

RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0131

A PHASE II TRIAL OF PRE-IRRADIATION AND CONCURRENT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED ANAPLASTIC OLIGODENDROGLIOMAS AND MIXED ANAPLASTIC OLIGOASTROCYTOMAS

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SCHEMA

R	<u>Pre-irradiation Therapy*</u>	R	<u>Radiation Therapy:</u>	
E	Temozolomide, 150 mg/m ² /day, p.o., for days 1 to 7 and days 15 to 21, repeated at 28 day intervals (<i>i.e.</i> , 7 days on, 7 days off) for 6 months for a total of 6 cycles*	E-	Stable Disease (SD), Partial Response (PR): <i>(to begin no later than 6 weeks after completing the final cycle of Temozolomide)</i> 59.4 Gy (1.8 Gy x 33 fractions, 5 days/week for 6.5 weeks) plus Temozolomide 75 mg/m ² /day, p.o., for 42 days	
G		R		
I		E		
S		G		
T		I		Complete Response (CR), Absence of Evaluable Disease:
E		S		Observation
R		T		
		E		
		R		

*Duration of Therapy (*Pre-irradiation*): Responding patients will receive treatment until 2 cycles after maximum response. Patients with stable disease will receive 6 cycles before radiation. In the absence of evaluable disease, a total of 6 cycles will be given before radiation. MRI scans will be performed every 8 weeks to evaluate response. Patients will receive chemotherapy according to the table below:

Response (<i>see Section 11.4 for definitions</i>)	Duration of Pre-irradiation Therapy
Complete or partial response	2 cycles after the time best response was noted*
Stable disease	6 cycles
Absence of evaluable disease	6 cycles
Progressive disease	Discontinue therapy

Eligibility: (*See Section 3.0 for details*)

- Unifocal or multifocal supratentorial pure or mixed anaplastic oligodendroglioma confirmed by central pathology review (*see Section 10.0*);
- Zubrod 0, 1;
- Laboratory studies: AGC \geq 1500/mm³, platelets \geq 100,000/mm³, hemoglobin \geq 10.0 gm/dl; creatinine \leq 1.5 x normal; bilirubin, alkaline phosphatase \leq 2 x normal, AST \leq 3 x normal;
- No prior radiotherapy to the brain or head/neck;
- No prior chemotherapy for this malignancy; no prior temozolomide;
- No spinal cord tumors or spinal cord metastases;
- No prior invasive malignancy unless disease-free \geq 3 years;
- No active infectious process;
- No surgery requiring general anesthesia \leq 14 days before start of treatment;
- Life expectancy $>$ 12 weeks;
- No pregnant or lactating women;
- Study-specific signed informed consent.

Required Sample Size: 37

RTOG Institution # _____

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ELIGIBILITY CHECK - STEP 1 (7/30/02)(12/23/02)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have a unifocal or multifocal supratentorial pure or mixed anaplastic oligodendroglioma confirmed by central pathology review?
- _____(Y) 2. Is the Zubrod performance status 0, 1?
- _____(Y) 3. Are the pre-treatment laboratory studies within the parameters of Section 3.1.3?
- _____(N) 4. Has the patient had prior radiotherapy to the brain or head/neck?
- _____(N) 5. Has the patient had prior chemotherapy for this malignancy?
- _____(N) 6. Has the patient had prior temozolomide?
- _____(N) 7. Is there evidence of spinal drop metastasis or spread to non-contiguous meninges?
- _____(Y/N) 8. Has the patient had prior invasive malignancy?
_____(Y) If yes to prior invasive malignancy, have they been disease free ≥ 3 years?
- _____(N) 9. Does the patient have an active infectious process?
- _____(N) 10. Has the patient had surgery requiring general anesthesia ≤ 14 days before start of treatment?
- _____(Y) 11. Does the patient have a life expectancy > 12 weeks?
- _____(N) 12. Is the patient pregnant or lactating?

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 (*Last, First*)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race

(continued on next page)

RTOG Institution # _____

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ELIGIBILITY CHECK - STEP 1 (7/30/02)(12/23/02)(7/24/03)

Case # _____

(page 2 of 2)

- _____ 10. Ethnic Category (*Hispanic or Latino, Not Hispanic or Latino, Unknown*)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Medical Oncologist
- _____ (Y/N) 18. Tissue/Blood kept for cancer research?
- _____ (Y/N) 19. Tissue/Blood kept for medical research?
- _____ (Y/N) 20. Allow contact for future research?
- _____ (Y/N) 21. Has the Central Pathology Report been received?

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 _____

Institution # _____

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ELIGIBILITY CHECKLIST – STEP 2 (7/30/02)

Case # _____
(assigned for Step 1)

- _____ 1. Name of institutional person registering this case.
- _____(Y/N) 2. Is the patient going to continue protocol treatment, i.e., radiation therapy plus temozolomide?
- _____ 3. If no, the reason that the patient cannot continue to Step 2: 1) progression of disease; 2) patient refusal; 3) physician preference; 4) other.
- _____ 4. **If no, call RTOG HQ to “discontinue” the case; provide reason _____**
(*progression, patient refusal, physician preference, other specify _____*)
- _____ 5. Patient’s Initials
- _____ 6. Verifying Physician
- _____ 7. Patient ID Number
- _____ 8. Calendar Base Date (*for Step 2*)
- _____ 9. Registration Date (*for Step 2*)
- _____ 10. Results of Central Scan Review: 1) stable disease; 2) partial response 3) complete response; 4) absence of evaluable disease

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Anaplastic Oligodendroglioma/Mixed Anaplastic Oligoastrocytomas

Anaplastic oligodendrogliomas represent 5% of primary brain tumors.¹ Standard post-surgical therapy for these tumors has been chemotherapy and radiation therapy. Some patients with anaplastic oligodendrogliomas (*AO*) or mixed anaplastic oligoastrocytomas (*MOA*), however, have unusually chemosensitive tumors.² Recently, a subset of these tumors has been found to be very responsive to chemotherapy.³ Those patients who had tumors with deletion of the 1p chromosome had a 100% response rate and a median survival in excess of 10 years. With these data, an approach using pre-irradiation chemotherapy is appealing.

1.2 Pre-irradiation Chemotherapy

Pre-irradiation or neoadjuvant chemotherapy has several potential advantages. First, in the absence of radiation-induced vascular sclerosis, drug delivery to the tumor is maximized. Secondly, neoadjuvant chemotherapy allows early treatment of infiltrating tumor cells that may be at or beyond the border of the radiation port. Finally, pre-irradiation chemotherapy allows a true assessment of the efficacy of chemotherapy.

Pre-irradiation chemotherapy of brain tumors has been tested in several clinical trials.⁴ This approach has proved to be feasible and in certain settings, efficacious. It is anticipated that the population of patients having chemosensitive tumors could be safely managed with this approach.

1.3 Temozolomide

Temozolomide is a cytotoxic alkylating agent that has an acceptable toxicity profile and demonstrated clinical antitumor activity against malignant gliomas both at initial diagnosis and relapse. Unlike standard chemotherapy nitrosourea-based regimens such as BCNU or PCV, temozolomide appears to have essentially no cumulative myelotoxicity. In addition, temozolomide is generally much better tolerated than PCV.

Pre-clinical Data

Temozolomide has exhibited antitumor activity against a range of mouse and human tumors.^{5,6,7} Antitumor activity was shown to be schedule-dependent as confirmed in phase I testing.^{8,9,10} Temozolomide has been found to penetrate the blood brain barrier in both preclinical and phase I testing.¹¹⁻¹⁵

Phase I Clinical Experience

The pharmacokinetics, efficacy and toxicity profile of temozolomide has been studied in several phase I clinical trials conducted in Europe by Schering-Plough and the Cancer Research Campaign (*CRC*).¹⁶ Oral bioavailability is complete. Multiple dose pharmacokinetics were studied in one patient. Plasma levels were obtained on Days 1 and 5. No accumulation of drug was found.¹⁵ The most common adverse events were nausea, vomiting and myelosuppression. The nausea and vomiting were usually mild to moderate (*WHO grades 1-2*) at doses up to 700 mg/m²; at higher doses, some patients experienced more severe vomiting, controlled by standard antiemetic treatment. Myelosuppression was dose-limiting. The maximum tolerated dose was established at 1000 mg/m² or 200 mg/m²/d for 5 days. Extended phase I results were reported by the *CRC* in 1993 in 28 patients with recurrent malignant glioma.^{12,14} The initial dose was 150 mg/m²/day for 5 days which was subsequently escalated to 200 mg/m²/day. Major clinical improvement was observed in 6/10 evaluable patients and major radiographic improvement in 5/10. Similar changes were seen in 4/7 patients with newly diagnosed high-grade astrocytomas given two to three doses of temozolomide prior to irradiation.

