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CHILDREN'S ONCOLOGY GROUP

ACNS0126

A PHASE II STUDY OF TEMOZOLOMIDE IN THE TREATMENT OF CHILDREN WITH HIGH GRADE GLIOMA OR DIFFUSE INTRINSIC PONTINE GLIOMAS

A Groupwide Phase II Study

Target Tumors

1. Anaplastic Astrocytoma (WHO III)
2. Glioblastoma Multiforme (WHO IV)
3. Gliosarcoma
4. Diffuse Intrinsic Pontine Gliomas

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AGENT AND NSC#

Temozolomide (Temodar ®) NSC# 362856

STATEMENT OF CONFIDENTIALITY

CHILDREN'S ONCOLOGY GROUP

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ABSTRACT

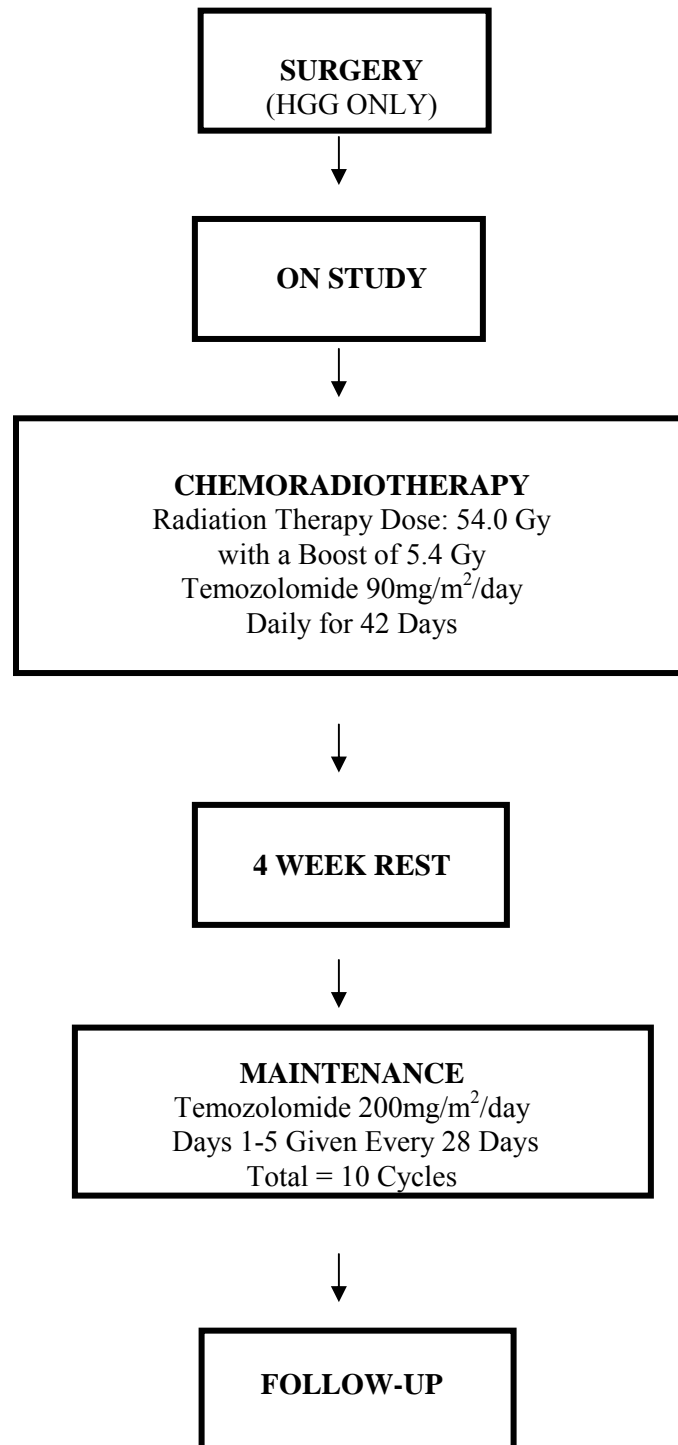
Children with high-grade gliomas (HGG) continue to have a poor prognosis, despite the use of multimodality therapy including surgery, XRT and chemotherapy. Surgery is necessary for histologic diagnosis although the impact of the extent of resection on outcome has been variable. While the benefit of extensive tumor resection is of some debate in adults,¹ there is general consensus that extent of tumor resection correlates with outcome in children.^{2,3} However, surgery alone is rarely curative – wide regional tumor infiltration beyond the primary tumor frustrates complete resections in all but the occasional tumor confined to polar locations. For older children and adults, radiation therapy (RT) remains the mainstay of therapy for HGG. With the exception of very young children, where an attempt has been made to eliminate or delay the use of RT because of concerns regarding neurodevelopmental morbidity, all patients are considered candidates for RT following surgery.

