with recurrent high-grade gliomas.<sup>11</sup> Temozolomide has been shown to provide better, six month progression-free survival, overall survival, and better overall quality of life when compared to Procarbazine alone in GBM patients.<sup>12</sup> Temozolomide also has demonstrated clinically meaningful efficacy in anaplastic astrocytoma (AA) patients in first relapse.<sup>4,5</sup> Patients benefited from the use of temozolomide irrespective of the exact tumor histology.<sup>4</sup>

### **1.3 Irinotecan (CPT-11)**

A phase II trial at Duke University of CPT-11 given at a starting dose of 125 mg/m<sup>2</sup> weekly to patients with recurrent high grade glioma has accrued 60 patients<sup>13</sup>. Evaluation of efficacy indicates that 10 patients have demonstrated a partial response, 3 patients a minimal response (25-50% disease regression), 13 patients continue with stable disease, 31 patients have progressed, 2 patients are too early to evaluate and 1 patient is non-evaluable for a response. Of note, the toxicity appears to be less than predicted from the colon carcinoma phase II experience. In the Duke trial, diarrhea was seen in only approximately 15% of patients and virtually no myelosuppression was observed that warranted dose reduction. A possible explanation for this lower than anticipated toxicity may be that these patients are being treated with anticonvulsants and corticosteroids.

Studies have demonstrated that patients receiving enzyme-inducing anti-epileptic drugs (EIAED) show decreased plasma levels of certain chemotherapeutic drugs when administered at conventional doses.<sup>14-16</sup> Failure to achieve adequate plasma levels of such drugs may account for lack of efficacy in past brain tumor trials. Based on the results of preclinical studies, phenobarbital (an EIAED) may enhance the conversion of CPT-11 to SN-38 and the formation of SN-38G from SN-38.<sup>17</sup> Additionally, phenobarbital has been combined with CPT-11 to successfully treat a patient with Gilbert's syndrome, which is associated with decreased UDP-GT enzyme activity.<sup>11,18</sup> However, in preclinical studies, valproic acid (not an EIAED) inhibits the primary clearance mechanism of the CPT-11 metabolite, SN-38 resulting in nearly a three-fold increase in AUC for this active compound.<sup>17</sup>

#### **1.4 Rationale for Using Temozolomide During Radiation Therapy**

Temozolomide has been given in a more extended dosing schedule without unacceptable toxicity.<sup>19</sup> Brock et al described results using a daily schedule for seven weeks in recurrent glioma. Stupp used this schedule in a pilot study in which newly diagnosed glioblastoma patients were treated with radiation therapy and 6 weeks of daily temozolomide at 75mg/m<sup>2</sup>/day, followed by temozolomide with the 5-day schedule.<sup>19</sup> The results showed the combination of radiation therapy and daily temozolomide were very tolerable and the survival data was highly encouraging. At the 2004 ASCO meeting, Stupp et al reported a multicenter, randomized prospective trial comparing external beam radiation therapy alone to adjuvant temozolomide 75mg/m<sup>2</sup> per day during radiation therapy followed by temozolomide in the 5 day schedule every 28 days for 6 cycles. This demonstrated a survival benefit in the chemotherapy arm.<sup>29</sup>

#### **1.5 Rationale for Using Temozolomide and Irinotecan (CPT-11)**

CPT-11 and temozolomide have both been tested in recurrent malignant gliomas after radiation and chemotherapy, with temozolomide being the most recently registered drug by the FDA for treatment of patients with this stage of disease. Although in contrast to the Duke study noted above, CPT-11 has demonstrated modest activity in a prior NABTC phase 2 study of recurrent GBM and anaplastic astrocytoma<sup>20</sup>, preclinical studies in glioma xenograft models suggested that there was a schedule dependent enhancement of antitumor activity when CPT-11 is combined with temozolomide<sup>21</sup>. The enhanced activity seems to require exposure to the alkylating agent prior to or concomitant with exposure to CPT-11. The mechanism for this schedule dependent enhancement of cytotoxicity may be in part related to the creation of topoisomerase 1-DNA covalent complexes by O6 alkylation of guanine residues by temozolomide.

In a recent phase 1-2 study of temozolomide and CPT-11 in patients with recurrent malignant glioma conducted by the NABTC, the MTD for CPT-11, when administered on days 1 and 15 with temozolomide 150mg/m<sup>2</sup> on days 1-5, for patients receiving enzyme inducing antiepileptic drugs, was 500mg/m<sup>2</sup>.<sup>22</sup> Dose limiting toxicities were primarily diarrhea and myelosuppression. In the phase 2 component of the trial, the 6-month progression-free survival was 38% and 5 GBM patients demonstrated partial responses. In the phase 1 component, there were 4 responses (1 CR and 3 PR) in 21 patients entered. In another phase 1 study using a different schedule involving temozolomide 200mg/m<sup>2</sup> on days 1-5 with weekly infusions of CPT-11 during the first 4 weeks of 6-week cycles, the MTD was not reached at 100mg/m<sup>2</sup> of CPT-11, and 1 CR and 2PRs were noted.<sup>23</sup> In yet another phase 1 study involving only subjects on EIAEDs, temozolomide was given on days 1-14, and CPT-11 on day 7 or 8 and both drugs were escalated to their single agent MTD. In this study, the phase 2 doses were determined to be 100mg/m<sup>2</sup> of temozolomide and 350mg/m<sup>2</sup> of CPT-11. Median survival for the GBM cohort was 9.5 months. There were 4 CR and 6 PR in this study<sup>24</sup>. Gruber<sup>25</sup> tested 2 schedules of CPT-11 and temozolomide in a single institution phase 2 study. In the first cohort, 6 patients were treated with temozolomide 200mg/m<sup>2</sup> per day on day 1-5 and irinotecan 125mg/m<sup>2</sup> on days 6, 13, and 20 of 28-day cycles. In the second, 24 patients received temozolomide 200mg/m<sup>2</sup> on days 1-5 and CPT-11 350mg/m<sup>2</sup> on day 6 of 28-day cycles. Two patients began on the first schedule and were switched to the second. Of 18 GBM, there were 2 complete and 3 partial responses. The median duration of response was 24 weeks and 6-month progression free survival was 39%.

These data suggest that the combination of CPT-11 and temozolomide is one of the most active regimens yet tested in recurrent malignant glioma. This regimen should be tested in the adjuvant setting to determine whether overall survival will exceed that of historical controls in the RTOG database<sup>26-28</sup>.

## **2.0 OBJECTIVES**

- 2.1 To determine if this treatment regimen improves the overall survival of patients with newly diagnosed supratentorial glioblastoma multiforme, compared with historical controls from the RTOG database.
- 2.2 To evaluate short- and long-term toxicity of this treatment regimen.
- 2.3 To report progression-free survival of patients with newly diagnosed supratentorial glioblastoma multiforme treated with this regimen.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility**

- 3.1.1 Histopathologically confirmed newly diagnosed glioblastoma multiforme.
- 3.1.2 Diagnosis must be made by surgical biopsy or excision.
- 3.1.3 The tumor must be supratentorial in location.
- 3.1.4 The patient must have recovered from the effects of surgery, or post-operative infection and other complications before entry into the study.
- 3.1.5 Therapy must begin  $\leq$  5 weeks after surgery.
- 3.1.6 Patients must have an estimated survival of at least 8 weeks.
- 3.1.7 Zubrod performance score 0-1
- 3.1.8 Age  $\geq$  18.
- 3.1.9 Patients receiving steroids should be on stable or decreasing doses for at least 2 weeks prior to study entry.
- 3.1.10 Patients requiring antiepileptic drugs must be receiving only non-enzyme inducing antiepileptic drugs (NEIAED) for 14 days prior to initiation of irinotecan. Patients receiving EIAEDs may be switched to NIEAEDs during the period of radiation therapy if the EIAED is discontinued 14 days prior to day 1 of the first cycle containing irinotecan.
- 3.1.11 Patients of reproductive potential must practice an effective method of birth control during and for 2 months after treatment.
- 3.1.12 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams, and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.  
Hematologic: Hemoglobin  $\geq$  10 grams  
Absolute neutrophil count  $\geq$  1500 (ANC) per  $\text{mm}^3$   
Platelets  $\geq$  100,000 per  $\text{mm}^3$   
Renal: BUN  $\leq$  25 mg  
Creatinine  $\leq$  1.5mg  
Hepatic: Bilirubin  $\leq$  0.5 mg/dL  
ALT or AST  $\leq$  2 x institutional uln
- 3.1.13 A diagnostic contrast-enhanced MRI or CT must be performed preoperatively and postoperatively before study entry, **within 28 days prior to registration** (preferably within 72 hours of surgery), prior to the initiation of radiotherapy. The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.
- 3.1.14 **Within 14 days prior to registration:** complete history and general physical examination; detailed neurological examination immediately prior to beginning protocol treatment; steroid and anti-convulsant doses must be documented; CBC with differential, platelet count, blood chemistries (total protein, albumin, calcium, phosphorus, glucose, BUN creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, AST, ALT, triglycerides and cholesterol).
- 3.1.15 Negative serum pregnancy test **within 5 days prior to registration** for females of child-bearing potential.
- 3.1.16 The patient must sign a study-specific informed consent prior to study entry. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