A phase I study of temozolomide on an every other week schedule was recently presented.¹⁷ The MTD was 150 mg/m²/day resulting in a 2.8 fold higher drug exposure than the standard daily for 5 day schedule. The dose-limiting toxicity was thrombocytopenia. No grade 3 or 4 non-hematologic toxicity occurred.

Phase II Clinical Experience

The results of a phase II clinical trial again conducted by the *CRC* in patients with recurrent high grade glioma were reported at the First Congress of the European Association for Neuro-Oncology (*EANO*) in October 1994. One hundred and three patients were entered. Temozolomide was administered in daily multiple doses of 750 to 1000 mg/m² over 5 to 10 days. Clinical response was measured largely by improvement in neurologic status. Eleven patients had an objective response, 48 were unchanged and 26 worsened. Mild to moderate nausea and vomiting was dose-related and, again, readily controlled with antiemetics. Leucopenia and thrombocytopenia (*WHO grade 3 or above*) occurred in 2 and 5 evaluable courses, respectively.

Preliminary results of three large clinical trials conducted by Schering-Plough in both Europe and the United States for patients with recurrent malignant glioma are available. In the first (194-122), 138

patients were entered. One hundred twenty-eight patients had GBM or gliosarcoma. On central imaging review, objective response rates were: 1% (2/138) CR, 8% (11/138) CR or PR, 51% (73/138) CR, PR, or stable disease (SD). Median progression-free survival was 2.1 months; 19% were progression-free at 6 months; 17% of patients were event free at six months. Median overall survival was 5.4 months. The six month death rate was 54%.

Results of a randomized phase II trial (C94-091) for patients with recurrent GBM were reported by Yung et al. at the European Association of Neuro-Oncology (EANO) in September 1996. Two hundred twenty-six patients were randomized: 112 to the temozolomide arm and 114 to the procarbazine arm. Patient characteristics including age, sex, and Karnofsky Performance Status were similar between the two arms. Progression-free survival (PFS) at six months was 21% for temozolomide and 9% for procarbazine with a p-value of 0.016 favoring temozolomide. The median overall survival was 7.34 months for temozolomide and 5.82 months for procarbazine also suggesting a trend in favor of temozolomide. Major hematologic toxicity was thrombocytopenia and commonly observed non-hematologic toxicities were nausea, vomiting and constipation. The study showed that treatment with temozolomide resulted in significantly better PFS and median PFS than procarbazine for patients with recurrent GBM.

Results are now available for a phase II multi-institutional trial (C/194/123) for patients with recurrent anaplastic astrocytoma and mixed anaplastic astrocytoma/oligodendroglioma. Median age was 42 years; 57% were male, and KPS was 80. Treatment at initial diagnosis was as follows: surgical resection in 68%; radiation therapy in 100%; and nitrosourea-based chemotherapy in 60%. Temozolomide 150 to 200 mg/m²/d was given for five days every 28 days for a maximum of two years from initial treatment until unacceptable toxicity or disease progression occurred. PFS was 46% at 6 months and 24% at 12 months. Median PFS was 5.4 months. The overall response rate (CR + PR) was 35% (57/162); 24% of patients had stable disease (SD). The drug was generally well-tolerated. Toxicities included nausea and vomiting in 3.6%. Grade 3/4 neutropenia and thrombocytopenia occurred in 3.6% and 5.7% of patients respectively. The investigators concluded that temozolomide was a safe and effective single agent for patients with recurrent anaplastic astrocytoma. It is of note that 30% of patients (N = 47) entered onto this trial were determined to be ineligible because of undergrading when the pathologic specimens were reviewed.

Recently, preliminary results of a phase II trial evaluating the activity of temozolomide administered prior to radiation therapy for patients with GBM were reported.¹⁸ Patients were treated with 200 mg/m² p.o. every day for five days every 28 days for up to four cycles. Tumor response for 24 patients was as follows: 3 complete response, 12 partial response, 3 stable disease and 6 progressive disease.

1.4 Radiation Therapy with Concurrent Chemotherapy

Chemotherapy concurrent with radiation therapy may synergistically increase the sensitivity of brain tumors to treatment. Previous studies have examined the concurrent administration of radiation therapy with a variety of chemotherapeutic agents (including cisplatin, BCNU, and etoposide).¹⁹⁻²² Some of these studies have documented increased hematologic toxicity with some concurrent chemotherapeutic regimens. The lack of cumulative myelosuppression in temozolomide may make this drug more favorable for use in concurrent regimens. In vitro, temozolomide increases the sensitivity of GBM cells to ionizing radiation.²³

1.5 Deferred Radiation Therapy in Patients with a Complete Response to Chemotherapy

Recently, it has become apparent that some patients with AO's or MAO's demonstrate prolonged complete responses to chemotherapy.^{3,29-31} While an association of chemosensitivity with a specific set of chromosomal losses has been made in these tumors, some data are conflicting and the results of a prospective, multicenter trial, have not been reported to date. Hence, it is premature to try to predict chemoresponsiveness based upon specific genetic alterations in a tumor. However, the median survival of patients whose tumors exhibit complete responses to chemotherapy has not yet been defined and survivals of greater than ten years have been observed without further treatment. The long-term risks associated with radiation therapy may not be warranted in this subset of patients with AO or MAO.

1.6 Rationale for Current Study

The phase II experience with single agent temozolomide for patients with malignant gliomas has been favorable. Response rates for patients with newly diagnosed and recurrent malignant astrocytomas are at least comparable to those obtained using the nitrosoureas. Temozolomide is well absorbed after oral administration and is generally well-tolerated. The dose-limiting toxicity for myelosuppression is tolerable and, importantly, is not cumulative, as with nitrosoureas and procarbazine. Furthermore, pre-irradiation and concurrent chemotherapy for this group of patients with responsive tumors has several potential advantages as noted above. The goal is to assess the efficacy of pre-irradiation chemotherapy and toxicity

of concurrent chemoradiation therapy in this patient population. This trial will evaluate response rate, time to progression, toxicity and, secondarily, survival.

2.0 OBJECTIVES

- 2.1 The primary endpoint of this trial is the rate of post-chemotherapy, pre-irradiation therapy progression.
- 2.2 The study will assess the toxicity of concurrent administration of temozolomide and radiation therapy in this patient population.
- 2.3 A secondary endpoint will be survival.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Pathologic evidence of unifocal or multifocal supratentorial pure or mixed anaplastic oligodendroglioma confirmed by central pathology review (*see Section 10.0*). Patients with prior suspected or proven low grade glioma are eligible provided they now have a biopsy-proven pure or mixed anaplastic oligodendroglioma and have not been treated previously with either RT or chemotherapy.
- 3.1.2 Zubrod 0, 1.
- 3.1.3 Absolute granulocyte count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin $\geq 10 \text{ gm/dl}$; serum creatinine $\leq 1.5 \times$ normal; bilirubin, alkaline phosphatase $\leq 2 \times$ normal, AST $\leq 3 \times$ normal.
- 3.1.4 Life expectancy > 12 weeks.
- 3.1.5 Patients must have no medical problems unrelated to the malignancy that would pose an undue risk or that would limit full compliance with the study.
- 3.1.6 Patients must sign a study-specific informed consent prior to study entry.

3.2 Ineligibility Criteria

- 3.2.1 Equivocal oligodendroglial element (*see Section 10.0*).
- 3.2.2 Tumor that is predominantly located in the posterior fossa (*i.e. brain stem or cerebellum*).
- 3.2.3 Spinal cord tumors.
- 3.2.4 Evidence of spinal drop metastasis or spread to non-contiguous meninges (*MRI of the spine is not required in asymptomatic patients and patients will not be excluded based on pathologic evidence of local meningeal infiltration by underlying tumor*).
- 3.2.5 Prior malignancy (*excluding carcinoma in situ of the cervix or non-melanomatous skin cancer*) unless disease free for at least three years.
- 3.2.6 Prior radiotherapy to the brain or head/neck.
- 3.2.7 Prior chemotherapy for this malignancy; no prior temozolomide.
- 3.2.8 Active infectious process.
- 3.2.9 No surgery requiring general anesthesia ≤ 14 days before the start of treatment.
- 3.2.10 Pregnant or nursing women. It is unknown what effects temozolomide may have on the developing fetus. Women of childbearing potential and sexually active men must agree to use a reliable form of birth control.