The efficacy of chemotherapy in addition to surgery and irradiation has been studied in several clinical trials during the last 2 decades. These clinical trials have provided data to support the use of adjuvant therapy in the treatment of patients with high-grade glioma; however, which agents to build upon in the adjuvant setting remains unsettled. This protocol is intended to pilot therapeutic strategies in a small number of patients and compare their outcome to those of historical controls culled from prior POG and CCG trials. This approach should allow for the rapid assessment of new therapeutic designs and serve as a model for the further study of treatment strategies in children with HGG.

Treatment options for DIPG are limited primarily due to their location as well as their frequent high grade pathology. Debulking surgery is not feasible, and surgical interventions are limited to biopsies in questionable cases. Radiation therapy has been the primary treatment modality for DIPG but, while useful in providing a period of disease stabilization and improved function, is not curative.^{4,5} Death in the vast majority of patients occurs within 6 months to 2 years from diagnosis. A variety of alternative interventions have been utilized including: adjuvant chemotherapy following XRT,^{6,7} high-dose therapy with stem cell rescue;⁸ and the use of radiosensitizing chemotherapy (e.g. cisplatin) during XRT.^{9,10} However, none of these approaches have resulted in an appreciable improvement in long-term survival. It is the poor prognosis associated with this tumor that warrants further exploration of novel treatments.

This trial will determine whether temozolomide given during radiation therapy and as adjuvant therapy results in an improvement in event-free survival compared to historical control cohorts. Temozolomide will be given concurrently with radiation therapy to newly diagnosed children with HGG or DIPG on a 42-day schedule. Four weeks following the completion of radiation therapy the patient will receive temozolomide daily for 5 days beginning a new cycle every 28 days for a total of 10 cycles.

July 6, 2004

EXPERIMENTAL DESIGN SCHEMA

July 6, 2004

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1

To determine whether temozolomide given during radiation therapy and as adjuvant therapy results in an improvement in event-free survival compared to historical control cohorts.

Target tumors are:

- Anaplastic Astrocytoma
- Glioblastoma Multiforme
- Gliosarcoma
- Diffuse Intrinsic Pontine Gliomas

1.2

To further assess the toxicity of temozolomide in a larger group of patients treated during XRT and during adjuvant treatment.

1.3

To evaluate the efficacy of temozolomide in the treatment of children with diffuse intrinsic pontine gliomas.

1.4

To monitor the toxicity of this therapy in the treatment of children with diffuse intrinsic pontine gliomas.

1.5 Laboratory Correlates (HGG Patients Only)

1.5.1

Investigate MGMT expression in formalin-fixed, paraffin-embedded biopsy specimens of brain tumors using immunohistochemical methods.

1.5.2

Identify those tumors in which MGMT expression is silenced by determining promoter CpG methylation in DNA isolated from formalin-fixed, paraffin-embedded tumor samples.

1.5.3

Investigate whether a functional MMR system is present in tumor cells by using microsatellite instability assays to compare DNA isolated from formalin-fixed paraffin-embedded tumor samples with DNA isolated from the patient's peripheral blood white cells.