### **3.2 Conditions for Patient Ineligibility**

- 3.2.1 Gliomas graded less than glioblastoma multiforme.
- 3.2.2 Recurrent malignant gliomas.
- 3.2.3 Tumor foci are detected below the tentorium or beyond the cranial vault.
- 3.2.4 Major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of the protocol therapy.

- 3.2.5 Previous malignancies except for non-melanomatous skin cancers and carcinoma in situ of the uterine cervix or bladder, unless disease free for  $\geq 5$  years.
- 3.2.6 Prior radiation to the head or neck (except T1 glottic cancer), resulting in overlap of radiation fields
- 3.2.7 Pregnant or lactating women, as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- 3.2.8 Patients who cannot be regularly followed by the investigator.
- 3.2.9 Known diagnosis of clinical Acquired Immune Deficiency (AIDS), due to the potential for increased complications from treatment.

#### **4.0 RECOMMENDED PRETREATMENT EVALUATIONS**

Not applicable. See all required evaluations in Section 3.0.

#### **5.0 REGISTRATION PROCEDURES**

##### **5.1 Pre-Registration Requirements**

Each institution must submit a Study Agent Shipment Form (Appendix III) to 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.

##### **5.2 Registration**

###### **5.2.1 Online Registration**

Patients can be registered only after eligibility criteria are met. The RA will 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. A username and password is required. 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, as discussed in Section 5.2.2.**

###### **5.2.2 Dial-in Registration**

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

## **6.0 RADIATION THERAPY [NOTE: INTENSITY MODULATED RT (IMRT) IS NOT ALLOWED.]**

### **6.1 Dose Definition and Schedule**

Radiotherapy must begin within  $\leq 5$  weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over 6 weeks (As described in Section 6.3). All portals shall be treated during each treatment session. Doses are specified as the target dose that shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

- 6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams
- 6.1.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams
- 6.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation
- 6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
- 6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity; however, if this technique is utilized, the dose shall be specified at the center of the target volume.
- 6.1.6 Other or complex treatment arrangements: at the center of the target volume

### **6.2 Technical Factors**

Treatment shall be delivered with megavoltage machines of a minimum energy of Cobalt 60. Selection of the appropriate photon energy (ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies  $> 10$  MV should be utilized only in dual energy beam arrangements using at least one beam with energy  $\leq 10$  MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Electron, particle or implant boost is not permissible.

### **6.3 Localization, Simulation, and Immobilization**

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility.

### **6.4 Treatment Planning**

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at RTOG Headquarters reviews.

The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. This initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast enhancing lesion plus a 2.5 centimeter margin. The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the tumor volume for the conedown treatment should include the contrast-enhancing lesion (without edema) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity within the target volume shall be kept to  $\leq 10\%$ .

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. The use of vertex fields requires either a diagram or a photograph of the treatment position to be submitted to RTOG Headquarters.

### **6.5 Dose Limitation to Critical Structures**

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 54 Gy, the retina of at least one eye (but preferably both) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

## **6.6 Radiation Toxicity**

### **6.6.1 Acute**

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting, or temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

### **6.6.2 Early Delayed**

Possible early delayed radiation effects include lethargy, transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

### **6.6.3 Late Delayed**

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, or radiation-induced neoplasms.

## **6.7 Treatment Delays**

RT will be delayed or interrupted if the platelet count is < 20,000. RT will not begin or resume until the platelet count is ≥ 20,000. Hematological toxicities should be rated on a scale of 0-5 as defined in the revised NCI Common Toxicity Criteria v.3.

## **6.8 Documentation Requirements**

At the completion of treatment, the following should be forwarded to RTOG Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the large and conedown fields, and the radiotherapy summary per Section 12.1. In addition, CT/MRI documentation must be submitted per Section 12.2.

## **6.9 RT Quality Assurance Review**

**6.9.1** The Radiation Oncology Co-Chair, Christina Tsien, M.D., will perform an RT Quality Assurance Review after complete data for the first 30 cases enrolled has been received at RTOG Headquarters. Dr. Tsien will perform the next review after complete data for the next 30 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first. These reviews will be on going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

## **6.10 Radiation Adverse Event Reporting — RTOG AE TELEPHONE LINE (215) 717-2762**

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). **Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

### **6.10.1 Documentation**

Radiation therapy is combined with chemotherapy administration in this protocol; therefore, ALL serious adverse events are reported using the appropriate reporting form (MedWatch/AdEERS) as stated in Section 7.0 of this protocol.

### **6.10.2 Summary of AE Reporting in Protocols Involving Radiation Treatment**

#### **6.10.2.1 RT Treatment With Chemotherapy Administration**

- Report Grade 4/Grade 5 AEs;
- Telephone report within 24 hours of discovery;
- Document using the appropriate report — MedWatch or AdEERS within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required;
- For **DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT:**
  - Telephone report to RTOG within 24 hours of discovery;
  - Follow guidelines outlined in Section 7.0 of this protocol for AE reporting.

## **7.0 DRUG THERAPY**

**Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.**

### **7.1 Concurrent Chemotherapy During Radiation Therapy**

Temozolomide, 75mg/m<sup>2</sup>/day will be given orally daily for 6 weeks during radiation therapy, beginning the night before the first fraction of radiation, including weekends and holidays. The last dose of temozolomide will be given the night before the last fraction of radiation. Doses will be rounded to the nearest 5 mg to accommodate capsule strength. Capsules are available in 250 mg, 100 mg, 20 mg, and 5 mg strengths.

Temozolomide should be taken on an empty stomach, either prior to eating in the morning or no less than 2 hours after eating or drinking other than water if taken in the evening before bedtime. Taking the daily dose before bedtime may minimize gastrointestinal toxicity. The timing of the dose is left to the discretion of the investigator. Temozolomide should be taken with water.

**7.1.1** Drug therapy for prophylaxis of pneumocystis pneumonia: Beginning within 48 hours of beginning temozolomide and radiation therapy, subjects will receive pneumocystis carinii prophylaxis with either trimethoprim-sulfamethoxazole or pentamidine. For subjects allergic to sulfa compounds, pentamidine will be the drug used, for other subjects the choice is left to the discretion of the investigator.

**7.1.1.1** Trimethoprim-sulfamethoxazole: 1 double strength tablet (equivalent to trimethoprim 160mg and sulfamethoxazole 800mg)/day for 3 days consecutively each week during radiation treatment and for 2 weeks after the completion of radiation treatment.

**7.1.1.2** Aerosolized pentamidine: Beginning within 48 hours of beginning radiation therapy, subjects will receive 300mg of pentamidine every 28 days either by nebulizer mask or an inhalation tent until 14 days post conclusion of radiation therapy.

The decision to continue pneumocystis prophylaxis beyond the endpoints noted above is left to the discretion of the investigator. Subjects who continue to demonstrate lymphopenia after the continuous daily temozolomide has been discontinued should be considered for ongoing prophylaxis.