4.0 PRETREATMENT EVALUATIONS

- 4.1 **Central pathology review prior to registration is mandatory to confirm eligibility.** Stereotactic biopsies are permitted but the tissue sampled must be adequate for unequivocal pathologic diagnosis.
- 4.2 History and physical examination (*including neurological examination*) with documentation of all symptoms and signs.
- 4.3 Laboratory and radiology evaluation:
All tests and scans must be performed within two weeks prior to study entry:

Hematology: ◦ CBC with differential

Biochemistry: ◦ Electrolytes

 ◦ Glucose

 ◦ Creatinine

 ◦ Bilirubin

 ◦ AST/ALT

 ◦ Alkaline phosphatase

Immunology ◦ Pregnancy test for women of child-bearing age

Radiology: ◦ Chest x-ray

 ◦ CT or MRI scan without and with contrast. (*Please see Appendix VI, Neuroimaging*)

Guidelines, for recommended imaging parameters and methods for handling and archiving images). **Note: Patients may be followed by either CT or MRI but must have an MRI scan after pre-irradiation chemotherapy is completed for RT treatment planning.**

- RT will be planned with an MRI scan obtained after pre-irradiation chemotherapy is completed, within two weeks of the start of radiotherapy.

4.4 Mini-Mental Status Examination within two weeks prior to study entry.

5.0 REGISTRATION PROCEDURES

5.1 **Central pathology review (Appendix III; also see Section 10.0) must be completed prior to study entry.**

5.2 **Registration for Pre-Irradiation Therapy-Step 1:** Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered 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.

5.3 Registration Following Pre-Irradiation Therapy-Step 2:

Within six weeks following the completion of pre-irradiation therapy and the evaluation of response, **all patients must be re-registered** by calling RTOG Headquarters (*see Section 5.2*). At this time, the response results and the second phase of the study (*RT plus temozolomide or observation*) will be recorded and a new data collection calendar generated.

5.3.1 The following information must be supplied:

- original case number;
- results of central scan review;
- treatment start date (*or observation*).

5.3.2 The treatment option registered at RTOG Headquarters and the new data collection calendar will be based on the parameters specified by the protocol. If the investigator or the patient deviates from the protocol specified treatment, documentation of this and data submission as outlined in Section 12.0 is required.

5.3.3 Patients who have developed progressive disease during the pre-irradiation phase of treatment and who will not continue therapy will remain on the original calendar schedule for continued follow-up only. This information must be relayed to RTOG Headquarters (*see Section 5.2*).

6.0 RADIATION THERAPY Central radiology review must be completed prior to the start of radiation therapy.

6.1 General Requirements

Treatment will be delivered with megavoltage machines of energy ≥ 4 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. The patient will be treated in the supine or other appropriate position. There must be at least two shaped treatment fields with each field treated daily. Treatment with a single beam is not acceptable. Port films of each field will be taken weekly, except for opposed fields with identical blocking where one film from each of the opposed fields should be taken weekly.

6.1.1 Treatment Volumes

6.1.1.1 Stable Disease (SD), Partial Response (PR):

The target volumes will be based on an MRI scan (*T2 and T1 gadolinium-enhanced images*) obtained within two weeks of start of radiotherapy. The "initial target volume" is the same as the "planning target volume". Margins are to the block edge. The initial target volume will include the T2 abnormality plus a 2 cm margin. The boost volume will include all tumor visible on the T1 gadolinium-enhanced scan plus a 1 cm margin. The target volumes are to receive 95-105% of the prescribed dose.

6.1.1.2 Complete Response (CR), Absence of Evaluable Disease:

If there is no measurable disease on MRI following the completion of 6 cycles of temozolomide, then radiotherapy will not be given and the patient will be observed until the study endpoint (*post-chemotherapy pre-irradiation therapy progression*) is reached. If, on central review of the post-chemotherapy MRI, the response is judged to be less than a CR, the patient will be re-stratified into the SD/PR group and start combined radiation therapy/chemotherapy accordingly. If central review agrees that a patient has had a CR but on confirmatory MRI four weeks later the patient has evidence of

progression, then they will have reached the primary endpoint and will be treated at the discretion of their treating physician.

6.1.2 Dose and Schedule

Treatment will be given in 1.8 Gy fractions (*to isocenter*), 1 fraction per day, 5 days per week, to a total dose of 59.4 Gy in 33 fractions. The initial 50.4 Gy in 28 fractions will include the initial target volume (*T2-MRI plus 2 cm margin*). The final 9 Gy in 5 fractions will include the boost volume (*T1 enhanced MRI plus 1 cm margin*). RT must begin no later than 6 weeks after completing the final cycle of temozolomide, (*i.e., within 6 weeks of day 33 of the final cycle of temozolomide*) blood counts permitting (*see Section 6.1.7*).

6.1.3 Treatment Summary

Volume	Includes	Daily Dose	No. of Fractions	Total Dose
Initial	T2-MRI + 2 cm	1.8 Gy	28	50.4 Gy
Boost	T1 (<i>Gad</i>) MRI + 1 cm	1.8 Gy	5	9 Gy
Total	-	-	33	59.4 Gy

6.1.4 Dosimetry

Two central axis isodose plots, one showing the initial tumor volume, and one showing the boost tumor volume, should be submitted with the following isodose lines in Gy: 25.2 Gy, 45.4 Gy, 47.9 Gy, 50.4 Gy, 52.9 Gy, 53.5 Gy, 55.4 Gy, 56.4 Gy, 59.4 Gy, 62.4 Gy, and 65.3 Gy. The following quality assurance guidelines will apply:

6.1.4.1 If the initial target volume receives < 45.4 Gy or > 55.4 Gy (*i.e., < 90% or > 110% of the prescribed total dose*) a major deviation will be scored. If the boost volume receives < 53.5 Gy or > 65.3 Gy (*i.e., < 90% or > 110% of the prescribed total dose*), a major deviation will be assigned.

6.1.4.2 If the initial target volume receives 45.4-47.8 Gy or 53.0-55.4 Gy (*i.e., 90-94% or 106-110% of the prescribed total dose*) a minor deviation will be scored. If the boost volume receives 53.5-55.8 Gy or 63.0-65.3 Gy (*i.e., 90-94% or 106-110% of the prescribed total dose*) a minor deviation will be assigned.

6.1.4.3 If the initial target volume receives 47.9-52.9 Gy (*i.e., 95-105% of the prescribed total dose*) no deviation will be scored. If the boost volume receives 56.4 -62.4 Gy (*i.e., 95-105% of the prescribed total dose*) no deviation will be assigned.

6.1.5 Dose Specification

Doses are specified as the target dose which shall be the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.5.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.1.5.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.1.5.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.1.5.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

6.1.5.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots due to unacceptable tissue inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target area.

6.1.5.6 Other or complex treatment arrangements: at the center of the target area.

6.1.5.7 **The use of IMRT is not allowed.**

6.1.6 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 60 Gy, the retina of at least one eye (*but preferably both*) to 50 Gy, and the brain stem to 60 Gy.

6.1.7 Treatment Delays

RT will be delayed or interrupted if the absolute granulocyte count is < 500 or the platelet count is < 20,000. RT will not begin or resume until the absolute granulocyte count is \geq 500 and the platelet count is \geq 20,000.

6.1.8 Toxic Reactions

Expected RT toxic reactions include hair loss, scalp redness or soreness, dry mouth or altered taste, hearing impairment, fatigue, or temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness. Unusually severe reactions should be noted and reported to the study chair. All

early delayed or late delayed neurotoxicities (eg. *transient demyelination syndromes, dementia, or brain necrosis*) must be documented and reported.

6.1.8.1 Acute toxicity monitoring: Acute (≤ 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 2.0.

6.1.8.2 Late toxicity monitoring: Late (> 90 days from RT start) side effects will be documented using the RTOG Late Radiation Morbidity Scoring Scheme (*Appendix IV*).

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 Drug Information - Temozolomide (Temodar™)

7.1.1 Dose Formulation

Temozolomide is supplied in white opaque, preservative free, 2-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg and 250 mg. Capsules should not be opened or chewed. If capsules are accidentally opened or damaged, inhalation or contact with the skin and mucous membranes should be avoided. 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.

