

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0513

### A PHASE I/II TRIAL OF TEMOZOLOMIDE, MOTEXAFIN GADOLINIUM, AND 60 GY FRACTIONATED RADIATION FOR NEWLY DIAGNOSED SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

NCI-supplied agent: Motexafin Gadolinium (NSC# 695238; IND# 55583)

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**Activation Date: February 9, 2006**

**Update Date: February 24, 2006**

**Version Date: August 14, 2008**

**Includes Amendment 1 (Broadcast September 4, 2008)**

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**A PHASE I/II TRIAL OF TEMOZOLOMIDE, MOTEXAFIN GADOLINIUM, AND 60 GY FRACTIONATED RADIATION FOR NEWLY DIAGNOSED SUPRATENTORIAL GLIOBLASTOMA MULTIFORME**

**SCHEMA (8/14/08)**

<b>R E G I S T E R</b>	<b><u>Phase I</u></b>	<p><u>Radiation Therapy:</u> 2.0 Gy x 30 fractions, 5 days/week x 6 weeks for a total dose of 60.0 Gy</p> <p><u>Concurrent Motexafin Gadolinium (MGd) During Radiation Therapy:</u> --22 total doses at MTD of phase I portion of the study (5 mg/kg) over 6 weeks --Weeks 1 &amp; 2, IV daily Mon-Fri 2-5 hrs before radiation therapy --Weeks 3-6, IV Mon, Wed, Fri 2-5 hrs before radiation therapy</p> <p><u>Concurrent Temozolomide During Radiation Therapy:</u> --Daily during radiation therapy, beginning the night before the first dose of radiation &amp; ending the night before the last dose of radiation</p> <p><u>Post-Radiation Temozolomide:</u> --Daily for 5 days every 28 days for up to 12 cycles, starting 28 days after the completion of radiation therapy</p>
	<p>ARM 1: MGd 3 mg/kg</p> <p>ARM 2: MGd 4 mg/kg</p> <p>ARM 3: MGd 5 mg/kg</p>	
	<b><u>Phase II</u></b>	
	<p>ARM 4: MGd MTD of phase I (5 mg/kg)</p>	

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

- Newly diagnosed histologically confirmed supratentorial glioblastoma multiforme or gliosarcoma
- Therapy must begin within ≤ 5 weeks of surgery

**Required Sample Size: 113**

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

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**ELIGIBILITY CHECKLIST** (2/9/06, 8/14/08)

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

(page 1 of 3)

- \_\_\_\_\_(Y) 1. Is there histologically confirmed, newly diagnosed, supratentorial glioblastoma multiforme or gliosarcoma?
- \_\_\_\_\_(Y) 2. Was the diagnosis made by surgical biopsy or resection?
- \_\_\_\_\_(Y) 3. Has a diagnostic contrast-enhanced MRI been performed preoperatively prior to study entry?
- \_\_\_\_\_(Y, N) 4. Has a diagnostic contrast-enhanced MRI been performed postoperatively within 28 days of study entry?  
\_\_\_\_\_(Y) If no, was the diagnosis was made by stereotactic biopsy?
- \_\_\_\_\_(Y) 5. Have all pretreatment evaluations been performed within the timelines specified in Section 3.1, with results within the specified parameters?
- \_\_\_\_\_(Y) 6. Will protocol therapy begin within 5 weeks of surgery?
- \_\_\_\_\_(Y) 7. Has the patient recovered from the effects of surgery or any postoperative complication?
- \_\_\_\_\_(Y) 8. Is the patient's age  $\geq$  18 years?
- \_\_\_\_\_(N) 9. Does the patient have any major medical or psychiatric illness, which in the investigator's opinion will prevent administration or completion of the protocol therapy?
- \_\_\_\_\_(N) 10. Has the patient had prior malignancies, except for non-melanomatous skin cancers or carcinoma in situ of uterus, cervix or bladder, unless disease free for  $\geq$  3 years?
- \_\_\_\_\_(N) 11. Has the patient received any prior radiation to the head or neck (except for T1 glottic cancer) resulting in overlap of radiation fields?
- \_\_\_\_\_(N) 12. Has the patient received any prior chemotherapy for the current glioblastoma multiforme?
- \_\_\_\_\_(N) 13. Is the patient pregnant or breast feeding?
- \_\_\_\_\_(N) 14. Does the patient have known Acquired Immune Deficiency Syndrome (AIDS)?
- \_\_\_\_\_(Y/NA) 15. If applicable, is the patient willing to use an acceptable method of contraception during study (see Section 3.2.9)?
- \_\_\_\_\_(N) 16. Does the patient have a history of porphyria or G6PD deficiency?
- \_\_\_\_\_(N) 17. Does the patient have a gadolinium allergy or other contraindication to MRI?

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

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

**ELIGIBILITY CHECKLIST** (2/9/06)

(page 2 of 3)

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (above) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- \_\_\_\_\_ 5. Patient's Initials (First Middle Last) [If no middle initial, use hyphen]
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code (U.S. Residents)
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Treatment Start Date
- \_\_\_\_\_ 17. Medical Oncologist
- \_\_\_\_\_ (Y/N) 18. Tissue kept for cancer research?
- \_\_\_\_\_ (Y/N) 19. Tissue kept for medical research?

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

RTOG 0513

**ELIGIBILITY CHECKLIST** (2/9/06)

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

(page 3 of 3)

\_\_\_\_\_ (Y/N) 20. Allow contact for future research?

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

Completed by \_\_\_\_\_ Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background (2/24/06, 8/14/08)**

Malignant gliomas are the most common primary central nervous system tumor in adults, and glioblastoma multiforme (GBM) represents the most aggressive and prevalent subtype of these tumors. Approximately 12,000 cases of GBM are diagnosed in the United States each year, and the incidence of GBM has been increasing over the past decade, with the peak occurrence after the age of 40.<sup>1</sup>

After surgical resection of all or part of the tumor, radiation therapy remains the most effective single adjuvant treatment for newly diagnosed GBMs. Median survival for surgery followed by standard courses of radiation is 36 weeks, compared with 14 weeks for surgery alone.<sup>2</sup> Radiation is generally targeted to the gross tumor volumes seen on radiographic studies with a margin that extends beyond the edema surrounding the tumor. Up to a point, patient survival time correlates with the total dose delivered; however, a further increase in the total dose of radiation to significant volumes of brain is limited by increasing late normal tissue damage.<sup>3,4</sup> Therefore, the current standard of care delivers a total of 59.4 to 60.0 Gray (Gy) in 1.8 to 2.0 Gy daily fractions. Data from several GBM studies utilizing this radiation regimen have been collected and gathered into a large database by the Radiation Therapy Oncology Group (RTOG), and this database has provided GBM survival information and has aided in the identification of prognostic variables in this malignancy.<sup>5</sup>

Although radiation therapy prolongs median survival, most patients eventually experience in-field recurrences that ultimately lead to death. Increasing doses of conventional radiation therapy beyond the standard of 60 Gy is limited by potential toxicity to the normal brain and has not resulted in improved survival.<sup>6-9</sup> Furthermore, complications of radiation correlate directly with the overall target volume treated.<sup>10,11</sup> Considering that 90% of recurrences in malignant gliomas are located within 2 cm of the enhancing edge of the original tumor on computed tomography (CT) scans<sup>12,13</sup> and that the occurrence of multicentric disease or metastatic spread is rare,<sup>14,15</sup> treatments that increase the dose or dose effectiveness to a localized tumor without increasing radiation to the adjacent normal brain tissue are attractive approaches that may improve the therapeutic ratio. To improve local control of the tumor, various attempts have been made to selectively intensify the radiation dose and/or its effects at the tumor site. Studies of two of these techniques, stereotactic radiosurgery (SRS)<sup>16-18</sup> and brachytherapy,<sup>11</sup> have been undertaken by various groups and suggest further dose responsiveness of the tumor to radiation effects.

However, the applicability of these techniques is limited to smaller tumors in accessible locations and, as currently investigated, neither has resulted in extending overall survival in GBM patients in randomized trials when compared to standard fractionated radiotherapy.<sup>11,19</sup> Temozolomide (Temodar<sup>®</sup>) is an oral alkylating agent that, when given during radiation to patients with newly diagnosed GBMs, has been shown in both a phase II and a randomized phase III trial to result in a modest improvement in overall survival without undue toxicity.<sup>20,21</sup> Motexafin gadolinium (MGd) (Xcytrin<sup>®</sup> Injection) is an agent that in nonclinical models interacts with tumor cells to enhance local radiation effects and has shown promise in phase I and phase II clinical trials in several tumors, including GBMs.<sup>22-27</sup> An international randomized phase III trial (the "SMART" trial; Pharmacyclics Corp, Sunnyvale, CA USA) combining MGd with radiation therapy in brain metastasis from lung cancer has recently closed, having met its accrual goal of over 550 patients; no results are available yet. Additional preclinical data suggest MGd and a variety of chemotherapeutic agents (including temozolomide) may be synergistic in the absence of radiation.<sup>28-30</sup> A phase I dose escalation clinical trial currently underway at the Barrow Institute in Phoenix, AZ (PI: William Shapiro, M.D.) utilizing the two agents concurrently in patients with recurrent GBM has demonstrated no overlapping toxicity at doses of MGd up to 5 mg/kg along with temozolomide (at 200 mg/m<sup>2</sup>, 5 days/month) for up to 10 months (W. Shapiro, personal communication 3/2005).

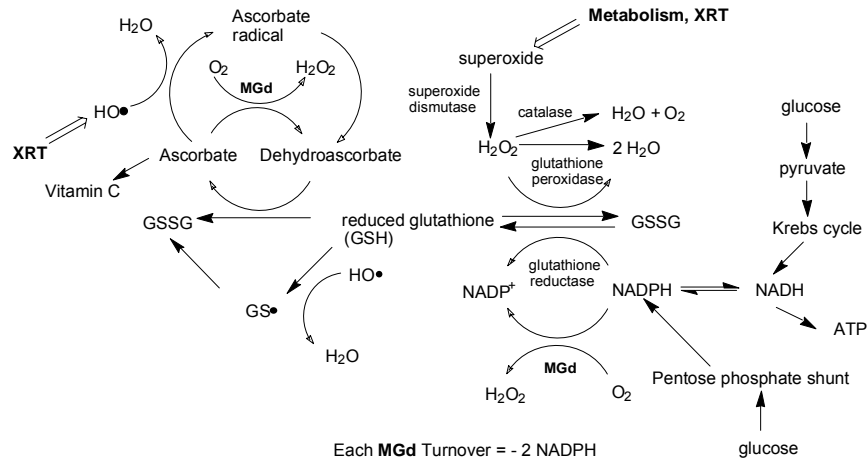
Although all available information suggests no overlapping or untoward toxicities are expected from this combination of therapies, no phase I data exist for this exact treatment combination. The current study is therefore a phase I/II design, with the dose escalation of MGd in the phase I portion. Patients with newly diagnosed supratentorial GBM will be treated with a combination of 60 Gy fractionated radiotherapy at 2 Gy/day, daily temozolomide during

radiotherapy at 75 mg/m<sup>2</sup>/day, and 22 doses of MGd at an initial dose of 3 mg/kg/day. MGd will be given as 5 once-daily doses (Monday-Friday), 2 to 5 hours prior to radiotherapy during weeks 1 and 2 and three times/week (Monday-Wednesday-Friday) during weeks 3 through 6. Subsequent temozolomide will be given at 150 to 200 mg/m<sup>2</sup>/day for 5 days every 28 days starting 28 days from the completion of radiation and continuing for up to 12 cycles. Cohorts will consist of up to 7 patients per MGd dose, and each cohort will be treated at only one dose level. In this study the dose-limiting toxicity (DLT) is defined as a grade 4 neurologic adverse event that is considered to be related to the radiation/temozolomide/MGd combination occurring within 21 days of the conclusion of radiotherapy, and the dose level of MGd will be considered acceptable if no more than one patient per cohort experiences a DLT. If < 2 DLTs are observed after the accrual of 7 patients at the first or second dose levels, accrual will be halted until the last patient at the currently open dose level has passed the 21-day mark from the end of radiation therapy. If the current level is considered acceptable, then the study will reopen to accrual at the next dose level. Otherwise, the preceding dose level will be declared the maximum tolerated dose (MTD). There will be a maximum of two MGd dose level escalations (4 mg/kg x 22 doses and 5 mg/kg x 22 doses). The goal of the phase I portion of this study is to establish the MTD of MGd when given in combination with temozolomide and radiation therapy. If, at any time, a grade 5 adverse event is observed, then accrual will be suspended and the study chairs will review the event. **If the study chairs determine that the grade 5 toxicity is treatment related, the Executive Steering Committee will be notified; this committee will determine whether the dose level should be closed.** The phase II trial will employ the same schema outlined above using the MTD established in the phase I setting. The combination of the administration of temozolomide and MGd along with standard radiation and subsequent temozolomide may enhance local control rates for GBM and prolong survival.