### **7.2 Post-Radiation Chemotherapy**

Beginning 4-6 weeks after completion of radiotherapy, temozolomide, 150mg/m<sup>2</sup>/day will be given orally for 5 days (Days 1-5) during week one and irinotecan 200mg/m<sup>2</sup> on days 1 and 15. This schedule will continue without interruption for one year or 12 complete 28-day treatment cycles (whichever is longer), as long as there is no tumor progression and toxicity is ≤ grade 3. Self-administration of temozolomide is permitted. One course of therapy is defined as 2 complete 28-day treatment cycles (a total of 2 sets of 5 days of administration of temozolomide and 4 doses of irinotecan at 14-day intervals. Zofran (4mg) or Kytril (1-2mg) po may be used for prevention of nausea associated with temozolomide on Days 1 – 5.

Temozolomide should be taken on an empty stomach, either prior to eating in the morning or no less than 2 hours after eating or drinking other than water if taken in the evening before bedtime. Taking the daily dose before bedtime may minimize gastrointestinal toxicity. The timing of the dose is left to the discretion of the investigator. Temozolomide should be taken with water. If temozolomide is taken prior to breakfast, the subject should wait at least 1 hour prior to eating or drinking liquids other than water.

### **7.3 Temozolomide (Temodar®)**

#### **7.3.1 Formulation**

Other Names: - methazolastone; Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lauryl sulfate NF.

#### **7.3.2 Mode of Action**

Alkylating agent of imidazotetrazinone class.

- 7.3.3** Storage and Stability  
The capsules are packaged in 30 cc, 28 mm, 48 Type I amber glass bottles (30 capsules/bottle) and should be stored between 2 and 30 degrees centigrade. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.
- 7.3.4** Supply  
Temozolomide is manufactured by Schering-Plough and is available commercially. For this study, commercial drug will be used. Capsules are available in 250 mg, 100 mg, 20 mg, and 5 mg strengths.
- 7.3.5** Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and  $T_{max}$  increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.  
Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.
- 7.3.6** Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m<sup>2</sup>.
- 7.3.7** Special Populations
- 7.3.7.1** Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m<sup>2</sup> has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CL<sub>cr</sub> < 36 mL/min/m<sup>2</sup>). Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.
- 7.3.7.2** Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.
- 7.3.7.3** Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.
- 7.3.7.4** Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.
- 7.3.8** Drug-Drug Interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the  $C_{max}$  or AUC values for temozolomide or MTIC.  
Population Analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known.  
Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H<sub>2</sub>-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.
- 7.3.9** Known Potential Adverse Events  
Hematological: Thrombocytopenia and leukopenia.

Gastrointestinal: Nausea, vomiting, anorexia.

Hepatic: Elevated liver enzymes (reversible)

Skin: Rash, alopecia

Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

**7.3.10** Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.

**7.3.11** Contraindications: Temozolomide is contra-indicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

**7.3.12** Pregnancy Category D:

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.**

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

#### **7.3.13** Temozolomide Dose Modifications

|  | <b>ANC (mm<sup>3</sup>)</b>    |                 | <b>Platelets (mm<sup>3</sup>)</b>          | <b>Modification</b>  |
|--|--------------------------------|-----------------|--|--|
| <b>Nadir</b>                               | ≥ 750<br>250-749<br>< 250      | and<br>or<br>or | ≥ 75,000<br>25,000 –<br>74,999 <<br>25,000 | No Change<br>Decrease dose 25%<br><br>Decrease dose 50%                                |
| <b>At scheduled time of administration</b> | ≥ 1500<br>< 1500               | and<br>and      | ≥ 100,000<br>< 100,000                     | Dose modified for nadir only<br>Hold for 1 week  |
| <b>* After 1 week</b>                      | ≥ 1500<br>1000 –1499<br>< 1000 | and<br>or<br>or | ≥ 100,000<br>75,000-99,999<br>< 75,000     | Dose modified for nadir<br>75% dose<br>Contact study chair before further chemotherapy |

\*Repetition of severe marrow depression, persistent neutropenia (<1500/mm<sup>3</sup>), or thrombocytopenia (< 25,000/mm<sup>3</sup>) at time of treatment and after dose reduction will require contacting the study chair before any further chemotherapy is administered. Further chemotherapy will be given only if there is joint agreement between the study chair and the individual investigator, and only 2 dose reductions will be allowed.

#### **7.4** Irinotecan (CPT-11)

**7.4.1** Chemistry: Irinotecan hydrochloride trihydrate {CPT-11, (4S)-4, 11-diethyl-4-hydroxy-9-((4-piperidinopiperidino) carbonyloxy)-1H-pyrido[3,4':6,7]indol[2,3-b]quino line-3, 14(4H, 12H)dione hydrochloride trihydrate} is a topoisomerase I inhibitor.

**7.4.2** Formulation: The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

**7.4.3** Administration: Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90 minutes. Nothing else should be added to the bag.

**7.4.4** Storage and Stability: Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years

at room temperature. CPT-11 is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D5W.

#### 7.4.5

**Toxicity:** Virtually all phase I and II studies of CPT-11 have reported neutropenia and/or late diarrhea (diarrhea occurring more than 8 hours after CPT-11 administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia.

Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after CPT-11 administration; this syndrome is thought to be cholinergically mediated. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials (note: this dosage regimen exceeds the usual dosage recommendations for loperamide) consisted of the following: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea.

Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed. CPT-11 may cause local irritation at infusion sites. Extravasation necrosis of the skin has not been reported in U.S. studies.

#### 7.4.6

**Supply:** Irinotecan is commercially available. It is manufactured by Pfizer and will be supplied by Pfizer for this study. The drug will be distributed by a vendor (I.V. Solutions, Inc.) under contract to RTOG.

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. Irinotecan will be distributed by I.V. Solutions, Inc. The Study Agent Shipment Form must be submitted 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 patient-specific drug supply 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 Canadian shipments, allow 7 to 10 days lead 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:

**Gary F. Mead, R.Ph, MHA  
I.V. Solutions, Inc.  
162 North Main Street  
Old Forge, PA 18518  
(570) 457-9201  
Fax (570) 457-0465**

#### 7.4.7 Dose Modifications

- 7.4.7.1 Dose Levels: Blood counts will be monitored every week during drug therapy.
- 7.4.7.2 Dose adjustments during treatment: treatment will continue without dose adjustment for the first 28-day cycle as long as there are no toxicities  $\geq$  grade 3. For grade 3 or greater toxicities, day 15 treatment will be withheld and the patients will be monitored weekly until toxicities resolve to grade 2 or better.
- 7.4.7.3 Dose adjustments for the subsequent courses: subsequent course will start (as long as the treatment is beneficial) after complete resolution of toxicities to grade 2 or better. A minimum of a two-week rest period will be required if there is grade 3 or greater toxicity. Dosage for the subsequent course will be 25% below the dose that produced toxicity. There will be no dose re-escalation after dose reduction. If subjects develop grade 3 toxicity during treatment at the 25% dose reduction, they will be removed from the protocol treatment.
- 7.4.7.4 Use of growth factors and blood products for hematologic toxicity: if the only grade 3 toxicity requiring further dose reduction or dose delay is neutropenia, subjects may receive G-CSF as clinically indicated. If the only grade 3 toxicity is anemia, subjects may receive R-epoetin and/or transfusion of packed red cells at the clinical discretion of the investigator.

#### 7.5 Modality review

The Medical Oncology Chair, Frank Lieberman, MD will perform a Chemotherapy Assurance Review of all patients in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review; incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

#### 7.6 Adverse Event Reporting—RTOG AE TELEPHONE LINE (215) 717-2762 OR (800) 227-5463 X4189

- 7.6.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.
- 7.6.2 All serious adverse events (SAEs) will be reported using 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)).