7.1.2 Mechanism of Action

Temozolomide belongs to a group of compounds known as imidazotetrazinones. The chemical name is 8-carbamoyl-3-methylimidazo [5,1-d]1,2,3,5-tetrazin-4 (3H)-one.²⁴ Temozolomide undergoes chemical degradation at physiologic pH to form MTIC (3-methyl- [triazene-1-yl]) imidazole-4-carboxamide, the active metabolite of dacarbazine, frequently used in the treatment of malignant melanoma.²⁵ Dacarbazine differs, however, in that MTIC is formed only following drug metabolism in liver. Hepatic metabolism can be affected by a variety of drugs, commonly used in brain tumor patients, including most anticonvulsant agents and corticosteroids. The implication is that the bioavailability of MTIC may be more consistent during treatment with temozolomide. The cytotoxicity of MTIC is thought to be primarily due to alkylation at the O6 position of guanine residue 18 with additional alkylation occurring at the N7 position.²⁶ Temozolomide is rapidly absorbed in humans after oral administration, with a maximum plasma concentration occurring 7 hours post dosage. Over the concentration range studied [single oral (200 - 1200 mg/m²) or intravenous (50-200 mg/m²)], temozolomide pharmacokinetics were independent of the dose, and the relationship between dose and area under the plasma concentration-time curve (AUC) was linear. Complete oral bioavailability was demonstrated in five patients receiving temozolomide at 200 mg/m². The drug does not accumulate in the plasma upon multiple dosing.

7.1.3 Drug Availability

Temozolomide is commercially available as Temodar™.

7.1.4 Storage

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.

7.1.5 Side Effects

Hematological: Thrombocytopenia, leukopenia and lymphocytopenia;

Gastrointestinal: Nausea, vomiting, anorexia;

Hepatic: Elevated liver enzymes (*reversible*);

Skin: Rash, alopecia;

Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache, pneumocystis carinii pneumonia.

7.2 Therapeutic Plan

7.2.1 Schedule

Pre-Irradiation: Temozolomide, p.o., 150 mg/m²/d for days 1-7 and 15-21, repeated at 28 day intervals (*i.e., 7 days on/7 days off*). This 4 week schedule defines a cycle of treatment.

During Irradiation: Temozolomide, p.o., 75 mg/m²/d for 42 days.

7.2.1.1 Pneumocystis Pneumonia Prophylaxis

During concurrent radiation-temozolomide therapy, patients will be treated with trimethoprim sulfamethoxazole (Bactrim™) double strength tablets (DS), 1 p.o. 3 times/week. Acceptable alternatives to trimethoprim sulfamethoxazole include either dapsone 50 mg p.o. bid or aerosolized pentamidine, 300 mg by nebulizer every 4 weeks (*i.e., two doses during radiation*). Therapy will be discontinued at the end of radiation.

7.2.2 Administration: Temozolomide will be administered on an empty stomach (*i.e., at least 1 hour before and 2 hours after any oral intake*). Granisetron, 1 mg p.o., or dolasetron, 100 mg p.o., will be given 1 hour before each dose of temozolomide. Antiemetics may be prescribed as required, but steroids may not be used as anti-emetics.

7.2.3 Duration of Therapy:
Pre-Irradiation: Responding patients will receive treatment until 2 cycles after maximum response. Patients with stable disease will receive 6 cycles before radiation. In the absence of evaluable disease, a total of 6 cycles will be given before radiation. CT/MRI scans will be performed every 8 weeks to evaluate response. Patients will receive chemotherapy according to the following table:

Response	Duration of Pre-irradiation Therapy
Complete or partial response *	2 cycles after the time at which the best response was noted
Stable disease	6 cycles
Absence of evaluable disease	6 cycles
Progressive disease	Discontinue therapy

* see Section 11.4 for definitions

Temozolomide will be discontinued (*and RT started*) for:

- treatment delays in excess of 8 weeks between cycles;
- unacceptable toxicity as defined in Section 7.3.4.1.2;
- any reason at the request of the patient or guardian;
- CT or MRI documented tumor progression (*see Section 11.6*);
- clinical deterioration, which in the judgment of the treating physician, is due to disease progression. (*Note: if the scan is unchanged, the investigator should be careful to exclude causes of clinical deterioration that mimic tumor progression such as anticonvulsant or other drug toxicity, occult infection, pulmonary embolism with hypoxemia, precipitous steroid withdrawal, intratumoral hemorrhage, etc.*)

Temozolomide Concurrent with Radiation Therapy (SD, PR only): Toxicity permitting, there will be 42 days of concurrent temozolomide.

7.3 Dose Modification

7.3.1 Hematologic Toxicity: Temozolomide dosage modification for each cycle of therapy will be based upon hematologic toxicity of the previous cycle according to the following table:

Temozolomide Dose Modification Table				
	AGC* (mm ³)		Platelets (mm ³)	Modification
Nadir	< 500 with fever or < 500 for 5 days	or	< 20,000	80%
At scheduled time of administration	≥ 1500	and/	≥ 100,000	Dose modified for nadir only.
	< 1500	or	< 100,000	Hold dose for 1 week and recheck CBC**
** After 2 weeks of treatment delay	≥ 1500	and	≥ 100,000	Dose modified for nadir;
	1000-1499	or	75,000-99,999	75% dose;
	< 1000	or	< 75,000	Contact study chair before further chemotherapy

* AGC = absolute granulocyte count

** Repetition of severe marrow depression, persistent neutropenia (< 1500/mm³) or thrombocytopenia (< 20,000/mm³) at time of treatment and after dose reduction will require contacting the chemotherapy study chair before any further chemotherapy is given. Further chemotherapy will be given only if there is joint agreement between the study chair and the individual investigator.

7.3.2 Nonhematologic toxicity: Dose reductions for reversible nonhematologic toxicity will be as follows:

Toxicity Grade	Temozolomide Dose (mg/m ² /d)
3	100%
4	80%

7.3.3 Toxicity Criteria: The NCI Common Toxicity Criteria version 2.0, available at <http://ctep.info.nih.gov> will be employed to grade observed toxicity.

7.3.4 Discontinuation/Reinstitution:

7.3.4.1 Patients will be removed from protocol treatment for the following reasons:

7.3.4.1.1 Disease progression or relapse; see Section 11.4.

7.3.4.1.2 Unacceptable toxicity: reversible nonhematologic grade 3 or 4 toxicity per se does not necessitate patient removal from study. However, the risks and benefits of further therapy must be discussed with the patient prior to subsequent courses.

7.3.4.1.3 Patient request or noncompliance.

7.3.4.1.4 Serious intercurrent illness which compromises patient safety or full participation in the trial.

7.3.4.1.5 Delay in therapy for > 2 weeks.

7.3.4.2 Criteria for the initiation of additional cycles:

7.3.4.2.1 Resolution of therapy-related toxicity to grade ≤ 1 with the exception of alopecia.

7.3.4.2.2 AGC $\geq 1500/\text{mm}^3$ and platelets $\geq 100,000/\text{mm}^3$.

7.3.4.3 Further cycles of therapy may be delayed up to 2 weeks to allow for recovery from toxicity.

7.4 Adverse Reaction Reporting

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

7.4.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for grading of chemotherapy and acute radiation (≤ 90 days) toxicity. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0. See Appendix V for Adverse Event Reporting Guidelines. This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.4.2 The following guidelines for reporting adverse drug reactions (ADR's) apply to any research protocol that uses commercial anticancer agents. The following ADR'S experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery and then a written report sent to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within ten working days:

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

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

7.4.2.3 Any death on study if clearly related to the commercial agent(s).

7.4.3 The ADR report should be documented on FDA Form 3500 and mailed or faxed to the address on the form, as well as to the IDB and RTOG Data Management Department:

Investigational Drug Branch	RTOG Data Management
P.O. Box 30012	1101 Market Street, 14 th floor
Bethesda, MD 20824	Philadelphia, PA 19107
(301) 230-2330, available 24 hours	Phone (215) 574-3214
Fax (301) 230-0159	Fax (215) 923-1737

All MedWatch 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.

7.4.4 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within ten days of discovery.

7.4.5 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. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

Investigational Drug Branch
(NCI/CTEP)
P.O Box 30012
Bethesda, MD 20824

and
RTOG Headquarters
AML/MDS Report
1101 Market Street, 14th floor
Philadelphia, PA 19107

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.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Steroid Use

Steroids may be used as required to control CNS symptoms due to tumor-associated or RT-associated cerebral edema, but wherever possible, should be tapered and stopped. Steroid doses will be recorded at specific time points during and after treatment (*see Section 11.0*). Investigators should avoid radical changes in steroid dose during periods critical for response evaluation so as not to complicate the assessment of response to temozolomide.