## **1.2 Motexafin Gadolinium (MGd)**

MGd belongs to a class of compounds termed texaphyrins, which are expanded porphyrin macrocycles capable of forming stable pentadentate complexes with large cations. Like naturally occurring porphyrins, MGd shows selective uptake and retention in tumor tissues relative to surrounding normal tissue. Murine studies utilizing [153Gd] MGd or [14C] MGd injected into tumor-bearing animals showed rapid clearance of the drug from blood and normal tissues, with delayed clearance from tumors, resulting in up to 8-fold greater concentrations in tumors than in surrounding tissues.<sup>24</sup> Because MGd contains the paramagnetic ion gadolinium, the drug can be detected using magnetic resonance imaging (MRI) scans. MRI studies of BALB/c mice bearing EMT-6 tumors have demonstrated a selective accumulation of MGd in tumors.<sup>25</sup>

MGd has favorable electron transfer capabilities that contribute to the disruption of tumor cell metabolism and an increase in the susceptibility of those cells to irradiation and chemotherapy effects. In vitro studies have shown that MGd catalyzes the intracellular reactions that deplete the antioxidants NADPH, ascorbate, and glutathione.<sup>24</sup> In the presence of oxygen, this results in the formation of supraoxide and hydrogen peroxide (fig. 1).



**Figure 1. Disruption of Cellular Metabolism by Motexafin Gadolinium (MGd)**

Incubation of MES-SA cells (a human uterine cancer cell line) with L-buthionine-[S,R]-sulfoximine and MGd resulted in a cooperative decrease in proliferation and increase in anaerobic radiation response.<sup>24,31</sup> Consistent with the resulting disruption in tumor cell metabolism, nuclear magnetic resonance measurements on MCa tumors (a mouse mammary carcinoma) implanted subcutaneously show changes in levels of high-energy phosphates.<sup>24,31</sup> Phosphocreatine and nucleotide triphosphate levels were depressed and corresponding levels of inorganic phosphate were increased for at least 6 hours after injection in the absence of ionizing radiation. Also, fluorescent microscopy has shown that MGd localizes intracellularly to the mitochondrial membrane. These findings are consistent with the proposal that MGd sensitizes cancer cells to ionizing radiation by altering their metabolic state. SMT-F tumor-bearing mice given a single dose of MGd and irradiated 2 to 5 hours later had greater tumor regrowth delay and improved survival compared to mice treated with radiation alone, and similar results were found using EMT-6 and MCa tumor-bearing mice.<sup>24</sup> Giving MGd alone resulted in no difference compared to untreated mice, and giving MGd after radiation resulted in no difference compared to mice treated with radiation alone.<sup>24</sup>

### **1.3 Temozolomide**

Temozolomide is an oral cytotoxic alkylating agent that has demonstrated clinical antitumor activity in gliomas, has been relatively well tolerated, and has an acceptable safety profile in phase I and II trials in patients with various advanced cancers, including malignant gliomas.<sup>32-37</sup> Temozolomide has an uncomplicated and well-defined pharmacokinetic profile.<sup>37</sup> Temozolomide was shown to be effective in prolonging progression-free survival and maintaining or improving health-related quality of life (HRQL) in adult patients with recurrent high-grade gliomas.<sup>38</sup> Temozolomide has been shown to provide better 6-month progression-free survival, overall survival, and overall quality of life when compared to procarbazine alone in GBM patients.<sup>38,39</sup> Temozolomide also has demonstrated clinically meaningful efficacy in anaplastic astrocytoma patients in first relapse.<sup>40</sup> Patients benefited from the use of temozolomide irrespective of the exact tumor histology.<sup>32</sup>

### **1.4 MGd During Radiotherapy**

#### **1.4.1 Brain Metastasis Trials: Phase I, II and III**

A phase I clinical trial (PCI- P120-9401) examined the single-dose safety profile of MGd as a radiation sensitizer.<sup>22</sup> A single intravenous dose of MGd was followed 2 or more hours later by radiation therapy. The MGd dose was escalated from 0.6 to 29.6 mg/kg in cohorts of 3 to 5 patients. Thirty-eight patients with locally advanced and/or metastatic cancers of the lung (n = 26), cervix (n = 3), or other solid tumors (n = 9) received a total of 41 single administrations of MGd; irradiated sites included the thorax, brain, pelvis, bone, soft tissue, and sites of nodal spread. The MTD was 22.3 mg/kg for single-dose administration and was

determined by the incidence of reversible acute tubular necrosis as the DLT, which was noted at 29.6 mg/kg. This toxicity occurred in two patients, and normal creatinine levels returned within 2 weeks in both patients. MGd selectively accumulated in primary and metastatic tumors, as demonstrated by MRI. No increase was seen in radiation toxicity of normal tissues.<sup>22</sup>

A multidose phase IB/II trial (PCI-P 120-9501) carried out in patients with brain metastases from a variety of tumors utilized 10 daily administrations of MGd in conjunction with 10 daily radiation therapy treatments of 3 Gy each.<sup>23</sup> The objectives were to determine the MTD, DLT, and biolocalization of MGd when given on a multidose schedule in a phase IB trial and to determine the radiologic response rate and pharmacokinetics in a phase II trial. Ten daily intravenous injections of MGd were each followed by whole-brain radiotherapy (WBRT) of 3 Gy each. The study enrolled 61 patients (n = 39, phase IB; n = 22, phase II), with brain metastases from lung cancer (n = 35), breast cancer (n = 10), melanoma (n = 4), renal cell carcinoma (n = 3), adenocarcinoma of unknown primary (n = 4), or other tumors (n = 5).

Applying the RTOG recursive partitioning analysis (RPA) classification<sup>16</sup> to the 61 patients, 2/61 (3%) were class 1, 48/61 (80%) were class 2, and 11/61 (16%) were class 3. Seventy-nine percent had one or more sites of extracranial metastases. Overall, 10 daily treatments were well tolerated. The MTD on repeat dosing was 6.3 mg/kg, with reversible grade 3 or 4 liver function test abnormalities as the DLT (increased ALT, 4%; abnormal liver function tests, 4%; bilirubinemia, 4%; increased AST, 3%). There was no evidence of enhanced radiation toxicity to normal tissues.<sup>23</sup> Tumor selectivity of MGd was established using MRI, which showed selective uptake and accumulation in the metastases but not in the normal brain. Of 41 patients available for radiologic response, one achieved a complete response and 26 had a partial response, for an overall response rate of 66%. The median survival for all patients (phase IB and phase II, including all dose levels) was 4.7 months. The median survival of the RPA class 2 patients (n = 48) was 5.9 months (compared with 4.2 months in the RTOG database), and 3.8 months in the RPA class 3 patients (n = 11), (compared with 2.3 months in the RTOG database).<sup>41,42</sup> Of 33 patients whose cause of death was available, 4 (12%) died of brain metastasis progression, 3 (9%) of meningeal carcinomatosis, 2 (6%) of cerebrovascular accidents, 1 (3%) of an extension of a cerebral hemorrhage present at study entry, and the remainder (70%) of systemic tumor progression or its complications.<sup>23</sup>

A randomized phase III trial (PCI-P120-9801) for patients with brain metastasis from solid tumors compared standard WBRT (3 Gy/day for 10 fractions) to WBRT plus MGd given 5 mg/kg/day before each fraction. The trial included 401 patients with brain metastasis from various sources including non-small cell lung cancer (61%) breast cancer (19%), and melanoma (6%). Treatment compliance was excellent, with over 95% of the doses being delivered in both arms and 94% of the intended MGd dose delivered in the MGd arm. The most common MGd-related effects were temporary greenish discoloration of the skin (83%), urine (47%), and sclera (24%); hypertension (30%); nausea (41%); diarrhea (24%); vesicubullous rash (19%); and paresthesias (15%). These events were typically National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 1 and 2. The most common possibly drug-related grade 3 or 4 adverse events were hypertension (6%), asthenia (3%), hyponatremia (2%), leucopenia (2%), hyperglycemia (2%), and vomiting (2%). There was no significant difference by treatment arm in survival time (median 5.2 months for MGd vs. 4.8 months for WBRT alone), but the MGd-treated patients had a prolonged time to neurologic progression (4.3 months for MGd vs. 3.8 months for WBRT, p = 0.018).<sup>43</sup> A second randomized phase III trial (the "SMART" trial; Pharmacyclics Corp, Sunnyvale, CA USA) combining MGd with radiation therapy in brain metastasis from lung cancer has recently closed, having met its accrual goal of over 550 patients; no results are available yet.

#### 1.4.2 GBM Trials: Phase I and II

A phase I dose escalation trial (NCI Protocol No. T97-0108) of MGd and radiation in the treatment of newly diagnosed GBM was completed at the University of California, Los Angeles (UCLA), under an Investigational New Drug (IND) application held by the NCI. The purpose of this phase I study was to establish in GBM patients a safe dose and schedule of MGd treatments combined with a 6½-week course of radiation therapy (thirty-three 1.8 Gy fractions per day, for a total of 59.4 Gy). The initial daily MGd dose of 4 mg/kg/day was about two thirds of the MTD (6.3 mg/kg/day) from the phase IB/II trial for 10 daily doses. The first

cohort received 10 total doses of MGd given once daily for the first week of radiation therapy and then given on Mondays, Wednesdays, and Fridays afterwards. In each subsequent cohort, dose escalation consisted of adding 3 more doses of MGd, given on the Monday, Wednesday, Friday schedule. Cohort 5 (22 doses) was prescribed a 6½-week schedule of MGd treatments that coincided with the full radiation therapy course. Subsequent cohorts received the same schedule as cohort 5, but the daily dose administered was increased.<sup>42</sup>

All cohorts have completed the study. Data from 27 patients enrolled in cohorts 1 through 6 were available for analysis. The median age was 51 years (range 23-72 years). Seventeen (63%) patients were male and 10 (37%) were female. The previously defined DLT, grade 3 or 4 liver function abnormalities, occurred in cohort 6 with 22 doses of 5.3 mg/kg/day. Two patients developed increases in their liver transaminases during the study treatment period. After the transaminase abnormalities occurred, subsequent scheduled doses of drug were skipped. The transaminase concentrations returned to the normal range without sequelae, and both patients were able to complete their course of cranial radiation. Preliminary survival data suggest a median survival of 16.8 months for the patients in this study, with a median follow-up of 11.4 months.<sup>42</sup>

Based on the experience from protocol T97-0108, a phase II trial (PCYC-0206) was initiated to evaluate a regimen of 22 doses of MGd at 5 mg/kg/day in combination with a 6-week course of cranial radiation. MGd was administered 2 to 5 hours before radiation therapy, daily for the first 10 fractions and then 3 times per week thereafter. Patients received 46 Gy (2 Gy × 23 fractions) to the MRI T2 abnormality (with a 2-cm margin) and an additional boost dose of 14 Gy (2 Gy × 7 fractions; total dose 60 Gy) to the MRI-enhancing abnormality with a 2-cm margin. Twenty-five patients enrolled (17 male, 8 female, age range 33-80, median age 59 years). Of the 25 GBM patients, 4 underwent total resection, 14 a partial resection, and 7 a biopsy only. By the RTOG RPA prognostic classification system, there were 4 class III patients, 10 class IV, 10 class V, and 1 class VI. Eighteen patients completed all 22 MGd doses and 22 completed > 80%. Twenty-four patients completed the planned radiation therapy.<sup>26</sup>

The following ≥ grade 3 toxicities occurred during the treatment period: deep vein thrombosis (16%), pneumonia (16%), asthenia (12%), convulsion (12%), GBM progression (12%), increased GGTP (12%), brain edema (8%), dyspnea (8%), and pulmonary embolus (8%). Grade 3 hypophosphatemia was seen in 52% of patients but did not cause any clinical sequelae. Two patients had protocol-specified interruptions in treatment for reversible grade 3 liver function abnormalities. Reversible grade 3 leukopenia was seen in one patient who had baseline leukopenia at study entry. Common drug-related grade 1 or 2 toxicities included reversible skin (88%) and urine (76%) discoloration, vesicubullous rash (68%), reversible paresthesias (52%-56%), and asthenia (44%). In general, the safety profile for the treatment regimen was similar to that seen in other clinical trials of MGd. With a median follow-up of 5.5 months, median survival has not been reached.<sup>26</sup>

The RTOG recently completed an analysis of the above noted UCLA phase I study (NCI Protocol No. T97-0108) of 31 GBM patients treated with radiotherapy and MGd, matched to 31 patients in the RTOG database by the prognostic variables of Karnofsky performance status, surgery (total/partial resection vs. biopsy), histology (all GBM), and age (within 5 years). The Kaplan-Meier estimate of median survival time for the UCLA cases was 16.1 months, compared with 11.8 months for the RTOG cases. A matched pair Cox analysis of overall survival comparing the UCLA cases to the RTOG cases calculated a hazard ratio of 2.3 in favor of the UCLA cases, with p = 0.03.<sup>44</sup>

An analysis of the combined outcome of the 56 patients in the two series (NCI T97-0108 and PCYC 0206) noted above has demonstrated a median survival of 14.7 months; patients who received ≥ 60 mg MGd (45/56 enrolled patients) appeared to have the greatest benefit, with 75% of this subset of patients alive at 12 months (C. Phan, personal communication 1/2005). Based upon these findings, MGd (22 doses, 5 mg/kg/day) in combination with cranial radiation (60 Gy in 30 fractions) can be safely completed by the majority of GBM patients and may offer a therapeutic advantage over radiotherapy alone.

