

RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-13

A PHASE III (PHASE I CLOSED) RANDOMIZED STUDY OF RADIATION THERAPY AND TEMOZOLOMIDE (IND #60,265) VERSUS RADIATION THERAPY AND BCNU FOR ANAPLASTIC ASTROCYTOMA AND MIXED ANAPLASTIC OLIGOASTROCYTOMA (ASTROCYTOMA DOMINANT)

Study Chairmen

RTOG (98-13)

(Coordinating Group)

Neuro-Oncology

Susan M. Chang, M.D.
(Primary Protocol Chair)
University of California-SF
400 Parnassus Avenue, 8th Fl
San Francisco, CA 94143-0372
(415) 353-2966
FAX (415) 353-2167
chang@neuro.ucsf.edu

Medical Oncology

Gregory J. Cairncross, M.D.
(403) 944-1260
FAX (403) 270-7878
jgcairn@ucalgary.ca

Mark R. Gilbert, M.D.
(713) 792-2883
FAX (713) 794-4999
mgilbert@mdanderson.org

Radiation Oncology

Jean-Paul Bahary, M.D.
(514) 890-8254
FAX (514) 412-7537
jean-paul.bahary@ssss.gouv.qc.ca

ECOG (R9813)

David Schiff, M.D. (5/17/04)
(434) 982-4415
FAX (434) 982-4467
DS4JD@virginia.edu

Neuroradiology

Carol A. Dolinskas, M.D.
(215) 829-6741
FAX (215) 829-7547
cadoli@pahosp.com

NCCTG (R9813)

Kurt Jaeckle, M.D.
Medical Oncology
(904) 953-7102
FAX (904) 953-7233
jaeckle.kurt@mayo.edu

Neuropathology and
Molecular Genetics

Ken Aldape, M.D.
(713) 792-7935
FAX (713) 745-1105
kaldape@mdanderson.org

Paul D. Brown, M.D.
Radiation Oncology

SWOG (R9813)

Neuro-Oncology
Geoffrey R. Barger, M.D.
(313) 577-1242
FAX (313) 745-4468
gbarger@med.wayne.edu

Activation Date:

June 16, 2000

Update Date:

May 17, 2004

Version Date:

October 19, 2004

Broadcast Date:

Includes Amendments 1-6
(November 4, 2004)

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

INDEX

Schema

Eligibility Check

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

References

- Appendix I - Sample Consent Form
- Appendix II - Karnofsky Performance Status
- Appendix III - Pre Randomization Central Pathology Review Form
- Appendix IV - Toxicity Criteria
- Appendix V - Adverse Reaction Reporting Guidelines
- Appendix VI - Intergroup Guidelines
- Appendix VII - Temodar™ Shipping Form

RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-13

A PHASE III (PHASE I CLOSED) RANDOMIZED STUDY OF RADIATION THERAPY AND TEMOZOLOMIDE (IND #60,265) VERSUS RADIATION THERAPY AND BCNU FOR ANAPLASTIC ASTROCYTOMA AND MIXED ANAPLASTIC OLIGOASTROCYTOMA (ASTROCYTOMA DOMINANT) SCHEMA (6/23/03)

S	R
T	A
R	N
A	D
T	O
I	M
F	I
Y	Z
	E

Age
1. < 50
2. ≥ 50

KPS
1. 60-80
2. 90-100

Surgery
1. Biopsy only
2. Resection

Arm 1: Radiation Therapy: 59.4 Gy (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) plus Temozolomide 200 mg/m² daily on days 1-5 of the first week of radiotherapy. Repeat Temozolomide every 28 days for a total of 12 cycles.

Arm 2: Radiation Therapy: 59.4 Gy (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) plus BCNU (80 mg/m²) on days 1,2, and 3 of the first week of radiotherapy and on days 56, 57, and 58, then every eight weeks for four cycles for a total of six cycles (maximum BCNU dose 1440 mg/m²).

Arm 3: (Radiation Therapy, BCNU, Temozolomide) **Dropped**; See Section 1.3

Pilot #1, Arm 4: Radiation Therapy: 59.4 (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) plus BCNU 200 mg/m² on day 1 of radiotherapy and Temozolomide 150 mg/m² on days 1-5 of the first week of radiotherapy. Repeat every six weeks for a total of six cycles (maximum BCNU dose 1200 mg/m²). (closed 3/15/01)

Pilot #2, Arm 5: Radiation Therapy: 59.4 (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) plus BCNU 150 mg/m² on day 5 of radiotherapy and Temozolomide 150 mg/m² on days 1-5 of the first week of radiotherapy. Repeat every eight weeks for a total of six cycles; BCNU will be given on day 5 of Temozolomide in these cycles. (maximum BCNU dose 900 mg/m²). (closed 1/25/02)

The first 15 patients were registered to Arm 4 in order to obtain additional toxicity data using temozolomide and BCNU. The second fourteen patients were registered to Arm 5 prior to the initiation of the phase III component of the study. Refer to Sections 7.1.4 and 7.1.5 for details. Based on the high proportion of dose reductions seen and the toxicities encountered in Arms 4 and 5, the phase III component of the study will consist of randomization to Arms 1 and 2 (The proposed Arm 3 has been dropped).

Eligibility (See Section 3.0 for details) (6/23/03) (12/22/03)

All questions regarding eligibility should be directed to RTOG Headquarters

- Histologically confirmed anaplastic astrocytoma by central review or mixed oligodendroglial/astrocytic tumors if the oligodendroglial component is ≤ 25%.
- No prior irradiation to the head, neck, or chemotherapy for any reason
- Karnofsky performance status ≥ 60

(continued on next page)

- Hgb \geq 10, absolute neutrophils \geq 1500, platelets \geq 150,000; liver function tests (AST/SGOT, alkaline phosphatase, total bilirubin $<$ 2 x upper limit of normal); serum creatinine $<$ 1.5 x normal.
- Therapy must begin within 6 weeks after tissue diagnosis
- No spinal cord tumors or spinal cord metastases
- No prior invasive malignancy unless disease free $>$ 5 years
- No active infectious process
- No pre-existing lung disease that in the investigator's opinion will prevent administration or completion of therapy with BCNU
- Signed study-specific consent form prior to randomization

**Required sample size: 15 phase I, 15 phase I, part 2
454 phase III (8/15/02)**

RTOG Institution # _____

RTOG 98-13

RTOG Case # _____

ELIGIBILITY CHECKLIST (6/23/03,12/22/03,1/28/04)

(page 1 of 2)

- _____(Y) 1. Has the patient's surgical specimen been reviewed by the central pathologist (*Section 10.0*) and has it been confirmed as anaplastic astrocytoma or oligodendroglial/astrocytic tumor with $\leq 25\%$ oligodendroglial component?
- _____(Y) 2. Is the KPS ≥ 60 ?
- _____(Y) 3. Are the laboratory results within the limits stated in Section 3.1.3?
- _____(Y) 4. Will protocol therapy start within 6 weeks of the tissue diagnosis?
- _____(N) 5. Any pre-existing lung disease that will prevent administration or completion of therapy with BCNU?
- _____(Y) 6. Is the disease unifocal?
- _____(N) 7. Does the patient have tumor located in the spinal cord or posterior fossa?
- _____(Y/N) 8. Was the patient diagnosed with a previous low grade astrocytoma?
_____(N) If yes, was the patient treated with either RT or chemo?
- _____(Y/N) 9. Was the patient diagnosed with any other malignancy except cancer *in situ* of cervix or non-melanomatous skin cancer?
_____(Y) If yes, has the patient been disease free for at least 5 years?
- _____(N) 10. Has the patient had any RT to the head and neck area or to the brain?
- _____(N) 11. Has the patient had any systemic chemotherapy?
- _____(Y/NA) 12. Is the patient willing to practice effective contraception if indicated?
- _____(Y/NA) 13. If female, has the patient had a negative pregnancy test within the last 7 days?
- _____(N/NA) 14. If female, is the patient breast feeding?
- _____(N) 15. Does the patient have an active infectious process?

(continued on next page)

RTOG Institution # _____

RTOG 98-13

RTOG Case # _____

ELIGIBILITY CHECKLIST (6/23/03) (12/22/03)

(page 2 of 2)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Initials (First, Middle, Last)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 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. Medical Oncologist's Name
- _____ 17. Patient's Age
- _____ 18. KPS
- _____ 19. Extent of Surgery (*Biopsy only vs. Resection*)
- _____ 20. Body Surface Area (*BSA*) (m^2)
- _____ (Y) 21. Is patient eligible by Central Pathological Review?
- _____ 22. Treatment Start Date
- _____ 23. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background

Approximately 17,400 new primary brain tumors are diagnosed each year in the United States.²⁴ The incidence of malignant glial neoplasms account for more than 60 % of which about 75 % are Glioblastoma Multiforme (*GBM*) (*Grade IV*) and 25 % anaplastic astrocytomas (*AA*) (*Grade III*). Advances in treatment of malignant gliomas lags behind that of most systemic neoplasms for several reasons including the location in a confined space, their tendency to infiltrate normal brain, both of which preclude good cancer surgery, brain tolerance to radiation therapy, inadequate to effectively kill the tumor cells, and the presence of the blood brain barrier which interferes with optimal penetration of pharmacological agents.

Despite recent technological advances in neuro-surgery, neuro-imaging, and radiation-oncology, patients with malignant gliomas are seldom cured.⁶ New treatment modalities^{3,18,19,31,35,43} have focused on control of local disease taking advantage of the observation that most gliomas recur within 2 to 3 centimeters of the original mass seen on imaging.²¹ However, it is well established that infiltrating tumor cells are present in regions of altered signal intensity due to edema and beyond.⁶ Thus, most patients relapse and ultimately die of their disease. Effective blood-born treatment modalities, able to reach infiltrating tumor cells, are needed. New drugs with demonstrated activity against malignant glioma should be investigated either alone or in combination with older agents in multi-institutional clinical trials so that adequate numbers of patients are available enabling valid statistical analysis.

Accurate pathologic classification of grade III and IV astrocytomas has been problematic. It has become clear, on the basis of sub-analyses of data from multi-institutional clinical trials, that tumor grade significantly influences survival independent of treatment.^{9,10,16,45} Patients with GBM have median survivals of 8 to 10 months, whereas patients with AA have median survivals of 11.1 to 58.6 months.⁹ Only recently have these two grades of astrocytoma been examined individually in prospective clinical trials.^{26,41}

Malignant astrocytomas are histologically very heterogeneous tumors. Inter-observer and intra-observer variability is common.³³ The practice of obtaining tissue by stereotactic biopsy, hence relatively unrepresentative tissue samples, has made it difficult for the pathologist to correctly classify these tumors. The incidence of AA is significantly increased in patients who undergo stereotactic biopsy compared to those who undergo open biopsy, where the incidence of GBM is higher. Re-examination of tissue by central pathology reviewers in two large AA trials has demonstrated greater than 20% upgrading.^{26,41} The effect of misclassification of AA is to produce a 45% under-estimation of median survival in small clinical trials ($n < 25$) and 59% under-estimation in large randomized trials ($n > 200$).⁴⁶ Several investigators have recommended that imaging studies be correlated with histologic findings.^{6,49} Also, it is becoming clear that chromosomal analyses of neoplastic tissue may also contribute to better delineation of histologic grade and be of prognostic value.^{8,13,22,32,44} Examples include losses of 10q and amplification of the epidermal growth factor receptor (*EGFR*), restricted almost exclusively to GBMs, and p53 mutations, more common in lower grade gliomas.^{8,23,29,50,52} In a retrospective analysis of patients with anaplastic oligodendroglioma, allelic loss of chromosome 1p or coincident losses of chromosomes 1p and 19q predicted response to PCV chemotherapy and long survival times, whereas CDKN2A deletions predicted short survival.⁸ Higher Ki-67 proliferation indices have been associated with more aggressive astrocytomas.³⁶ These findings suggest that genetic alterations rather than clinical pathologic features better predict chemo-sensitivity and survival.