10.0 PATHOLOGY

10.1 Central pathology review is mandatory prior to study entry to confirm eligibility. It should be initiated as soon as the diagnosis has been made. Central pathology review will be performed by Dr. Bernd Scheithauer, Mayo Clinic. All slides for pre-entry review will be sent directly to the Mayo Clinic (*see Section 10.3.3*) and not through Group Headquarters.

10.2 To be eligible for this study, the patient's tumor must contain an unequivocal (*at least 25%*) oligodendroglial element and have two or more anaplastic features (*one of which must be frequent mitoses [e.g., 5 or more per 10 40X fields] or endothelial proliferation*). For mixed tumors, the non-oligodendroglial element must be astrocytic and either the oligodendroglial or astroglial component may be anaplastic. The "home" pathologist will assess the tumor and complete the Pathology Checklist (*Appendix III*). First, the tumor will be designated as a pure anaplastic oligodendroglioma or a mixed anaplastic glioma, and if mixed, further described as oligodendroglioma-dominant, astrocytoma-dominant, or equally mixed. For subsequent analyses and reporting, pure oligodendrogliomas and oligodendroglioma-dominant mixed tumors will be considered "pure" and the others considered "mixed". The degree of anaplasia will be based on the presence or absence of high cellularity, nuclear pleomorphism, frequent mitoses, vascular proliferation, and necrosis. For stratification, tumors with 2 or 3 anaplastic features will be considered moderately anaplastic and those with 4 or 5 features considered highly anaplastic.

10.3 (12/23/02) The following materials will be sent by overnight mail to the Mayo Clinic for central review:
-Pathology Checklist ([Appendix III] with the left hand side completed by the "home" pathologist) and Specimen Transmittal Form;

All H&E stained slides **and**

representative paraffin block(s) (*or ten representative unstained slides of the highest grade tumor-containing block*);

name, phone, and fax number of person to whom the results of the central pathology review should be transmitted.

10.3.1 The data manager will initiate the Pathology Checklist. The top right-hand corner of the form is to be filled out and submitted along with the operative and pathology reports, when requesting the slides and blocks from the pathology department.

10.3.2 The primary pathologist will complete the Pathology Checklist and return it to the data manager, along with the slides, blocks and pathology and operative reports.

10.3.3 (12/23/02) The data manager will check the form for completeness and send all materials (*Section 10.3*) to the central neuropathology reviewer in care of:

**Russ Hamilton
Charlton Building SL, Room S215
Mayo Clinic
200 First Street SW
Rochester, MN 55905
(507) 266-3385
FAX (507) 284-0079**

Please alert Mr. Hamilton prior to sending the materials.

- 10.3.4 After the pathology materials have been reviewed, a call will be made to the institution notifying them whether or not the case is eligible. This will be confirmed by fax.
- 10.3.4.1 If the patient enters the study, the patient's RTOG case number will be added to the Pathology Checklist by the data manager and a copy of the completed form will be sent to RTOG. A copy of the Specimen Transmittal Form must be included. All materials will be returned to the submitting institution along with all slides except the one(s) selected by the neuropathologist for the study files.
- 10.3.4.2 If the patient does not enter the study, *all* slides, blocks and forms will be returned to the participating submitting institution.
- 10.4 **RTOG Tissue Bank** *(for patients who have consented to participate in the tissue component of the study).*
- 10.4.1 Submit materials for patients entered on this study to the RTOG Tissue Bank. These materials can include slides/blocks that were returned to the institution from the Mayo Clinic following the mandatory central pathology review.
- 10.4.2 The following must be provided:
 - 10.4.2.1 One H&E stained slide.
 - 10.4.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
 - 10.4.2.3 Pathology report documenting that submitted block or slides contain tumor.
 - 10.4.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
- 10.4.3 RTOG will reimburse pathologists from submitting institutions \$100 per case if proper materials are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS that they have received the appropriate number of slides/blocks.
- 10.4.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.4.5 Materials will be sent to:

LDS Hospital (7/24/03)
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
ldhflinn@ihc.com

- 10.4.6 FISH analysis for 1p/19q will be performed on paraffin sections retrospectively at the Cleveland Clinic Reference Laboratory. Specimens will be shipped to the Cleveland Clinic Reference Laboratory from the RTOG Tissue Bank when requested.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Parameter	Pre-Treatment	Temozolomide Pre-irradiation cycles 2,3,4,5,6	Pre-RT	During RT/Temozolomide End of weeks 2, 4 and 6 (<i>SD, PR only</i>)	F/U per Sec. 12.0
Clinical Assessment, ZPS	X	X	X	X	X
Hematology: CBC w/diff	X ^a	X	X	X	X
Biochemistry: Electrolytes, Glucose, Creatinine, Bilirubin, AST/ALT, Alkaline Phosphatase	X ^a	X	X	X	X
Pregnancy Test	X ^a				
CT or MRI without/with contrast ^b	X ^a	X ^d	X ^c		X
Chest X-ray	X ^a				
Record Steroid Dose	X	X	X	X	X
Toxicity Evaluation		X	X	X	X
MMSE	X ^a	X ^c		X ^f	X

- All tests and scans must be performed within two weeks prior to study entry.
- The baseline and all follow-up scans to assess response/progression must be of the same type, that is either CT or MRI.
- MRI (*T2 and T1 gad*) to plan RT within 2 weeks of RT start; if patient has CR, confirmatory MRI 4 weeks later.
- CT/MRI every 8 weeks to evaluate response.
- At 3 and 6 months and at end of chemotherapy.
- At end of radiation therapy.

11.2 Survival

Patients will be followed until death. The cause of death will be recorded for each patient and if possible the histologic type and extent of tumor reassessed at autopsy. Survival time will be the interval between the date of entry and the date of death.

11.3 Time to Progression

Patients will be followed clinically and radiologically as outlined in Section 11.0. The date at which the tumor is documented to have first enlarged by 25% (*steroid dose stable or increased, neurologically stable or worse*) will be considered the date of tumor progression. Time to progression will be the interval between the date of study entry and the date of tumor progression. In the event of a discrepancy and for the purposes of analysis, the treating physician's date of tumor progression will be deemed to be correct. Tissue confirmation of tumor progression by stereotactic biopsy or other surgical procedure is encouraged. Thallium-SPECT or PET imaging of all "recurrent lesions" is recommended for patients at centers with access to these technologies.

11.4 Overall Response Assessment (*Call Dr. Vogelbaum With Questions*)

11.4.1 Definition of response to temozolomide is adapted from Macdonald et al.²⁷

Residual enhancing, non-enhancing, or minimally enhancing tumor:

Complete Response (CR): shall be defined as the circumstance when the tumor is no longer seen by neuroimaging, with the patient off all steroids, or on adrenal maintenance only; CR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan coding a response.

Partial Response (PR): Decrease of >50% in the product of two diameters with the patient off all steroids, or on adrenal maintenance only; PR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan.

Stable Disease (SD): shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids. This will not need a confirmatory scan.

Progression (P): shall be defined as a > 25% increase in tumor area (*two diameters*) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. This will not need

a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the first two months after completion of XRT. (*Note: Under exceptional circumstances disease progression may be declared in the absence of an increase in tumor size - see Section 7.2.3*)

11.5 Toxicity Evaluation

11.5.1 Acute Toxic Reactions

A complete blood count and biochemistry screening evaluation will be done prior to each cycle of temozolomide. PFTs and other tests will be performed as necessary to assess pulmonary and other toxicity due to chemotherapy. All unexpected radiation reactions will be reported.

11.5.2 Other Toxicities

All second malignancies, myelodysplastic syndromes, respiratory illnesses, neuromuscular disorders, dementias and other illnesses probably or possibly related to temozolomide or RT will be reported.

11.6 Treatment at Progression

See Section 11.4 for the definition of tumor progression.

11.6.1 Progression during Temozolomide

Immediate external beam RT is strongly recommended for tumor progression during pre-irradiation temozolomide, but other therapies are permitted. The MRI scan for RT treatment planning may need to be repeated.

11.6.2 Progression during RT

Those whose tumors progress during RT will be treated at the discretion of the investigator. All subsequent treatments will be recorded.