1.5.4

Determine p53 expression using standardized immunohistochemical techniques. p53 mutation analysis will incorporate microdissection-based topographic genotyping and direct sequence analysis.

1.5.5

Determine MIB-1 indices in tumor samples using standardized immunohistochemical techniques.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Children with high-grade gliomas (HGG) continue to have a poor prognosis, despite the use of multimodality therapy including surgery, XRT and chemotherapy. Surgery is necessary for histologic diagnosis although the impact of the extent of resection on outcome has been variable. While the benefit of extensive tumor resection is of some debate in adults,¹ there is general consensus that extent of tumor resection correlates with outcome in children.^{2,3} However, surgery alone is rarely curative – wide regional tumor infiltration beyond the primary tumor frustrates complete resections in all but the occasional tumor confined to polar locations. For older children and adults, radiation therapy (RT) remains the mainstay of therapy for HGG. With the exception of very young children, where an attempt has been made to eliminate or delay the use of RT because of concerns regarding neurodevelopmental morbidity, all patients are considered candidates for RT following surgery. Newer techniques, such as conformal RT, which permit more precise delivery to the tumor bed are being investigated with respect to the ability to reduce treatment related morbidity.

The efficacy of chemotherapy in addition to surgery and irradiation has been studied in several clinical trials during the last 2 decades. The Children's Cancer Group (CCG) in study CCG-943 compared postoperative RT with prednisone, CCNU, and vincristine (pCV). In this study of 58 patients the addition of adjuvant chemotherapy was reported to result in a statistically significant improvement in outcome; 5 yr PFS was 46% for the group that received chemotherapy in addition to irradiation versus 18% for the group that received radiation therapy alone.¹¹ Further studies have not shown this same degree of improvement. In a later study, CCG-945 compared the "8-in-1" regimen¹² against the pCV of their prior 943 study. Median PFS and OS for the entire group was 16 and 26 months and there was no significant difference between treatment groups: 5-yr OS and PFS for the "8-in-1" vs. pCV regimens were 39 (\pm 7)% vs 29 (\pm 8)% and 33 (\pm 7)% vs 26 (\pm 8)%, respectively. Of note is that the survival associated with the pCV regimen was substantially inferior to that noted in the original 943 study,¹³ although this difference does not appear to reach statistical significance.¹⁴ In addition, a re-review of the initial histology has suggested that a substantial proportion of patients did not fit the definition of malignant glioma with 37.7% of patients classified by central consensus review as not having a HGG.¹⁵

As an alternate strategy, the Pediatric Oncology Group (POG) 8832 study utilized a pre-irradiation chemotherapy regimen with cisplatin-cytosine arabinoside in children with incompletely resected supratentorial neoplasms. The results of this study were similarly disappointing in that neither survival nor median time to progression (12 months) was improved over prior trials or historic controls. POG 9135 studied the use of cisplatin-BCNU versus cyclophosphamide-vincristine. The cisplatin-BCNU arm was associated with a 27 (\pm 9)% 5-yr. OS vs. 7% (\pm 7%) for cyclophosphamide-vincristine. Event-free survival was similarly contrasted at 20 (\pm 9)% vs. < 5%. Anecdotally encouraging results regarding the combination of cisplatin/BCNU have also been reported in adult patients with HGG.^{16,17} It remains uncertain whether cisplatin provides any incremental benefit beyond that of the nitrosoureas. In that context, prior experience utilizing cisplatin in children with brain tumors has suggested a limited role of this agent for patients with high-grade gliomas.¹⁸⁻²¹ Moreover, Grossman and colleagues recently reported the results of the Phase III study of neoadjuvant cisplatin-BCNU followed by XRT vs. XRT with adjuvant BCNU,²² which noted no advantage to the use of neoadjuvant chemotherapy in this trial, and suggested a limited role for cisplatin. The NCCTG 93-72-52 trial, a randomized study specifically evaluating the benefit for addition of cisplatin to BCNU, should be reported this year. Barring substantial evidence supporting a clear role for cisplatin in this trial, the further use of this agent in the treatment of HGG patients seems unwarranted.