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

Several recent clinical trials have been published that have demonstrated the relative safety and efficacy of combined radiotherapy and temozolomide in newly diagnosed GBM.<sup>20, 21</sup> In these studies, temozolomide has typically been given on a daily dosing schedule throughout 6 to 7 weeks of radiation without unacceptable toxicity. Lanzetta et al<sup>20</sup> described results using a daily schedule of 75 mg/m<sup>2</sup>/day for 6 weeks as initial treatment of GBM, followed by temozolomide 200 mg/m<sup>2</sup>/day every 28 days for up to 6 cycles. Median survival was 15.7 months, with a 1-year survival rate of 58%. Stupp et al<sup>21</sup> recently reported a randomized, multicenter trial in which 573 newly diagnosed GBM patients were treated with radiation therapy alone (n = 286) or radiation therapy and 6 weeks of daily temozolomide (n = 287) at 75 mg/m<sup>2</sup>/day, followed by adjuvant temozolomide at 150 to 200 mg/m<sup>2</sup>/day on a 5-day schedule every 28 days for up to 6 cycles. The treatment arms were well balanced with regard to age, gender, and performance status. With a median follow-up of 2 years, the median survival for the radiation therapy alone arm was 12.0 months versus 15.0 months for the radiation therapy plus temozolomide arm (p < 0.001). The 2-year overall survival rate for the radiation alone group was 8% versus 26% for the group receiving radiation with concurrent and adjuvant temozolomide (p < 0.001). The toxicities reported were quite modest, and the combined modality arm experienced no significant increase in radiation-related toxicity. These results demonstrate the combination of radiation therapy and daily temozolomide is very tolerable; in addition, the survival data are highly encouraging, with the result that the combination of radiation therapy and temozolomide has rapidly become the new defacto standard of care for newly diagnosed GBM.

### **1.6 Rationale for Using MGd and Temozolomide (2/24/06)**

In nonclinical models, the combination of MGd and selected chemotherapy agents was more effective against tumor cells than chemotherapeutic agents alone.<sup>28,29</sup> In vivo studies of the combined treatment of MGd with bleomycin or doxorubicin showed significant delay in tumor growth compared with control animals treated with either agent alone. The combination of docetaxel and MGd in an in vivo study performed on A549 human lung cancer demonstrated that MGd enhanced the antitumor activity of docetaxel and showed a significant tumor growth delay compared with docetaxel alone (tumor growth delay of 22 days, p = 0.04).<sup>30</sup> MGd has been shown to increase the chemotherapeutic effect of temozolomide in a murine spontaneous lung cancer model. In that study, C57BL/6 mice were injected intramuscularly with Lewis lung carcinoma cells. Mice were treated with 5 days of MGd, temozolomide, or both agents. Compared with control animals and animals treated with temozolomide or MGd alone, the combination therapy significantly decreased the rate of spontaneous metastasis.<sup>30</sup> A phase I dose escalation study combining MGd and temozolomide is underway at the Barrows Neurological Institute for patients with recurrent GBM. The dose of temozolomide is 150 mg/m<sup>2</sup>/day x 5 doses for the first 28-day cycle and may be adjusted in subsequent cycles to 200 mg/m<sup>2</sup> x 5 doses. Patients are also receiving 5 consecutive days of cohort-prescribed MGd with sequential cohorts treated with escalating doses of MGd; an individual patient is treated at only one MGd level. New cohorts are initiated only after cycle 1 is completed and toxicity has been evaluated for all patients in the current cohort. Four cohorts are specified, with temozolomide given as described above and MGd given every 28 days at doses of 1 mg/kg/day x 5 days, 3 mg/kg/day x 5 days, 5 mg/kg/day x 5 days, or 7 mg/kg/day x 5 days. To date, cohorts 1, 2, and 3 have been completed and no patients in either cohort 1 (1 mg/kg/day) or cohort 2 (3 mg/kg/day) experienced any grade 3 or higher events; the DLT has not been reached. Accrual to cohort 4 (MGd at 7 mg/kg/day x 5 days) is proceeding; no data on tumor response in these patients is yet available (W. Shapiro, personal communication 3/2005).

### **1.7 Rationale for the Study Design and Dosing Regimen (8/14/08)**

Despite the recent multicenter trial demonstrating a modest survival advantage for the use of concurrent and adjuvant temozolomide over radiotherapy alone in patients with newly diagnosed GBM, the overall survival remains poor and treatment for the vast majority of patients must still be viewed as palliative, as most patients fail to survive even 18 months. Although the combination of radiotherapy with temozolomide is an advance, other combinations of treatment, including the data presented above for radiotherapy with MGd in newly diagnosed GBM, have produced similar overall survivals, albeit in smaller, more provisional studies. Since preclinical data suggest a possible synergy between MGd and a

variety of chemotherapeutic agents, including temozolomide, the investigation of the combination of radiotherapy, temozolomide, and MGd in newly diagnosed GBM would appear wholly reasonable. MGd has different known DLTs than temozolomide or radiotherapy; MGd affects the hepatic and renal systems whereas the primary toxicity of temozolomide is on the hematologic system, and neither appears to potentate significantly the acute central nervous system or scalp dermatologic effects that can be seen with cranial radiotherapy. The single-dose MTD of MGd with radiotherapy is 22.3 mg/kg (established by PCI-P 120-9401), and previous trials in patients with newly diagnosed GBM treated with MGd in combination with 6.5 weeks of radiation demonstrated an acceptable safety profile for MGd regimens with a daily dose of 5 mg/kg (for a cumulative dose of 110 mg/kg). Temozolomide at 75 mg/m<sup>2</sup>/day combined with 6 weeks of fractionated radiation (and subsequent monthly temozolomide) has been shown to be well tolerated, and the ongoing phase I clinical trial looking at MGd with temozolomide in recurrent GBM at the Barrow Neurological Institute has thus far demonstrated no overlapping toxicities at up to 5 mg/kg/day x 5 days/month of MGd for up to 10 months; the accrual to the final planned cohort of MGd at 7 mg/kg/day is underway, a dose level higher than in this study. Although all available information suggests no overlapping or untoward toxicities are expected from this combination of therapies, no phase I data for this exact treatment combination exist. This study proposal is therefore a phase I/II design, with the dose escalation of MGd in the phase I portion. Patients with newly diagnosed supratentorial GBM will be treated with a combination of 60 Gy fractionated radiotherapy at 2 Gy/day, daily temozolomide during radiotherapy at 75 mg/m<sup>2</sup>/day and 22 doses of MGd at an initial dose of 3 mg/kg/day. MGd will be given as 5 once-daily doses (Monday-Friday), 2 to 5 hours prior to radiotherapy during weeks 1 and 2 and three times/week (Monday-Wednesday-Friday) during weeks 3 through 6. Subsequent temozolomide will be given at 150 to 200 mg/m<sup>2</sup>/day for 5 days every 28 days starting 28 days from the completion of radiation and continuing for up to 12 cycles. Cohorts will consist of up to seven patients per MGd dose, and each cohort will be treated at only one dose level. In this study the DLT is defined as a grade 4 neurologic adverse event that is considered to be related to the radiation/temozolomide/MGd combination occurring within 21 days of the conclusion of radiotherapy, and the dose level of MGd will be considered acceptable if no more than one patient per cohort experiences a DLT. If < 2 DLTs are observed after the accrual of 7 patients at the first or second dose levels, accrual will be halted until the last patient at the currently open dose level has passed the 21-day mark from the end of radiation therapy. If the current level is considered acceptable, then the study will reopen to accrual at the next dose level. Otherwise, the preceding dose level will be declared the MTD. There will be a maximum of two MGd dose level escalations (4 mg/kg x 22 doses and 5 mg/kg x 22 doses).

The goal of the phase I portion of this study is to establish the MTD of MGd when given in combination with temozolomide and radiation therapy. If, at any time, a grade 5 adverse event is observed, then accrual will be suspended and the study chairs will review the event. **If the study chairs determine that the grade 5 toxicity is treatment-related, the Executive Steering Committee will be notified; this committee will determine whether the dose level should be closed.** The phase II trial will employ the same schema outlined above utilizing the MTD established in the phase I setting.

## **2.0 OBJECTIVES**

### **2.1 Phase I**

**2.1.1** To determine the MTD of MGd given concurrently with temozolomide and radiation therapy in patients with newly diagnosed supratentorial GBM.

### **2.2 Phase II**

**2.2.1** To estimate the overall survival of patients with newly diagnosed supratentorial GBM treated with concurrent radiation, temozolomide, and MGd followed by post-radiation temozolomide.

**2.2.2** To determine the short- and long-term adverse effects of this treatment regimen.

**2.2.3** To estimate the progression-free survival of patients with newly diagnosed supratentorial GBM treated with concurrent radiation, temozolomide, and MGd followed by post-radiation temozolomide.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility (8/14/08)**

- 3.1.1 Histopathologically confirmed newly diagnosed GBM or gliosarcoma within 5 weeks of registration
- 3.1.2 Diagnosis must be made by surgical biopsy or excision
- 3.1.3 The patient must have recovered from the effects of surgery or postoperative infection and other complications
- 3.1.4 The tumor must be supratentorial in location as determined by:
  - 3.1.4.1 A diagnostic contrast-enhanced MRI performed preoperatively: an MRI performed postoperatively within 28 days prior to registration (preferably within 72 hours of surgery), prior to the initiation of radiotherapy; a postoperative scan is not required if the patient was diagnosed by stereotactic biopsy and a pre-operative MRI was performed.
- 3.1.5 Zubrod performance status 0-1
- 3.1.6 Neurologic function status 0-2
- 3.1.7 Age  $\geq 18$
- 3.1.8 Therapy must begin  $\leq 5$  weeks after surgery
- 3.1.9 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:
  - 3.1.9.1 Absolute neutrophil count (ANC)  $\geq 1800$  cells/mm<sup>3</sup>
  - 3.1.9.2 Platelets  $\geq 100,000$  cells/mm<sup>3</sup>
  - 3.1.9.3 Hemoglobin  $\geq 8$  g/dL. If anemia is present to the extent that the hemoglobin is  $< 8$  g/dL, then correction by transfusion is indicated before entry into the study
- 3.1.10 Blood chemistries (to include total protein, albumin, calcium, phosphorus, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT) within 14 days of registration, as defined as follows:
  - 3.1.10.1 BUN  $\leq 25$  mg
  - 3.1.10.2 Creatinine  $\leq 1.5$  mg
  - 3.1.10.3 Total bilirubin  $\leq 1.5$  mg/dL
  - 3.1.10.4 ALT or AST  $\leq 2$  x institutional upper limit of normal
- 3.1.11 Within 14 days prior to registration: Complete history and general physical examination; detailed neurological examination; documentation of steroid and anticonvulsant doses
- 3.1.12 Patients of reproductive potential must practice an effective method of birth control during and for 2 months after treatment; negative serum pregnancy test within 5 days prior to registration for females of child-bearing potential
- 3.1.13 The patient must sign a study-specific informed consent prior to study entry; if the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member
- 3.2 Conditions for Patient Ineligibility**
  - 3.2.1 Gliomas graded less than GBM
  - 3.2.2 Recurrent malignant gliomas
  - 3.2.3 Tumor foci detected below the tentorium or beyond the cranial vault
  - 3.2.4 Multifocal disease or leptomeningeal spread
  - 3.2.5 Prior invasive malignancies (except for non-melanomatous skin cancers and carcinoma in situ of the uterine cervix or bladder), unless disease free for a minimum of 3 years
  - 3.2.6 Prior systemic chemotherapy (including Gliadel wafers) for the current GBM; note that prior chemotherapy for a different cancer is allowable. See Section 3.2.5.
  - 3.2.7 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields
  - 3.2.8 Severe, active comorbidity, defined as follows:
    - 3.2.8.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
    - 3.2.8.2 Transmural myocardial infarction within the last 6 months
    - 3.2.8.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
    - 3.2.8.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration
    - 3.2.8.5 Coagulation defects; note, however, that laboratory tests coagulation parameters are not required for entry into this protocol
    - 3.2.8.6 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

- 3.2.9 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic
- 3.2.10 Prior allergic reaction to the study drugs involved in this protocol
- 3.2.11 Patients who cannot be regularly followed by the investigator
- 3.2.12 History of porphyria or G6PD deficiency
- 3.2.13 Allergy to gadolinium or contraindications to MRI scan

#### **4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT**

(In addition to the mandatory pre-testing for eligibility in Section 3.0)

**Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient's eligibility for this study, please contact RTOG HQ immediately (215) 574-3189**

##### **4.1 Additional Mandatory Pretreatment Evaluations/Interventions**

See Section 11.1; note that failure to perform this test may result in assessment of a protocol violation

- 4.1.1 Mini-mental status examination (MMSE)

#### **5.0 REGISTRATION PROCEDURES**

##### **5.1 Regulatory Pre-Registration Requirements (8/14/08)**

- 5.1.1 **U.S. sites and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, [http://www.rtog.org/pdf\\_file2.html?pdf\\_document=CTSUSIRBCECertifForm.pdf](http://www.rtog.org/pdf_file2.html?pdf_document=CTSUSIRBCECertifForm.pdf), prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

##### **5.1.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS**

- 5.1.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

- 5.1.2.2 Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See [http://www.rtog.org/pdf\\_forms.html?members/forms=Intl\\_LOI\\_Form.doc](http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc)

Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form, [http://www.rtog.org/pdf\\_forms.html?members/forms=RTOG%20International%20REC%20Certification.doc](http://www.rtog.org/pdf_forms.html?members/forms=RTOG%20International%20REC%20Certification.doc) to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- REC approval letter;
- Informed Consent (English Version);
- Federalwide Assurance (FWA) number.

##### **5.2 Registration**

Patients can be registered only after eligibility criteria are met.

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

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

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

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

Institutions can contact RTOG web support for assistance with web registration at [websupport@phila.acr.org](mailto:websupport@phila.acr.org).