Current management of malignant gliomas is multi-modality. A radical surgical resection resulting in less than 5% residual tumor impacts favorably on prognosis.⁵⁶ Other independent favorable prognostic factors include young age and KPS. Radiation therapy remains the single most effective adjuvant treatment for malignant astrocytomas as demonstrated by the Radiation Therapy Oncology Group (*RTOG*) and Brain Tumor Cooperative Group (*BTCG*) in prospective, randomized, controlled clinical trials^{42,54} Also demonstrated in these trials is a dose-response relationship with a significant survival advantage for patients receiving 60.0 compared to 50.0 Gy.⁵⁵ Most studies now support administration of limited field irradiation to tumor and surrounding edema plus a margin of 2 to 3 cm because of the high local recurrence rate.^{21,42}

Chemotherapy's role in the management of malignant astrocytomas has been controversial. The first prospective trial to suggest a role was reported by the BTCG in 1978.⁵³ A variety of single agents and drug combinations have been studied since publication of this report, but none have been shown to be more effective than the nitrosoureas or procarbazine.^{16,17,27,57,58} Some patients seem to have sensitive tumors,

and live longer as a result, but clinicians are unable to predict who will benefit and thus treat accordingly.⁸ A recent meta-analysis using survival data from 16 randomized trials showed an estimated increase in survival of 10% at one year and 9% at two years for patients treated with radiation and chemotherapy, in most cases, BCNU, compared to patients who received radiation therapy only.¹²

In 1989, the Northern California Oncology Group (NCOG) published the results of a Phase III prospective, randomized trial comparing BCNU to a three drug regimen (PCV) consisting of Lomustine (CCNU), Procarbazine, and Vincristine, administered following standard radiation therapy, to patients with malignant gliomas (Grades III and IV).²⁸ Patients were randomized to receive either BCNU or PCV within two weeks of completion of radiation. There was no statistical difference in survival between patients who received the two regimens. However, a retrospective analysis of the data demonstrated a statistically significant difference in time to tumor progression and survival for patients with anaplastic astrocytoma (Grade III) compared to patients with glioblastoma (Grade IV). Median survival was 157 weeks in 36 patients who received PCV compared to 82 weeks in 37 patients who received BCNU. At the time, this was the first study to show that any chemotherapy regimen was superior to the nitrosoureas in the treatment of anaplastic astrocytoma. As a result, PCV chemotherapy became the standard of care for patients with anaplastic astrocytoma against which newer agents were measured in phase III clinical trials. It is important to note, however, that these survival data were generated retrospectively, and that the number of patients in each group was small. Indeed, the results of two studies, published in abstract form in 1998, do not show a survival advantage for patients with malignant astrocytoma (grades III and IV) treated with PCV chemotherapy.

The first, a phase III, randomized trial from the United Kingdom compared radiation therapy alone to radiation therapy followed by PCV chemotherapy. The results of this trial were presented at the May 1998 meeting of the American Society of Clinical Oncology in Los Angeles. Six hundred and seventy four patients were entered. Subset analyses of survival data were performed by grade. There were no survival differences between the various treatment groups. Then, in October 1998, at the American Society for Therapeutic Radiology and Oncology, Prados et al. presented the results of a retrospective analysis of survival data for AA patients from 4 different RTOG clinical trials. Two hundred and fifty-seven patients were treated with radiation therapy and BCNU and 175 patients with radiation therapy and PCV. Median survivals ranged between 36 and 48 months. Subset analyses failed to demonstrate a survival advantage for patients treated with PCV compared to patients treated with BCNU. The results of these two analyses demonstrate that there is no survival advantage for AA patients treated with radiation therapy and adjuvant PCV compared to either radiation therapy alone or radiation therapy and single agent BCNU. For patients with anaplastic oligodendroglioma (*oligo*) and anaplastic oligo-astrocytoma, on the other hand, the PCV chemotherapy regimen has been shown to be effective with response rates as high as 75%.^{7,15,30}

It is clear that chemotherapy for malignant astrocytomas is inadequate, hence the need to find new agents or combinations of agents that are unequivocal benefit. It is also clear that grading criteria need to be expanded to include genetic analyses and/or radiographic characteristics to better distinguish AA from GBM to enhance the credibility of survival data obtained in clinical trials. Finally, patients whose tumors may be responsive to chemotherapy need to be identified.

1.2 Temozolomide

Temozolomide is a cytotoxic alkylating agent with an acceptable toxicity profile and demonstrated clinical anti-tumor activity against malignant gliomas both at relapse and first diagnosis.

1.2.1 Chemical Characteristics

Temozolomide belongs to a group of compounds known as imidazotetrazinones. Its chemical name is 8-carbamoyl-3-methylimidazo [5,1-d]1,2,3,5-tetrazin-4 (3H)-one.⁴⁷

1.2.2 Mechanism of Action

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.¹⁴ 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 residues¹⁸ with additional alkylation occurring at the N7 position.²⁰

1.2.3 Pre-clinical Data

Temozolomide has exhibited antitumor activity against a range of mouse and human tumors.^{40, 47,48,51} Antitumor activity was shown to be schedule dependent confirmed in phase I testing.^{2, 11, 25} Temozolomide has been found to penetrate the blood brain barrier in both preclinical and phase I testing.^{1,4,5,37,39}

1.2.4 Phase I Clinical Experience

The pharmacokinetics, efficacy and toxicity profile of Temozolomide have been studied in several phase I clinical trials conducted in Europe by Schering-Plough and the Cancer Research Campaign (CRC).³⁴ Oral bioavailability was studied in five patients at a dose of 200 mg/m² and found to be complete.³⁴ Multiple dose pharmacokinetics were studied in one patient. Plasma levels were obtained on Days 1 and 5. No accumulation of drug was found. The AUC was 34.8 mg/h/L on Day 1 and 23.1 on Day 5.³⁴ The most common adverse events were nausea and 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 x 5 days. Extended phase I results were reported by the CRC in 1993 in 28 patients with recurrent malignant glioma.^{37,38} The initial dose was 150 mg/m²/day for 5 days 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 2 to 3 doses of Temozolomide prior to irradiation.

1.2.5 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 anti-emetics. 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 6 months. Median overall survival was 5.4 months. The 6-month death 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. 225 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). Twenty four percent 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.⁵⁸ Patients were treated with 200 mg/m² PO qd for five days q 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.

The phase II experience with single agent Temozolomide for patients with malignant gliomas has been favorable with response rates for patients with recurrent and newly diagnosed malignant astrocytomas at least comparable to those obtained using the nitrosoureas. Temozolomide is well absorbed after oral administration and is generally well tolerated. Myelosuppression, the dose limiting toxicity is tolerable and, importantly, is not cumulative, as are the nitrosoureas and Procarbazine.

1.2.6 Temozolomide/BCNU Combination Regimen

There is one on-going phase II clinical trial using the combination of Temozolomide and BCNU for patients with recurrent malignant glioma. In this study, Temozolomide is administered as a single p.o. dose two hours following BCNU every 6 weeks. The MTD and sequencing of drugs was established in a phase I clinical trial. Pharmacokinetic studies of Temozolomide were also performed during the first treatment cycle and shown to be unaffected by the treatment schedule. Phase II data are not yet available; however, in the phase I study, 7/33 patients with malignant glioma had a partial response defined as a 50% reduction in tumor size; 12 of 33 had stable disease (*privileged communication*). Toxicity was predominantly hematologic. There were three cases of pulmonary toxicity: two in patients with lung cancer metastatic to brain who received the MTD and one in a patient who received the dose and schedule one level above the MTD. A phase I trial is currently in progress using the established five-day p.o. schedule of Temozolomide and BCNU. The MTD for BCNU in this schedule is 200 mg/m² and Temozolomide 150 mg/m² is given on days 1-5 (*privileged communication*). Only anecdotal toxicity data for patients with malignant glioma are available from this trial. The rationale for the drug combination is clear, e.g. two active drugs given together are more efficacious than single agent therapy. Furthermore, it has been demonstrated that Temozolomide can deplete O6-alkylguanine-DNA acyltransferase (*AT*), the DNA repair enzyme, high levels of which are thought to contribute to glioma cell resistance to the nitrosoureas.²⁵

1.2.7 (8/15/02) Two pilot studies (*Arms 4 and 5*) of RTOG 98-13, enrolling 15 and 14 patients respectively, have been completed. On Arm 4, the median number of cycles was 5 (1-6). There were two grade 3 infections and one grade 4 infection, as well as one each of the following grade 3 toxicities noted: dyspnea, hyperglycemia, and dermatologic. More than 50% of the patients required dose reductions by the second cycle because of toxicity. One patient stopped all therapy; 2 patients stopped BCNU, and 1 patient stopped temozolomide because of toxicity. On the second pilot arm (*Arm 5*), there were five grade 3 hematologic toxicities (3 *thrombocytopenia* and 2 *neutropenia*), and three grade 4 toxicities (*neutropenia*). Two patients developed pulmonary toxicity by the second cycle, and the BCNU was discontinued in these patients. Nine patients required a dose reduction by the second cycle of therapy because of toxicity. Based on the toxicities seen in Arms 4 and 5, the proposed Arm 3 of the phase III component of the study (*RT, 59.4 Gy + BCNU, 150 mg/m² + Temozolomide, 150 mg/m²*) has been dropped; the study will randomize patients between radiation therapy and temozolomide (*Arm 1*) or radiation therapy and BCNU (*Arm 2*).

1.3 Summary (8/15/02)

We had proposed to conduct a three-arm phase I/III clinical trial to compare single agent BCNU, standard treatment for anaplastic astrocytoma, to both single agent temozolomide and the combination of temozolomide and BCNU. Although there is little phase I or II data available for the five-day temozolomide schedule and BCNU combination, all major phase II trials for temozolomide have used the five-day schedule based on extensive pre-clinical and phase I testing that demonstrated that drug efficacy was schedule dependent. To obtain additional toxicity data rapidly for the five-day temozolomide using the MTD that has been established and BCNU combination, the first 15 patients entered were placed on a pilot arm (*Arm 4*). The toxicity profile for this arm was unacceptable, and a subsequent group of 14 patients were treated on pilot Arm 5. Unfortunately, toxicity was again unacceptable; therefore, patients in the phase III component of the study will be randomized between the two arms of single agent BCNU versus temozolomide, and the third arm will be deleted.

Another important goal of this study is to better understand the biology of malignant astrocytomas. Grading criteria need to be expanded to include genetic analyses and/or radiographic characteristics to better distinguish AA from GMB to enhance the credibility of survival obtained in clinical trials. To this end, there will be central pathology review, central radiographic review and evaluation of pathologic specimens to identify molecular predictors of response to chemotherapy and survival, specifically 1p, 10q, 19q, p53 mutations, RB, CDKN2A and EGFR status, and Ki-67 proliferation index. Clearly, it would be desirable to be able to identify patient whose tumors may be responsive to chemotherapy.

2.0 OBJECTIVES (8/15/02)

- 2.1.1 To compare overall survival.
- 2.1.2 To compare time to tumor progression.
- 2.1.3 To compare the relative toxicities of the two drug regimens.
- 2.1.4 To correlate molecular analyses with Sections 2.1.1 and 2.1.2.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (6/23/03) (12/22/03)

- 3.1.1 Histologically-confirmed unifocal anaplastic astrocytoma by central review (*See Section 5.1*), or mixed oligodendroglial/astrocytic tumors where the oligodendroglial component is $\leq 25\%$. Patients with prior biopsy-proven low grade astrocytoma who now have a biopsy-proven anaplastic astrocytoma and have not been previously treated with either radiation or chemotherapy are eligible.
- 3.1.2 Karnofsky performance status ≥ 60 (*Appendix II*).
- 3.1.3 Adequate bone marrow reserve hemoglobin ≥ 10 grams, absolute neutrophil count $\geq 1500/\text{mm}^3$, platelets $\geq 150,000/\text{mm}^3$; liver function tests (AST/SGOT, alkaline phosphatase, total bilirubin) < 2 x upper limit of normal; serum creatinine < 1.5 x normal
- 3.1.4 Therapy must begin within 6 weeks after tissue diagnosis.
- 3.1.5 Patient must sign a study-specific informed consent form prior to randomization.

3.2 Ineligibility Criteria (8/17/01, 2/18/02, 12/22/03)

- 3.2.1 Major medical illnesses or psychiatric impairments, which in the investigator's opinion will prevent administration or completion of the protocol therapy and/or interfere with follow-up.
- 3.2.2 Any oligodendroglial component $> 25\%$
- 3.2.3 Tumor predominately located in the posterior fossa (*i.e. brainstem or cerebellum*).
- 3.2.4 Spinal cord tumors.
- 3.2.5 Evidence of spinal drop metastases or spread to non-contiguous meninges (*MRI of the spine not required in asymptomatic patients; patients will not be excluded based on pathologic evidence of local meningeal infiltration by underlying tumor*).
- 3.2.6 Prior malignancy (*excluding in situ carcinoma of the cervix or non-melanomatous skin cancer*) unless disease free for at least 5 years.
- 3.2.7 Prior radiation to the brain or head/neck.
- 3.2.8 Prior chemotherapy.
- 3.2.9 Active infectious process.
- 3.2.10 Pregnant or nursing. The effects of protocol agents in the fetus are unknown.
- 3.2.11 Inability or unwillingness to use effective contraception. This applies to both female and male patients.
- 3.2.12 Known or suspected hypersensitivity to one of the components of BCNU or temozolomide or to any other nitrosourea or Dacarbazine.
- 3.2.13 Any pre-existing lung disease that in the investigator's opinion will prevent administration or completion of therapy with BCNU.