Both CCG and POG have examined a number of other neoadjuvant approaches during the last several years. CCG-9933 compared three different alkylating agents (carboplatin, ifosfamide, and cytoxan) with etoposide. Results, while preliminary, suggested an unacceptably high rate of disease progression with an overall survival of 32% (± 6) and PFS of 15% (± 5) at 24 months. The arm containing carboplatin had the lowest rate of progressive disease.²³ POG 9436, which recently closed, utilized an upfront window design to assess the activity of procarbazine and topotecan in previously untreated patients. Survival data is too early to report, but neither procarbazine²⁴ nor topotecan²⁵ showed sufficient activity in the neoadjuvant setting to warrant further study. Given the results in these studies, enthusiasm has shifted away from pursuing additional neoadjuvant strategies at this time.

While there is data to support the use of adjuvant therapy in the treatment of patients with HGG, particularly those with anaplastic gliomas,²⁶ which agents to build upon in the adjuvant setting remains unsettled. Nitrosoureas have been an integral component of most trials, and this observation might argue for the inclusion of CCNU or BCNU in the design of further clinical trials. A retrospective analysis by Prados et al. suggests that BCNU alone showed comparable efficacy to PCV.²⁷ More compelling is the recently published report from the Medical Research Council Brain Tumour Working Party where 674 patients with high-grade astrocytoma were randomized to receive either XRT alone or XRT followed by adjuvant PCV. Median survival was 9.5 months for XRT and 10 months for XRT plus PCV with the trial showing no benefit to PCV chemotherapy.²⁸ Newer therapeutic approaches are warranted. This protocol is intended to pilot therapeutic strategies in a small number of patients and compare their outcome to those of historical controls culled from the prior POG 9135 and CCG-945 trials. This approach should allow for the rapid assessment of new therapeutic designs and serve as a model for the further study of treatment strategies in children with HGG.

The design of this study takes into account the fact that, in addition to the therapeutic challenges posed by these tumors, malignant gliomas have historically proven difficult to reliably classify by institutional neuropathologists. This factor has complicated analyses of prior studies of malignant glioma (MG), in which the frequency of discrepancies between institutional and central review diagnoses has been as high as 30%. This can, and has, resulted in incorrect conclusions regarding response and survival. A mechanism to address this issue prospectively is essential to ensure that the results of this study will establish a reliable baseline against which other adjuvant approaches for these tumors can be compared. Accordingly, all patients will have central review of their tumor by a panel of review pathologists. Final diagnosis will require a consensus opinion.

Known mechanisms of resistance to the DNA methylating action of temozolomide include both O⁶-methylguanine methyltransferase (MGMT, also referred to as alkylguanine-DNA alkyltransferase; AGT) and DNA mismatch repair (MMR) deficiency. MGMT is the proximal mechanism of resistance; removal of the methyl group from the O⁶ position of guanine to a cysteine residue within MGMT restores DNA to the intact state, thus abolishing the cytotoxicity of chloroethylating and methylating agents such as the nitrosoureas, procarbazine, and temozolomide. MGMT is reported to be commonly increased in many human tumors including malignant gliomas, and human studies have suggested that there is a relationship between clinical outcome and tumor MGMT levels.²⁹⁻³¹ Unlike chloroethylating agents, the DNA adduct resulting from temozolomide requires the presence of an intact MMR system. The ultimate cytotoxic event associated with temozolomide is the initiation of futile repair efforts and subsequent induction of apoptosis.^{32,33} *In vitro* and early clinical studies strongly suggest that a similar relationship exists between MMR and tumor response.^{34,35} Thus, an issue to explore in the treatment of malignant gliomas is the potential relationship between outcome and drug (temozolomide) resistance phenotype (tumor MMR and MGMT status). A report by Friedman et al suggested a relationship between response to temozolomide

and the immunocytochemical quantitation of MMR proteins (MSH2, MLH1) and MGMT among a small group of newly diagnosed adults with glioblastoma multiforme.³⁴ To better understand these relationships and their impact on the outcome of patients treated with temozolomide, the current study will incorporate a biologic analysis of these resistance mechanisms as potential correlates of clinical response. The information obtained may be of future value for predicting patient response to temozolomide and suggesting the use of alternative treatments in those with unfavorable biologic profiles.