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. The following AEs experienced by patients accrued to this protocol and attributed to the protocol treatment (**definitely, probably, or possibly related**) should be reported:

- Death on study (from start of protocol treatment to 30 days post protocol treatment)
- Hospitalization or prolongation of hospitalization on study (from start of protocol treatment to 30 days post protocol treatment)
- Life threatening event
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Intervention required to prevent permanent impairment/damage

- 7.6.3 The following steps must be taken to report Serious Adverse Events that occur while the patient is on this trial:
- Within **24 hours of discovery** of the adverse event, **call** the RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762, or to (800) 227-5463, X4189;
  - Within **10 working days**, file a report using the **Adverse Event Expedited Reporting System (AdEERS)**. **Use the patient's case number as the patient ID when reporting via AdEERS;**
  - Reporting requirements and timing of reporting are dependent on the Phase of the trial, grade, attribution, and whether the event is expected or unexpected as determined by the protocol and/or Investigator's Brochure. **Please read the protocol thoroughly for this important information.**

- AEs reported through AdEERS also **must be reported in routine study data submissions (appropriate case report forms).**

**7.6.4** Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of the FDA Form 3500 (MedWatch) or a report via the AdEERS system and **must be mailed within 30 days of AML/MDS diagnosis** to the following addresses:

|   |                                     |
|---|-------------------------------------|
| Investigational Drug Branch<br>(NCI/CTEP) | RTOG Headquarters<br>AML/MDS Report |
| P.O Box 30012                             | 1818 Market Street, Suite 1600      |
| Bethesda, MD 20824                        | Philadelphia, PA 19103              |

**All forms** submitted to RTOG Headquarters **must include the RTOG study and case numbers**; the non-RTOG intergroup study and case numbers must be included, when applicable. *NCI will be creating a pathway for this on the AdEERS site in the future.*

**Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment must be telephoned to RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762, or to 1-800-227-5463, X4189 within 24 hours of discovery.** Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG Headquarters via the AE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 10 days.

**7.6.5** The table below summarizes the requirements for reporting serious adverse events (SAEs).

### Summary of Expedited Reporting Requirements for All Studies

| Attribution | ADVERSE EVENT |          |            |          |                                    |          |                                    |          |                                    |          |
|-------------|---------------|----------|------------|----------|------------------------------------|----------|------------------------------------|----------|------------------------------------|----------|
|             | Grade 1       |          | Grade 2    |          | Grade 3 and/or<br>*Hospitalization |          | Grade 4 and/or<br>*Hospitalization |          | Grade 5 and/or<br>*Hospitalization |          |
|             | Unexpected    | Expected | Unexpected | Expected | Unexpected                         | Expected | Unexpected                         | Expected | Unexpected                         | Expected |
| Unrelated   |               |          |            |          | *                                  | *        | AdEERS                             | AdEERS   | AdEERS                             | AdEERS   |
| Unlikely    |               |          |            |          | *                                  | *        | AdEERS                             | AdEERS   | AdEERS                             | AdEERS   |
| Possible    |               |          | AdEERS     |          | AdEERS                             | *        | AdEERS                             | AdEERS   | AdEERS                             | AdEERS   |
| Probable    |               |          | AdEERS     |          | AdEERS                             | *        | AdEERS                             | AdEERS   | AdEERS                             | AdEERS   |
| Definite    |               |          | AdEERS     |          | AdEERS                             | *        | AdEERS                             | AdEERS   | AdEERS                             | AdEERS   |

#### AdEERS – ADVERSE EVENT EXPEDITED REPORTING SYSTEM

**\*For Hospitalization Only: Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected attribution.**

Expedited reporting may not be appropriate for specific expected adverse events for certain Phase II and Phase III protocols. In those situations, the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. For example, an expected Grade 3 event that is definitely related to an investigational agent is only to be reported if the patient is hospitalized using the generic reporting criteria. In a trial of an investigational agent in which Grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

RTOG telephone number available 24 hours daily: (215) 717-2762 or (800) 227-5463, ext. 4189.

Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

A list of agent specific expected adverse events can be found in the protocol document and/or consent form.

**Known/expected** adverse events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, noted in the drug insert, or in the Investigator’s Brochure.

**Unknown/unexpected** adverse events are those thought to have resulted from the protocol treatment.

## **8.0 SURGERY**

(Not applicable to this study)

## **9.0 OTHER THERAPY**

### **9.1 Pneumocystis prophylaxis**

All patients must receive prophylactic therapy to prevent pneumocystis pneumonia during the concomitant administration of temozolomide and radiation therapy. Acceptable regimens are: trimethoprim 160mg/sulfamethoxazole 800mg daily for 3 days each week, beginning on day 1 of radiation therapy and continuing for 14 days after completion of radiation therapy; or aerosolized pentamidine 300mg every 28 days beginning on day 1 of radiation therapy and concluding 14 days after completion of radiation therapy. Aerosolized pentamidine may cause (occur in 10-25% of patients): headache, bronchospasm, shortness of breath, chills, cough, metallic taste; uncommonly (1-10% of patients): low white cell counts, low red cell counts, low platelet counts may occur; rarely (fewer than 1%): liver injury that resembles hepatitis, collapsed lung (pneumothorax), and severe allergic reactions may occur. Sulfatrimethoprim may cause nausea, malaise, neutropenia, thrombocytopenia. Uncommonly, allergic reactions including Stevens-Johnson syndrome, hepatic injury, pseudomembranous enterocolitis, renal failure, aplastic anemia, clotting disorders, hyperkalemia, hyponatremia may occur. Rarely, diuresis and hypoglycemia may occur.

### **9.2 Permitted Supportive Therapy**

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

**9.2.1** Steroids may be given as clinically indicated. The total dose must be recorded pre-treatment, and at the time of each treatment evaluation. Steroids will be used in the smallest dose that will afford the patient satisfactory neurologic function and the best possible quality of life

**9.2.2** Antiepileptic drugs: Subjects requiring antiepileptic drugs must be managed using NEIAEDs. For subjects who have been started on EIAEDs, a NEIAED may be substituted during interval between the end of radiation therapy and the beginning of the first cycle of irinotecan and temozolomide administration. The subject must be off the EIAEDs at least 14 days prior to day 1 of cycle 1 of irinotecan and temozolomide. Subjects who require NEIAED for seizure control should be maintained on the same drug throughout the study. Dose adjustments may be made as clinically indicated.

The choice of NEIAED is left to the clinical judgment of the investigator. In the absence of a contraindication or indication for another NEIAED, levetiracetam is one appropriate choice. Patients may be converted to levetiracetam as follows: patients > 60 years old 250 PO BID mg x 2 days, then 500 mg PO BID x 2 days (at which time EIAED taper will begin), then 1000 mg BID. Patients 60 or younger may start at 500 mg PO BID. A taper for phenytoin will be at 100 mg/day; carbamazepine 200 mg/day; phenobarbital 30 mg/day.

**9.2.3** Loperamide (Imodium®): For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in one day or (3) a significant increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every four hours during the night. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

**9.2.4** Anticholinergics: lacrimation, diaphoresis, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur shortly after receiving irinotecan. Patients should be instructed to contact their treating physician promptly in case such events occur while they are taking their irinotecan. In past studies, atropine, 0.25-1 mg given intravenously or subcutaneously, has been used as therapy for these symptoms in patients receiving intravenous irinotecan. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may additionally affect irinotecan metabolism. Patients who have troublesome cholinergic symptoms may receive prophylactic intravenous or subcutaneous atropine in subsequent courses. Anticholinergics

should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

- 9.2.5** Antiemetics: patients should receive dexamethasone (Decadron®) 10 mg IV as a pretreatment antiemetic for treatment with irinotecan. (Please Note: patients should only receive this dose just prior to the irinotecan treatment, and should not use Decadron beyond this point to control nausea between treatment). Patients should also be given ondansetron (Zofran®) at 8 mg IV or granisetron (Kytril®) at 1-2 mg IV. Atropine 1mg IV is also given prior just prior to irinotecan infusion and may be repeated in 1-2 hours if abdominal cramping occurs. The addition of lorazepam (Ativan®) at 1-2 mg IV or PO prior to irinotecan infusion may also be considered if clinically indicated. Zofran may be used for prevention of nausea associated with temozolomide on Days 1 – 5 (Section 7.2). Because late nausea and vomiting may occur for several days following irinotecan administration, prochlorperazine (Compazine®) 10 mg PO every six hours as needed might be considered to ameliorate these events. Other antiemetics such as 5HT3 antagonists or lorazepam (Ativan®) PO bid may be used at the discretion of the investigator for late nausea and vomiting.
- 9.2.6** Anticoagulants: patients who are taking Coumadin® may participate in this study; however, it is recommended that INR or prothrombin time be monitored carefully. Irinotecan may modify the effectiveness of warfarin anticoagulation. It is recommended that subjects receiving warfarin while on study have PT and INR determinations at least weekly during the first cycle of irinotecan and temozolomide. The frequency of INR determinations in subsequent cycles is left to the clinical judgment of the investigator. Subcutaneous heparin or fractionated heparin products are also permitted.
- 9.2.7** Growth Factors: routine prophylactic use of G-CSF in the first course of therapy is not permitted and secondary prophylaxis with G-CSF in subsequent courses is not generally recommended. Use of GM-CSF is not permitted at any time. However, prophylactic administration of G-CSF in a patient who is experiencing recurrent difficulties with neutropenia in subsequent cycles, or therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion.
- 9.2.8** Infections are to be treated with the appropriate antibiotics and recorded.
- 9.2.9** Analgesics and any other medications are to be specified and their doses recorded.