4.0 PRETREATMENT EVALUATIONS (6/23/03, 12/22/03)

- 4.1 Central pathology review is mandatory to confirm eligibility. Stereotactic biopsies are permitted but the tissue sample must be considered adequate for an unequivocal pathologic diagnosis.
- 4.2 Preoperative MRI scan. A contrast-enhanced postoperative MRI must be obtained (*preferably within 72 hours after the surgical procedure*) to determine the extent of residual tumor prior to further treatment. If patient had only a stereotactic biopsy, then a post biopsy scan is not necessary. CT scans are allowed for patients who cannot undergo MRI. The same type of scan must be used throughout the protocol treatment period. (**TESTS AND SCANS MUST BE PERFORMED WITHIN 3 WEEKS PRIOR TO REGISTRATION**)

- 4.3 Complete history and physical examination (*including neurological examination*) with documentation of all signs and symptoms to determine the extent of residual tumor prior to further treatment
- 4.4 CBC with differential (*absolute granulocyte count*) and platelet count.
- 4.5 Electrolytes, glucose, BUN, serum creatinine, total bilirubin, SGOT, AST, alkaline phosphatase.
- 4.6 Pulmonary function tests (*PFTs*) and carbon monoxide diffusion capacity (*DLCO*).
- 4.7 Chest x-ray.
- 4.8 Pregnancy test for women of childbearing age (*within one week prior to study entry*).
- 4.9 Karnofsky Performance Status.
- 4.10 Mini-Mental Status Examination.

5.0 REGISTRATION PROCEDURES (6/23/03, 8/20/03)

- 5.1 **Central pathology review is mandatory prior to study entry to confirm eligibility. It should be initiated as soon as the diagnosis has been made. All slides for pre-entry review will be sent directly to the central reviewer and not through RTOG Headquarters. Same-day review cannot be guaranteed. See Section 10.0.**
- 5.2 Each institution must submit a Temodar™ Shipment Form (*Appendix VII*) to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Temodar™ Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of its first case (the shipment form is only submitted once). Allow adequate processing time (*7-10 days*) before calling to register your first case.
- 5.3 **RTOG Members (8/17/01)**
Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

5.4 SWOG Participants

- 5.4.1 **SWOG Member and CCOP Institutions**
Institutions will call the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 a.m. and 1:30 p.m. (*PT*) Monday through Friday, excluding holidays. The SWOG Statistical Center will confirm the eligibility criteria as per Section 3.1. The SWOG Statistical Center will then contact the RTOG Headquarters at 215-574-3191 to enter and randomize the patient after which the SWOG Statistical Center will contact the institution to relay the treatment assignment for that patient. RTOG Headquarters will forward a confirmation of treatment assignment to the SWOG Statistical Center for routing to the SWOG institution. Please note: Southwest Oncology Group institutions will follow their normal procedures for documentation of IRB approval.
- 5.4.2 **SWOG CCOP Institutions**
Institutions will call the Southwest Oncology Group CCOP Office at 206/652-CCOP (206/652-2267) between the hours of 7:00 a.m. and 1:30 p.m. (*PT*) Monday through Friday, excluding holidays. The SWOG CCOP Office will confirm the eligibility criteria as per Section 3.1. The SWOG CCOP Office will then contact the RTOG Headquarters at 215-574-3191 to enter and randomize the patient after which the SWOG CCOP Office will contact the institution to relay the treatment assignment for that patient. The RTOG Headquarters will forward a confirmation of treatment assignment to the SWOG CCOP office for routing to the SWOG CCOP institution. Please note: Southwest Oncology Group CCOP institutions will follow their normal procedures for documentation of IRB approval.

5.5 ECOG Institutions (6/23/03, 9/15/03, 12/22/03, 10/19/04)

- 5.5.1 **NOTE:** Each institution must submit a Temodar™ shipment form (*See Appendix VII*) to CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Institutional IRB approval must be obtained prior to submitting this form. Allow adequate processing time (*7-10 days*) before calling to register the first case.
- 5.5.2 **RANDOMIZATION ECOG INVESTIGATORS:**
Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.3. A. CTSU IRB Certification Form.

- Or
- B. HHS 310 Form.

Or

 - C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB.
- Full protocol title and number.
- Version Date
- Type of review (full board vs. expedited).
- Date of review.
- Signature of IRB official.

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp.

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00 am - 6:00 pm.

Patients must not start protocol treatment prior to randomization. Therapy should start within 6 weeks after tissue diagnosis.

5.5.3 **NOTE: Central pathology review is mandatory prior to study entry to confirm eligibility. See Section 10.0 for pre-registration pathology requirements.**

5.5.4 Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG webpage using the Web-based Patient Registration Program (<http://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's initials, chart number, social security number and demographics (sex, birth date, race, nine-digit zip code and method of payment)); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. After completing the checklist on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the RTOG directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

5.5.5 If a patient does not receive any protocol therapy, written notification and an explanation must be received at ECOG Headquarters (*who will route it to RTOG*) as soon as this has been determined. The Onstudy form (11) and Eligibility Checklist should also be submitted. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given protocol treatment, all forms must be submitted.

5.5.6 Additional Intergroup information is in Appendix VI.

5.6 **NCCTG Institutions (6/23/03, 9/15/03, 11/5/03)**

IRB approval(s) is required for each treating site. A signed Clinical Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2page.asp Guidelines can be found under the Quick Fact Sheets.

To register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the Randomization Center between 8 a.m. and 3:30 p.m. central time Monday through Friday.

At the time of registration/randomization, Randomization Center personnel will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (U.S.A. institutions only)

Upon confirmation of eligibility, the NCCTG Randomization Center will contact the RTOG to register the patient. The NCCTG Randomization Center will then contact the registering institution with the treatment assignment.

All investigators must be registered with CTEP, DCTD by the annual submission of the FDA Form 1572 and a current C.V. To obtain an NCI/CTEP investigator number, investigators should complete and submit (by US Mail or Express Courier, faxes are not acceptable) an FDA Form 1572, with an original signature, and a current curriculum vitae to the PMB at:

Pharmaceutical Management Branch, CTEP, DCTD, NCI
6130 Executive Boulevard, Room 7149
Rockville, MD 20852
Phone: 301-496-5725

A copy of this submission should be sent to the NCCTG Operations Office.

The FDA Form 1572, with instructions, is available on the NCI home page (<http://ctep.info.nih.gov>) or by calling PMB at 301-496-5725.

6.0 RADIATION THERAPY (all questions regarding treatment should be directed to the RTOG Study chairs)

6.1 Dose Definition and Schedule

Limited volume irradiation will be used for treatment in this protocol. Treatment will be given in 1.8 Gy fractions (to isocenter), 1 fraction per day, 5 days per week to a dose of 59.4 Gy in 33 fractions. The initial 50.4 Gy in 28 fractions will include the initial target volume (T2-MR plus 2 cm margin) or contrast-enhancing lesion +2.5 cm when no edema is present. The final 9 Gy in 5 fractions will include the boost volume (T1 enhanced MR plus 1 cm margin). See table below:

Volume	Includes	Daily Dose	Fraction #	Total Dose
Initial	T2-MR + 2 cm	1.8 Gy	28	50.4 Gy
Boost	T1 (Gad) MR + 1 cm	1.8 Gy	5	9.0 Gy
Total			33	59.4 Gy

6.2 Physical Factors (12/22/03)

Treatment will be delivered with megavoltage machines of energies ranging from 4 to 18 MV photons. Source skin distance for SSD techniques or source axis distance for SAD techniques must be ≥ 80 cm. 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.

6.3 Simulation, Immobilization, Localization

6.3.1 The patient may be treated in the supine or other appropriate position. Adequate immobilization and reproducibility of position will be ensured. The treatment volume for both the initial volume and the cone down volume will be based on MRI scan.

6.3.1.1 The post-operative MRI scan will determine the treatment volume for patients without complete tumor resection.

- 6.3.1.2** The pre-operative MRI scan will determine the treatment volume for patients without a post-operative MRI scan (*per Section 3.1.6.1*).
- 6.3.2** The initial treatment volume will include the T2 abnormality plus a 2 cm margin. If there is no surrounding edema, the initial treatment volume should include the contrast and noncontrast-enhancing lesion plus a 2.5 cm margin. The boost volume will include the contrast and noncontrast-enhancing lesion plus a 1 cm margin. If the tumor has been completely resected and the MR scan for RT planning is normal, the initial volume will be the surgical defect plus a 2 cm margin. The boost volume will be the surgical defect plus a 1 cm margin. The target volumes are to receive 95-105% of the prescribed dose.
- 6.4** **Dosimetry (8/15/02)**
Two sets of composite isodose distributions drawn in a plane containing the central axis, one showing the initial target volume and one showing the boost target 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:
- 6.4.1** If the initial target volume receives < 45.4 Gy or > 55.4 Gy, (*i.e.*, < 90% or > 110% of the prescribed total dose), a deviation unacceptable 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 deviation unacceptable will be assigned.
- 6.4.2** 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 variation acceptable 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 variation acceptable will be assigned.
- 6.4.3** 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.
- 6.5** **Dose Specification**
Doses are specified as the target dose that shall be prescribed to the isocenter of the target volume. For the following portal arrangements, the target dose shall be specified as follows:
- 6.5.1** For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
- 6.5.2** For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
- 6.5.3** For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
- 6.5.4** Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
- 6.5.5** The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots due to unacceptable dose inhomogeneity. However, if this technique is utilized the dose shall be specified at the center of the target area.
- 6.5.6** Other or complex treatment arrangements: at the center of the target area.
- 6.6** **Dose Limitation to Critical Structure (12/22/03)**
The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 54 Gy, the retina of at least one eye (*but preferably both*) to 50 Gy, and the brain stem to 60 Gy.
- 6.7** **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. Hematological toxicities should be rated on a scale of 0-5 as defined in the revised NCI Common Toxicity Criteria.
- 6.8** **Radiation Toxicities**
- 6.8.1** *Acute*
Expected acute radiation-induced toxicities include hair loss, erythema or soreness of the scalp, nausea and vomiting, dry mouth, altered taste, fatigue, or temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically.
- 6.8.2** *Early Delayed*
Possible early delayed radiation effects include lethargy, transient worsening of existing neurological deficits.
- 6.8.3** *Late Delayed*
Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, accelerated atherosclerosis, or radiation-induced neoplasms.

6.10.4 Unusually Severe

Unusually severe reactions should be noted and reported to the study chair. All early delayed or late delayed neurotoxicities must be documented and reported.

7.0 DRUG THERAPY (all questions regarding treatment or dose modifications should be directed to RTOG HQ)

RTOG Institutional Participation in Chemotherapy Studies Must be in Accordance with the Medical Oncology Quality Control Guidelines Stated in the RTOG Procedures Manual.

7.1 Treatment Plan (8/15/02, 12/22/03)

Patients should take BCNU and Temozolomide on consecutive days with no interruptions for weekends or holidays.

7.1.1 Arm 1: Temozolomide Schedule

Temozolomide: 200 mg/m² on days 1-5 of the first week of radiotherapy. Repeat every 28 days for a total of 12 cycles. Temozolomide will be given orally at least one hour prior to or one hour following food ingestion.

7.1.2 Arm 2: BCNU Schedule (8/17/01, 2/18/02)

7.1.2.1 BCNU (80 mg/m²) will be administered on days 1, 2, and 3 of the first week of radiotherapy and on days 56, 57, and 58. The BCNU administered on days 1, 2, and 3 of the first week of radiotherapy can be given any time on those days. It will then be administered every eight weeks for four more cycles for a total of 6 cycles (maximum BCNU dose 1440 mg/m²).

7.1.2.2 BCNU will be given as an intravenous infusion over 1-2 hours at a dose of 80 mg/m² per day for each 3-day course.

7.1.3 Arm 4: Temozolomide and BCNU Schedule (closed 3/15/01)

7.1.3.1 BCNU 200 mg/m² will be administered on day 1 of radiotherapy. Temozolomide 150 mg/m² daily will be administered daily on days 1-5 of the first week of radiotherapy. BCNU and Temozolomide will be repeated every six weeks for a total of six cycles (maximum total BCNU dose 1200 mg/m²).

7.1.3.2 BCNU will be given as an intravenous infusion over 3 hours.

7.1.3.3 Temozolomide is to be given two hours following BCNU infusion.

7.1.3.4 Temozolomide will be given orally at least one hour prior to or one hour following food ingestion.

7.1.3.5 Early stopping rule for Arm 4, phase I component: Arm 4 will be terminated if two or more of the first 15 patients develop grade 3 or worse pulmonary toxicity, or five or more patients develop a grade 4 thrombocytopenia (< 25,000 for 5 days) and grade 4 neutropenia (< 500/microl for 7 days) or grade 4 neutropenia of any duration with fever requiring hospital admission after one dose reduction of 50% in BCNU.

7.1.4 Arm 5: Temozolomide and BCNU Schedule (closed 1/25/02)

7.1.4.1 BCNU 150 mg/m² will be administered on day 5 of radiotherapy. Temozolomide 150 mg/m² daily will be administered daily on days 1-5 of the first week of radiotherapy. BCNU and Temozolomide will be repeated every eight weeks for a total of six cycles; BCNU will be given on day 5 of temozolomide in these cycles (maximum total BCNU dose 900 mg/m²).