In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

## **6.0 RADIATION THERAPY (Note: Intensity Modulated RT (IMRT) Is Not Allowed)**

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

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

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

### **6.2 Technical Factors**

Treatment shall be delivered with megavoltage (MV) equipment with energies up to and including 18 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiotherapy dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies  $> 10$  MV should be utilized only in dual energy beam arrangements using at least one beam with energy  $\leq 10$  MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible.

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

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

## **6.4 Treatment Planning**

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

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

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

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

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

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

## **6.6 Radiation Adverse Events**

### **6.6.1 Acute**

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea, altered taste, loss of appetite, and vomiting and 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; these reactions could result in short-term hearing impairment.

### **6.6.2 Early Delayed**

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

### **6.6.3 Late Delayed**

Possible late delayed effects of radiotherapy include radiation necrosis, neurocognitive defects, endocrine dysfunction, dry mouth, blindness, metal status changes, and radiation-induced neoplasms. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

## **6.7 Treatment Delays**

Radiation therapy will be delayed or interrupted if the absolute granulocyte count is  $< 500$  or the platelet count is  $< 20,000$ . Radiation therapy will not begin or resume until the absolute granulocyte count is  $\geq 500$  and the platelet counts is  $\geq 20,000$ . Hematologic toxicities should be rated on a scale of 0 to 5 as defined in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

## **6.8 Documentation Requirements**

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

## **6.9 Radiation Therapy Quality Assurance Reviews**

**6.9.1** The Radiation Oncology Chair, David Brachman, M.D., will perform a Radiation Therapy Quality Assurance Review after complete data for the first 30 cases enrolled have been received at RTOG Headquarters. Dr. Brachman will perform the next review after complete data for the next 30 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as

soon as complete data for all cases enrolled have been received at RTOG Headquarters, whichever occurs first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

## **6.10 Radiation Adverse Event Reporting**

(See Sections 7.7 and 7.8)

## **7.0 DRUG THERAPY**

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

### **7.1 Concurrent Drug Therapy During Radiation Therapy (8/14/08)**

**7.1.1** Temozolomide 75 mg/m<sup>2</sup>/day will be taken orally continuously during radiation therapy, including weekends and holidays for a maximum of 49 days. The first dose of temozolomide will begin the night before the first fraction of radiation. The last dose will be taken the night before the last fraction of radiation. Doses will be rounded to the nearest 5 mg to accommodate capsule strength. Capsules are available in 250 mg, 180 mg, 140 mg, 100 mg, 20 mg, and 5 mg strengths.

#### **7.1.2** MGd

**7.1.2.1** Phase I: MGd will be given intravenously over 30 minutes Monday through Friday during weeks 1 and 2, and then three times per week (preferably Monday, Wednesday, and Friday) during weeks 3 through 6 of radiation therapy, for a total of 22 doses. MGd will begin on the first day of radiation treatment. MGd will be given 2 to 5 hours prior to each fraction and will not be given if the patient is not to receive a fraction of radiation that day. Arm 1 of the trial will treat patients at an MGd dose of 3 mg/kg/day, Arm 2 at 4 mg/kg/day, and Arm 3 at 5 mg/kg/day. See Section 13.1.1 for details on how the MTD of MGd will be determined.

**7.1.2.2** Phase II: Phase II will use the same administration schema as detailed above, with the MGd dose as determined from the phase I portion. **[NOTE:** The phase I portion of this study established the MTD of MGd as 5 mg/kg; the phase II portion of this study opened on 3/14/08, with MGd administered at that dose. ]

**7.1.3** MGd Administration Guidelines: Patients will be evaluated for any signs of dehydration prior to administration of MGd. Patients must have consumed at least 16 ounces of clear fluids prior to the MGd infusion. If physical examination or tachycardia indicates that a patient is dehydrated, hydration with 500 to 1000 mL of an appropriate intravenous fluid is recommended before treatment, unless contraindicated. Before administration of MGd, the intravenous tubing is to be cleared with at least 10 mL of normal saline without preservative. Undiluted, filtered MGd, at a dose of 3 to 5 mg/kg/day (See Sections 7.1.2.1 and 7.1.2.2), will be given intravenously over approximately 15-30 minutes, 2 to 5 hours before irradiation. For all dosing calculations, the weight measured at baseline will be used, unless a > 15% change of weight has occurred during the course of treatment. If such a change has occurred, the dose of MGd will be adjusted to the most recent weight measurement. After the administration, the intravenous tubing is to be flushed again with 10 mL of normal saline without preservative to clear it of MGd. Antiemetics will be given prior to MGd infusion and prior to each temozolomide dose to prevent nausea and vomiting (see Section 9.1.2 for dosing guidelines).

#### **7.1.4** MGd Dose Modifications

**7.1.4.1** Dose levels: Complete blood counts and chemistry panel will be monitored every week during drug therapy.

**7.1.4.2** Dose adjustments during treatment:

<b>Event</b>	<b>Modification</b>
Grade 3 or worse alkaline phosphatase, total bilirubin, or serum creatinine	Discontinue MGd Resume at 100% of dose if toxicity resolves to grade 2
Grade 3 AST or ALT	Reduce to 50% of dose Resume at 100% of dose if toxicity resolves to grade 2
Grade 4 AST or ALT	Discontinue MGd Resume at 100% of dose if toxicity resolves to grade 2
Any other laboratory test abnormalities deemed clinically significant by investigator	Discontinue MGd Resume at 100% of dose if toxicity resolves to grade 2

Patients who develop any of the following conditions should have their MGd treatment delayed; however, radiation treatments may continue:

- NCI CTCAE Grade 4 elevation in ALT or AST
- NCI CTCAE  $\geq$  Grade 3 elevation in alkaline phosphatase, total bilirubin, or serum creatinine
- Any other laboratory test abnormalities determined by the investigator to be clinically significant

MGd dosing may resume after the blood levels return to Grade 2 or lower.

If a patient has an NCI CTCAE Grade 3, but not Grade 4, AST or ALT value, the MGd dose should be reduced to 50% of the protocol-specified dose. If the toxicity reaches Grade 4, MGd should be discontinued. MGd may be resumed at the original dose if the toxicity drops to Grade 2 or lower.

If doses of MGd are missed due to toxicity, they should not be made up. If a dose is missed for other reasons, it may be made up during a week in which only three doses are planned.

During weeks 3 through 6, if holidays or other interruptions occur on a Monday, Wednesday, or Friday, the missed dose should be made up on a Tuesday or Thursday, so the patient still receives three doses of study drug that week. If unplanned interruptions make it such that only two doses are given in a week, study drug dosing should be continued three times per week into week 7 until the patient receives a total of 22 doses of study drug.

#### 7.1.5 Treatment of MGd Adverse Effects

**7.1.5.1** MGd is emetogenic. Before administration of MGd injection, premedication with antiemetics is mandatory. In previous trials, the incidence of nausea or vomiting in patients receiving 5 mg/kg of MGd was approximately 35% to 45%; the use of agents such as prochlorperazine, lorazepam, granisetron, and ondansetron effectively prevented nausea with subsequent doses of study drug.

**7.1.5.2** Patients have reported intermittent chills, noninfectious fevers, and in rare instances, transient rigors in association with MGd treatment. Premedication with bolus doses of dexamethasone (up to 10 mg by mouth [PO] or IV) and diphenhydramine (25 to 50 mg PO or IV) 30 to 60 minutes before administration has prevented these symptoms.

**7.1.5.3** Patients treated with MGd may develop hypophosphatemia. Serum phosphate should be monitored weekly with the blood chemistries. If serum phosphate decreases below 2.0 mg/dL (NCI CTCAE Grade  $\geq$  3) or if a patient becomes symptomatic, phosphate should be replaced orally.

**7.1.5.4** It is recommended that patients avoid direct sunlight and apply a sunscreen of at least SPF 45 to their hands and feet if exposed to aid in the prevention of blisters. Patients may experience recall blisters later in the course of their treatment. See Section 9.1.8 for management.

#### 7.1.6 Temozolomide Dose Modifications During Concomitant Radiation Therapy

	<b>ANC (mm<sup>3</sup>)</b>		<b>Platelets (mm<sup>3</sup>)</b>	<b>Modification</b>
<b>Nadir</b>	$\geq$ 750 250-749 < 250	and or or	$\geq$ 75,000 25,000-74,999 < 25,000	100% 75 Dose% 50% Dose
<b>At scheduled time of administration</b>	$\geq$ 1500 < 1500	and and	$\geq$ 100,000 < 100,000	Dose modified for nadir only Hold for 1 week
<b>* After 1 week</b>	$\geq$ 1500 1000-1499 < 1000	and or or	$\geq$ 100,000 75,000-99,999 < 75,000	Dose modified for nadir only 75% Dose Contact study chair before further chemotherapy

\*Repetition of severe marrow depression, persistent neutropenia ( $< 1500/\text{mm}^3$ ), or thrombocytopenia ( $< 25,000/\text{mm}^3$ ) at time of treatment and after dose reduction will require

contacting the study chair before any further chemotherapy is administered. Further chemotherapy will be given only if there is joint agreement between the study chair and the individual investigator, and only 2 dose reductions will be allowed.

No dose reduction will be made, but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and nonhematologic adverse events (AEs), as specified below. If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded on the Treatment Summary Form (TF).

If one or more of the following are observed:

- ANC < 1.0 x 10<sup>9</sup>/L
- Platelet count < 75 x 10<sup>9</sup>/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue) then treatment with concomitant temozolomide will be withheld until all of the following conditions are met:
  - ANC ≥ 1.0 x 10<sup>9</sup>/L
  - Platelet count ≥ 75 x 10<sup>9</sup>/L
  - Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose as used initially.

If one or more of the following are observed:

- ANC < 0.5 x 10<sup>9</sup>/L (Grade 4)
- Platelet count < 10 x 10<sup>9</sup>/L (Grade 4)
- Grade 3 or 4 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue) then treatment with concomitant temozolomide should be **stopped**.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide should be stopped after 49 days of temozolomide treatment.

#### Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Grade	Action
ANC	≥ 0.5 and < 1.5 x 10 <sup>9</sup> /L	2, 3	Delay temozolomide until: --ANC ≥ 1.5 x 10 <sup>9</sup> /L -- platelet ≥ 75 x 10 <sup>9</sup> /L --Non-hem AE ≤1
Platelet	≥ 25 and < 70 x 10 <sup>9</sup> /L	2, 3	
Non-Hematologic (except alopecia, nausea/vomiting unless on maximal anti-emetic therapy)	N/A	3	
ANC	<0.5 x 10 <sup>9</sup> /L	4	<b>STOP</b> concomitant temozolomide
Platelet	< 25 x 10 <sup>9</sup> /L	4	
Non-Hematologic (except alopecia, nausea/vomiting unless on maximal anti-emetic therapy)	NA	4	

#### 7.1.6.1 Concomitant temozolomide, if radiotherapy is interrupted

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide should stop.

#### 7.1.7 Drug Therapy for Prophylaxis of Pneumocystis Prophylaxis

Beginning within 48 hours of starting temozolomide and radiation therapy, patients will receive *Pneumocystis carinii* prophylaxis with either trimethoprim-sulfamethoxazole or pentamidine. For patients allergic to sulfa compounds, pentamidine (or dapsone or atovaquone) will be the drug used; for other patients the choice is left to the discretion of the investigator.

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

- 7.1.7.1 Trimethoprim-sulfamethoxazole: 1 double-strength tablet (equivalent to trimethoprim 160 mg and sulfamethoxazole 800 mg)/day for 3 days consecutively each week during radiation treatment and for 2 weeks after the completion of radiation treatment. See Section 9.1.4.
- 7.1.7.2 Aerosolized pentamidine: Beginning within 48 hours of starting radiation therapy, patients will receive 300 mg of pentamidine every 28 days either by nebulizer mask or an inhalation tent until 14 days after the conclusion of radiation therapy. See Section 9.1.4.
- 7.1.7.3 Intravenous pentamidine: Beginning within 48 hours of starting radiation therapy, patients will receive 300 mg of pentamidine intravenously every 28 days until 14 days after the conclusion of radiation therapy. See Section 9.1.4.
- 7.1.7.4 Dapsone: A 50-mg tablet BID or 100 mg PO QD will be given daily during radiation treatment and for 2 weeks after the completion of radiation treatment. A G6PD qualitative assay is suggested prior to starting dapsone therapy. The most common toxicity of dapsone is hemolytic anemia, usually dose related and occurring with increased frequency in patients with G6PDH deficiency. It is recommended that determination of G6PDH activity in peripheral blood be established prior to starting dapsone therapy. In patients who develop clinically significant hemolytic anemia, the drug should be discontinued. If patients develop grade 2 neuropathy, dapsone should be discontinued. Patients with a prior type 1 hypersensitivity reaction should not be given dapsone for prophylaxis. See Section 9.1.4.
- 7.1.7.5 Atovaquone: Atovaquone may be used as an alternative for *Pneumocystis carinii* prophylaxis in this study. Atovaquone should be administered 1500 mg PO daily with food beginning on the day prior to starting radiation therapy and continuing for 14 days after completion of radiation therapy. See Section 9.1.4.

## **7.2 Post-Radiation Therapy (2/24/06, 8/14/08)**

### **7.2.1 Dosing Schedule**

Temozolomide will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle. The starting dose for the first cycle will be 150 mg/m<sup>2</sup>/day, with a single dose escalation to 200 mg/m<sup>2</sup>/day in subsequent cycles if no adverse events > grade 2 are noted.

**First cycle** Temozolomide will be started at a dose of 150 mg/m<sup>2</sup>/day, 28 days from the end of radiation therapy.