### **9.3 Non-permitted Supportive Therapy**

- 9.3.1** No other chemotherapy treatment can be received while on protocol treatment.

## **10.0 TISSUE/SPECIMEN SUBMISSION**

### **10.1 Tissue/Specimen Submission**

The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Tissue Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. In this study, tissue will be submitted to the RTOG tissue bank for the purpose of tissue banking for patients who have consented to participate in the tissue banking component of the study.

### **10.2 Specimen Collection for Tissue Banking**

Tissue specimens for banking should be taken from pre-study diagnostic biopsy or surgery. The following must be provided in order for the case to be evaluable for the Tissue Bank:

- 10.2.1** One H&E stained slide
- 10.2.2** A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- 10.2.3** 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. The surgical pathology numbers and information must NOT be removed from the report.

- 10.2.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.
- 10.2.5** Submit materials for tissue banking to:

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

**10.3 Reimbursement**

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

**10.4 Confidentiality/Storage**

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

- 10.4.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
- 10.4.2** 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**

| Required Assessments                 | Pre-Treatment Evaluation | Each Week During RT | During Chemotherapy | Follow up Per Section 12.1 |
|--------------------------------------|--------------------------|---------------------|---------------------|----------------------------|
| History/Physical                     | X <sup>a</sup>           |                     | X                   | X                          |
| Zubrod                               | X                        |                     |                     | X                          |
| Neurological exam                    | X <sup>f</sup>           | X                   | X                   | X                          |
| CBC with diff; platelets             | X <sup>f</sup>           | X                   | X <sup>b</sup>      |                            |
| Blood chemistries <sup>e</sup>       | X <sup>f</sup>           |                     | X                   |                            |
| Steroid/anti-convulsant levels       | X <sup>f</sup>           |                     | X                   | X                          |
| MRI or CT with contrast <sup>c</sup> | X                        |                     | X <sup>c</sup>      | X <sup>d</sup>             |
| Serum pregnancy test                 | X <sup>g</sup>           |                     |                     |                            |
| Mini-Mental Status                   | X                        |                     |                     | X                          |

- a. A complete history and physical including documentation of all measurable disease as well as signs and symptoms must be performed within 14 days prior to registration.
- b. CBC with differential and platelet count are required for study treatment and must be done < 72 hours prior to the treatment cycle; CBC also will be performed every 2 weeks during chemotherapy.

- c. MRI or CT of the brain must be performed within 28 days prior to registration and prior to initiation of radiation therapy (preferably post-operatively within 72 hours of surgery) and every 2 months during therapy.
- d. Following completion of radiation therapy but just prior to post RT chemotherapy, then before every course. Note: Patients are to be followed with the same radiological study (Gd-MRI vs. Contrast CT) as the baseline study. The post-operative scan is not required if the patient was diagnosed by stereotactic biopsy.
- e. Blood chemistries include total protein, albumin, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH and SGOT(AST) or SGPT(ALT), triglycerides, and cholesterol.
- f. Within 14 days prior to registration.
- g. Within 5 days before study entry.

## **11.2 Evaluation During Study**

- 11.2.1 A neurologic examination should be performed once a week during radiation therapy, post radiation, every 2 months during chemotherapy and then at the time of neurologic deterioration.
- 11.2.2 A physical examination should be performed every two months; CBC, diff platelet every week during radiation and then every 2 weeks during chemotherapy; blood chemistry and anticonvulsant every 2 months.
- 11.2.3 Skin within the treatment portal shall be examined at least once per week during radiation therapy.
- 11.2.4 The Gd-MRI/contrast CT of the brain shall be obtained prior to radiotherapy, every 2 months during therapy, and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.
- 11.2.5 Considering that radio-necrosis is usually indistinguishable from tumor progression by CT/MRI imaging, Thallium-SPECT, PET or spectroscopic MRI imaging is encouraged in all cases at the time of suspected progression / necrosis.
- 11.2.6 Overall survival will be measured from registration until death.
- 11.2.7 Mental status will be measured by the Mini-Mental Status Exam (MMSE) prior to the start of protocol treatment and during follow-up.
  - 11.2.7.1 Instructions For Administration of MMSE  
The MMSE can be administered by physicians, nurses, or assistants trained in the administration of this assessment. The person administering the MMSE should be sensitive to patients who may be embarrassed by their inability to answer these questions. Patients should be assured by explaining that this is another way to see how treatment may be affecting their brain tumor. It also needs to be made clear to the patient that it is very important to obtain this type of information directly from them. The test administrator should understand that either the correct answer is given or not, and there is no partial credit given.

## **11.3 MRI/CT Review**

The serial MRI/CT scans shall be examined at the institution by an independent reviewer, a neuro-radiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course.

## **11.4 Overall Response**

- 11.4.1 Progression (P): shall be defined as a > 25% increase in tumor area (two diameters) provided that this scan was performed with the patient currently receiving, for at least 7 days, a dose of steroids that at least equals the dose he/she was taking at the time of the previous scan.
- 11.4.2 If the patient meets the criteria in Section 11.4.1, no further protocol chemotherapy will be administered.
- 11.4.3 Once progression is documented, subjects will be followed for overall survival but progression free survival will be determined by the time point at which progression is documented under protocol guidelines. Subjects who demonstrate progression and who are removed from the treatment protocol may receive other therapeutic agents including standard regimens or other experimental agents.

## **12.0 DATA COLLECTION**

Data should be submitted to:

**RTOG Headquarters  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### **12.1 Summary of Data Submission**

| <b><u>Item</u></b>   | <b><u>Due</u></b>   |
|--|---|
| Demographic Form <b>(A5)</b><br>Initial Evaluation Form <b>(I1)</b><br>Pretreatment MRI/CT scan (both pre- and post-surgery) <b>(C1)</b> and reports <b>(C3)</b><br>Pathology Report <b>(P1)</b><br>Slides/Blocks <b>(P2)</b><br>Mini Mental Status Exam <b>(MS)</b> | Within 2 weeks of study entry   |
| <u>Final Dosimetry Information:</u><br>Daily Treatment Record <b>(T5)</b><br>Isodose Distribution <b>(T6)</b><br>Simulation or DRRs and port films of all fields <b>(TP)</b><br>Protocol Calculation Form <b>(TL)</b><br>Radiotherapy Form <b>(T1)</b>               | Within 1 week of RT end   |
| Treatment Form <b>(TF)</b>   | Within 1 week of concurrent chemotherapy end then after every course (2 cycles) during post-RT chemotherapy   |
| Follow-up Form <b>(F1)</b><br>Mini Mental Status Exam <b>(MS)</b>  | Week 13 (Day 90 from the start of radiation therapy)<br>and then<br>Every 3 months from start of treatment for 2 years; q 6 months x 3 years, then annually.<br>Also at progression/relapse and at death. |
| Adverse Event Form <b>(AE)</b><br>Autopsy Report <b>(D3)</b>   | As applicable for toxicity assessment reporting.<br>As applicable.  |

### **12.2 CT/MRI Documentation**

The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins must be submitted within two weeks of registration. The patient should consistently be followed with the same diagnostic study.