11.6.3 Progression after Treatment

Those whose tumors progress after completing temozolomide and RT will be treated at the discretion of the investigator. Tissue confirmation of recurrent tumor should be considered. All subsequent treatments will be recorded.

Note: The investigator must be careful to exclude causes of clinical or radiologic deterioration that mimic tumor progression (*ie. pseudoprogression*) such as acute radiation reactions, precipitous steroid withdrawal, intratumoral hemorrhage, etc.

11.7 Film Review

Central radiology review must be completed prior to the start of radiation therapy. Baseline and follow-up scans will be reviewed on all patients who have responded, progressed, experienced an unexpected CNS toxicity, or died.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Pathology Checklist (P4) (copy, original to reviewer)	Within 1 week of study entry
Initial Evaluation Form (I1) Pathology Report (P1) Slides/Blocks (P2) Mini-Mental Status Exam (MS) CT/MRI Scans (C1) CT/MRI Report (C3)	Within 2 weeks of study entry
Treatment Summary Form (TF)	Monthly x 6
CT/MRI Reports (C3)* CT/MRI Scans (C2)	After cycles 2, 4, and 6 and at follow-up, within 1 week of scan date
Central Radiology Review Form	At end of chemotherapy; prior to second registration

Initial Follow-up Form (FS) Mini-Mental Status Exam (MS)	At 3 and 6 months or at end of chemotherapy and 90 days from the start of RT
Concurrent Treatment Form (SF)	At end of concurrent treatment (RT and temozolomide)
Radiotherapy Form (T1) Mini-Mental Status Exam (MS)	Within 2 weeks of RT end
Follow-up Form (F1) Mini-Mental Status Exam (MS)	At 9 and 12 months then q 4 months in year 2, q 6 months years 3 to 5, then annually. Also at progression/relapse. At death (F1 only)
Autopsy Report (D3)	As applicable

* CT/MRI scans and reports must be submitted on all patients who respond or progress on temozolomide and on all patients at progression. These must be submitted to RTOG within 1 week of scan date.

12.2 Dosimetry Submission for Patients Receiving Radiation Therapy

<u>Item</u>	<u>Due</u>
Items will be sent directly to RTOG Headquarters:	
MRI scan with contrast for treatment planning (MR) (T2 and T1 gad) MRI scan report (ME)	Within two weeks of RT start
Calculation data form for all fields (TL) Simulation and portal films for all fields (TP) Complete treatment record (T5) Isodose Distributions (T6) (see Section 6.1.4 for details) Boost Films (T8)	Within two weeks of RT end
FollowUp Scan (C2) Follow Up Scan Report (C3)	Within 4 months from RT end

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Rate of progression at six months (*postchemotherapy/pre-irradiation therapy progression*);

13.1.2 Acute and late toxicities associated with this treatment regimen;

13.1.3 Overall survival.

13.2 Sample Size

The primary endpoint of this study is six month progression rate for anaplastic oligodendroglioma patients who have received induction temozolomide. Chen and Ng²⁸ provide a flexible design that will have 80% power, at a 0.05 one-sided significance level, to detect the difference between the null hypothesis progression rate of 0.20 and the alternative progression rate of 0.05, with a maximum sample size of 35. Progression will be continuously monitored. If, at any time, it is determined that at least two of the first 16 patients, 3 of the first 17 to 27 patients, or 4 of the first 28 to 35 patients, have progressed within six months, then we will stop accrual with the result of *not* rejecting the null hypothesis. Otherwise, if less than 4 of all 35 patients have progressed within six months, then the null hypothesis will be rejected in favor of the alternative, and we will conclude that temozolomide merits further investigation in a phase III setting. This plan has an average estimated sample size of 17.8 and requires a maximum sample size of 35. Assuming an ineligibility/ inevaluability (*no data*) rate of 5%, we will need to accrue 37 patients.

13.3 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 minorities in clinical research, any pronounced differences in outcome between races or genders will be noted, but the small size of this study will not allow for meaningful subset analyses. The projected gender and minority accruals are shown below:

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	12	24	0	36
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	12	25	0	37
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	1	0	1
Black or African American	0	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	12	22	0	34
More than one race	0	0	0	0
Unknown	0	1	0	1
Racial Category: Total of all subjects*	12	25	0	37

13.4 Patient Accrual

The patient accrual is projected to be 3.3 patients per month. At this rate, it will take 12 months to accrue the maximum of 37 patients. If the average monthly accrual rate is less than two patients, the study will be re-evaluated with respect to feasibility.

13.5 Analyses Plans

13.5.1 Interim Analyses

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

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

By examining the above items, the statistician and study committee can identify problems with the execution of the study. If necessary, problems will be reported to the RTOG Executive Committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

If early termination occurs, results will be reported at that time. Otherwise, results will be reported when 35 eligible and evaluable patients have six month progression data. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting of institutional accrual;
- c) distribution of important prognostic baseline variables – (*age, ZPS, neurologic function, extent of surgery, mental status*);
- d) observed results with respect to the endpoints described in Section 13.1.

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APPENDIX IA

RTOG BR-0131

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II TRIAL OF PRE-IRRADIATION AND CONCURRENT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED ANAPLASTIC OLIGODENDROGLIOMAS AND MIXED ANAPLASTIC OLIGOASTROCYTOMAS

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 an uncommon cancerous brain tumor that is wholly or partly an oligodendroglioma.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good or bad) the chemotherapy agent temozolomide has on patients with your type of brain cancer.

This research is being done because doctors are trying to determine the best way that chemotherapy can be used in treating your type of tumor. Doctors want to see if temozolomide given before radiation therapy will delay growth of your tumor.

This study will also gather information about whether the addition of the drug temozolomide to radiation therapy will prolong the time to regrowth of the cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 37 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY

Chemotherapy: The chemotherapy drug to be used in this study is temozolomide. Temozolomide will be given by mouth in capsule form for days 1-7 and days 15-21, every 28 days. This means 7 days on and 7 days off. This comprises one cycle. You will receive temozolomide for six months for a total of six cycles. You will receive six cycles of temozolomide prior to your radiation therapy, and then you will receive temozolomide for 42 days during radiation therapy.

Radiation Therapy: You will receive radiation therapy once a day, five days a week, for six and a half weeks. All radiation therapy treatments will be given as an outpatient at your institution. Radiation therapy will not be given immediately after chemotherapy if your tumor has completely disappeared by the end of chemotherapy. In the event that your tumor has completely disappeared after chemotherapy, you will be given radiation therapy only if your tumor reappears on a subsequent MRI scan.

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

<i>Procedure</i>	<i>Schedule</i>
Physical and Neurological Exam	Prior to study entry, before each cycle of temozolomide, before radiation starts, at end of weeks 2, 4, and 6 during radiation and temozolomide, and at followup.
Blood Counts, Chemistries	Prior to study entry, before each cycle of temozolomide, before radiation starts, at end of weeks 2, 4, and 6 during radiation and temozolomide, and at followup
Pregnancy test (if applicable)	Prior to study entry.
Chest X-ray	Prior to study entry.
CT or MRI	Prior to study entry, every 8 weeks during temozolomide, and at followup.

MRI Within two weeks of start of radiation therapy. There may be another MRI four weeks after this one for confirmation of response.

MMSE (Mini-Mental Status Exam) Prior to study entry, at 3 and 6 months during temozolomide, at end of chemotherapy, at end of radiation therapy, and at follow-up.

Follow-up visits will be at 9 and 12 months in the first year, every 4 months in the second year, and every 6 months in years 3-5, then annually for the rest of your life.

Also, at the time of your diagnosis by biopsy, some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was completed, the tumor samples were sent to the Mayo Clinic for an additional review. These samples will be sent back to the submitting institution except for the one slide selected by the pathologist for the study files.

HOW LONG WILL I BE IN THE STUDY?