**Second cycle** The dose of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts.

- 7.2.1.1 The dose will be determined using the body surface area (BSA) calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit immediately before each cycle. Capsules of temozolomide are available in 5, 20, 100, 140, 180 and 250 mg. The daily dose will be rounded to the nearest 10 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.
- 7.2.1.2 Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). The start of the first cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days) after the first daily dose of temozolomide of the preceding cycle.
- 7.2.1.3 Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them.
- 7.2.1.4 If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- 7.2.1.5 Antiemetic prophylaxis with a 5-HT<sub>3</sub> antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration.
- 7.2.1.6 Duration of treatment

Patients will be treated with post-radiation temozolomide for 6 cycles unless there is evidence of tumor progression or treatment related toxicity. At the completion of 6 cycles, patients may receive up to an additional 6 cycles of treatment (therefore, a maximum of 12 cycles) if treatment has been well tolerated and at least one of the following criteria is met:

- Serial MR studies show continued tumor response as evidenced by reduction
- in tumor size
- The patient demonstrates progressive improvement in overall performance
- status
- The patient demonstrates clinical improvement by improvement in neurologic
- function
- The patient demonstrates ongoing treatment benefit by a decreasing
- requirement of corticosteroids

### 7.2.2 Dosing Modifications for Post-Radiation Temozolomide

Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

Dose Level	Dose, mg/m <sup>2</sup> /day	Remarks
-2	100	Reduction if prior AE
-1	125	Reduction if prior AE
0	150	Starting dose cycle 1 adjuvant
+1	200	Escalated dose at cycle 2, for cycles 2-12 in absence of AE

**Delay** On day 1 of each cycle (within the prior 72 hours), ANC  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$  and all grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade  $\leq 1$ ).

If AEs persists, treatment should be delayed by 1 week for up to 3 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with temozolomide should be stopped.

**Dose escalation** If, during the first cycle, all non-hematologic AEs observed were grade  $\leq 2$  (except alopecia, nausea and vomiting) and with platelets  $\geq 100 \times 10^9/L$  and ANC  $\geq 1.5 \times 10^9/L$ : then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing nonhematologic AEs of grade  $\geq 2$ , then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

**Dose reductions** If any non-hematologic AE observed was grade  $> 2$  (except alopecia, nausea and vomiting) and/or if platelets  $< 50 \times 10^9/L$  and/or ANC  $< 1 \times 10^9/L$ , then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level  $< 100$  mg/m<sup>2</sup>/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be stopped.

*Subsequent cycles (3-12):* Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

*Important:* If the dose was reduced or delayed for adverse events, there will be no dose escalation. The reason(s) for dose reduction and/or delay must be documented in the CRF.

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

<b>Worst Non-Hematologic AE (except alopecia, nausea and vomiting) During the Previous Cycles</b>	
<b>Grade</b>	<b>Dose Modification</b>
0-2	No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop.
4	Stop (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable.

Nadir Values		Platelets		
ANC		$\geq 100 \times 10^9/L$	50 -99 $\times 10^9/L$	$< 50 \times 10^9/L$
	$\geq 1.5 \times 10^9/L$	Escalation to L1 (cycle 2 only)	Dose Unchanged	Reduce by 1 dose level
	$\geq 1 \text{ \& } < 1.5 \times 10^9/L$	Dose Unchanged	Dose Unchanged	Reduce by 1 dose level
	$< 1 \times 10^9/L$	Reduce by 1 dose level	Reduce by 1 dose level	Reduce by 1 dose level

Note: A complete blood count must be performed 21 days (+/- 48 hours) after the first daily dose of each adjuvant treatment cycle.

<b>Hematologic AE on Day 1 of Each Cycle (within 72 hours before)</b>	
<b>AE</b>	<b>Delay</b>
ANC $< 1.5 \times 10^9/L$ and/or Platelet count $< 100 \times 10^9/L$	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

<b>Non- Hematologic AE (except alopecia, nausea and vomiting) on Day 1 of Each Cycle (within 72 hours before)</b>	
<b>Grade</b>	<b>Delay</b>
2-3	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

**7.3 MGd Agent Information (NSC# 695238) (8/14/08)**

**7.3.1** Chemical Name: Bis(acetato-Q)[9, 10 diethyl-20, 21-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl -8,11-imino-3,6:16, 13-dinitrilo-1,18-benzodiazacycloeicosine-5, 14-dipropanolato-N<sup>1</sup>,N<sup>18</sup>,N<sup>23</sup>,N<sup>24</sup>,N<sup>25</sup>]gadolinium hydrate

**7.3.2** Other Names: Xcytrin (motexafin gadolinium) Injection, Gd-tex, gadolinium texaphyrin (PCI-0120), gadolinium texaphyrin PEG, Gd texaphyrin, FP-GP1, MGd

**7.3.3** Classification: Antineoplastic (water soluble redox modulator)

**7.3.4** CAS Registry Number: 156436-89-4

**7.3.5** Molecular Formula: C<sub>52</sub>H<sub>72</sub>GdN<sub>5</sub>O<sub>14</sub>·xH<sub>2</sub>O (where x is typically between 0 and 2)

**7.3.6** M.W.: 1148.4(anhydrous)

**7.3.7** Mode of Action: MGd targets oxidative stress proteins such as metallothioneins and thioredoxin reductase. Targeting these proteins leads to oxidative damage, impaired metabolism and impaired metal ion homeostasis. These effects lead to apoptosis. Cells respond to this stress (MGd treatment) by upregulating cascades of genes under the transcriptional control of MTF-1, HIF-1 and NRF-2. These genes are primarily involved in cellular metabolism, redox balance and metal ion homeostasis (e.g. metallothioneins, HIF -1 alpha, heme oxygenase, heat shock protein and enzymes involved in glutathione synthesis).

MGd is tumor selective. Concentration of the drug in tumors occurs because cancer cells are under severe redox stress as a result of hypoxia, low pH and glycolytic metabolism. MGd has heightened or selective reactivity in cancers compared to normal tissues due to these abnormalities.

**7.3.8** Preparation and Administration: The MGd solution should be used without dilution. After the vial is opened, the study drug must be used within 8 hours or discarded. It must be filtered prior to use, using a sterile filter with a pore size of 5.0 µm (recommended supplier: Millipore Corporation; Bedford, Mass). The filtered solution must be transferred into a sterile IV bag (polypropylene, ethylvinyl acetate, or polyvinyl chloride) or sterile glass IV bottle. Motexafin gadolinium should not be administered through an in-line filter. The MGd solution should be administered through a peripheral IV site or a peripherally inserted central catheter or other indwelling catheter. If a central catheter, heparin or saline lock is used, it should be capped and maintained according to the study center's usual procedures.

The MGd solution should be infused IV over approximately 15 to 30 minutes as appropriate for the volume to be administered. The volume must be calculated to supply the protocol specified dose based on the patient's body weight. Dose calculations should be rounded to the nearest whole mL. For all dosing calculations, the patient's weight at screening will be used, unless a >15% change in body weight occurs during study participation. If such a change occurs, the MGd dose should be adjusted. When using an existing IV line, central catheter, heparin or saline lock, or other venous access device already in place, the tubing must be flushed with at least 10 mL of normal saline without preservative immediately before MGd administration. After administration, the IV tubing is to be flushed again with 10 mL of normal saline without preservative to clear it of MGd.

MGd provided for this study by the Sponsor is to be used only in patients enrolled specifically in this trial and may not be used in other persons or released to any third party, laboratory, or clinic for use in humans, or for in-vivo or in-vitro laboratory research, or for any other use, without the express written consent of the Sponsor. No investigative procedures other than those detailed in this protocol may be undertaken with MGd on enrolled patients or otherwise without prior written consent from the Sponsor.

**7.3.9** Storage: Store intact vials under refrigeration (2-8°C). Do not freeze. Protect from light.

**7.3.10** Stability: Intact vials are stable for at least 36 months at the labeled storage conditions (2-8°C). Stability studies of intact vials are ongoing. CAUTION: The single-use vial contains no antibacterial preservatives. Discard any unused portion immediately.

**7.3.11** Route of Administration: Intravenous

**7.3.12** Accountability and Supply

The Principal Investigator (or authorized designee listed by the Investigator on the site's most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request motexafin gadolinium from NCI's Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Room 7149, Bethesda, MD 20892.] All forms can be accessed on the NCI web site, <http://ctep.cancer.gov/forms/index.html>. The Investigator Brochure (IB) for this drug will be

supplied by the PMB/NCI. All requests for IBs should be e-mailed to [ibcoordinator@mail.nih.gov](mailto:ibcoordinator@mail.nih.gov) <mailto:ibcoordinator@mail.nih.gov> or the IB Coordinator may be contacted at 301-496-5725.

MGd is supplied by Pharmacyclics, Inc., and is distributed by the DCTD/NCI as a dark green 2.5 mg/mL solution in single use 50 mL vials. The solution is an isotonic solution in 5% mannitol that is adjusted to pH 5.4 with a small amount of acetic acid. (Please note that supplies distributed before December 2003, had a 2.3 mg/mL strength.)

### 7.3.13 Clinical Trials Agreement

The agent supplied by CTEP, DCTD, NCI used in this protocol (**motexafin gadolinium, or MGd**) is provided to the NCI under a Collaborative Agreement (CRADA) between the Pharmaceutical Company (**Pharmacyclics, Inc.**) (hereinafter referred to as “Collaborator”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (<http://ctep.cancer.gov/industry>) contained within the terms of award, apply to the use of the Agent in this study:

Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.

Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.-Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164

When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator’s wish to contact them.

Any data provided to Collaborator for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator for courtesy review at least five (5) days prior to submission. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

**Regulatory Affairs Branch, CTEP, DCTD, NCI**  
**Executive Plaza North, Suite 7111**  
**Bethesda, Maryland 20892**  
**FAX 301-402-1584**  
**Email: [anshers@ctep.nci.nih.gov](mailto:anshers@ctep.nci.nih.gov)**

The Regulatory Affairs Branch will then distribute them to Collaborator. No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

### 7.3.14 Adverse Events

The Comprehensive Adverse Events and Potential Risks List (CAEPR) for MGd is presented in the table below.

#### Comprehensive Adverse Events and Potential Risks List (CAEPR) for Motexafin Gadolinium (NSC 695238)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Motexafin Gadolinium.

Version 1.1, July 5, 2006<sup>1</sup>

Category (Body System)	Adverse Events with Possible Relationship to Motexafin Gadolinium (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
<b>ALLERGY/IMMUNOLOGY</b>		
	Allergic reaction/hypersensitivity (including drug fever)	<b><i>Allergic reaction/hypersensitivity (including drug fever)</i></b>
<b>BLOOD/BONE MARROW</b>		
	Blood/Bone Marrow - Other (G6PD hemolytic crisis)	<b><i>Blood/Bone Marrow - Other (G6PD hemolytic crisis)</i></b>
	Hemoglobin	<b><i>Hemoglobin</i></b>
	Platelets	<b><i>Platelets</i></b>
	Splenic function	<b><i>Splenic function</i></b>
<b>CARDIAC GENERAL</b>		
	Hypertension	<b><i>Hypertension</i></b>
	Hypotension	<b><i>Hypotension</i></b>
<b>CONSTITUTIONAL SYMPTOMS</b>		
	Fatigue (asthenia, lethargy, malaise)	
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	
	Rigors/chills	
<b>DERMATOLOGY/SKIN</b>		
	Dermatology/Skin - Other (Porphyria cutanea tarda)	
	Dermatology/Skin - Other (Transient greenish color of the skin)	
	Dermatology/Skin - Other (Pseudoporphyria)	
	Flushing	<b><i>Flushing</i></b>
	Injection site reaction/extravasation changes	<b><i>Injection site reaction/extravasation changes</i></b>
	Pruritus/itching	<b><i>Pruritus/itching</i></b>
	Rash/desquamation	
	Urticaria (hives, welts, wheals)	<b><i>Urticaria (hives, welts, wheals)</i></b>
<b>ENDOCRINE</b>		
	Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	<b><i>Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)</i></b>
	Neuroendocrine: gonadotropin secretion abnormality	<b><i>Neuroendocrine: gonadotropin secretion abnormality</i></b>
	Neuroendocrine: growth hormone secretion	<b><i>Neuroendocrine: growth hormone</i></b>