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

**13.1.1** Overall survival.

**13.1.2** Short- and long-term toxicities.

**13.1.3** Progression-free survival.

### **13.2 Background**

Stupp et al. report median survival time per RPA class from the European Organisation for Research and Treatment of Cancer (EORTC) phase III study of radiation therapy combined with temozolomide as 17.0, 14.6, and 11.8 months, for RPA class III, IV, and V, respectively.<sup>29</sup> These median survival times correspond to hazard rates of 0.0281, 0.0502, and 0.0753, respectively. The RTOG current GBM database contains 1457 RPA class III through V patients (from RTOG studies 74-01 (arms 3 and 4), 79-18, 83-02, 90-06, 94-11), with a distribution of 17%, 45%, 38%, respectively. Combining the hazard rates from the EORTC trial based on the RPA distribution from the RTOG GBM database results in a combined hazard rate of 0.0506, which corresponds to a median survival time of 13.69 months. The sample size calculation will be based upon this fixed survival rate.

### **13.3 Sample Size**

The primary objective of this study is to determine whether standard radiation therapy with temozolomide followed by temozolomide plus irinotecan improves overall survival in GBM RPA class III-V patients, compared to the published survival results from the EORTC phase III trial (see Section 13.2). The sample size calculation uses a Z-test comparing the logarithm of the hazard ratio found in Schoenfeld and Richter (1982)<sup>27</sup> (adjusted for a single-arm trial). A similar formulation can be found in D. Collett's *Modelling Survival Data in Medical Research* (Sections 9.2, 9.3).<sup>30</sup> This trial aims to improve median survival time by 35% from 13.69 months to 18.48 months. Assuming at least an approximately exponential distribution of survival times, this improvement corresponds to a 26% reduction in hazard rate from 0.0506 to 0.0375 deaths per month, which is equivalent to a hazard ratio of 0.74. Sixty deaths are required for a Type I error rate of 0.10 (1-sided) with 85% statistical power to detect a decrease in hazard rate at least this large. These figures require 94 patients accrued over 12 months and at least 18 months of follow-up for each patient (i.e., 18 months of follow-up after accrual ends).

Adjusting for a 95% eligibility/evaluability rate, 99 patients are needed in order to accrue 94 eligible patients. In summary, **this study requires a total sample size of 99 patients.**

### **13.4 Inclusion of Women and Minorities**

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.<sup>26</sup> The RTOG found no difference in survival of glioblastoma multiforme patients by race.<sup>28</sup> Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

The projected gender and ethnicity accruals appear below:

| <b>Ethnic Category</b>                    | <b>Females</b> | <b>Males</b> | <b>Total</b> |
|---|----------------|--------------|--------------|
| Hispanic or Latino                        | 3              | 4            | 7            |
| Not Hispanic or Latino                    | 42             | 50           | 92           |
|   |                |              |              |
| <b>Ethnic Category: Total</b>             | <b>45</b>      | <b>54</b>    | <b>99</b>    |
|   |                |              |              |
| <b>Racial Category</b>                    |                |              |              |
| American Indian or Alaskan Native         | 0              | 0            | 0            |
| Asian                                     | 0              | 1            | 1            |
| Black or African American                 | 5              | 6            | 11           |
| Native Hawaiian or other Pacific Islander | 1              | 0            | 1            |
| White                                     | 39             | 47           | 86           |
|   |                |              |              |
| <b>Racial Category: Total</b>             | <b>45</b>      | <b>54</b>    | <b>99</b>    |

### **13.5 Patient Accrual**

The study is projected to accrue 12 cases per month, based upon the monthly accrual for prior RTOG GBM studies. Allowing for low accrual during the first six months while institutions are obtaining IRB approval, accrual should be completed within 12 months of study activation. If the average monthly accrual rate (excluding the first six months) is less than six patients, the study will be re-evaluated with respect to feasibility.

### **13.6 Analyses Plans**

#### **13.6.1 Interim Analyses**

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) accrual by institution;
- c) the frequency and severity of the toxicities;
- d) the results of any completed study chair modality reviews.

Through examining the above items, the statistician and study chairs can identify problems with the execution of the study. These problems will be reported to the RTOG Brain Committee and, if necessary, the RTOG Research Strategy Committee, so that corrective action can be taken.

#### **13.6.2 CDUS Tracking**

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

#### **13.6.3 Analysis for Reporting the Initial Treatment Results**

This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. All information reported in the interim analyses (Section 13.6.1) will be included in the final report. All eligible patients receiving any protocol drug will be included in the efficacy analysis. Patients not included in the final analysis will be listed, with the reason for exclusion. Survival will be calculated as the time from study entry until death, regardless of cause. Patients who are alive at the time of the last follow-up will be analyzed as censored observations. The hazard (death) rate will be calculated, using the Kaplan-Meier estimate of 18-month survival [hazard rate =  $-\ln(18\text{-month survival})/18$ ]. A one-sided Z-test, at a 0.10 significance level, will be performed to test the difference between the logarithm of the observed hazard rate and the logarithm of the fixed hazard rate of 0.0506 per month. The variance of the Z-statistic will be estimated by the reciprocal of the number of deaths at 18 months. A statistically significant result will support the development of a phase III trial comparing this regimen to the current standard at that time.

Because the distribution of patients in this by RPA class may differ from that assumed in the study design, a fixed hazard rate based on the observed distribution may be recalculated, such that the observed hazard rate is also compared to this recalculated fixed hazard rate.

## REFERENCES

1. Levin VA, Leibel SA, Gutin PH. Neoplasms of the central nervous system. In: DeVita VT, Jr., Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott-Raven Publishers, 1997: 2022-2073.
2. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer*. 71: 2585-2597,1993.
3. Levin, VA. The morbidity and mortality of brain tumors: A perspective on recent advances in therapy. Salcman M. *Neurologic Clinics*. 3: 229-257, 1985.
4. Bower M, Newlands ES, Bleehen NM, et al. Multicenter CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol*. 40: 484-488. 1997.
5. Newlands ES, O'Reilly SM, Glaser MG, et al. The Charing Cross Hospital experience with temozolomide in patients with gliomas. *Eur J Cancer*. 32A: 2236-2241, 1996.
6. Newlands ES, Blackledge GR, Slack JA, et al. Phase I trial of temozolomide (CCRG 81045: M&B 39831: NSC 362856). *Br J Cancer*. 65: 287-291, 1992.
7. O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: A new oral cytotoxic agent with promising activity against gliomas. *Proceedings Amer Soc Clin Onc*. 12: 499-499, 1993.
8. Plowman J, Waud WR, Koutsoukos AD, Rubinstein LV, Moore TD, Grever MR. Preclinical antitumor activity of temozolomide in mice: Efficacy against human brain tumor xenografts and synergism with 1,3-bis(2- chloroethyl)-1-nitrosourea. *Cancer Res*. 54: 3793-3799, 1994.
9. Brock CS, Newlands ES, Wedge SR, et al. Phase I trial of temozolomide using an extended continuous oral schedule. *Cancer Res*. 58: 4363-4367, 1998.
10. Dhodapkar M, Rubin J, Reid JM, et al. Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. *Clin Cancer Res*. 3: 1093-1100, 1997.
11. Yung WK, Albright R, Olson J, et al. Randomized trial of temodal vs. procarbazine in glioblastoma multiforme at first relapse. *Br J Cancer*. 83: 588-593, 2000.
12. Osoba D, Brada M, Yung WK, Prados M. Health-related quality of life (HRQL) benefits of treatment with temozolomide vs. procarbazine in patients with glioblastoma multiforme. *Eur J Cancer*. 36:1788-1795, 2000.
13. Friedman HS, Petros WP, Friedman AH et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol*;17:1516-1525, 1999.
14. Grossman SA, Hochberg F, Fisher J, et al. Increased 9-aminocamptothecin (9-AC) dose requirements in patients on anticonvulsants. *Proc Am Soc Clin Oncol* 1997;16: 1387.
15. Chang S, Kuhn, Ruzzo J, et al. Phase I study of paclitaxel in patients with recurrent malignant glioma: A North American Brain Tumor Consortium Report. *J Clin Oncol* 16: 2188-2194, 1998.
16. Fetell MR, Grossman SA, Fisher JD, et al. Preirradiation paclitaxel in glioblastoma multiforme: efficacy pharmacology and drug interactions. *J Clin Oncol* 1997; 15: 3121-3128.
17. Gupta E, Wang X, Ramirez J, et al. Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. *Can Chemotherapy Pharmacol* 1997b; 39: 440-444.