This study will also provide correlative data on tumor biological and genotypic factors that may be associated with treatment response. In particular, recent publications from the group;³⁶⁻³⁸ based on the CCG-945 clinical study cohort have demonstrated that several biological markers are strongly associated with outcome in childhood malignant gliomas. In particular, a significant association was apparent between p53 overexpression and outcome. Five-year progression-free survival was 44 +/- 6 percent in 74 tumors with low levels of p53 expression versus 17 +/- 6 percent in 41 tumors with p53 overexpression ($P < 0.001$).³⁶ A weaker association was observed between TP53 mutations and outcome, although a strong interaction between age and frequency of p53 mutations was noted.³⁷ The association between p53 overexpression and adverse outcome was apparent even after stratifying for histologic subgrouping (e.g., anaplastic astrocytoma or glioblastoma multiforme, $P = 0.005$), as well as age, extent of resection, and tumor location ($P < 0.001$).³⁶ A similarly strong association was observed between MIB-1 labeling and outcome. Five-year event-free survival was 44% +/- 6% among 71 tumors with MIB-1 indices $< 18\%$, 30% +/- 8% in 33 tumors with indices between 18 and 36%, and 10% +/- 6% in 29 with indices $> 36\%$ ($P < 0.0001$).³⁸ Prognostic value transcended histologic subgroups ($P < 0.0001$), and was apparent in tumors classified as anaplastic astrocytoma (AA) ($P = 0.002$) and glioblastoma multiforme (GBM) ($P = 0.002$), notwithstanding the independent association between MIB-1 labeling index and histologic diagnosis (18.2 +/- 2.36 for AA versus 29.2 +/- 2.82 for GBM, $P = 0.004$).

Brainstem gliomas occur at any age but most commonly in children with a peak in the first decade of life.³⁹ Brainstem tumors are broadly divided into tectal, cervicomedullary and diffuse intrinsic pontine lesions. Diffuse intrinsic pontine gliomas (DIPG) are the most common and are associated with a very poor prognosis,⁴⁰ with death occurring in almost all children between 6 months and 2 years from diagnosis. The pathology of the diffuse intrinsic pontine tumor is a fibrillary astrocytoma. While some low-grade fibrillary tumors are seen (which may reflect sampling error, since most biopsies of such tumors are exceedingly small), the majority are high-grade lesions of both anaplastic astrocytoma and glioblastoma multiforme. Regardless of grade, prognosis is equally poor, and given the diagnostic appearance of these lesions on imaging evaluation, biopsy is currently reserved strictly for the rare cases in which the imaging features raise concern about an alternate diagnosis.

Treatment options for DIPG are limited primarily due to their location as well as their infiltrative, biologically malignant, growth characteristics. Debulking surgery is not feasible, and surgical interventions are limited to biopsies in questionable cases. Radiation therapy has been the primary treatment modality for DIPG but, while useful in providing a period of disease stabilization and improved function, is not curative.^{4,5} Death in the vast majority of patients occurs within 6 months to 2 years from diagnosis. A variety of alternative interventions have been utilized including: adjuvant chemotherapy following XRT;^{6,7} high-dose therapy with stem cell rescue;⁸ and the use of radiosensitizing chemotherapy (e.g. cisplatin) during XRT.^{9,10} However, none of these approaches have resulted in an appreciable improvement in long-term survival. It is the poor prognosis associated with this tumor that warrants further exploration of novel treatments.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Temozolomide, the methyl analog of mitozolomide, is a second-generation imidazotetrazine. Temozolomide demonstrated activity against murine tumor models⁴¹ and demonstrated preclinical activity against brain tumor xenografts⁴². Effectiveness appeared to be schedule dependent with oral dosing improving survival over single IP dosing.⁴¹