	abnormality	<b>secretion abnormality</b>
	Neuroendocrine: prolactin hormone secretion abnormality	<b>Neuroendocrine: prolactin hormone secretion abnormality</b>
	Thyroid function, high (hyperthyroidism, thyrotoxicosis)	<b>Thyroid function, high (hyperthyroidism, thyrotoxicosis)</b>
	Thyroid function, low (hypothyroidism)	<b>Thyroid function, low (hypothyroidism)</b>
<b>GASTROINTESTINAL</b>		
	Dehydration	<b>Dehydration</b>
	Diarrhea	
	Nausea	<b>Nausea</b>
	Necrosis, GI: small bowel NOS	<b>Necrosis, GI: small bowel NOS</b>
	Vomiting	<b>Vomiting</b>
<b>HEMORRHAGE/BLEEDING</b>		
	Hemorrhage, GI: lower GI NOS	<b>Hemorrhage, GI: lower GI NOS</b>
	Hemorrhage, GI: upper GI NOS	<b>Hemorrhage, GI: upper GI NOS</b>
	Hemorrhage, GU: urinary NOS	<b>Hemorrhage, GU: urinary NOS</b>
	Hemorrhage, pulmonary/upper respiratory: respiratory tract NOS	<b>Hemorrhage, pulmonary/upper respiratory: respiratory tract NOS</b>
<b>INFECTION</b>		
	Infection with unknown ANC - Select	<b>Infection with unknown ANC - Select</b>
<b>LYMPHATICS</b>		
	Edema: head and neck	<b>Edema: head and neck</b>
	Edema: limb	
<b>METABOLIC/LABORATORY</b>		
	Alkalosis (metabolic or respiratory)	<b>Alkalosis (metabolic or respiratory)</b>
	ALT, SGPT (serum glutamic pyruvic transaminase)	<b>ALT, SGPT (serum glutamic pyruvic transaminase)</b>
	AST, SGOT (serum glutamic oxaloacetic transaminase)	<b>AST, SGOT (serum glutamic oxaloacetic transaminase)</b>
	Bilirubin (hyperbilirubinemia)	<b>Bilirubin (hyperbilirubinemia)</b>
	Creatinine	<b>Creatinine</b>
	GGT (gamma-glutamyl transpeptidase)	
	Glucose, serum-high (hyperglycemia)	<b>Glucose, serum-high (hyperglycemia)</b>
	Phosphate, serum-low (hypophosphatemia)	
	Potassium, serum-low (hypokalemia)	<b>Potassium, serum-low (hypokalemia)</b>
	Proteinuria	<b>Proteinuria</b>
	Sodium, serum-low (hyponatremia)	<b>Sodium, serum-low (hyponatremia)</b>
<b>NEUROLOGY</b>		
	Ataxia (incoordination)	<b>Ataxia (incoordination)</b>
	CNS cerebrovascular ischemia	<b>CNS cerebrovascular ischemia</b>
	CNS necrosis/cystic progression <sup>2</sup>	
	Confusion	<b>Confusion</b>
	Mood alteration: agitation	
	Mood alteration: anxiety	<b>Mood alteration: anxiety</b>
	Neuropathy: motor	<b>Neuropathy: motor</b>
	Neuropathy: sensory	
	Seizure	<b>Seizure</b>
<b>OCULAR/VISUAL</b>		
	Ocular/Visual - Other (Transient greenish discoloration of sclera)	
	Vision-photophobia	<b>Vision-photophobia</b>
<b>PAIN</b>		
	Pain - abdomen NOS	<b>Pain - abdomen NOS</b>
	Pain - extremity-limb	
	Pain - head/headache	<b>Pain - head/headache</b>
	Pain - muscle	<b>Pain - muscle</b>
	Pain NOS	<b>Pain NOS</b>

<b>PULMONARY/UPPER RESPIRATORY</b>		
	Dyspnea (shortness of breath)	
	Hypoxia	<b>Hypoxia</b>
	Pneumonitis/pulmonary infiltrates	<b>Pneumonitis/pulmonary infiltrates</b>
	Pulmonary/Upper Respiratory - Other (Respiratory failure)	<b>Pulmonary/Upper Respiratory - Other (Respiratory failure)</b>
<b>RENAL/GENITOURINARY</b>		
	Renal failure	<b>Renal failure</b>
	Urine color change	
<b>VASCULAR</b>		
	Thrombosis/thrombus/embolism	<b>Thrombosis/thrombus/embolism</b>
	Vascular - Other (Vasodilation)	

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [ADEERSMD@tech-res.com](mailto:ADEERSMD@tech-res.com). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>CNS necrosis was observed only when Motexafin Gadolinium is administered along with radiation therapy.

**Also reported on Motexafin Gadolinium trials but with the relationship to Motexafin Gadolinium still undetermined:**

**BLOOD/BONE MARROW** - hemolysis

**CARDIAC ARRHYTHMIA** - sinus bradycardia; sinus tachycardia

**COAGULATION** - fibrinogen; INR

**CONSTITUTIONAL SYMPTOMS** - weight loss

**DERMATOLOGY/SKIN** - alopecia; bruising

**GASTROINTESTINAL** - anorexia; GI perforation; heartburn; mucositis/stomatitis (functional/symptomatic); small bowel obstruction; taste alteration

**HEPATOBIILIARY/PANCREAS** - liver dysfunction/failure; pancreatitis

**INFECTION** - febrile neutropenia

**MUSCULOSKELETAL/SOFT TISSUE** - muscle weakness

**NEUROLOGY** - apnea; dizziness; memory impairment; mental status; somnolence/depressed level of consciousness; speech impairment

**OCULAR/VISUAL** - optic disc edema; retinal detachment

**PAIN** - chest/thorax pain; joint pain; pain

**PULMONARY/UPPER RESPIRATORY** - ARDS; hiccoughs; hypoxemia

**RENAL/GENITOURINARY** - nephrolithiasis; renal tubular necrosis

**VASCULAR** - phlebitis

**Note:** Motexafin Gadolinium in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

#### **7.4 Temozolomide Agent Information (8/14/08)**

**7.4.1 Formulation:** Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lauryl sulfate NF.

**7.4.2 Other Names:** Temodar, methazolastone;

**7.4.3 Supply:** Temozolomide is manufactured by Schering-Plough and is commercially available. Temozolomide is IND exempt. For additional information, please refer to the complete prescribing information for temozolomide.

**7.4.4 Mode of Action:** Alkylating agent of imidazotetrazinone class.

**7.4.5 Storage and Stability:** The capsules are packaged in 30 cc, 28 mm, 48 Type I amber glass bottles (5 or 20 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.

- 7.4.6** Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and  $T_{max}$  increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

- 7.4.7** Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m<sup>2</sup>.

**7.4.8** Special Populations

- 7.4.8.1** Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m<sup>2</sup> has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CL<sub>Cr</sub> < 36 mL/min/m<sup>2</sup>).

Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

- 7.4.8.2** Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

- 7.4.8.3** Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

- 7.4.8.4** Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

- 7.4.9** Drug-Drug Interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the  $C_{max}$  or AUC values for temozolomide or MTIC.

Population Analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H<sub>2</sub>-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

- 7.4.10** Known Potential Adverse Events (Please see the temozolomide package insert for a comprehensive list of adverse events)

Hematologic: Thrombocytopenia, leukopenia, lymphocytopenia

Gastrointestinal: Nausea, vomiting, anorexia

Hepatic: Elevated liver enzymes (reversible)

Skin: Rash, alopecia

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

- 7.4.11** Dose-Limiting Adverse Events: Thrombocytopenia, neutropenia
- 7.4.12** Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.
- 7.4.13** Contraindications: Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.
- 7.4.14** Pregnancy Category D: Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.**

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

#### **7.5 Criteria for Removal From Protocol Treatment**

- Progression of disease;
- Adverse events unacceptable to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- A delay in chemotherapy > 2 weeks; call the Protocol Chair (David Brachman, M.D., 602-406-3170)
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.

#### **7.6 Modality Review**

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

Dr. Ashby will perform a Quality Assurance Review after complete data for the first 30 cases enrolled has been received at RTOG Headquarters. Dr. Ashby will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

#### **7.7 Adverse Events (8/14/08)**

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

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

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

**In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

#### 7.7.1 **Adverse Events (AEs)**

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

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via AdEERS.**

**NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.**

#### 7.7.2 **Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.**

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

**Definition of an SAE:** Any adverse drug experience occurring during any part of protocol treatment and for so days after that results in any of the following outcomes:

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.] Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically sponsored studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

**All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS.** Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

**SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

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

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

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

## 7.8 AdEERS Expedited Reporting Requirements (8/14/08)

CTEP defines routine AE reporting requirements for phase 1 and 2 trials as described in the tables below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

### Phase 1 Trials Utilizing an Agent Under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent [Motexafin Gadolinium]

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

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

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

**Phase 2 Trials Utilizing an Agent Under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent [Motexafin Gadolinium]**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:  
 AdEERS 24-hour notification followed by complete report within 5 calendar days for:  
 • Grade 4 and Grade 5 unexpected events  
 AdEERS 10 calendar day report:  
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization  
 • Grade 5 expected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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

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

## **8.0 SURGERY**

Not applicable to this study.

## **9.0 OTHER THERAPY**

### **9.1 Permitted Supportive Therapy (8/14/08)**

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

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

**9.1.2** Antiemetics: Patients should also be given antiemetics prior to each daily dose of temozolomide and MGd. The antiemetic and dosing will be left to the treating physician's discretion. Other antiemetics such as 5HT3 antagonists or lorazepam (Ativan®) PO BID may be used at the discretion of the investigator for late nausea and vomiting.

**9.1.3** Anticoagulants: Patients who are taking warfarin (Coumadin®) may participate in this study; however, it is recommended that international normalization ration (INR) or prothrombin time be monitored carefully. The frequency of INR determinations is left to the clinical judgment of the investigator. Subcutaneous heparin or fractionated heparin products are also permitted.

**9.1.4** Pneumocystis prophylaxis: All patients must receive prophylactic therapy to prevent *Pneumocystis pneumonia* during the concomitant administration of temozolomide and radiation therapy. Acceptable regimens are:

**9.1.4.1** Trimethoprim-sulfamethoxazole: Trimethoprim will be given at 160 mg/sulfamethoxazole 800 mg daily for 3 days each week, beginning on day 1 of radiation therapy and continuing for 14 days after completion or radiation therapy. Sulfa-trimethoprim may cause nausea, vomiting, malaise, pruritus, rash, fever, anemia, leukopenia, neutropenia, and thrombocytopenia. Allergic reactions including Stevens-Johnson syndrome, hepatic injury, pseudomembranous enterocolitis, renal problems that may lead to renal failure/diuresis, aplastic anemia, clotting disorders, hyperkalemia, hyponatremia, and hypoglycemia have occurred. (Please see the trimethoprim-sulfamethoxazole package insert for a comprehensive list of adverse events.)

**9.1.4.2** For subjects allergic to sulfa compounds, pentamidine (or dapsone or atovaquone) will be the drug used. The choice is left to the discretion of the investigator.

**9.1.4.2.1** Pentamidine: Aerosolized or intravenous pentamidine will be given at 300 mg every 28 days beginning on day 1 of radiation therapy and concluding 14 days after completion of radiation therapy. Pentamidine may cause: headache, allergic reaction leading to bronchospasm, shortness of breath, chills, rash, chest pain, cough, and metallic taste (occur in 10%-25% of patients); low white cell counts, low red cell counts, low platelet counts (uncommon; occur 1%-10% of patients); and liver injury that resembles hepatitis, vomiting, fatigue, fever, dizziness, hypotension, tachycardia, hypoglycemia, hyperglycemia, pancreatitis, kidney damage, collapsed lung (pneumothorax), and severe allergic reactions (rare; occur in fewer than 1%).

**9.1.4.2.2** Dapsone: A 50-mg tablet BID or 100 mg PO QD will be given daily during radiation treatment and for 2 weeks after the completion of radiation treatment. A G6PD qualitative assay is suggested prior to starting dapsone therapy. The most common toxicity of dapsone is hemolytic anemia, usually dose related and occurring with increased frequency in patients with G6PDH deficiency. It is recommended that determination of G6PDH activity in peripheral blood be established prior to starting dapsone therapy. Dapsone should be discontinued: (1) in patients who develop clinically significant hemolytic anemia; and (2) in patients who develop grade 2 neuropathy. Patients with a prior type 1 hypersensitivity reaction should not be given dapsone for prophylaxis. Uncommon side effects include peripheral neuropathy (usually dose related), abdominal pain, nausea, vomiting, pancreatitis, kidney injury, vertigo, blurred vision, tinnitus, fever, headache, lupus-like syndrome, and retinal and optic nerve damage. In some patients, visual loss associated with ischemic/hypoxic retinopathy or optic neuropathy related to severe hemolytic anemia has been irreversible. (Please see the dapsone package insert for a comprehensive list of adverse events.)

**9.1.4.2.3** Atovaquone: Atovaquone should be administered at 1500 mg PO daily with food beginning on the day prior to starting radiation therapy and continuing for 14 days after completion of

radiation therapy. Commonly seen side effects with atovaquone include rash, nausea, vomiting, diarrhea, headache, hyponatremia, cough, altered sense of taste, dizziness, insomnia, and fever/sweating. Uncommon side effects are fatigue, anemia, neutropenia, hypoglycemia, elevated amylase levels, and elevated transaminase levels. Rarely, vortex keratopathy, pancreatitis, acute renal impairment, and hypersensitivity rash are seen. (Please see the atovaquone package insert for a comprehensive list of adverse events.)

- 9.1.5** Growth Factors: Routine prophylactic use of granulocyte colony-stimulating factor (G-CSF) in the first course of therapy is *not* permitted, and secondary prophylaxis with G-CSF in subsequent courses is not generally recommended. Use of granulocyte macrophage colony-stimulating factor (GM-CSF) is not permitted at any time. However, prophylactic administration of G-CSF in a patient who is experiencing recurrent difficulties with neutropenia in subsequent cycles or therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion.
- 9.1.6** Infections are to be treated with the appropriate antibiotics and recorded.
- 9.1.7** Analgesics and any other medications are to be specified and their doses recorded.
- 9.1.8** Recall blisters post-sun exposure can be treated with Domeboro soaks. If neuropathy occurs, patients may be placed on gabapentin.
- 9.2** **Non-Permitted Therapy**
- 9.2.1** No other chemotherapy treatment is permitted during protocol treatment.

## **10.0** **TISSUE/SPECIMEN SUBMISSION**

### **10.1** **Tissue/Specimen Submission (8/14/08)**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking for patients who have consented to participate in the tissue banking component of the study.