18. Gupta E, Mich R, Ramirez J, et al. Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. *J Clin Oncol* 1997a;15: 1502-1510.
19. Stupp R, Ostermann Kraljevic S, Dietrich P, Pica A, et al. Promising survival with concomitant and adjuvant temozolomide [TMZ] for newly diagnosed glioblastoma multiforme [GBM]. *Proceeding Amer Soc Clin Onc.* 19: 163a (Abstract), 2000.
20. Yung WKA, A phase I/II trial of irinotecan in patients with recurrent malignant glioma. *103 patients (accrual complete; phase I manuscript submitted, phase II manuscript in preparation)* personal communication, 2004.
21. Patel VJ, Elion GB, Houghton PJ, et al. Schedule dependent activity of temozolomide plus CPT-11 against a human central nervous system tumor derived xenograft. *Clin Cancer Res* 6:4154-4157, 2000.
22. Gilbert MR, Wen P, Lieberman F, et al. Phase I/II study of combination temozolomide an irinotecan for recurrent malignant gliomas. A North American Brain Tumor Consortium Study. *ASCO Proceedings* 2003, p102.
23. Badruddoja MA, Reardon D, Beason R, et al. Phase I study of temozolomide plus irinotecan in adults with recurrent malignant glioma. *ASCO Proceedings* 2003, p 102
24. Stupp, R, Ostermann S, Calderone A, Uhlmann C, Leyvraz S. Temozolomide and irinotecan for primary brain tumors. A dose escalation study. *ASCO Proceedings* 2003, p104.
25. Gruber ML, Buster WP. Temozolomide in combination with irinotecan for treatment of recurrent malignant glioma. *Am J Clin Oncol* 27:33-38, 2004
26. Curran WJ Jr., Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst.* 85: 704-710, 1993.29.
27. Schoenfeld D, Richter J. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics.* 38: 163-70, 1982.
28. Simpson JR, Horton J, Scott C, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *Int J Radiat Oncol Biol Phys.*26: 239-244,1993.
29. Stupp R, Mason WP, Van Den Bent, MJ, et al. Concomitant and adjuvant temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme. Conclusive results of a randomized phase III trial by the EORTC Brain and RT Groups and NCIC Clinical Trials Group. *ASCO Proceedings* 23:1. 2004
30. Collett D. *Modelling Survival Data in Medical Research* (1<sup>st</sup> Edition). London: Chapman and Hall; 1994: Section 9.

## **APPENDIX I**

**RTOG 0420**

### **SAMPLE CONSENT FOR RESEARCH STUDY**

#### **A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME**

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 a brain tumor called a supratentorial glioblastoma multiforme (GBM).

#### **WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to find out what effects (good and bad) radiation therapy combined with temozolomide followed by treatment with the combination of chemotherapy drugs temozolomide and irinotecan have on you and your cancer. Temozolomide is a chemotherapy agent approved by the FDA for treating some brain tumors. Irinotecan is a chemotherapy drug that has been tested alone and in combination with temozolomide in patients with recurrent glioblastoma.

This research is being done because currently, there is no proven curative treatment for newly diagnosed glioblastoma.

#### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 99 people will take part in this study.

#### **WHAT IS INVOLVED IN THE STUDY?**

There are two parts of treatment to this study:

1. Radiation therapy along with temozolomide (75mg/m<sup>2</sup>/day) chemotherapy.

Radiation treatments will be given once a day, 5 days a week for 6 weeks. During the radiation therapy treatment, you will take temozolomide, which is supplied as capsules,

every day (7 days a week), by mouth at bedtime beginning the night before the first radiation treatment and continuing until the night before the last radiation treatment.

## 2. Chemotherapy with irinotecan and temozolomide

Beginning 4 to 6 weeks after completion of treatment with radiation therapy with temozolomide, you will begin treatment with irinotecan and a higher dose of temozolomide. A complete set of treatments with the combination of drugs is called one cycle. For the combination of temozolomide and irinotecan, one cycle takes 1 month (28 days). You will be treated with 12 complete cycles of chemotherapy unless your tumor grows during treatment or you have side effects that require stopping treatment.

The irinotecan is given twice during each treatment cycle, on the first and 15<sup>th</sup> day of each 28- day cycle. Irinotecan is given as an intravenous infusion.

On the first 5 days of each 28- day cycle, you will take temozolomide 150mg/m<sup>2</sup>. Temozolomide is taken by mouth in pill form.

Because there is a risk of contracting a type of pneumonia called pneumocystis pneumonia when you are receiving temozolomide at the same time as radiation therapy to the brain, you will receive one of two preventive treatments:

Trimethoprim-sulfamethoxazole tablets: You will take these antibiotic pills daily for 3 days in a row every week while you are receiving radiation therapy and for 4 weeks after the conclusion of radiation.

or

Aerosolized pentamidine: If you take this inhaled antibiotic, called aerosolized pentamidine, you will receive breathing treatments through an inhaler mask similar to an oxygen mask for 45 minutes once a month beginning on the day prior to radiation therapy and ending one month after the conclusion of radiation therapy. Alternatively, you may sit inside a small tent and breathe in the antibiotic in spray form in the air inside the tent.

### **IF YOU TAKE PART IN THIS STUDY, YOU WILL HAVE THE FOLLOWING TESTS AND PROCEDURES**

#### **Procedures that are part of regular cancer care and may be done even if you do not join the study.**

- Initial surgery to remove your tumor or biopsy to determine the type of tumor. Biopsy is the surgical removal of a small bit of tissue for examination under the microscope to determine the type of tumor.
- Routine blood tests: blood counts, glucose testing, blood tests to check liver and kidney function, urine tests
- Blood tests to determine the level of antiseizure medicine in your blood
- MRI or CT scans

- Monthly neurological examination and physical examination
- Mini mental status exam with the monthly neurologic examination
- Blood pregnancy test

**Standard procedures being done because you are in this study.**

- Routine blood tests: blood counts, glucose testing, blood tests to check liver and kidney function, urine tests. These tests are done weekly during the period of time you are receiving chemotherapy.
- Blood tests to determine the level of antiseizure medicine in your blood performed monthly or as clinically needed.
- MRI or CT scans prior to radiotherapy, every 2 months during chemotherapy, and at neurologic deterioration.
- Neurological examination once a week during radiation therapy, post radiation, every 2 months during chemotherapy, and neurologic deterioration and physical examination every 2 months.
- Mini mental status exam prior to the start of protocol treatment and follow-up.
- Blood pregnancy test within 5 days before study entry and as needed during the trial if there is any question about your becoming pregnant.

**Procedures that are being tested in this study.**

None

**HOW LONG WILL I BE IN THE STUDY?**

You will receive radiation therapy and chemotherapy with temozolomide for 6 weeks. Four to six weeks after the radiation therapy with temozolomide ends, you will receive chemotherapy with a higher dose of temozolomide and with irinotecan for 12 complete cycles of chemotherapy as long as your cancer does not progress and you do not experience severe side effects. You will be seen in follow-up visits every month during the year of temozolomide and irinotecan chemotherapy, then every 2 months for the next 2 years, and then every 6 months for the rest of your life.

Your doctor may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the investigator who is treating you and your regular doctor first.

## **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 radiation therapy and chemotherapy are stopped, but in some cases side effects can be serious or long lasting or permanent.

Risks and side effects related to the procedures and drugs we are studying include:

### **Risks Associated with Temozolomide:**

#### **Common (more than 10 out of 100 patients)**

Nausea and/or vomiting  
Decreased appetite  
Headache  
Constipation  
Drowsiness/fatigue

#### **Uncommon (more than 1 but less than 10 patients out of 100)**

Decrease in blood counts that may cause infection, bleeding, and bruising  
Diarrhea  
Fever  
Weight loss  
Weakness  
Sores in your mouth  
Hair loss  
Numbness or tingling  
Abdominal pain/jaw pain  
Skin rash  
Weakness of hands and feet  
Injury to the liver: this usually is detected by blood tests  
Elevated liver enzymes (reversible)

When temozolomide is given during radiation therapy, there is a risk of a type of pneumonia called pneumocystis pneumonia, which is caused by a parasite that infects the lungs. This can cause shortness of breath, difficult breathing, and even death. You will receive an antibiotic either as a pill treatment or using a type of inhaled antibiotic to prevent pneumocystis pneumonia.