As an alkylating agent, temozolomide is considered to exert its effect by cross-linking DNA with site-specific alkylation at the O⁶-position of guanine⁴³ with some effect also at the N7 position.⁴⁴ Cytotoxicity of temozolomide requires the absence of mismatch repair proficiency in the tumor. As expected, temozolomide was more effective in tumors deficient in O⁶-guanine methyl transferase; this suicide enzyme is the proximal mechanism of drug resistance.⁴⁵

2.3 Adult Studies

The initial Phase I trial of temozolomide enrolled 51 patients who received temozolomide intravenously at doses between 50 and 200 mg/m², and 42 patients who received temozolomide orally.⁴⁶ The dose-limiting toxicity was myelosuppression. Grade 3 or 4 nausea and vomiting were noted in 9% of patients at the maximum tolerated dose (MTD). Other toxicities noted in the 180 evaluable courses of oral temozolomide included grade 3 or 4 anemia (5 courses), constipation (5), headache (3), alopecia (2), rash (1), renal (3), burning sensation of skin (2), esophagitis (1), pain (3), diarrhea (1), lethargy (1), and hepatotoxicity (4). A dosage of 750 mg/m² p.o. divided daily over 5 days (150 mg/m²/day) was recommended, with a dose escalation to 1000 mg/m² for patients who did not have significant myelosuppression by day 22. Among the responders were patients with gliomas.

A Phase II study of temozolomide against newly diagnosed and recurrent high-grade astrocytomas⁴⁷ identified major responses in 5 of 10 (50%) recurrent astrocytomas and 4 of 7 (57%) newly diagnosed patients. An additional Phase II study was reported for patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse.⁴⁸ This open-label, multicenter trial enrolled 162 patients of which 111 patients were confirmed to have eligible histology. Patients with no prior exposure to chemotherapy received dosing at 200 mg/m²/day x 5 days and those with prior chemotherapy began at 150 mg/m²/day x 5 days (the dose could be increased to 200 mg/m²/day in the absence of grade 3/4 toxicity). Oral therapy was scheduled on the first 5 days of each 28-day cycle. Objective responses were noted in 35% patients (8% CR, 27% PR) with an additional 26% with SD.

SP-138 was an industry-sponsored trial in which 33 patients with GBM and 18 patients with AA were enrolled. Patients received 4 cycles of the 5-day dosing schedule of temozolomide. The response rate for GBM was 48% (4CR/12PR/8SD) and for AA was 39% (2CR/5PR/6SD).

Stupp and colleagues recently reported on the use of temozolomide given during radiation therapy and in the adjuvant setting. Preliminary results were encouraging with an estimated one-year survival of 71% in these 37 patients.⁴⁹

2.3.1 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Temodar® (SCH 52365; temozolomide, TMZ) is a prodrug of the cytotoxic triazine MTIC (also the active metabolite of DTIC). Unlike DTIC, temozolomide spontaneously degrades to the active compound. Temozolomide has been shown to cross the blood brain barrier.⁴⁶ When administered either intraoperitoneally or orally, there is a rapid absorption phase with an elimination half-life of 1.29 hours po. Oral bioavailability was 0.98.⁴¹ Temodar® exhibits linear pharmacokinetics with increasing doses.

⁴⁶ The AUC seen in the British Phase I trial of 200 mg/m² of Temodar® was: single dose schedule 31.6 ± 3.95 (n=6); repeat dose schedule (Day 1) 32.9 ± 2.9 (n=4), repeat dose schedule (Day 5) 36.6 ± 2.4 (n=4).