You will receive temozolomide for six months, followed by six and a half weeks of radiation therapy during which you will also receive temozolomide. We think you will be in the study for approximately nine months. Followup visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, if your condition worsens, or if 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 researcher 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

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

Risks Associated with Temozolomide:

Very Likely

Nausea and/or Vomiting
Headache
Constipation
Drowsiness/Fatigue

Less Likely, But Serious

Decrease in blood counts that may cause infection and bleeding
Decreased ability to carry out daily activities
Pneumonia

Less Likely

Loss of appetite
Diarrhea
Fever
Weight loss and/or a decrease in appetite
Weakness
Sores in your mouth
Hair loss
Numbness or tingling
Abdominal pain/jaw pain
Skin rash
Weakness of hands and feet
A temporary elevation in the blood tests that show how your liver is functioning

Risks Associated with Radiation Therapy:

Very Likely

Scalp redness or soreness
Hair loss
Dry mouth or altered taste
Fatigue, sleepiness

Less Likely, But Serious

Permanent hair loss
Hearing loss
Eye injury resulting in blindness
Mental slowness, behavioral changes
Severe damage to normal brain tissue that may require additional surgery

Less Likely

Fever, chills, heavy sweating
Upset stomach, nausea and/or vomiting
Loss of appetite, taste changes
Thrombophlebitis (blood clots)
Headaches, seizure, weakness

Reproductive Risks: You cannot enroll in this study if you are pregnant. You should not nurse your baby while on this study. Women of childbearing potential should use birth control throughout participation in this study. If you suspect that you have become pregnant, you must notify the study doctor immediately.

Risks associated with drawing blood from your arm may include pain, bruising, lightheadedness, and, on rare occasions, infection.

Risks of Delaying Radiation Therapy: If your tumor completely disappears as a result of chemotherapy, you may not receive radiation therapy unless the tumor reappears on a subsequent MRI scan. The risk associated with delaying radiation therapy until the tumor reappears is unknown; delaying radiation could be harmful and reduce its effectiveness.

Your condition may not improve or may worsen while participating in this study.

There may be other risks or side effects that are unknown at this time.

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. You are being offered this experimental drug along with radiotherapy because temozolomide has shown some anticancer activity in certain kinds of brain cancer. We hope the information learned from this study will benefit other patients with brain tumors in the future as well as possibly you.

WHAT OTHER OPTIONS ARE THERE?

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

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

WHAT ABOUT CONFIDENTIALITY?

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

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

WHAT ARE THE COSTS?

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

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

You or your insurance company will be charged for continuing medical care and/or hospitalization.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT? (12/23/02)

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. 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 new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

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

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

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

Patient's Name

Signature

Date

Name of Person Obtaining Consent

Signature

Date

APPENDIX IB

RTOG BR-0131 CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

ABOUT USING TISSUE FOR RESEARCH

You are going to have 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 may be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue be returned to you or your designee.

In the future, people who do research may need to know more about your health. While the treating physician/ institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research 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. The treating physician/institution will protect your records so that your name, address, and phone number 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”. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at (IRB’s phone number).

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 from (treating physician, institution) may contact me in the future to ask me to take part in more research.

Yes No

Please sign your name here after your circle your answers.

Your Signature: _____ Date: _____

Signature of Doctor/Nurse: _____ 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 pre-disease activities without restriction (<i>Karnofsky 90-100</i>).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<i>Karnofsky 70-80</i>).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).

APPENDIX III

<p>P4</p> <p align="center">Radiation Therapy Oncology Group</p> <p align="center">PRE-Registration Pathology Form</p> <p><input type="checkbox"/> If this is a revised or corrected form, indicate by checking box.</p>	<p align="center">RTOG Study BR-0131 Case# _____</p> <p>Institution _____ Institution # _____</p> <p>Patient Name _____ Patient ID# _____</p>																																				
<p>INSTRUCTIONS: Please refer to Section 10.0 of protocol regarding completion and submission of this form. <input type="checkbox"/> DE</p>																																					
<p>ELIGIBILITY (6/2/03): To be eligible for this study, tumors must contain an unequivocal (<i>at least 25%</i>) oligodendroglial component and have two (<i>one of which must be frequent mitoses or endothelial proliferation</i>) or more of the following anaplastic features: high cellularity, nuclear pleomorphism, frequent mitoses, endothelial proliferation, or necrosis. For mixed tumors, the non-oligodendroglial element must be astrocytic (<i>either element may be anaplastic</i>).</p>	<p>TISSUE SOURCE:</p> <p>STEREOTACTIC BX: DATE ____/____/____</p> <p>OPEN BX/RESECTION: DATE ____/____/____</p>																																				
<p align="center">“HOME” PATHOLOGY REVIEW</p> <p>Tumor Type:</p> <p>Oligodendroglioma _____</p> <p>Mixed Glioma _____</p> <p>If mixed,</p> <p> Oligo dominant _____</p> <p> Oligo=astro _____</p>	<p align="center">“CENTRAL” PATHOLOGY REVIEW</p> <p>Tumor Type:</p> <p>Oligodendroglioma _____</p> <p>Mixed Glioma _____</p> <p>If mixed,</p> <p> Oligo dominant _____</p> <p> Oligo=astro _____</p>																																				
<table border="0" style="width:100%;"> <tr> <td>Anaplastic Features:</td> <td align="center">Yes</td> <td align="center">No</td> </tr> <tr> <td>High cellularity</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Nuclear pleomorphism</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Frequent mitoses</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Endothelial proliferation</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Necrosis</td> <td align="center">_____</td> <td align="center">_____</td> </tr> </table>	Anaplastic Features:	Yes	No	High cellularity	_____	_____	Nuclear pleomorphism	_____	_____	Frequent mitoses	_____	_____	Endothelial proliferation	_____	_____	Necrosis	_____	_____	<table border="0" style="width:100%;"> <tr> <td>Anaplastic Features:</td> <td align="center">Yes</td> <td align="center">No</td> </tr> <tr> <td>High cellularity</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Nuclear pleomorphism</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Frequent mitoses</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Endothelial proliferation</td> <td align="center">_____</td> <td align="center">_____</td> </tr> <tr> <td>Necrosis</td> <td align="center">_____</td> <td align="center">_____</td> </tr> </table>	Anaplastic Features:	Yes	No	High cellularity	_____	_____	Nuclear pleomorphism	_____	_____	Frequent mitoses	_____	_____	Endothelial proliferation	_____	_____	Necrosis	_____	_____
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<p>Total No. of Anaplastic Features: _____</p>	<p>Total No. of Anaplastic Features: _____</p>																																				
<p>Stratification: For the purposes of subsequent analysis, pure oligodendrogliomas and oligodendroglioma-dominant mixed tumors will be considered “pure” whereas oligodendroglioma=astrocytoma and astrocytoma-dominant mixed tumors will be considered “mixed”. Tumors with 2 or 3 anaplastic features will be considered moderately anaplastic and those with 4 or 5 features will be considered highly anaplastic.</p>																																					
<p><u>Institution</u> (<i>must be completed</i>)</p> <p>Completed by: _____ Date: _____</p> <p>Telephone #: _____ Fax #: _____</p>																																					
<p>Central Pathology Reviewer (<i>must be completed and faxed to RTOG HQ, 215-574-0300 after notifying submitting institution</i>)</p> <p>Completed by: _____ Date: _____</p> <p>Approved for Study Entry _____ Yes _____ No Reason _____</p>																																					

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected 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, or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite:	The adverse event is <i>clearly related</i> to the treatment/procedure.
Probable:	The adverse event is <i>likely related</i> to the treatment/procedure.
Possible:	The adverse event <i>may be related</i> to the treatment/procedure.
Unlikely:	The adverse event is <i>doubtfully related</i> to the treatment/procedure.
Unrelated:	The adverse event is <i>clearly NOT related</i> to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.
3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

- a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
- b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.
5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).
6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.
7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).
8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.
9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.
10. All neuro-toxicity (\geq grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.
2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.
3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE¹	Hospitalization During Treatment²	Secondary AML/MDS³
FDA Form 3500 ^{4,5} within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis ^{4,5}				X
Call RTOG within 24 hrs of event ⁷	X ⁶			

1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
5. Copy to RTOG Data Management labeled: Attention: Adverse Event Report.
6. All grade 5 known toxicity.
7. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators' reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. Expedited Reporting for Phase 1 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Grade 2: Expedited report within 10 working days. Grade 3: Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

APPENDIX VI

Neuroimaging Guidelines

Imaging Protocol

Neuroimaging examinations are performed at multiple time points during the trial, as detailed in Section 11.1. Contrast-enhanced CT or MRI studies are acceptable; however, the baseline and all follow-up scans must be of the same type. It is also understood that with clinical changes or deterioration, additional scans may be obtained at the investigator's discretion at different time points than stated above. These additional examinations should also be considered as trial data, and all CT or MRI examinations on enrolled patients during the period of the study will be evaluated. All imaging studies will require central review, but of particular importance are those that are necessary to determine stratification; i.e., at the end of pre-irradiation chemotherapy. The following are a set of imaging guidelines that are recommended for use in this study.