#### **Reproductive**

Temozolomide given in the dose and frequency used in this study may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant

even after the chemotherapy has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

### **Risks Associated with Radiation Therapy**

#### Common (more than 10 out of 100 patients)

Temporary partial hair loss with some areas of permanent hair loss

Headache

Fatigue Sleepiness

Dry mouth

Altered sense of taste

Scalp redness or soreness

#### Uncommon (more than 1 but less than 10 patients out of 100)

Hearing loss, Dryness of the ear canal and redness of the external ear if in radiated area

#### Rare (less than 1 out of 100 patients)

Eye injury resulting in blindness

Mental slowness, behavioral changes

Severe damage to normal brain tissue that may require additional surgery

Brain swelling in the area receiving the radiation therapy

Seizure

### **Risks Associated with Irinotecan (CPT-11)**

#### Likely- occurs in more than 25% of people (more than 25 out of 100 people)

Delayed diarrhea (occurring within hours of receiving study drug and lasting up to 5-7 days)

Sweating

Flushing

Abdominal cramping

Runny nose

Teary eyes

Sudden urge to have a bowel movement occurring shortly after the irinotecan infusion.

*Note:* Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Diarrhea that occurs at a time when the white blood cell count is low can be especially dangerous, which can make you more susceptible to severe infections that could be life-threatening. Should you experience a fever or other sign of infection when your white blood cell count is very low, you may need to be admitted to the hospital for precautionary measures and receive intravenous antibiotics until your blood cell counts rise to safe levels.

Diarrhea has been the most frequent severe side effect associated with receiving irinotecan. When severe diarrhea has occurred, some patients have had to be admitted

to the hospital to receive intravenous fluids until the diarrhea resolved (usually in 5-7 days). With early recognition and proper treatment, the likelihood of severe diarrhea may be decreased. In order to minimize the severity of the diarrhea, you are advised to follow these directions:

1. Be aware of your bowel movements. If they become softer than usual or if you have any increase in the number of bowel movements over what is normal for you, begin taking loperamide tablets right away.
2. Take two loperamide (Imodium®) tablets immediately after the onset of diarrhea or increased frequency of bowel movements, and then take one tablet every two hours until you have been without a bowel movement for 12 hours straight. At night, you may take two tablets every four hours so that you won't have to wake up so often. Make sure that you drink plenty of fluids (soups, juices, etc.) to replace the fluids lost in the bowel movements. If your soft bowel movements or diarrhea do not stop within 36 hours, call your doctor. Should you become weak, lightheaded, or feel faint, call your doctor immediately. Don't take loperamide tablets unless you have loose or frequent stools or diarrhea.

Common- occurs in 10% to 25% of people (10-25 people out of 100 people)

Nausea and vomiting

Lack of appetite

Delayed abdominal cramping (stomach pain that can last for 5-7 days)

Hair loss

Weakness

Decrease in blood cells (due to the drug preventing your body from making and keeping new blood cells)

Uncommon-occurs in 1% to 10% of people (1 to 10 out of 100 people)

Mouth sores

Frequent bowel movements (sometimes with blood noted in your bowel movements)

Serious kidney problems

Rare- occurs in less than 1% of people (less than 1 out of 100 people)

Lung problems with symptoms shortness of breath, nonproductive (dry) cough, and abnormal chest x-ray

Abnormal blood, kidney and liver lab results

Redness or irritation of your skin at infusion sites

*Note:* If you are on a blood thinner (coumadin), you will need to be monitored for any interaction between irinotecan and coumadin. If you have any bleeding or bruising, you should let your physician know.

There have been deaths reported from these combinations of side effects. Although the risk of death is low, you should tell your doctor immediately if you experience any of these side effects.

## Reproductive

Irinotecan has been shown to cause birth defects in animals. To avoid risk to the fetus, it is important that you not become pregnant during the conduct of this study. It is also advised that study participants (or their female sexual partner) not become pregnant for one week after injection of the study drug. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. If you choose to be sexually active during this study, you should understand that even with use of these birth control measures, pregnancy could still result. The risks of receiving the study drug while pregnant include potential loss of pregnancy or possible birth defects.

Irinotecan given in the dose and frequency used in this study may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is not enough information about irinotecan in men and woman of childbearing age who subsequently try to have children to know how likely problems will be.

As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe, or life threatening.

## **Risks of antibiotic treatments to prevent pneumocystis pneumonia**

### **Risks of oral trimethoprim- sulfamethoxazole:**

#### Common (occurring in 10-25% of people)

Nausea,  
Loss of appetite  
Vomiting  
Skin rash

#### Uncommon (1-10 of 100 patients)

Rash  
Low white blood cell counts  
Low blood platelet counts (problems with blood clotting)  
Liver irritation resembling hepatitis  
Low red cell counts,  
Abnormalities in blood tests that measure liver functions

#### Rare (less than 1 out of 100 patients)

Stevens-Johnson syndrome (a severe skin reaction similar to a bad burn that can involve the lining of the mouth and eye)  
Very low white cell counts, platelet counts, red cell counts  
Allergic reaction similar to severe asthma with difficulty breathing  
Life threatening injury to the liver or kidneys

## **Risks of aerosolized pentamidine**

### Common (more than 10 of 100 patients)

Nausea

Loss of appetite

Bronchospasm (difficulty breathing due to squeezing closed breathing passages in the lungs)

Cough

Shortness of breath

Dizziness

Rash

### Uncommon (1-10 out of 100 patients)

Headache

### Rare (less than 1 in 100 patients)

Abnormal heart rhythms

Low white blood cell counts

Low blood sugar

High blood sugar

Pancreatitis (inflammation of the pancreas causing belly pain)

Kidney damage

Liver irritation resembling hepatitis

Eye irritation

Blurred vision

## **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. The treatments in this study are being tested to determine if they are more effective than other treatments for newly diagnosed glioblastoma based on the results of studies of patients with glioblastomas, which had recurred after the initial treatment. The treatments being tested in this study may be no different or worse in comparison to other treatments that are considered standard therapy for newly diagnosed glioblastoma. We hope the information learned from this study will benefit other patients with brain cancer 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: radiation therapy without chemotherapy, radiation therapy with other types of chemotherapy than the combination being tested in this study, radiation treatments using a

technique called radiosurgery, or other experimental treatments. Experimental treatments may include experimental drugs or other types of treatments. You could also decide to have no further antitumor treatment.

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 the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, and qualified representatives of Pfizer, Inc.

### **WHAT ARE THE COSTS?**

Irinotecan will be provided free of charge by Pfizer, Inc. for this study. Temozolomide is commercially available.

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

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

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider. You will receive no payment for taking part in this study.

### **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study,

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

A group of experts in brain cancer from the RTOG Brain Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically 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

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

*Consent Form for Use of Tissue for Research*

### **About Using Tissue for Research**

You are going to have (or have had) a biopsy (or surgery) to see if you have cancer. Your doctor 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 is left over 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.

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.

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. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While (doctor/hospital) 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 and will not be sold. The research done with your tissue may help to develop new products in the future.

### **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**

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

## **Making Your Choice**

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

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

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

Yes                  No

2. 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

3. Someone may contact me in the future to ask me to take part in more research.

Yes                  No

## **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  
**[www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials)**

or

For NCI's general information about cancer visit  
**[www.cancer.gov/cancerinfo/](http://www.cancer.gov/cancerinfo/)**

## **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 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<br>( <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<br>( <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> )   |
| 5 | Death ( <i>Karnofsky 0</i> )  |

**APPENDIX III**

**RTOG 0420**

**STUDY AGENT (Irinotecan) SHIPMENT FORM**

Each institution must submit a Study Agent Shipment 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. Allow adequate processing time (7-10 days) before calling to register the first case.

**SHIP TO:**

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

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

(No P.O. addresses)

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

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

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

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

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

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

Investigator (PI) Signature \_\_\_\_\_

Date: \_\_\_\_\_

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

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

Send Completed Form to:  
**CTSU Regulatory Office**  
**1818 Market Street, Suite 1100**  
**Philadelphia, PA 19103**  
**FAX 215-569-0206**

RTOG Headquarters Approval \_\_\_\_\_

Date: \_\_\_\_\_