7.1.4.2 BCNU will be given as an intravenous infusion over 3 hours.

7.1.4.3 Temozolomide is to be given two hours following BCNU infusion.

7.1.4.4 Temozolomide will be given orally at least one hour prior to or one hour following food ingestion.

7.1.4.5 Early stopping rule for Arm 5, phase I component: Arm 5 will be terminated if two or more of the 15 patients develop grade 3 or worse pulmonary toxicity, or five or more patients develop a grade 4 thrombocytopenia (< 25,000 for 5 days) and grade 4 neutropenia (< 500/microl for 7 days) or grade 4 neutropenia of any duration with fever requiring hospital admission after one dose reduction of 50% in BCNU.

7.2 Temozolomide (Temodar™) Information (IND #60,265)

7.2.1 Supply (6/23/03, 8/20/03)

Temozolomide is manufactured by Schering-Plough and will be supplied free of charge for this study. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. Temozolomide will be distributed by Biologics, Inc. The Study Agent Shipment Form must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case.

The patient-specific drug supply will not be shipped by Biologics, Inc. until the patient has been randomized. The shipment will be processed, using two-day express delivery, the next business day after the randomization of each patient assigned to the temozolomide treatment arms. Note: Biologics does not ship drug on Fridays. RTOG will notify Biologics, Inc. to initiate each of these shipments. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

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

Leigh Hancock, Clinical Trials Manager
Biologics, Inc.
625 Oberlin Road
Raleigh, NC 27605
(800) 850-4306 ext. 106
Fax (919) 546-9816
lhancock@biologicstoday.com

7.2.2 Pharmaceutical Data

Other Names: CCRG 81045; SCH 52365; M&B 39831, NSC 362856, methazolastone. 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.

7.2.3 Mode of Action

Alkylating agent of imidazotetrazinone class.

7.2.4 Storage and Stability

The capsules are packaged in 30 cc 28 mm-48- Type I amber glass bottles (30 capsules/bottle) and should be stored between 2 and 30 degrees Centigrade. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.

7.2.5 Temozolomide Toxicities

7.2.5.1 Hematological: Thrombocytopenia and leukopenia.

7.2.5.2 Gastrointestinal: Nausea, vomiting, anorexia.

7.2.5.3 Hepatic: Elevated liver enzymes (*reversible*)

7.2.5.4 Skin: Rash, alopecia

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

7.2.6 Dose Modifications/Treatment Delays (10/19/04)

TEMOZOLOMIDE DOSE MODIFICATION TABLE				
	ANC (mm³)		Platelets (mm³)	Modification
Nadir	≥ 750	or	≥ 75,000	100% dose
	250-749	or	25,000 –74,999	75%
	< 250	or	< 25,000	50%
At scheduled time of administration	≥ 1500	or	≥ 100,000	Dose modified for nadir only
	< 1500	or	< 100,000	Hold dose for 2 weeks*
* After 2 weeks	≥ 1500	or	≥ 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

* Repetition of severe marrow depression, persistent neutropenia (<1500/mm³) or thrombocytopenia (< 25,000/mm³) at time of treatment and after dose reduction will require contacting the chemotherapy study chair before any further chemotherapy. Further chemotherapy will be given only if there is joint agreement between the study chair and the individual investigator.

7.2.7 **(8/17/01)** Temozolomide will be discontinued at documentation of disease progression. Schering Plough will not supply temozolomide free of charge for patients who go off study (*per protocol definition*) for either progression or toxicity.

7.3 BCNU Information

7.3.1 Supply

BCNU (*bis-chlorethyl nitrosourea*) is available commercially.

7.3.2 Preparation

BCNU should be reconstituted by adding 3 ml of accompanying diluent (*absolute ethanol*), then 27 ml of sterile water for injection, USP. This results in a concentration of 100 mg/30 ml. For infusion, dilute total dose in 250 ml of 5% Dextrose in water, USP, or Sodium Chloride injection, USP in glass bottle. Severe local discomfort can occur especially during infusion in less than 100 ml of fluid. The final dosage form prepared in glass at 0.2 mg/ml is stable for 48 hours at 4°C and for eight hours at room temperature.

7.3.3 Discontinuation of BCNU

At documentation of progression, BCNU will be discontinued. At the discretion of the investigator, the patient may be treated with additional chemotherapy, biological therapy, surgery, or supportive care. Such therapy shall be documented in detail and reported to RTOG on the appropriate data forms.

7.3.4 BCNU Toxicity (8/17/01, 10/19/04)

7.3.4.1 Possible progressive pulmonary toxicity may occur with BCNU chemotherapy. The risks of developing pulmonary toxicity appear to increase sharply above a total cumulative dose of 1200-1500 mg/m². Pulmonary toxicity usually presents as progressive interstitial pneumonitis and interstitial fibrosis on chest x-ray. Worsening pulmonary function tests or progressive pulmonary symptoms should alert the investigator to consider stopping BCNU. **It is mandatory that BCNU be stopped at a maximum of 1440 mg/m² or 1 full year of therapy.** If symptoms or signs of BCNU pulmonary toxicities occur, chest x-ray and pulmonary function studies including DLCO should be obtained to document toxicity.

7.3.4.2 Toxicities may include myelosuppression which may be delayed and severe; mild to moderate nausea and vomiting 2-12 hours after administration; mild and reversible liver enzyme changes; alopecia; pain along the vein of injection; increased pigmentation along the vein of injection; pulmonary impairment; and very rarely renal impairment. See Section 7.4 for reporting adverse drug reactions.

7.3.5 Dose Modification (6/23/03)

7.3.5.1 BCNU dose is calculated upon actual weight and must not exceed 125% of ideal weight. Should the patient weigh more than 125% of ideal weight, the maximum BCNU dose is calculated based upon ideal body weight PLUS 25%.

7.3.5.2 There will be no dose escalation.

7.3.5.3 Dose reduction due to hematologic toxicity: The blood counts immediately prior to the next cycle of chemotherapy and the nadirs from the weekly CBC and platelets recorded in the previous cycle will both be examined to determine whether the next cycle of chemotherapy is to be given at a reduce dose. The dose modification will be as follows: (10/19/04)

BCNU DOSE MODIFICATION TABLE			
Nadir:			
<u>Absolute Neutrophil Count (ANC)</u>		<u>Platelets</u>	<u>Modification</u>
≥ 750	or	≥ 75,000	100% dose
250 < 750	or	25,000 < 75,000	75% dose
< 250	or	< 25,000	50% dose
At scheduled time of administration:			
<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	or	≥ 100,000	Dose modified for nadir only
< 1500	or	< 100,000	Hold dose for 2 weeks* and repeat
* After 2 weeks:			
<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	or	≥ 100,000	Dose modification for nadir only
1000 < 1500	or	75,000 < 100,000	75% dose
< 1000	or	< 75,000	Contact Chemotherapy Chairman before further chemo administration

- 7.3.5.4 Repetition of severe marrow depression, persistent neutropenia (<1500) or thrombocytopenia (< 25,000) at time of treatment and after dose reduction shall require contacting the chemotherapy chairman before any further chemotherapy. Further chemotherapy shall be given only if there is joint agreement between the Chemotherapy Study Chairman and the individual investigator.
- 7.3.5.5 When liver enzyme (*SGOT, SGPT or bilirubin*) level is greater than three times the upper limit of the institutional normal value, BCNU should be held until SGOT or SGPT drops to less than two times the upper limit of normal and bilirubin drops within the normal range. Then, BCNU should be administered at 50% of the previous dose level.
- 7.3.5.6 **When the DLCO is < 60%, BCNU will be discontinued, unless a reversible cause is found and the DLCO improves to ≥ 60%, in which case the BCNU can be restarted.**
- 7.3.5.7 **When the serum creatinine level is greater than 3 times the upper limit of normal value for the institution, BCNU will be held until the serum creatinine drops to less than 1.5 times the upper limit of normal. Then, BCNU should be administered at 50% of the previous dose level.**
- 7.3.5.8 All dose modifications made for nadir counts or counts at the time of administration must be maintained in all subsequent cycles of chemotherapy. Any subsequent modifications must be made on already reduced dose levels.

7.4 RTOG Members: Adverse Drug Reaction Reporting

- 7.4.1 The revised NCI Common Toxicity Criteria (*CTC*) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities and can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). This study will be monitored by the Clinical Data Update System (*CDUS*) Version 3.0. Cumulative CDUS date will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol, which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.
 - 7.4.1.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected (*phone report within 24 hours; written report within 10 days*).
 - 7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
 - 7.4.1.3 Any death on study if clearly related to the commercial agent(s).
 - 7.4.1.4 Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
 - 7.4.1.5 Any grade ≥ 3 pulmonary toxicity or grade ≥ 4 thrombocytopenia or neutropenia after one dose reduction of drug(s) must be called into RTOG HQ within 24 hours of discovery.
- 7.4.2 The completed FDA Form 3500 must be **mailed or faxed to ALL** the following addresses: (1/27/04, 10/19/04)

FDA	Investigational Drug Branch	RTOG Headquarters
MedWatch	P.O. Box 30012	1818 Market St., Suite 1600
5600 Fishers Lane	Bethesda, MD 20824	Philadelphia, PA 19103
Rockville, MD 20852	301-230-2330 (24 hrs.)	215-717-2762 (24 hrs.)
Fax 800-332-0178	Fax 301-230-0159	Fax 201-928-0153

- 7.4.3 Any death regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

7.5 SWOG Members: Adverse Event (AE)/Drug Reaction (ADR) Reporting for SWOG Institutions
AE/ADR Reporting should be based on the NCI Common Toxicity Criteria.

All Southwest Oncology Group (*SWOG*) investigators are responsible for reporting of adverse events/adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. SWOG investigators must:

Call the SWOG Operations Office at 210/667-8808 within 24 hours of any suspected adverse event deemed either drug- or treatment-related, or possibly drug- or treatment-related which meets these criteria:

- (a) Any AE/ADR which is life threatening (Grade 4) or fatal (Grade 5) and unknown. Any occurrence of secondary AML or MDS must also be reported.
- (b) Any increased incidence of a known AE/ADR which has been reported in the protocol.
- (c) Any AE/ADR which is fatal (Grade 5) and known.

Instructions will be given as to the necessary steps to take depending on whether the reaction was previously reported, the grade (*severity*) of the reaction, study phase, and whether the patient was receiving investigational agent. The SWOG Operations Office will immediately notify the RTOG Headquarters.

Within 10 days of the initial telephone report, the investigator must send the completed (*original*) Adverse Reaction Form for Investigational Drugs (*if the adverse event/reaction is attributable to the investigational agent*) or the FDA 3500 Form (*if the adverse event/reaction is attributable to the commercial agents*), to the NCI:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824**

In addition, within 10 days the investigator must send:

- a copy of the above report,
- copies of prestudy forms
- copies of treatment and toxicity forms from prestudy through event,
- documentation of IRB notification, to the following address:

**ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217**

At the SWOG Operations Office a multilayered review will be performed and pertinent findings and supporting documentation will be forwarded to the RTOG Headquarters, NCI, study coordinator, and SWOG Statistical Center.

7.6 Adverse Event Reporting for ECOG Investigators (6/23/03, 10/19/04)

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the RTOG reporting guidelines in section 7.4 and Appendix V. Both 24 hour and written/electronic adverse reports should be made directly to the RTOG according to the instructions in that section.

Reporting of AML/MDS

	NCI/CTEP Secondary AML/MDS Report Form ¹
AML/MDS	X

¹To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and RTOG accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

ECOG Telephone Number: (617) 632-3610

ECOG Fax Number: (617) 632-2990

ECOG Mailing Address:

ECOG Coordinating Center

FSTRF

ATTN: Adverse Event

900 Commonwealth Avenue

Boston, MA 02215

NCI Fax Number: (301) 230-0159

NCI Mailing Address:

Investigational Drug Branch

P.O. Box 30012

Bethesda, MD 20824

FDA Fax Number 1-800-332-0178

FDA Mailing Address:

Medwatch

5600 Fishers Lane

Rockville, MD 20852-9787

RTOG Headquarters Mailing Address:

AML/MDS Report

1818 Market Street

Philadelphia, PA 19103

7.7 NCCTG Members: Adverse Drug Reaction Reporting (6/23/03)

This study will utilize the Common Toxicity Criteria (*CTC*) version 2.0 for adverse event monitoring and reporting. The *CTC* version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm). All appropriate treatment areas should have access to a copy of the *CTC* version 2.0.

Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the *CTC*. Next, determine whether the event is expected or unexpected (*refer to protocol and/or product literature*) and if the adverse event is related to the medical treatment or procedure. With this information, determine whether an adverse event should be reported as an expedited report or as part of the routinely reported clinical data.