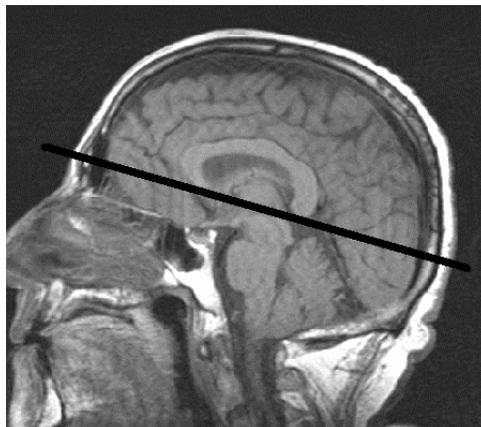
Guidelines for Brain MRI Studies:

All MRI examinations in the protocol are to be performed on high field strength MRI scanners (1.0 – 1.5 T). The MRI images critical to the efficacy and safety analyses are the following: 1. unenhanced T1-weighted spin echo scans of the brain (any orientation); 2. Axial T2-weighted (conventional or FSE) scans; 3. Axial post- gadolinium T1-weighted spin echo scans. Specific MRI imaging protocols are defined at each investigating site, and it is understood that the patient's brain examinations may have additional imaging sequences, such as images in different orientations. MRI scanning guidelines are provided only for the three sequences listed above, which will be used for quantitative analyses. These parameters should be saved in your MRI scanner's protocol directory. The suggested protocol is designed such that single measurements will be made for each required scan, avoiding "full gap and fill" methods that double the measurement time. Specific parameter ranges are given that should be accommodated by all manufacturers.

(MRI) 1. Patient Positioning: Patients should be positioned in the head coil using normal, comfortable, standard positioning techniques. It is always best to place an intravenous line with extension tubing prior to patient positioning, so that the table does not need to be repositioned for gadolinium injection during the examination. The head should be aligned straight, minimizing rotation or head tilt, using laser marker or head coil landmarks. The chin position is not critical, but avoid extremes of head flexion and extension. The patient's head is padded, and firmly secured in the head coil. There is no need for external markers or fiducials. The patient table is then positioned with the laser line over the frontonasal suture region (center of head coil), the scan line is marked, and the table is advanced to isocenter.

(MRI) 2. Scout Scans: A quick three plane scout is used to determine gross head size and position. From this, a three slice, sagittal T1 weighted SE scout should be performed in midline sagittal position, if necessary, using oblique positioning to obtain true anatomic midline sagittal slices. These scout images must be of sufficient quality to allow for reliable positioning of axial slices.

(MRI) 3. T1-weighted axial SE scans: Pre-contrast, axial-oblique, T1-weighted SE scans will be positioned with reference to the undersurfaces of the anterior (genu) and posterior (splenium) aspects of the corpus callosum (see figure below). The stack of slices should be positioned with respect to this reference for all three sequences defined, with the stack giving



whole head coverage. Once the stack is positioned for the T1-weighted SE scans, this positioning should be saved and reproduced on the axial T2-weighted and post-gadolinium T1-weighted scans.

T1-weighted SE scan parameters are as follows:

TE: 12-20 ms (motion / flow compensation suggested)
TR: 600 – 800 ms
No Magnetization Transfer
Slices: 7 mm slices, no gap, interleaved slice excitation, 24 – 28 slices
Matrix: 192 – 256 phase x 256 frequency, L-R phase encoding
FOV: 230 mm, may use 6/8 rectangular FOV
Ave: 2
Time: @ 4 – 5 minutes

(MRI) 4.T2-weighted axial FSE scans: These must be performed with the same number of slices and identical axial-oblique slice positioning as the previous T1-weighted SE scans. Most centers are expected to be using FSE methods, but conventional SE scans are also acceptable if there is identical slice coverage and positioning and comparable resolution. Additionally, FSE FLAIR scans with identical slice coverage and positioning and comparable resolution are acceptable. T2-weighted FSE scan parameters are as follows:

TE: 90 - 105 ms
TR: 4000 – 6000 ms
ETL 4 – 8
Slices: 7 mm slices, no gap, interleaved slice excitation, 24 – 28 slices
Matrix: 192 – 256 phase x 256 frequency, L-R phase encoding
FOV: 230 mm, may use 6/8 rectangular FOV
Ave: 1- 2
Time: @ 3 - 6 minutes

(MRI) 5.Gadolinium: A standard, single dose of gadolinium based upon patient's weight is to be used (0.1 mmol/kg = 0.2 ml/kg) (Example: a 70 kg patient receives 14 ml of gadolinium). Any FDA- approved gadolinium product is acceptable. After injection, approximately five minutes equilibration time is needed prior to performing the axial, post – contrast T1-weighted SE scans. In case of contrast allergy or contrast refusal, note the problem, and relay the information to the site investigator.

(MRI) 6.Post-gadolinium axial T1-weighted SE scans: The post-gadolinium, axial- oblique, T1-weighted SE scans are performed in the exact positioning and slice coverage as the pre-contrast scans. Identical scan parameters are to be used, and importantly, no magnetization transfer.

(MRI) 7.Other: The sites may acquire any additional scans per their routines, though these may not be used for quantitative analyses.

(MRI) 8.Stereotactic Pre-operative MRI study: The patient's routine pre-operative stereotactic MRI study may be substituted for an appropriate timepoint. These studies may include an axial T2-weighted (or FLAIR) scan, and a high resolution, T1-weighted, post-gadolinium 3D gradient echo (MPRAGE or other GRE) scan.

Guidelines for Cerebral CT Studies:

(CT) 1. CT scans should be performed with iodinated contrast media. Selection of contrast agent is per local institution guidelines. Recommended i.v. dose = 100 ml of 280 -300 mg % contrast media for adult patients.

(CT) 2. Patients should be injected with the contrast agent ten minutes prior to scanning.

(CT) 3. Scans are performed in an axial plane from the base of the skull to the vertex, using 5-8 mm thick slices, at contiguous intervals parallel to the orbito-meatal line.

(CT) 4. Images should be printed with 12-on-1 to 20-on-1 format on 14 x 17 laser film. This should be a direct, digital, laser-printed set of images, and not from a photographic duplication stand.

(CT) 5. The scout image with slice positions should be filmed.

(CT) 6. Brain “soft tissue” window and center are needed. No bone images are needed.

(CT) 7. There must be a measurement ruler with centimeter markings in the image frame

(CT) 8. The investigational site must keep unadulterated, original films (as required by the institution) in the patient files as source documentation.

Image Format

Images may be filmed for routine clinical purposes at the site. It is recommended that an image format of no greater than 20:1 be used. For film studies, it is essential that calibration rulers be included in each image segment. Analysis of imaging data for the purposes of this trial will be from digitized film studies or on DICOM – 3 digital data.

Image Transfer/Storage

The study sites should maintain a film hardcopy of all imaging data, as well as digital, DICOM – 3 permanent archival. Either film hardcopy or digital imaging data must be forwarded to RTOG Headquarters. The easiest, least expensive, and most reliable method for transferring digital data is to copy data to a CD-ROM. Most MRI facilities will have some sort of digital PACS network, and there should be workstations or PC's where data can either be directly saved to CD-ROM, or exported to a Windows directory as DICOM data, and then burned to CD-ROM. This CD-ROM can then be shipped to RTOG Headquarters at the address below:

RTOG Headquarters
Radiation Therapy Quality Assurance Department
1101 Market Street, 14th Floor
Philadelphia, PA 19107

Sites should maintain a second copy of the studies on CD-ROM. Each CD can hold more than one patient examination; it is likely that a patient's entire set of MRI examinations for this study could be stored on one or two CD's.

Data Analysis

Enrollment and baseline studies will be reviewed to check that imaging- based inclusion and exclusion criteria are met. Neuroimaging data will be analyzed for treatment response to temozolamide, as per Section 11.4.1. Patient studies will be followed to date of tumor progression, as defined in Section 11.3, using bi-dimensional product measurement methodology. Tumor size will be determined as the product of the bi-dimensional measurements of measurable (> 1.0 cm in two perpendicular dimensions) enhancing tumor and non-enhancing tumor (if present) , using electronic calipers. Progressive disease is defined as a 25 % or greater increase in size of measurable tumor, or the appearance of new lesions (measurable or non-measurable), consistent with progressive tumor, as determined by central review. Studies will also be analyzed to help determine safety and toxicities of treatment, according to the Adverse Event Reporting Guidelines, as detailed in Appendix V.