Following oral administration of temozolomide to participants in the CCG Phase I study, TMZ was rapidly absorbed with maximal concentrations usually observed within 60 minutes of administration. Based on the assumption of 100% bioavailability (as previously documented in adult Phase I studies), the total apparent body clearance of Temodar® was ~100 ml/min/m² and the plasma elimination half-life was ~100 minutes. Plasma elimination half-life and apparent total body clearance values were constant over the dose range of 100-260 mg/m². Further, there was no appreciable difference in TMZ plasma elimination within patients when determined on Days 1 and 5 of the five day schedule. These findings were quite consistent with those previously reported in an adult Phase I European study⁴⁶ and in a recent U.S. Phase I adult trial.⁵⁰ The similarity in plasma elimination in adult and pediatric patients, across a substantial dose range, and between days 1 and 5 are all consistent with chemical degradation following administration. Temodar® is a chemically reactive alkylating species known to degrade in aqueous solutions relatively rapidly, and these results are consistent with chemical degradation playing a major role in TMZ plasma elimination.

2.4 Pediatric Studies

The Children's Cancer Group (CCG) conducted a Phase I study of temozolomide in children and adolescents with recurrent solid tumors.⁵¹ Twenty-two patients had received prior craniospinal irradiation (CSI) and 27 had not. The MTD was determined at 215 mg/m²/day x 5 days for children in the non-CSI group and 180 mg/m²/day x 5 days in the CSI-treated group. As in the adult studies, DLT was hematologic in all cases.

The United Kingdom Phase I study enrolled 27 children of whom 22 were evaluable for toxicity.⁵² For children with no prior craniospinal radiotherapy, the recommended Phase II dose was 200 mg/m²/day x 5 days. The trial was stopped prior to defining the dose for the craniospinal stratum. While not the primary endpoint of the trial, stable disease or partial responses were seen in children with brainstem gliomas and in those with high-grade gliomas with 7 of 16 (64%) demonstrating stable disease or a partial response after two cycles. One high-grade astrocytoma had a CR after 10 cycles.

A recent Phase II trial for children and adolescents with recurrent central nervous system tumors has just finished accruing patients in a combined intergroup trial between CCG and the Pediatric Oncology Group (POG). Non-CSI patients were treated at 200 mg/m²/day x 5 days and prior CSI patients at 150 mg/m²/day x 5 days. Activity in children with HGG was disappointing, although perhaps anticipated. This likely stems from the fact that the proximal mechanism of resistance to temozolomide (alkylguanine alkyltransferase removal of DNA adducts) is the same as for the nitrosoureas. The vast majority of patients in the Phase II setting have received prior nitrosoureas, thus selecting for a patient population anticipated to have developed resistance to this agent. This assertion is supported by the improved response rate for patients treated in the "up-front setting" as detailed above.

As mentioned previously, temozolomide has been previously utilized in combination with radiation therapy.⁵³ While there is no evidence to suggest a direct radiosensitizing effect, there is *in vitro* data to support the use of temozolomide and XRT concurrently.^{54,55} The temozolomide dosing will be modeled after the trial by Stupp.⁴⁹ Preliminary results of a multi-institutional Phase I trial in children utilizing a 42-day dosing schedule of TMZ has shown the regimen to be well tolerated (Cohen, personal communication).

Temozolomide is increasingly utilized in the treatment of fibrillary astrocytomas with evidence of activity in both high-grade gliomas⁵⁶ and low-grade gliomas.^{57,58} Efficacy of temozolomide appears to be most pronounced when given in the upfront setting^{49,53,56} although partial responses and prolonged periods of stable disease have been seen at the time of recurrence (Nicholson, personal communication and⁵⁹). It has been utilized for the treatment of diffuse intrinsic pontine gliomas (DIPG) at low-dose in the Phase I setting^{60,61} and as adjuvant therapy at the time of DIPG progression.⁶² Informal surveys of the neuro-oncologists within the COG indicate that many providers are utilizing temozolomide according to the schema of ACNS0126 for newly diagnosed children with DIPG. It seems prudent to capture this experience more formally.

2.5 Gender and Race Differences

Differences in ethnicity or gender from previous clinical trials have not been analyzed to date for response rate.

3.0 PATIENT ELIGIBILITY AND STUDY ENTRY

Note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). It must also be documented in the patient's medical research record that the criteria below have been satisfied.