Expedited adverse event reporting requires submission of a written report to the NCCTG Operations Office. Expedited reports are to be completed within the time frames specified below. All expedited adverse event reports should also be submitted to the local Institutional Review Board (*IRB*).

Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite – The adverse event *is clearly related* to the agent(s).

Probable – The adverse event *is likely related* to the agent(s).

Possible – The adverse event *may be related* to the agent(s).

Unlikely – The adverse event *is doubtfully related* to the agent(s).

Unrelated – The adverse event *is clearly NOT related* to the agent(s).

	Grade 3, 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE ¹	Secondary AML/MDS ²
FDA Form 3500 (MedWatch) to NCCTG within 24 hours ³	X	X	
NCI/CTEP Secondary AML/MDS Report Form to NCCTG within 15 working days ⁴			X

1. Any increased incidence of a known AE that has been reported in the package insert or the literature, including adverse event resulting from a drug overdose.
2. Reporting for this AE required during or after treatment.
3. Fax to the NCCTG Operations Office, Fax 507-284-1902. NCCTG will forward the report to RTOG (Fax: 301-230-0159) within 24 hours of receipt. RTOG is responsible for reporting to Schering-Plough, FDA, and NCI.
4. Fax or mail to the NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax 507-284-1902. NCCTG will forward the report to RTOG. RTOG is responsible for reporting to Schering-Plough, FDA, and NCI as applicable.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Dexamethasone

9.1.1 Use

Dexamethasone may be used as required to control CNS symptoms due to tumor-associated or radiation-associated cerebral edema, but whenever possible should be tapered and stopped. Steroid doses will be recorded at time of entry onto the protocol and at specified times during and after treatment. Investigators should avoid radical changes in steroid dose during periods of response evaluation so as not to complicate response assessment. In patients who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice.

9.1.2 Toxicity

Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, peptic ulcer, skin changes (*thinning*), convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic changes.

9.1.3 Pharmaceutical Data

- **Formulation:** Dexamethasone is available in a variety of potencies in capsule or tablet form.
- **Storage and Stability:** Dexamethasone is to be stored at room temperature.
- **Administration:** The drug is administered orally or intravenously.

9.2 Other Drugs

Other drugs including anticonvulsants and pain medications may be given at the discretion of the patient's oncologist but should be recorded on a flow sheet. No other treatment specifically for anaplastic astrocytoma should be given until a recurrence is detected.

10.0 PATHOLOGY (RTOG and SWOG Members) (6/23/03)

10.1 Central pathology review

Central review is mandatory prior to study entry to confirm eligibility. It should be initiated as soon as the diagnosis has been made. All slides for pre-entry review will be sent directly to the central reviewer and not through RTOG Headquarters. Central review of slides will be completed within a few days of arrival. Immediate review, on the day of arrival, cannot be guaranteed.

- 10.2** To be eligible for this study, the patient must have an anaplastic astrocytoma, WHO grade III or IV or mixed oligodendroglial/astrocytic tumors if the oligodendroglial component is less than 25%. Mitotic activity, nuclear pleomorphism, and increased cellularity should be present. Microvascular proliferation and necrosis must be absent.

- 10.3** The following materials will be required for central review of eligibility prior to study entry:
- 10.3.1** PreRandomization Pathology Submission Form. See Appendix III.
- 10.3.2** Surgical pathology report.
- 10.3.3** All prepared H&E stained slides that were used for diagnosis.
- 10.4** The institutional research associate will initiate the PreRandomization Pathology Submission Form. The form will be submitted to the primary pathologist with the surgical pathology report when requesting the slides.
- 10.5** The primary pathologist will complete the “Local Pathology Review” section of the PreRandomization Pathology Submission Form and return it to the research associate along with the slides and the surgical pathology reports. The research associate will check the form for completeness and send the materials in Section 10.3 to:

Ken Aldape, M.D.
Department of Pathology, Box 85
UT MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
(713) 792-7935
FAX (713) 745-1105
kaldape@mdanderson.org

- 10.6** After the pathology materials have been reviewed, Dr. Aldape will call the institution notifying them whether or not the case is eligible for randomization. This will be confirmed by fax. **Same day review cannot be guaranteed.**
- 10.6.1** If the patient enters the study, the patient's RTOG case number will be added to the PreRandomization Pathology Submission Form by the research associate. A copy of the completed form will be sent to RTOG. 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.
- 10.6.2** If the patient does not enter the study, all materials will be returned to the submitting institution.
- 10.7** After randomization, the institution entering the patient will be required to send the following for molecular analysis:
- 10.7.1** Pathology Submission Form;
- 10.7.2** Representative paraffin block(s) are preferred for molecular analysis. If a representative paraffin block is not available for distribution, then five to ten representative slides of unstained tumor sections should be submitted;
- 10.7.3** In addition, One serum separator tube of blood preferably frozen or on ice pack/wet ice if freezing is not possible will be required for molecular analysis. Blood may be drawn before or after start of protocol treatment; however, a pre-treatment blood draw is preferable.
- 10.7.4** Materials must be shipped to Dr. Aldape (Section 10.5) in an appropriate container between Monday and Thursday for delivery between Tuesday and Friday. Do not send samples on Friday or on the day before a holiday. Samples may be sent by Air Express, Federal Express or another appropriate carrier for overnight delivery. Notify Dr. Aldape by fax of pending deliveries.
- 10.7.5** Any questions regarding blood samples and shipping should be directed to Dr. Aldape per Section 10.5.
- 10.7.6 Reimbursement (12/22/03, 10/19/04)**
 RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue, \$200 per case for a block or core of material and \$100 per case for unstained slides. Once materials have been shipped to the appropriate institution, an invoice with the RTOG study and case number and your institutional name and address should be sent to RTOG Headquarters. The invoice should be mailed to the American College of Radiology, Clinical Trials Administration, 1818 Market Street, Suite 1600, Philadelphia, PA 19103, Attn: Linda Bomba. This does not apply to the pre-randomization central pathology review. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.8 ECOG Investigators

10.8.1 Pre-Randomization

Central pathology review is mandatory prior to study entry to confirm eligibility. Five to ten stained slides confirming the presence of astrocytic tumor containing mitotic figures will be required to confirm eligibility. The slides, along with the completed ECOG Pathology Material Submission Form (#638), RTOG PreRandomization Pathology Submission Form, and surgical pathology report should be submitted as soon as diagnosis is made to Dr. Ken Aldape, Department of Pathology, Box 85, M.D. Anderson Cancer Center, Houston, TX 77030. Copies of the ECOG Pathology Material Submission Form (#638), RTOG PreRandomization pathology report, and surgical pathology report should also be submitted to the ECOG Pathology Coordinating Office. After the pathology materials have been reviewed, Dr. Aldape will call the institution notifying them whether or not the case is eligible for randomization. This will be confirmed by fax. If the patient enters the study, the RTOG case number will be added to the Pre-Randomization Pathology Submission Form. A copy of the completed form will be sent to ECOG's Coordinating Center for routing to RTOG. All material will be returned to the submitting institution along with all slides except the one(s) selected by the neuropathologist for the study files.

10.8.2 After Randomization (6/23/03)

Representative paraffin block(s) are preferred for molecular analysis. If a representative paraffin block is not available for distribution, then five to ten representative slides of non-heated, unstained tumor sections will be used. In addition, one serum separator tube of blood frozen if possible, or on ice pack/wet ice, will be required for molecular analysis. The blood may be drawn after the start of study treatment, however a pre-treatment blood draw is preferable. The blood must be shipped directly to Dr. Ken Aldape, while the slides, along with the completed ECOG Pathology Material Submission Form (#638) and the institutional pathology report should be submitted to the ECOG Pathology Coordinating Office within two weeks of study entry. Materials shipped directly to Dr. Aldape must be sent between Monday and Thursday for overnight delivery between Tuesday and Friday. If insufficient tissue is available following diagnostic pathology to provide the paraffin block, a letter stating this must be sent to the ECOG Pathology Coordinating Office within 6 months of patient registration. The slides/blocks and original forms should be sent to the: ECOG Pathology Coordinating Office, Robert H. Lurie Comprehensive Cancer Center of Northwestern University Medical School, Olson Pavilion, Room 8501, 710 North Fairbanks Court, Chicago, IL 60611. Include both the ECOG and RTOG protocol number and patient number. The ECOG Pathology Coordinating Office will forward the slides (*or blocks*) to RTOG. A copy of the completed submission forms will be sent to the ECOG Coordinating Center by the Pathology Coordinating Office. The submitting pathologist should be informed that the blocks submitted for this protocol will be banked for future laboratory studies, and therefore, will not be returned to the submitting institution unless requested. In order to facilitate tissue collection, ECOG is requesting that, when possible, extra blocks of tumor be made for patients entering the study.

RTOG will reimburse submitting institutions for cutting slides and shipping costs if proper materials are submitted. See Section 10.7 for details.

10.9 NCCTG Institutions

10.9.1 Pre Study Entry

Per Section 10.1, central pathology review is mandatory prior to study entry and patient's tumor must meet the requirements as stipulated in Section 10.2. Central pathology review (*see Sections 10.3 – 10.6.2*) [**representative blocks/slides only**] will be performed by Dr. Ken Aldape.

10.9.2 After Randomization (6/23/03)

10.9.2.1 The institution entering the patient will be required to send the following to the NCCTG Pathology Coordinator, NCCTG Operations Office, Plummer 4, 200 1st Street, SW, Rochester, MN 55905, where they will be catalogued. The NCCTG Operations Office will forward the material to Dr. Wilma Lingle's laboratory, Mayo Clinic Rochester. Dr. Lingle will then forward the appropriate material to Dr. Ken Aldape.

- Pathology report
- RTOG Pathology Submission Form
- Paraffin block(s) with tumor present
- Representative unstained slides (*if blocks are not available for distribution*)

Each block(s) or slide(s) should be labeled with the NCCTG membership name, study patient number, patient's initials, protocol number, surgical accession number, and source (*e.g., primary, nodal*).

Material not used for the study will be stored for future research of astrocytoma. If there is an insufficient amount of tissue available, a letter from the pathologist stating such must be submitted to the NCCTG Operations Office.

10.9.2.2 Two yellow-topped (*ACD, Solution A*) standard-sized tubes of blood on ice pack or wet ice within 24 hours. Blood may be drawn before or after start of protocol treatment; however, a pre-treatment blood draw is preferable.

Materials must be shipped to Dr. Wilma Lingle, Tissue Acquisition and Cellular/Molecular Analysis Shared Resource laboratory, Guggenheim 1036, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Attention: Biospecimen Acquisition Specialist, who will process the sample and forward it to Dr. Wilma Lingle's laboratory. Ship materials in an appropriate container between Monday and Thursday for delivery between Tuesday and Friday. **Do not send samples on Friday or on the day before a holiday.** Samples may be sent by Air Express, Federal Express or another appropriate carrier for overnight delivery. Each institution will be responsible for assembling and shipping their own kit(s). **NCCTG will not be providing kits.**

Dr. Lingle will catalogue the samples, retain one tube of blood for future research of astrocytoma, and forward the remaining tube of blood to Dr. Ken Aldape. RTOG will reimburse submitting institutions for cutting slides and shipping costs if proper materials are submitted. See Section 10.7.6 for details.

Any questions from NCCTG members regarding blood samples and shipping should be directed to Linda S. Long, (507) 266-3853.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (12/22/03, 10/19/04)

Required	Pre-Treatment Evaluation	Each Week During RT	Before Each Course of Chemo	Followup Per Section 12.1
Physical Exam, KPS	X ^{a,d}		X	X
Neurologic Exam	X	X	X	X
CBC w/Diff, Platelets	X	X	X ^b	
Sodium, Potassium, CO ₂ , Calcium	X		X	
Serum Creatinine, BUN	X		X	
Required	Pre-Treatment Evaluation	Each Week During RT	Before Each Course of Chemo	Followup Per Section 12.1
Alkaline phosphatase, SGOT/AST, total bilirubin	X		X	
Chest X-Ray	X			X ^f
Anticonvulsant Levels	X		X	X
MRI or CT Brain/contrast ^c	X ^c		X ^c	X ^c
Pregnancy Test	X ^g			
Mini Mental Exam	X			X ^d
PFT and DLCO	X		X ^e	

- a. A complete history and physical including documentation of all measurable disease as well as signs and symptoms must be performed prior to study entry.
- b. CBCs (*with differential and platelet count*) required for study treatment must be done < 24 hours prior to the treatment cycle.
- c. Preoperative MRI; MRI of the brain should be performed post-operatively within 72 hours of surgery, following completion of radiation therapy but just prior to chemotherapy, then q 2 months. MRIs should be obtained sooner if there is a change in clinical status. CT scans allowed for patients who cannot undergo MRI—same type of scan must be used throughout protocol treatment..
- d. KPS and MMSE will be done pretreatment, then with every follow-up.
- e. If symptoms or signs of BCNU pulmonary toxicities occur, chest x-ray and pulmonary function studies including DLCO should be obtained to document toxicity. **(8/17/01, 12/22/03)**
- f. Every 3 months in year 1; q 6 months in year 2.
- g. As applicable, within 1 week prior to study entry.