### **10.2** **Specimen Collection for Tissue Banking (8/14/08)**

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

- 10.2.1** One H&E stained slide
- 10.2.2** A paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Biospecimen Resource. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- 10.2.3** A Pathology Report documenting that the submitted block, core, or slides contain tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.2.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource. The form must include the RTOG protocol number and patient's case number.
- 10.2.5** Submit materials for tissue banking to:

**Mailing Address: For Non-frozen Specimens Only**  
RTOG Biospecimen Resource  
University of California San Francisco  
Campus Box 1800  
1657 Scott Street, Room 223  
San Francisco, CA 94143-1800

**Courier Address (FedEx, DHL, etc.): For Frozen Specimens**  
RTOG Biospecimen Resource

University of California San Francisco  
1657 Scott Street, Room 223  
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu)

**10.3 Reimbursement (8/14/08)**

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

**10.4 Confidentiality/Storage (8/14/08)**

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

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

**10.4.2** Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

## 11.0 PATIENT ASSESSMENTS

### 11.1 Study Parameters (8/14/08)

Required Assessments	Pre-Treatment Evaluation	During Radiation Therapy	During Post-Radiation Chemotherapy	Follow up Per Section 12.1
History/Physical <sup>a</sup>	X <sup>g</sup>	X <sup>d</sup>	X <sup>d</sup>	X
Zubrod	X <sup>g</sup>			X
Neurological exam	X <sup>g</sup>	X <sup>d</sup>	X <sup>d</sup>	X
Skin Assessment		X <sup>f</sup>		
CBC with differential, platelets, ANC	X <sup>g</sup>	X <sup>b</sup>		X <sup>i</sup>
Blood chemistries <sup>e</sup>	X <sup>g</sup>	X <sup>b</sup>	X <sup>b</sup>	X <sup>i</sup>
Steroid/anticonvulsant levels	X <sup>g</sup>	X <sup>b</sup>		X <sup>i</sup>
Contrast-enhanced MRI	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>
Serum pregnancy test	X <sup>h</sup>			
Mini-mental status exam	X <sup>g</sup>	X <sup>i</sup>		X

- a. A complete history and physical and neurologic examination including documentation of all measurable disease as well as signs and symptoms.
- b. Blood chemistries and blood counts (CBC, differential, platelets, and ANC) will be done weekly during radiation therapy and until counts recover, then once per month (within 48 hours prior to the next chemotherapy cycle) during post-radiation chemotherapy. Counts will be continued monthly until they return to normal levels. Anticonvulsant levels, if applicable, will be done monthly during radiation therapy.
- c. Preoperatively, postoperatively within 28 days prior to registration (preferably within 72 hours of surgery), 21-28 days following completion of radiation therapy but prior to the start of the first post-chemoradiation temozolomide cycle, then every 2 months and at neurologic deterioration. A postoperative scan is not required if the patient was diagnosed by stereotactic biopsy and a pre-biopsy diagnostic MRI was performed.
- d. Neurologic and physical examinations will be performed weekly during radiation therapy, every month during chemotherapy, at completion of study therapy, then every 2 months at the end of study treatment, and at neurologic deterioration.
- e. Blood chemistries include total protein, albumin, calcium, phosphorus, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, and SGOT (AST) or SGPT (ALT).
- f. Weekly examination of skin in the treatment portal during radiation therapy.
- g. Within 14 days prior to registration.
- h. Within 5 days before study entry.
- i. At the physician's discretion.
- j. At the end of radiation treatment and then per follow-up schedule in Section 12.1.

### 11.2 Evaluation During Study

- 11.2.1 Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post-treatment and last up to 6 to 8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is therefore urged in diagnosing and treating recurrent tumor during the first 2 to 3 months post-irradiation.
- 11.2.2 Considering that radio-necrosis is usually indistinguishable from tumor progression by CT/MRI imaging, the use of Thallium-SPECT, PET, or spectroscopic MRI imaging is encouraged in all cases at the time of suspected progression/necrosis that have not been pathologically confirmed.
- 11.2.3 Overall survival will be measured from registration until death.

**11.2.4** Mental status will be measured by the mini-mental status exam (MMSE) prior to the start of protocol treatment, at the end of radiation therapy, and every 2 months thereafter.

**11.2.4.1** Instructions for Administration of MMSE

The MMSE can be administered by physicians, nurses, or assistants trained in the administration of this assessment. The person administering the MMSE should be sensitive to patients who may be embarrassed by their inability to answer these questions. Patients should be assured by explaining that this is another way to see how treatment may be affecting their brain tumor. It also needs to be made clear to the patient that it is very important to obtain this type of information directly from them. The test administrator should understand that either the correct answer is given or not and that there is no partial credit given.

**11.3** MRI Review

The serial MRI scans shall be examined at the institution by an independent reviewer, a neuro-radiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course. Preoperative and postoperative scans (if applicable) will be submitted to RTOG. The first follow-up scan done 21-28 days post radiation will be submitted within 6 weeks of the end of radiotherapy. Scans documenting progression will also be submitted.

**11.4** Overall Response

**11.4.1** Progression will be defined as a > 25% increase in tumor area (two diameters) provided that this scan was performed with the patient currently receiving, for at least 7 days, a dose of steroids that at least equals the dose he/she was taking at the time of the previous scan.

**11.4.2** If the patient meets the criteria in Section 11.4.1, no further protocol chemotherapy will be administered.

**11.4.3** Once progression is documented, subjects will be followed for overall survival but progression-free survival will be determined by the time point at which progression is documented under protocol guidelines. Subjects who demonstrate progression and who are removed from the treatment protocol may receive other therapeutic agents, including standard regimens or other experimental agents.

**11.5** Film Review

Dr. Brachman will review the baseline and follow-up scans on all patients who have responded, progressed, experienced an unexpected CNS toxicity, or died.

## **12.0 DATA COLLECTION**

Data should be submitted to:

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

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

### **12.1 Summary of Data Submission (8/14/08)**

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form <b>(A5)</b> Initial Evaluation Form <b>(I1)</b> Pretreatment MRI scan (both pre- and post-surgery) <b>(C1)</b> and reports <b>(C3)</b> Mini-Mental Status Exam <b>(MS)</b>	Within 2 weeks of study entry
<u>Final Dosimetry Information:</u> Daily Treatment Record <b>(T5)</b> Isodose Distribution <b>(T6)</b> in color Simulation or DRRs and port films of all fields <b>(TP)</b> Protocol Calculation Data <b>(TL)</b> Radiotherapy Form <b>(T1)</b> Follow-up MRI Scan & Report <b>(C1) (C3)</b>	Within 1 week of radiation therapy end      Within 6 weeks post-radiation therapy and at the time of progression/grade 3 adverse events
Treatment Form <b>(TF)</b> Adverse Event <b>(AE)</b>	Within 1 week of completion of concurrent chemotherapy, then after every cycle of post-radiation chemotherapy or early termination of chemotherapy
Follow-up Form <b>(F1)</b> Mini-Mental Status Exam <b>(MS)</b>	Every 2 months for 1 year, every 3 months for 2 years, every 6 months for 3 years, then annually; also at progression/relapse and at death if these events occur between scheduled follow-up intervals
Mini-Mental Status Exam <b>(MS)</b>	At the completion of the first, fourth, and sixth cycles of adjuvant chemotherapy
Adverse Event <b>(AE)</b>	At the conclusion of all protocol treatment, with each TF and F1 form as needed
Autopsy Report <b>(D3)</b>	As applicable

### **12.2 Scan Documentation**

The contrast-enhanced CT/MRI taken before surgery and the MRI after surgery (but prior to radiotherapy begins) must be submitted within 2 weeks of registration. Postoperative imaging is not required if a stereotactic biopsy was performed and the preoperative study was an MRI. If a postoperative MRI is required, it must be done within 28 days of registration and submitted to RTOG Headquarters. The follow-up MRI scan performed (1) 21-28 days post-radiation therapy but prior to the start of the first post-chemoradiation temozolomide cycle and (2) at the time of progression should also be submitted to RTOG Headquarters. The patient should consistently be followed with the same diagnostic study, with similar technique whenever possible.

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

#### **13.1.1 Phase I**

**13.1.1.1** To determine the MTD of MGd given concurrently with temozolomide and radiation therapy in patients with newly diagnosed supratentorial GBM.

#### **13.1.2 Phase II**

**13.1.2.1** To estimate the overall survival of patients with newly diagnosed supratentorial GBM treated with concurrent radiation, temozolomide, and MGd followed by post-radiation temozolomide.

**13.1.2.2** To determine the short- and long-term adverse effects of this treatment regimen.

**13.1.2.3** To estimate the progression-free survival of patients with newly diagnosed supratentorial GBM treated with concurrent radiation, temozolomide, and MGd followed by post-radiation temozolomide.

### **13.2 Background**

Stupp et al<sup>21</sup> report median survival time per recursive partitioning analysis (RPA) class from the European Organisation for Research and Treatment of Cancer (EORTC) phase III study of radiation therapy combined with temozolomide as 17.0, 14.6, and 11.8 months, for RPA class III, IV, and V, respectively. These median survival times correspond to hazard rates of 0.0281, 0.0502, and 0.0753, respectively. The RTOG current GBM database contains 1457 RPA class III through V patients (from RTOG studies 74-01 (arms 3 and 4), 79-18, 83-02, 90-06, 94-11), with a distribution of 17%, 45%, 38%, respectively. Combining the hazard rates from the EORTC trial based on the RPA distribution from the RTOG GBM database results in a combined hazard rate of 0.0506, which corresponds to a median survival time of 13.69 months. The sample size calculation will be based upon this fixed survival rate.

### **13.3 Sample Size**

**13.3.1** **Phase I:** The primary objective of this portion of this study is to establish the MTD of MGd when given in combination with temozolomide and radiation therapy. Patients will be followed for a minimum of 90 days from the start of radiation therapy and carefully evaluated with respect to treatment morbidity. A DLT is defined in this study as a grade 4 neurologic adverse event that is considered to be related to the radiation/temozolomide/MGd combination occurring within 21 days of the conclusion of radiation. If, at any time, a grade 5 adverse event is observed, then accrual will be suspended and the study chairs will review the event. **If the study chairs determine that the grade 5 toxicity is treatment related, the Executive Steering Committee will be notified; this committee will determine whether the dose level should be closed.** For each dose level, up to seven patients will be accrued to assure that there will be six eligible for treatment adverse event evaluation. A patient registered to the study who is found retrospectively not to meet the study eligibility criteria in Section 3 or who does not receive any MGd will be excluded from evaluation of treatment adverse events. A dose level of MGd will be considered acceptable if no more than 1 patient of the 6 experience a DLT. Should all seven patients be analyzable for adverse events, only the first six will be considered in the determination of DLTs. If the current level is considered acceptable, then dose escalation will occur. Otherwise, the preceding dose level will be declared the MTD. There will be a maximum of two dose level escalations. **Maximum sample size for the phase I portion of the study will be 21 patients.**

**13.3.2** **Phase II:** The primary objective of this portion of this study is to determine whether standard radiation therapy with temozolomide and MGd improves overall survival in GBM RPA class III-V patients, compared to the published survival results from the EORTC phase III trial (see 13.2). The sample size calculation uses a Z-test comparing the logarithm of the hazard ratio found in Schoenfeld and Richter (1982)<sup>45</sup> (adjusted for a single-arm trial). A similar formulation can be found in D. Collett's *Modelling Survival Data in Medical Research* (Sections 9.2, 9.3).<sup>46</sup> This trial aims to improve median survival time by 35% from 13.69 months to 18.48 months. Assuming at least an approximately exponential distribution of survival times, this improvement corresponds to a 26% reduction in hazard rate from 0.0506 to 0.0375 deaths per month, which is equivalent to a hazard ratio of 0.74. Sixty deaths are required for a Type I error rate of 0.10 (1-sided) with 85% statistical power to detect a decrease in hazard rate at least this large. These figures require 94 patients accrued over 12 months and at least 18 months of follow-up for each patient (i.e., 18 months of follow-up after accrual ends). Adjusting for a 95% eligibility/evaluability rate, 99 patients are needed in order to accrue 94 eligible patients. In summary, **the phase II portion of this study requires a total sample size of 99 patients.**

**13.3.3** Patients treated at the MTD from the phase I portion of the study will be included in the phase II portion of the study. Therefore, the maximum sample size needed is **113 patients**.

**13.4 Inclusion of Women and Minorities (8/14/08)**

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.<sup>47</sup> The RTOG found no difference in survival of GMB patients by race.<sup>48</sup> Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

The projected gender and ethnicity accruals appear below:

**Projected Distribution of Gender and Minorities**

<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	3	5	8
Not Hispanic or Latino	48	57	105
<b>Ethnic Category: Total</b>	<b>51</b>	<b>62</b>	<b>113</b>
<b>Racial Category</b>			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	6	7	13
Native Hawaiian or other Pacific Islander	1	0	1
White	44	54	98
<b>Racial Category: Total</b>	<b>51</b>	<b>62</b>	<b>113</b>

**13.5 Patient Accrual**

The study is projected to accrue five cases per month, based upon the monthly accrual for prior RTOG GBM studies and the fact that there will be another RTOG study in this patient population open simultaneously with this study. Allowing for low accrual during the first 6 months while institutions are obtaining institutional review board (IRB) approval, accrual should be completed within 28 months of study activation. If the average monthly accrual rate (excluding the first 6 months) is less than two patients, the study will be re-evaluated with respect to feasibility.