11.2 Imaging (12/22/03, 10/19/04)

- 11.2.1 Central imaging review will be performed as an adjunct to histopathologic diagnosis and for the purposes of determining response rate and time to tumor progression.
- 11.2.2 A contrast enhanced MRI or CT scan must be obtained (preferably within 72 hours after the surgical procedure) to determine the extent of residual tumor prior to further treatment.
- 11.2.3 All MR examinations should include short TR/TE images with and without contrast as well as a long TR/short TE or FLAIR sequence, and a long TR/TE sequence (*T2*) all in the same imaging plane.
- 11.2.4 Central imaging review will be performed by Dr. Carol Dolinskas.

11.3 Criteria for Evaluation and Endpoint Definitions (2/18/02)

11.3.1 Survival

The duration of survival will be from the date of randomization until death.

11.3.2 Response Rate

11.3.2.1 Complete Response (CR)

Total radiographic disappearance of brain tumor in conjunction with stabilization of the neurological examination off glucocorticoids.

11.3.2.2 Partial Response (PR)

Greater than 50% decrease in size of lesion radiographically in conjunction with improvement or stabilization of the neurological examination without an increase in glucocorticoid dose.

11.3.2.3 Stable Disease (SD)

A zero to 25% or zero to 50% decrease in size of the lesion radiographically in conjunction with improvement or stabilization of the neurological examination.

11.3.2.4 Progressive Disease (PD)

A radiographic increase in size of the lesion by > 25%, recurrence of the study lesion, or the development of new lesions. Time to progression is defined as time from initial diagnosis to tumor progression. Disease progression will be confirmed by imaging. Patients should undergo stereotactic biopsy in an effort to distinguish tumor from radiation necrosis.

11.3.3 Cause of Death

11.3.3.1 Neurological Death

Patients will be considered to have died neurological deaths if they have progressive neurological disease consisting of expanding intracranial masses, CNS hemorrhages, or hydrocephalus resulting in herniation.

11.3.3.2 Non-neurological Death

Death not due to the neurologic disease as defined in Section 11.3.4.1, will be considered the cause of death, if in neurologically stable patients, fatal infections, extracranial hemorrhage, or vital organ failure develops.

11.4 Patient Assessment

Measures to be assessed will include results of the mini-mental status examination (*MMSE*), changes in performance status, steroid dependence, radiographically-documented progression or recurrence of brain tumor, length of survival, and cause of death.

11.5 Period to Follow Patients

All patients will be followed for evidence of neurological progression of symptoms and evidence of treatment failure. Patients who show 1) objective evidence of progression or reappearance of brain tumor, or 2) progression of hard neurological signs will be reevaluated at that time. If progression or recurrence is

detected, further treatment may be given, consisting of surgery, additional radiation therapy, and/or chemotherapy at the discretion of the physicians involved in the patient's care.

11.6 Criteria for Removal from Protocol Treatment (8/17/01)

- 11.6.1 Unacceptable toxicity
- 11.6.2 The patient may withdraw from the study at any time for any reason.
- 11.6.3 **Schering Plough will not supply temozolomide free of charge for patients who go off study (per protocol definition) for either progression or toxicity.**

12.0 DATA COLLECTION (12/22/03, 10/19/04)

(RTOG, 1818 MARKET STREET, PHILADELPHIA, PA 19103, FAX# 215/928-0153)

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>	
Pre Randomization Pathology Submission Form (P4)	Within 2 weeks of study entry	
Initial Evaluation Form (I1)		
Pathology Report (P1)		
Pathology Slides (<i>unstained</i>)/Blocks (P2)		
See Section 10.7		
Pre-op and post-op MRI Scan (MR) and Reports (ME)	Within 1 week of RT end	
Baseline Mini Mental Status (MS)		
<u>Final Dosimetry Information:</u>		
Radiotherapy Form (T1)		
Daily Treatment Record (T5)		
Isodose Distribution (T6)		
Calculation Form (TL)		
External Beam Films (<i>simulation and portal</i>) (TP)		
MRI Scan (MR)		For grade ≥ 3 neuro-toxicity and for progression. See Section 12.2 for submission details.
MRI Report (ME)		
Treatment Summary (TF)	Monthly x 12	
Initial Follow-up (FS)	At 3 months from treatment start	
Follow-up Form (F1)	Every 3 months for 1 year; q 6 months x 2 years, then annually. Also at progression/relapse and at death. (F1 only)	
Mini Mental Status (MS)		
Autopsy Report (D3)	As applicable	

12.2 Dosimetry and Film Submission

- 12.2.1 **Items will be sent directly to RTOG Headquarters by all Groups.**
- 12.2.2 MRI scans and reports must be submitted to RTOG within 2 weeks of scan date.
- 12.2.3 Subsequent MRI scans and MRI reports, other than the pre-entry, should be forwarded to RTOG Headquarters **only** in the event of a suspected ≥ 3 neuro-toxicity and/or progression.

12.3 ECOG, SWOG AND NCCTG DATA SUBMISSION (6/23/03)

- 12.3.1 *ECOG:* The original data forms as listed in Section 12.1 should be submitted to the ECOG Coordinating Center, FSTRF, ATTN: DATA, 900 Commonwealth Avenue, Boston, MA 02215. Include the RTOG and ECOG study and case numbers. The ECOG Coordinating Center will forward the forms to RTOG. ECOG members should **NOT** send forms directly to RTOG.

- 12.3.2** SWOG:
 SWOG Member and
 CGOP Institutions
- Southwest Oncology Group Statistical Center
 Fred Hutchinson Cancer Research Center
 1100 Fairview Avenue, North, MP-557
 P.O. Box 19024
 Seattle, WA 98109-1024
- SWOG CCOP Institutions
- SWOG CCOP institutions should submit two copies of data forms as listed in this section at the required intervals to:
 Cancer Research and Biostatistics (CRAB)
 ATTN: SWOG CCOP Office
 1100 Olive Way, Suite 1150
 Seattle, WA 98101-1892

- 12.3.3** NCCTG (6/23/03, 10/19/04)
 Data forms are to be submitted to:

RTOG Headquarters
 1818 Market Street
 Philadelphia, PA 19103
 (Fax# 215-928-0153)

- 12.3.4** **Both the ECOG or SWOG or NCCTG and RTOG assigned case and study numbers must be recorded on all items submitted.** Unidentified data will be returned.

- 12.3.5** **Request for Study Information and Forms Request:**

Requests for additional information or clarification of data will be routed through ECOG/SWOG/NCCTG for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically (*generally two times per year*) computer generated lists identifying delinquent material are prepared and are routed through ECOG/SWOG/NCCTG for distribution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (8/15/02)

- 13.1.1** Overall survival.
13.1.2 Time to tumor progression.
13.1.3 Relative toxicities of the two regimens.
13.1.4 Correlate molecular analyses with Sections 13.1.1 and 13.1.2.

13.2 Sample Size (8/15/02)

13.2.1 Survival

The primary endpoint of this study is survival. The standard arm is radiotherapy (RT) plus BCNU. The experimental arm is: RT and temozolomide (Tem). Assuming that the MST for RT+BCNU is 36 months and the RT and Tem arm has a MST of 54 months, then a sample size of 216 evaluable patients per arm will provide overall statistical power of 90% with a one-sided significance level of 0.05. Since it is expected that 5% of the patients will be ineligible then **a total of 454 randomized patients will be required.**

According to Scott et al.⁵⁹ and Curran et al.⁹ the recursive partitioning analysis classes are prognostically important. Based upon eligibility criteria, patients may be in RPA classes I-IV which have decreasing estimated MST from 58.6 to 11.1. The distribution of patients by RPA class will affect the expected number of deaths during the study. It is assumed that 67% of the patients will be in class I, 25% in class III, and 8% in classes II and IV combined. If the percentage of RPA class II patients in the study sample is substantially higher than 25%, then the MST will be lower than 36 months, or if the percentage of RPA class I patients is higher than 75%, then the MST will be higher than 36 months. In either case the sample size may need to be adjusted. **(8/17/01, 2/18/02)**

13.2.2 Molecular Analyses

Cairncross et al. indicated that patients with chromosome 1p loss had a 17-fold decrease in death rate compared to patients with chromosome 1p.⁸ Patients with chromosome 19q loss had a 4-fold decrease in death rate compared to patients with chromosome 19q. These factors along with CDKN2A will be

examined for their association with survival. Assuming only 400 patients have sufficient pathology materials for assessment. If 50% of the patients have chromosome 19q loss then this study will have 80% power to detect at least a 33% improvement in death rate. If 33% of the patients have chromosome 19q then this study can detect at least a 38% improvement in death rate with 85% power.

13.2.3 Phase I Arm (8/17/01)

Prior to initiating randomization, 15 patients will be accrued to the RT+Tem+BCNU arm. A 20% rate of grade 3 or higher pulmonary toxicities or a 40% rate of grade 4-5 thrombocytopenia and neutropenia is considered unacceptable for the RT+Tem+BCNU arm. In order to ensure that the 80% confidence interval excludes the unacceptable toxicity rates then 15 patients will be accrued. If 2 or more patients in the first 15 experience a grade 3 or higher pulmonary toxicity; or 5 or more patients experience a grade 4-5 thrombocytopenia/neutropenia then the RT+Tem+BCNU arm will be discontinued.

Fifteen patients were accrued to the RT+Tem+BCNU arm and the above number of dose limiting toxicities was not exceeded; however, a sufficient number of patients had dose reductions to cause changes. The eligibility criteria were also changed in Section 3. Therefore, an additional 15 patients will be accrued to a Phase I arm to assess the tolerability. The same criteria for dose limiting toxicities will be used as stated above.

13.3 Patient Accrual (8/15/02)

Initially, 15 non-randomized patients will be accrued to the RT+Tem+BCNU arm. Accrual will be suspended for 3 months to assess morbidity. If the rate of grade 3 or higher pulmonary toxicity and grade 4-5 thrombocytopenia/neutropenia is acceptable then an additional 454 patients will be randomized to the two treatment arms discussed in Section 13.2. The patient accrual is projected to be 12 cases per month based upon accrual rates to RTOG 94-04. At that rate, it will take 38 months to reach the required total accrual of 454 cases. If the average monthly accrual rate is less than 6 patients, the study will be re-evaluated with respect to feasibility.

13.4 Randomization

Patients will be randomized according to a permuted block design, balancing by institution within strata. The randomization will be stratified by age (<50 vs ≥50), KPS (60-80 vs. 90-100), and prior surgery (*resection vs. biopsy*). These stratification factors will ensure balance by RPA classes as well.

13.5 Analyses Plans

13.5.1 Analysis of Phase I Patients

An analysis of the 15 non-randomized patients enrolled on the RT+Tem+BCNU arm will proceed after all patients have been on study for a minimum of 3 months. This analysis will pertain to treatment morbidity only. The purpose of this analysis is to determine the treatment arms available for the randomized phase of this study. Only eligibility, pretreatment characteristics, treatment morbidity, and treatment delivery will be reported on these patients.

13.5.2 Interim Analyses

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

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities.
- d) The distribution of patients by pretreatment characteristics including RPA classes.

13.5.3 Interim Analyses of Endpoints (8/15/02)

There will be three interim analyses of the primary study endpoint (*survival*). The interim analyses will proceed according to the following table.

Cumulative Events	Significance Level
63	.0041
126	.0158
188	.0285

If a significance level is smaller than the H₀ values listed then the null hypothesis will be rejected. These significance levels were calculated to ensure an overall significance level of 0.05. There will be two stochastic analyses: at 50% accrual and 75% accrual. If the any stochastic analysis indicates less than 15% power to observe the alternative hypothesis then the study will be recommended to be closed. The results of these interim analyses will only be reported, in a blinded fashion to the RTOG Data Monitoring Committee (DMC). A report with recommendations will be given to the study chairman.

Any problems or recommendations identified by the DMC, not results, will be reported to the Brain Committee, which is responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.5.4 Analysis for Reporting the Initial Treatment Results (8/15/02)

This analysis will be undertaken when all patients have been potentially followed for a minimum of 36 months or a maximum of 251 deaths. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables by treatment arm;
- d) observed results with respect to the endpoints described in Section 13.1.

13.5.4.1 Survival (8/15/02)

RT+BCNU will be compared to RT+Tem. A significance level of .0405 (*one-sided*) will be used, adjusting for prior analyses. Analyses within RPA classes, or other prognostic groups, may be performed if there are sufficient numbers of patients.

13.5.4.2 Tumor Progression (8/15/02)

Survival is made up of two components: time spent without tumor progression and time spent with tumor progression. For this reason, time to tumor progression is correlated with survival. We expect the results to be closely reflective of survival. Although, not all patients will have documented tumor progression at death or during survival which may account for differential outcome. Analyses within RPA classes, or other prognostic groups, selecting the best treatment may be performed if there is sufficient numbers of patients.

13.5.4.3 Toxicity

Overall toxicity will be compared across treatments. The comparison will be performed using the Pearson chi-square test.

13.5.4.4 Molecular Analyses

Pathologic samples will be analyzed for chromosomes 1p and 19q and CDKN2A. The distribution of the outcome of molecular analyses will be examined by treatment arm to identify any imbalance. If there is no imbalance then the treatment arms will be collapsed and survival and time to tumor progression will be compared by the groups identified by Cairncross et al.⁸ These groups will also be correlated with other pretreatment characteristics.

13.6 Inclusion of Women and Minorities (8/17/01)

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.⁹ Since there are no publications found to support a possible interaction between different radiation therapy schedules and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

Planned Gender and Minority Inclusion (8/15/02)

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	3	18	16	3	170	0	210
Male	0	3	28	16	3	223	0	273
Total	0	6	46	32	6	393	0	483

REFERENCES (8/15/02)

1. Baker SD, Wirth M, Statkevich P, et al. Absorption, metabolism and excretion of C- Temozolomide in patients with advanced cancer. *Am Soc Clin Oncol, ASCO, 33rd Annual Meeting, Denver, CO, May 17-20, 1997; 16:214.*
2. Brada M, Moore S, Judson I, Batra VJ, Quartey P, Dugan M. A phase I study of SCH 52365 (Temozolomide) in adult patients with advanced cancer. *Am Soc Clin Oncol, ASCO, 31st Annual Meeting, Los Angeles, CA, May 20-23, 1995; 14:470.*
3. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Schold SC. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet 1995; 345:1008-1012.*
4. Brock CS, Matthews JC, Brown G, Osman S, Luthra SK, Brady F. Temozolomide uptake in human astrocytomas demonstrated in vivo. *Am Soc Clin Oncol, ASCO, 33rd Annual Meeting, Denver, CO, May 17-20, 1997; 16:231.*
5. Brock CS, Matthews JC, Brown G, Luthra SK, Brady F, Newlands ES, Price P. The kinetic behavior of Temozolomide in man. *Am Soc Clin Oncol, ASCO, 32nd Annual Meeting, Philadelphia, PA, May 18-21, 1996; 15:475.*
6. Burger PC, Heinz ER, Shibata T, et al. Topographic anatomy and CT correlations in the untreated glioblastoma multiforme. *J Neurosurg 1988; 68:698-704.*
7. Cairncross JG, Macdonald DR: Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol 23: 460-464, 1988.*
8. Cairncross, GJ, Louis, DN., et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendroglioma. *J Natl Cancer Inst. (In press).*
9. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman, M, Asbell SO, Krisch RE, Nelson DF. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst 1993; 85:704-710.*
10. Curran WJ, Scott CB, Horton J, Nelson JS, Weinstein AS, Nelson, DF, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Powlis WD. Does extent of surgery influence outcome for astrocytoma with atypical or anaplastic foci (AAF)? A report from three Radiation Therapy Oncology Group (RTOG) trials. *J Neuro Oncol 1992; 12:219-227.*
11. Eckardt JR, Weiss GR, Burris HA, et al. Phase I and pharmacokinetic trial of SCH52365 (Temozolomide) given orally daily x 5 days. *Am Soc Clin Oncol, ASCO, 31st Annual Meeting, Los Angeles, CA, May 20-23, 1995; 14:484.*
12. Fine HA, Dear KBG, Loeffler JS, et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer 1993; 71:2585-2597.*
13. Ganju V, Jenkins RB, O'Fallon JR, Scheithauer BW, Ransom DT, Katzmann JA, Kimmel DW. Prognostic factors in gliomas: a multivariate analysis of clinical, pathologic, flow cytometric, cytogenetic, and molecular markers. *Cancer 1994; 74:920-927.*
14. Gibson NW, Hickman AJ, Erickson LC. DNA cross-linking and cytotoxicity in normal and transformed human cells treated in vivo with 8-carbamoyl-3-(2-chloroethyl) imidazo (5,1,d)-1,2,3,5-tetrazin-4(3H)-one. *Cancer Res 1984; 44:1772-5.*
15. Glass J, Hochberg FH, Gruber ML, Louis DN, Smith D, Rattner B: The treatment of oligodendrogliomas and mixed oligodendroglioma-astrocytoma with PCV chemotherapy. *J Neurosurg 76: 741-745, 1992.*
16. Green SB, Byar DP, Strike TA, et al. Randomized comparisons of BCNU, streptozotocin, radiosensitizer, and fractionation of radiotherapy in the post-operative treatment of malignant gliomas (Study 7702). *Proc Am Soc Clin Oncol 1984; 3:260.*

17. Green SB, Byar DP, Walker MD, Pistenmaa DA, Alexander E Jr, Batzdorf U, Brooks WH, Hunt WE, Mealey J Jr, Odom GL, Paoletti P, Ransohoff Jr, Robertson JT, Selker RC, Shapiro WR, Smith KR Jr, Strike TA. Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. *Cancer Treat Rep* 1983; 67:121-132.
18. Greenberg HS, Ensminger WD, Chandler WF. Intraarterial BCNU chemotherapy in the treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; 61:423-429.
19. Gutin PH, Philips TL, Wara WM, et al. Brachytherapy of recurrent malignant brain tumors with removable high-activity iodine-125 sources. *J Neurosurg* 1984; 60:61-68.
20. Hartley JA, Gibson NW, Kohn KW, et al. DNA sequence selectivity of guanine-N7 alkylation by three antitumor chloroethylating agents. *Cancer Res* 1986; 46:1943-7.
21. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology* 1980; 30:907-911.
22. Kleihues p, Burger PC, Scheithauer BW. *Histological typing of tumors of the Central Nervous System*, Berlin: Springer-Verlag, 1993.
23. Kraus JA, Koopman J, Kaskel P, et al. Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. *J Neuropathol Exp Neurol* 1994;53:11-12.
24. Landis SH, Murray T, Bolden S, Ningo P. Cancer Statistics. *J Amer Cancer Society* 1998; 48: 6-29.
25. Lee SM, Thatcher N, Crowther D, Margison GP. In vivo depletion of human O6-alkylguanine-dna-alkyltransferase by Temozolomide. 8th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Program and Abstract Book, March 15-18, 1995; abstract number 044.
26. Levin V, Yung A, Prados M, et al. Phase II study of Temodal (Temozolomide) at first relapse in anaplastic astrocytoma (AA) patients. *Am Soc Clin Oncol, ASCO, 33rd Annual Meeting, Denver, CO, May 17-20, 1997; 16:384.*
27. Levin VA, Edwards MS, Wright DC, Seager ML, Pischer-Schimberg T, Townsend JJ, Wilson CB: Modified procarbazine, CCNU and vincristine (PCV-3) combination chemotherapy in the treatment of malignant brain tumors. *Cancer Treat Rep* 64: 237-241, 1980.
28. Levin VA, Silver P, Hannigan J, Wara WM, Gutin PH, Davis RL, Wilson CB. Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 Final Report. *IJ Rad Oncol Bio Phys* 1990; 18:321-324.
29. Louis DN. The p53 gene and protein in human brain tumors. *J Neuropath Exp Neurol* 1994; 53:11-21.
30. Macdonald DR, Gaspar LE, Cairncross JG: Successful chemotherapy for newly diagnosed aggressive oligodendroglioma. *Ann Neurol* 27: 573-574, 1990.
31. Mahaley MS Jr, Whaley RA, Blue M. Central neurotoxicity following intracarotid BCNU chemotherapy for malignant gliomas. *J Neurooncol* 1986; 3:297-314.
32. Mason WP, Louis DN, Cairncross JG. Chemotherapy sensitive gliomas in adults: which ones and why? *J Clin Oncol* 1997;15:3423-3426.
33. Mittler MA, Walters BC, Stopla EG. Observer reliability in histological grading of astrocytoma stereotactic biopsies. *J Neurosurg* 1996; 85:1091-1094.
34. Newlands ES, Blackledge GRP, Slack JA, et al. Phase I trial of Temozolomide (CCRG 81045; M&B 39831: NSC 362856). *Br J Cancer* 1992; 65:287-91.

35. Neuwalt EA, Howieson J, Frenkel EP, et al. Therapeutic efficacy of multiagent chemotherapy with drug delivery enhancement by blood-brain barrier modification. *Neurosurgery* 1986; 19:573-582.
36. Ono Y, Tarniya T, Ichikawa T, et al. Malignant astrocytomas with homozygous CDKN2/p16 gene deletions have higher Ki-67 proliferation indices. *J Neuropath Exp Neurol* 1996;55:1026-1031.
37. O'Reilly SM, Newlands ES, Glaser, MG, Brampton M, Stevens MFG. Temozolomide: a new cytotoxic agent with promising activity against glioma. *Am Soc Clin Oncol, ASCO, 29th Annual Meeting, Orlando, FL, May 16-18, 1993; 12:176.*
38. O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumors. *Eur J Cancer* 1993; 29A:940-2.
39. Patel M, McCully C, Godwin K, Balis F. Plasma and cerebrospinal fluid pharmacokinetics of Temozolomide. *Am Soc Clin Oncol, ASCO, 31st Annual Meeting, Los Angeles, CA, May 20-23, 1995; 14:461.*
40. Plowman J, Waud WR, Koutsoukos AD, et al. Preclinical antitumor activity of Temozolomide in mice: efficacy against human brain tumor xenografts and synergism with 1,3-bis (2-chloroethyl)-1-nitrosourea. *Cancer Res* 1994; 54:3793-9.
41. Prados M, Scott C, Sandler H, Buckner J, Phillips T, Curran W, Byhardt R, Parliament M, Davis R. Interim Report A Phase III Randomized Study of radiotherapy with or without BudR plus PCV for the treatment of anaplastic astrocytoma. (RTOG: 94-04) *Int J Radiat Oncol Biol Phys* 39: 138, 1997.
42. Salazar OM, Rubin P. The spread of glioblastoma as a determining factor in the radiation treated volume. *In J Rad Oncol Bio Phys* 1976; 1:627-637.
43. Salzman, M. Experimental therapy for brain tumors. *Brain Tumors*, ed. Kaye & Laws, 1995, pp. 369-381.
44. Sandberg AA. The usefulness of chromosome analysis in clinical oncology. *Oncology* 1987; 1:21-33.
45. Schiffer, D., Adriano, C., Giordana, M.T., Leone, M., Soffietti, R. Prognostic value of histologic factors in adult's cerebral astrocytoma. *Cancer* 1988; 61(7):1386-1393.
46. Scott CB, Nelson JS, Farnan NC, Curran WJ, Murray KJ, Fischbach J, Gaspar LE, Nelson DF. Central pathology review in clinical trials for patients with malignant glioma. *Cancer* 1995; 76 (2):307-313
47. Stevens MFG, Hickman JA, Stone R, et al. Antitumor imidazotetrazines I. Synthesis and chemistry of 8-carbamoyl-3-(2-chloroethyl) imidazo (5,1,d)-1,2,3,5-tetrazin-4(3H)-one, a novel broad spectrum antitumor agent. *J Med Chem* 1984; 27:196-201.
48. Stevens MFG, Hickman JA, Langdon SP, et al. Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-(2-chloroethyl) imidazo (5,1,d)-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M&B 39831), a novel drug with potential as an alternative to dacarbazine. *Cancer Res* 1987; 47:5846-52.
49. Tchang S, Scott G, Terbrugge K, Melancon D, Belanger G, Milner C, Ethier R. Computerized tomography as a possible aid to histological grading of supratentorial gliomas. *J Neurosurg* 1977; 46:735-739.
50. Thapar K, Fukuyama K, Rutka JT. Neurogenetics and the molecular biology of human brain tumors. *Brain Tumors*, eds. Kaye & Laws, 1995, pp. 69-93.
51. Tsang LLH, Quarterman CP, Gescher A, Slack JA. Comparison of the cytotoxicity in vitro of Temozolomide and dacarbazine, prodrugs of 3-methyl-(triazin-1-yl) imidazole-4-carboxamide. *Cancer Chemother Pharmacol* 1991; 27:342-6.
52. Vom Deimlinga, Louis DA, von Ammonki, Petersen I, Wiestler OD, Seizinger BR. Evidence for a tumor suppressor gene on chromosome 19q associated with human astrocytomas, oligodendrogliomas and mixed gliomas. *Cancer Res* 1992;52:4277-4279.

53. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA, Strike TA. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas, a cooperative clinical trial. *J Neurosurg* 1978; 49:333-343.
54. Walker MD, Green SB, Byar DP, Alexander E Jr, Batzfork U, Brooks WH, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J, Owens G, Ransohoff J, Robertson JT, Shapiro WR, Smith KR, Wilson CB, Strike TA. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *New Eng J Med* 1980; 303:1323-1329.
55. Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationships in the radiotherapy of malignant gliomas. *Int J Radiation Oncology Biol Phys* 1979; 5:1725-1731.
56. Winger MJ, Macdonald DR, Cairncross JG: Supratentorial anaplastic gliomas in adults: the prognostic importance of extent of resection and prior low-grade glioma. *J Neurosurg* 71: 487-493, 1989.
57. Kornblith PL, M Walker. Chemotherapy for malignant gliomas. *J Neurosurg* 68: 1-17, 1988.
58. Friedman HS, Dugan M, Kerby T, Henry A, Lovell M, Rasheed K, Haglund M, Friedman A. Temodal (Temozolomide) therapy of newly diagnosed high grade glioma. 12th Int'l Conference on Brain Tumor Research and Therapy, Keeble College, Oxford, UK; September 20-23, 1997; *J. Neuro-Oncology* 35 Supp 1:186.
59. Scott, C. B., Scarantino, C., Urtasun, R., Movsas, B., Jones, C. U., Simpson, J. R., Fischbach, A. & Curran, W. J. Validation and Predictive Power of Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis Classes for Malignant Glioma Patients: A Report Using RTOG 90-06. *Int J Radiat Oncol Biol Phys* 40, 51-55, 1998.

APPENDIX I (12/22/03)

RTOG 98-13

A PHASE III (PHASE I CLOSED) RANDOMIZED STUDY OF RADIATION THERAPY AND TEMOZOLOMIDE (IND# 60,265) VERSUS RADIATION THERAPY AND BCNU FOR ANAPLASTIC ASTROCYTOMA AND MIXED ANAPLASTIC OLIGOASTROCYTOMA (ASTROCYTOMA DOMINANT) SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY (8/15/02)

You have been diagnosed with a malignant brain tumor called anaplastic astrocytoma or oligodendroglial/astrocytoma. Standard treatment for this kind of tumor is surgery followed by local radiation. BCNU chemotherapy is usually given with the radiation. If BCNU is planned, it continues for about a year after the radiation is finished. Although radiation therapy plus BCNU may delay tumors from growing back for many years, this kind of tumor eventually returns in many patients. Also, BCNU can hurt the blood cells and lungs. Doctors are trying to find new drugs that will both prevent the return of the tumor or delay its re-growth and not hurt the blood cells as much.

Temozolomide is an investigational chemotherapy drug that is recently being used for your kind of tumor. Your doctors have asked you to participate in this study to compare the effectiveness of temozolomide with radiation versus BCNU with radiation in preventing the return of tumor or delaying the re-growth of tumor.

DESCRIPTION OF PROCEDURES (6/23/03)

The treatment you will be given will be one of two treatment methods. You will be assigned to one of the two by chance (*at random*). It is not known right now which of these methods of treatment is better. The treatment you get will be assigned by a computerized selection process. Your doctor will call a statistical office where a computer will assign you to one of the two treatment methods. Your chance of receiving one of the two treatments is approximately equal. You will be assigned to one of the following:

Treatment 1: Radiation is given once daily five days a week for six weeks. You will also receive Temozolomide capsules on the same day you start your radiation therapy. Temozolomide will be taken by mouth for five days in a row, every four weeks for up to a year. Temozolomide must be taken at least one hour before, or at least one hour after, eating. Temozolomide capsules must not be opened or chewed.

Treatment 2: Radiation is given once daily five days a week for six weeks. You will receive BCNU by vein as an outpatient. The BCNU will begin on the first three days of radiation and will be given on days 56, 57, and 58. Then the BCNU will be repeated every 8 weeks for three days up to six times. The BCNU is given over 1-2 hours at each of these visits.

You will also be asked to complete a short questionnaire before treatment and at each follow-up visit. The questionnaire will measure your mental status by asking you to answer several questions and by completing a few drawings.

Also, at the time of your diagnosis by biopsy, all or 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 complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples and a small sample of your blood for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS (8/17/01)

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (*side effects*). The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks from Radiation Therapy: include some or all of the following side effects: scalp redness or soreness, hair loss, which may be temporary or permanent, dry mouth or altered taste, hearing impairment, fatigue, sleepiness or temporary aggravation of tumor symptoms such as headaches, seizure, or weakness. There is a risk of injury to the eyes from radiation therapy with the possibility of blindness. Radiation sometimes causes late side effects such as mental slowing or behavioral change. Occasionally radiation causes severe local damage to normal brain tissue, a condition called necrosis. Radiation necrosis can mimic recurrent brain tumor or those of a stroke and may require surgery.

Risks of BCNU

BCNU can cause nausea, vomiting, a burning sensation at the injection site, facial flushing, and low blood pressure. Rarely liver and/or kidney abnormalities may develop. It also can lower blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need antibiotics, hospitalization, and transfusions if these problems are severe. Rarely, it may cause scarring of the lungs, resulting in cough or shortness of breath.

Temozolomide (Temodar™): may cause headache, nausea, vomiting, loss of appetite, constipation, diarrhea, sores in your mouth, skin rash, or hair loss. If capsules are accidentally opened or damaged, inhalation or contact with the skin and mucous membranes should be avoided. Blood counts may drop making you bruise more easily or lead to infection. Your liver enzymes may also temporarily rise. You may also feel very tired.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized (*tubal ligation or hysterectomy*), you should have a pregnancy test before enrolling in this study. You (*both men and women*) must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on this study, you must tell your doctor immediately.

COSTS (8/17/01)

The temozolomide will be provided to you by the drug company at no cost to you while you are on-study. The BCNU should be covered by your insurance company. Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS

(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

ALTERNATIVES

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. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than the another treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY (8/17/01)

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**). If your doctor is a member of ECOG, NCCTG or SWOG, your records will also be kept in a confidential file at ECOG, NCCTG or SWOG, as applicable. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of 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 may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

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.

Patient Signature (or legal Representative)

Date

TISSUE AND BLOOD TESTING (RTOG 98-13)

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. You can participate in the treatment part of the study without participating in any or part of the tissue and blood research studies. 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/blood may be kept for use in research to learn about, prevent, treat, or cure cancer.

Yes
No

2. My tissue/blood may be kept for research about other health problems (*for example: causes of diabetes, Alzheimer's disease, and heart disease*).

Yes
No

3. My doctor (*or someone from the RTOG*) may contact me in the future to ask me to take part in more research.

Yes
No

Please sign your name here after you circle your answers.

Your Name:

Date:

Your Signature:

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

APPENDIX III (8/17/01, 12/22/03)

<p>P4</p> <p>Radiation Therapy Oncology Group Anaplastic Astrocytoma PRE-Randomization 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 9813 Case# _____</p> <p>Institution _____ Institution # _____</p> <p>Participant's Initials _____ Participant's 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:</p> <p align="center">See Protocol Section 3.1.1</p> <p>Slides with Pathology reports that indicate grade II tumor but reference anaplasia can be submitted to Dr. Aldape for central pathology review</p>	<p>TISSUE SOURCE:</p> <p>STEREOTACTIC BX: DATE ____/____/____</p> <p>OPEN BX/RESECTION: DATE ____/____/____</p>
<p>LOCAL PATHOLOGY REVIEW</p> <p>TUMOR GRADE/TYPE</p> <p><input type="checkbox"/> WHO GRADE III 1 No (<i>not eligible</i>) 2 Yes</p> <p><input type="checkbox"/> HISTOLOGIC TYPE 1 Anaplastic Astrocytoma 2 Oligodendroglioma (< 25%) 3 Oligoastrocytoma (<i>not eligible</i>)</p> <p><input type="checkbox"/> ASTROCYTOMA SUBTYPE 1 Diffuse Fibrillary 2 Gemistocytic 3 Protoplasmic</p> <p>FEATURES (<i>check all that apply</i>)</p> <p>_____ Atypia _____ Mitosis(es) _____ Microvascular (<i>endothelial</i>) proliferation _____ Necrosis</p>	<p>CENTRAL PATHOLOGY REVIEW</p> <p>TUMOR GRADE/TYPE</p> <p><input type="checkbox"/> WHO GRADE III 1 No (<i>not eligible</i>) 2 Yes</p> <p><input type="checkbox"/> HISTOLOGIC TYPE 1 Anaplastic Astrocytoma 2 Oligodendroglioma (< 25%) 3 Oligoastrocytoma (<i>not eligible</i>)</p> <p><input type="checkbox"/> ASTROCYTOMA SUBTYPE 1 Diffuse Fibrillary 2 Gemistocytic 3 Protoplasmic</p> <p>FEATURES (<i>check all that apply</i>)</p> <p>_____ Atypia _____ Mitosis(es) _____ Microvascular (<i>endothelial</i>) proliferation _____ Necrosis</p>
<p>Institution (<i>must be completed</i>) Circle Group ID: _____</p> <p>Completed by: _____ Date: _____</p> <p>Telephone #: _____ Fax #: _____</p>	
<p align="center">RTOG ECOG SWOG NCCTG</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

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman 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.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

**** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form**

APPENDIX VI (6/23/03, 10/19/04)

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

- I. REGISTRATION:** RTOG will be responsible for all registration/randomizations. The procedure is:
Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forwards a copy of the calendar to the participating institution.

For ECOG Registrations: Please follow the instructions in Section 5.5.

- II. PROTOCOL DISTRIBUTION:** Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.
- III. INSTITUTIONAL PARTICIPATION:** It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.
- IV. CONFIRMATION/CALENDARS:** A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code, which appears on the Calendars in the “key” columns, is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items that are not forms (*CT or MRI scan reports, pathology reports*) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

- V. FORMS (10/19/04):** Other groups will attach a forms appendix to their members' version. It will be the responsibility of the other group's member to copy the attached forms and to maintain a supply of available forms for data submission.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (*see below*), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to:

American College of Radiology
Radiation Therapy Oncology Group
1818 Market Street, Suite 1600
Philadelphia, PA 19103

VI. LABELS: Patient specific labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Research associates are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be canceled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission. RTOG requires all patients in randomized trials to be followed with data submission according to protocol schedule.

VI. RAPID REVIEW ITEMS: Time critical data which require rapid submission must be sent directly to RTOG. These items are:

- T2 - Protocol Treatment Form
- T3 - Photon Localization film (*for all fields treated initially*)
- T4 - Photon dose calculations (*for all fields treated initially*)

IX. REQUEST FOR STUDY INFORMATION

AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (*generally three times per year*) computer-generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

**Data/Eligibility/Treatment/
Adverse Events/Data Management Procedures**

RTOG Research Associate (215) 574-3214

Forms Packets (RTOG Members)

Registration Secretary (215) 574-3191

Pathology

Pathology Clerk (801) 321-1929
(*unless specified otherwise in Section 10.0*)

Protocols/Amendments

Director, Protocol Development (215) 574-3195

Radiotherapy data items (*films, radiographs, isodose summations, treatment records, scans, reports and calculations*)

Dosimetry Clerk (215) 574-3219

Randomization/Registration

Registration Secretary (215) 574-3191

If you are unable to reach the person noted, and your call is urgent, ask to speak to any HQ Research Associate.

XI. ADVERSE EVENTS AND TOXICITY

From Radiotherapy: Unusual toxicities, all grade 5 toxicities, and grade 4 toxicities in altered fractionation studies are reported by telephone within 24 hours of discovery to RTOG Headquarters, to the Group Chairman Dr. Walter Curran, to the Study Chair(s), and to the RTOG Research Associate for this study.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters, RTOG Data Management and the Study Chair(s) are to receive notification as outlined by the NCI procedures. If telephone notification is necessary, RTOG and the Study Chair(s) must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.

Data Submission: Events that require telephone reporting will require current updating of data forms through the date of the event. Submit within 10 working days of the telephone call.

Second Malignancy: All second primary tumors that are diagnosed during or following protocol treatment must be reported on the study data collection forms. AML/MDS must be reported on the NCI/CTEP Secondary Reporting Form. Instructions for submission are on the data form.

APPENDIX VII (6/23/03, 8/20/03, 12/22/03)

RTOG 98-13

A PHASE III (PHASE I CLOSED) RANDOMIZED STUDY OF RADIATION THERAPY AND TEMOZOLOMIDE (IND #60,265) VERSUS RADIATION THERAPY AND BCNU FOR ANAPLASTIC ASTROCYTOMA AND MIXED ANAPLASTIC OLIGOASTROCYTOMA (ASTROCYTOMA DOMINANT)

TEMODAR™ SHIPMENT FORM

Temodar™ will be shipped only to institutions who have identified a single individual for receipt of shipment. Each institution must submit this form to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of it's the institution's first case (*the shipment form is only submitted once*). Allow adequate processing time (*7-10 days*) before calling to register the first case.

SHIP TO:

Name: _____

Address: _____

(No P.O. Box Numbers)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

Group Affiliation: *(circle one)* RTOG ECOG NCCTG SWOG

IRB Approval Date: _____

(attach copies of IRB approval and sample consent form)

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # (Required) _____

Return to:

*CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206*

RTOG Headquarters Approval _____ Date: _____