**13.6 Analyses Plans**

**13.6.1 Interim Analyses**

Interim reports with statistical analyses are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

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

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

**13.6.2 CDUS Tracking**

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

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

This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. All information reported in the interim analyses (Section 13.6.1) will be included in the final report. All eligible patients receiving any protocol drug will be included in the

efficacy analysis. Patients not included in the final analysis will be listed, with the reason for exclusion. Survival will be calculated as the time from registration until death, regardless of cause. Patients who are alive at the time of the last follow-up will be analyzed as censored observations. The hazard (death) rate will be calculated for each arm, using the Kaplan-Meier estimate of 18-month survival [hazard rate =  $-\ln(18\text{-month survival})/18$ ]. A one-sided Z-test, at a 0.10 significance level, will be performed to test the difference between the logarithm of the observed hazard rate and the logarithm of the fixed hazard rate of 0.0506 per month. The variance of the Z-statistic will be estimated by the reciprocal of the number of deaths at 18 months. A statistically significant result will support the development of a phase III trial comparing this regimen to the current standard at that time.

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

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## APPENDIX I (2/21/06, 8/14/08)

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

RTOG 0513

#### **A PHASE I/II TRIAL OF TEMOZOLOMIDE, MOTEXAFIN GADOLINIUM, AND 60 GY FRACTIONATED RADIATION FOR NEWLY DIAGNOSED SUPRATENTORIAL GLIOBLASTOMA MULTIFORME**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a brain tumor called a supratentorial glioblastoma multiforme (GBM), for which you have not yet received treatment other than surgery to biopsy or remove your tumor (meaning your tumor is “newly diagnosed”).

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

The purpose of this study is to find out what effects (good and bad) radiation therapy combined with temozolomide and motexafin gadolinium have on you and your cancer.

Motexafin gadolinium, or MGd, is a drug that builds up in cancer cells. In earlier studies using MGd in patients with brain tumors, more drug stayed in the cancer cells than in the normal cells. MGd may weaken cancer cells and help some types of chemotherapy and radiotherapy work better. MGd is an investigational drug that has not been approved by the FDA for treating brain tumors.

Temozolomide is a chemotherapy agent approved by the FDA for treating some brain tumors.

The standard treatment for a GBM is a combination of surgery, radiation therapy, and chemotherapy. Although there are treatments for newly diagnosed GBM, they are not curative. This research is being done because currently there is no curative treatment for newly diagnosed GBM.

#### **HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

About 113 people will take part in this study.

#### **WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?**

##### **Before you begin the study... (8/14/08)**

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be

done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Initial surgery to remove your tumor or biopsy to determine the type of tumor. Biopsy is the surgical removal of a small bit of tissue for examination under the microscope to determine the type of tumor
- Routine blood tests: blood counts, blood chemistries to check electrolytes, liver and kidney function
- Blood tests to determine the level of antiseizure medicine in your blood if you are taking antiseizure medicines.
- MRI scans
- Neurologic and physical examination including an assessment of your level of activity
- A list of the medications you are taking
- Mini-mental status exam (a test looking at your mental status that takes 5-10 minutes)
- Blood pregnancy test if you are able to bear children

#### **During the study... (8/14/08)**

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures to see how the study is affecting your body:

- Routine blood tests: blood counts and blood chemistries will be done once a week during your radiation therapy (about 6 weeks), then once a month during your post-radiation chemotherapy (within 48 hours of the start of your chemotherapy) and until your counts recover if they decrease as a result of your treatment
- Blood tests to determine the level of antiseizure medicine in your blood will be done monthly during treatment if you are taking antiseizure medicines
- Neurologic and physical examination including an assessment of your level of activity will be done weekly during radiation treatment and then every 2 months
- A list of the medications you are taking
- A list of any side effects you may be having as a result of your treatment
- Mini-mental status exam (a test looking at your mental status that takes 5-10 minutes) will be done at the end of your radiation therapy; at the completion of the first, fourth, and sixth cycles of your post-radiation chemotherapy; and then every 2 months
- An MRI of your head 21-28 days after the end of radiation before the start of the monthly chemotherapy and then every 2 months
- You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience.

During the study, you will receive outpatient treatment with radiation therapy, temozolomide chemotherapy, and motexafin gadolinium (MGd). You will also receive drugs to prevent some of the side effects of these treatments. Your therapy will consist of:

- Radiation treatments: These treatments will be given once a day, 5 days a week (Monday-Friday) for 30 treatments over 6 weeks.
- Temozolomide: Temozolomide is supplied as capsules. You will take them every day (7 days a week), by mouth at bedtime beginning the night before the first radiation treatment and continuing until the night before the last radiation treatment. Beginning 28 days after your last radiation treatment, you will take temozolomide for 5 days every 28 days for up to 12 months.
- MGd: MGd is a dark green medicine that you will receive through a vein in your arm over 10-30 minutes. Before you receive each MGd treatment you will be instructed to drink at least 16 ounces (2 glasses) of a non-alcoholic, caffeine-free fluid so that your body has enough water. (If your doctor feels you need it, you might also receive fluids through a vein in your arm before your MGd treatment begins).
  - During weeks 1 and 2 you will receive MGd infusions daily Monday-Friday.
  - During weeks 3-6 you will receive MGd infusions 3 times a week, most likely on Monday, Wednesday, and Friday.
  - You will receive each MGd infusion 2-5 hours before your radiation treatment.
- Therapy to prevent nausea and vomiting: Before each dose of MGd and temozolomide, you may receive a medicine to prevent nausea and vomiting.
- Therapy to prevent pneumonia: Because there is a risk of contracting a type of pneumonia called Pneumocystis pneumonia when you are receiving temozolomide at the same time as radiation therapy to the brain, you will receive a preventive treatment chosen by your doctor. This treatment will be one of the following options:
  - Trimethoprim-sulfamethoxazole: You will take these antibiotic pills daily for 3 days in a row every week while you are receiving radiation therapy and for 2 weeks after the conclusion of radiation.  
**or**
  - Pentamidine: If you take the inhaled form of this antibiotic (called aerosolized pentamidine), you will receive breathing treatments through an inhaler mask similar to an oxygen mask for 45 minutes once a month beginning on the day before radiation therapy and ending 2 weeks after the conclusion of radiation therapy. Alternatively, you may sit inside a small tent and breathe in the antibiotic in spray form in the air inside the tent. Instead of aerosolized pentamidine, you may receive pentamidine by intravenous infusion once a month beginning within 2 days before starting radiation therapy and ending 2 weeks after the conclusion of radiation therapy.  
**or**
  - Dapsone: You will take dapsone by mouth daily during radiation and for 2 weeks after the conclusion of radiation. If your doctor chooses to use

dapsone, you will have a blood test to make sure your body can properly break down the drug.

or

- Atovaquone: You will take atovaquone by mouth with food beginning the day before you start radiation therapy and continuing for 14 days after the conclusion of radiation therapy.

### **WHEN I AM FINISHED TAKING THE STUDY TREATMENT**

When you are finished taking the drug and radiation therapy, you will need these tests and procedures to check on the status of your tumor:

- Neurologic and physical examination including an assessment of your level of activity: Every 2 months
- A list of the medications you are taking: Every 2 months
- MRI scans: Every 2 months
- Mini-mental status exam (a test looking at your mental status that takes 5-10 minutes): Every 2 months for the first year, every 6 months for the next 3 years, then every year
- Blood tests if your doctor thinks they are necessary

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

You will receive radiation therapy plus drug therapy with temozolomide and MGd for 6 weeks. After you are finished taking the drugs and radiation therapy, the study doctor will ask you to visit the office for a follow-up exam 28 days after treatment. You will then be started on temozolomide for 5 days every 28 days for 6 months, and you will be asked to return to the office monthly during that time. After that, you will be asked to return to the doctor for a follow-up exam every 2 months indefinitely.

### **CAN I STOP BEING IN THE STUDY?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the temozolomide, MGd, and radiation therapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

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

**Risks and side effects related to temozolomide include those that are:**

Likely

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

Less Likely

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Diarrhea
- Fever
- Sores in your mouth
- Hair loss
- Rash
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration

Rare but Serious

- Decreased ability to carry out daily activities
- Pneumonia and other infections (NOTE: To try to prevent these infections, your study doctor will treat you with an antibiotic)

**Risks and side effects related to radiation therapy include those that are:**

Likely

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, possibly resulting in short-term hearing loss
- Fatigue
- Feeling of sluggishness, inactivity, or indifference

Less Likely

- Mental slowness
- Permanent hearing loss
- Cataracts
- Behavioral change
- Nausea
- Vomiting
- Dry mouth or altered taste
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of the arms and legs
- Temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness of the arms and legs

### Rare but Serious

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

### **Risks and side effects related to MGd include those that are: (8/14/08)**

#### Likely

- Temporary olive-green color of the skin, the white part of the eye, and urine; this discoloration is due to MGd's green color and generally resolves 1 to 3 days after the last MGd dose
- Nausea and vomiting, which can usually be prevented by taking medicine before MGd is given
- Lack or loss of energy
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration
- Skin reactions, such as a rash or temporary blisters on the hands, occasionally accompanied by changes in the fingernails
- Tingling in the fingers, hands, or arms
- Swelling in the hands or feet
- Diarrhea
- Headache

#### Less Likely

- General pain, including pain in the muscles, stomach, and arms/legs
- High blood pressure
- Low blood pressure
- Fever
- Chills
- Dehydration
- Flushing
- Sensitivity to light
- Hives, welts, and wheals
- Reaction at the injection site
- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Decreased hemoglobin level (anemia)
- High or low hormone levels, which may cause tiredness or irritability

### Rare but Serious

- Severe allergic reaction, which could include shortness of breath and swelling of the head and neck
- Blood clots/infiltrates in the lungs or lung inflammation, possibly leading to lung failure
- Pooling of blood in the arms/legs
- Blood in your urine
- Gastrointestinal bleeding

- A decrease in blood supply to the bowel, leading to possible peritonitis (inflammation or irritation of the lining of the abdominal wall)
- Aplastic anemia (a form of anemia in which the bone marrow dramatically decreases or stops blood cell production)
- High or low blood chemistry levels indicating problems with kidney or pancreatic function; kidney failure has been reported, but at much higher doses than given in this study
- Lack of oxygen to your brain
- Seizures
- Confusion
- Agitation and anxiety
- Problems with coordination
- Severe problems with muscles, including weakness, contractions, twitching, and muscle changes in one side of the body
- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.

**Note:** When given in combination with other drugs, MGd may cause a worsening of any side effect known to be caused by the other drugs. The combination may also cause side effects not previously associated with any of the drugs.

**Risks and side effects related to antibiotic treatments to prevent Pneumocystis pneumonia include those that are:**

**Trimethoprim-sulfamethoxazole**

Likely

- Itching
- Rash

Less Likely

- Decreased hemoglobin level (anemia)
- Feeling of general discomfort or uneasiness
- Fever
- Nausea
- Vomiting

Rare but Serious

- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration
- Aplastic anemia (a form of anemia in which the bone marrow dramatically decreases or stops blood cell production)
- Other abnormalities in blood tests
- Liver irritation resembling hepatitis
- Problems with kidney function, which may lead to increased urination and kidney failure

- Pseudomembranous colitis (a diarrheal disease that can occur in patients taking antibiotics and can cause watery diarrhea, fever, and abdominal cramping)
- Stevens-Johnson syndrome (a severe skin reaction similar to a bad burn that can involve the lining of the mouth and eye)

### **Pentamidine**

#### **Likely**

- Bronchospasm (difficulty breathing due to the squeezing of breathing passages in the lungs)
- Cough
- Shortness of breath
- Chills
- Rash
- Chest pain
- Headache
- Increased potassium levels in your blood

#### **Less Likely**

- Metallic taste, which may lead to decreased appetite

#### **Rare but Serious**

- Dizziness
- Abnormal heart rhythms
- Low blood pressure
- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Low red blood cell count, which may cause fatigue
- Low blood sugar
- High blood sugar
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)
- Kidney damage
- Liver irritation resembling hepatitis
- Vomiting
- Fever
- Fatigue
- Severe allergic reactions
- Collapsed lung

### **Dapsone**

#### **Less Likely**

- Abdominal pain
- Nausea
- Vomiting
- Kidney injury
- Vertigo (spinning sensation)
- Blurred vision
- Tinnitus (noises or buzzing in the ears)

- Fever
- Headache
- Lupus-like syndrome (might include joint pain, aching, rashes, fever, sores in the mouth, kidney injury), which usually resolves when drug is stopped
- Numbness, pins and needles, and loss of strength and coordination in the hands and feet due to injury to nerves in the arms and legs. Usually this improves if the dapsone is stopped.
- Low red blood cell count, caused by speeding up the break down of red cells. If you develop this problem dapsone will be stopped.

#### Rare but Serious

- Retinal and optic nerve damage, which may cause permanent visual loss or blindness
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)

#### Atovaquone

##### Likely

- Rash
- Nausea
- Vomiting
- Diarrhea
- Headache
- Low blood sodium
- Cough
- Altered sense of taste
- Dizziness
- Inability to sleep
- Fever/sweating

##### Less Likely

- Fatigue
- Low red blood cell count, which may cause fatigue
- Low white blood cell count, which may cause problems with infection
- Low blood sugar
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration

##### Rare but Serious

- Inflammation of the cornea of the eye, which may cause visual problems
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)
- Kidney problems
- Serious rash requiring stopping the drug and treatment with anti-inflammatory medicine

**Reproductive Risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing age and have not