3.1 Timing of Enrollment and Start of Treatment

3.1.1

Patients must be scheduled to begin treatment within 42 days from the time of surgical resection.

3.1.2

Patients must be enrolled before treatment begins. The start of treatment must be planned to begin within 14 days of study enrollment.

3.2 Patient Status

3.2.1 Age

Patients must be ≥ 3 years and <22 years at the time of enrollment.

3.2.2 Histologic Diagnosis

3.2.2.1 High-Grade Glioma

Patients must have a newly diagnosed CNS tumor as: Anaplastic Astrocytoma, Glioblastoma Multiforme, Gliosarcoma. Patients must have histologic verification of diagnosis. Patients with primary spinal cord malignant gliomas are eligible.

Patients with M+ disease (defined as evidence of neuraxis dissemination by spinal MRI or metastatic disease) are not eligible. Diagnostic CSF cytology is not required. If, however, CSF is obtained and the cytology proves positive, the patient would be considered to have metastatic disease and would, therefore, be ineligible.

Either tissue blocks or paraffin fixed slides for pathology review and paraffin-fixed slides and micron sections for biology studies must be submitted prior to the start of maintenance. In addition, a 5ml pre-treatment peripheral blood specimen is also required (See Section 12.3). Failure to provide specimens will make patient ineligible.

3.2.2.2 Diffuse Intrinsic Pontine Gliomas

Patients with newly diagnosed diffuse intrinsic brain stem glioma as diagnosed by gadolinium enhanced MRI are eligible. BIOPSY IS NEITHER REQUIRED NOR RECOMMENDED. MRI must demonstrate that at least 2/3 of the tumor is situated in the pons and that the origin of the tumor is clearly in the pons.

Imaging studies of the spine should be undertaken if clinically indicated. Presence of diffuse leptomeningeal disease excludes the patient from eligibility. Tumors with features not typical of diffuse intrinsic brainstem glioma are not eligible. These include dorsally exophytic brainstem gliomas, cervico-medullary junction tumors, and focal low grade gliomas of the midbrain or brainstem which should undergo resection and pathologic evaluation. Patients with diffuse brainstem enlargement due to neurofibromatosis are not eligible.

3.2.3 Performance Level

Patients must have a Lansky/Karnofsky performance status of 50-100 (Appendix I).

3.2.4 Life Expectancy

Patients must have a life expectancy of ≥ 2 months.

3.3 **Prior Therapy**

Patients must be newly diagnosed and previously untreated for the current diagnosis.

3.4 **Concomitant Medications**

Patients with CNS tumors who are receiving steroids are eligible.

3.5 **Organ Function Requirements**

All patients must have:

3.5.1 Adequate Bone Marrow Function Defined As

- Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
- Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent)
- Hemoglobin $\geq 10.0 \text{ gm/dL}$ (transfusion independent)

3.5.2 Adequate Renal Function Defined As

- Serum creatinine $\leq 1.5 \times$ institutional upper limit of normal for age

3.5.3 Adequate Liver Function Defined As

- Total bilirubin $\leq 1.5 \times$ institutional upper limit of normal for age
- SGPT (ALT) or SGOT (AST) $< 2.5 \times$ institutional upper limit of normal for age.

3.5.4 Central Nervous System Function Defined As

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

3.6 Pregnancy/Contraception

Temozolomide is potentially mutagenic and cytotoxic. Therefore, there is reason to believe it can be harmful to a developing fetus. It is not known whether Temozolomide is excreted in human milk and therefore, should not be used by nursing women.

Females > 13 years of age or who have achieved menarche must have a negative pregnancy test within 2 weeks of starting treatment (urine or serum) to be eligible. Patients must agree not to become pregnant during the trial and for 2 months afterwards. Patients who have recently delivered an infant must agree not to breast feed while on study.

Male sexually active patients must agree to use an effective method of contraception.

3.7 Exclusion Criteria

Patients with second malignancies are not eligible. Patients with M+ disease are not eligible.

3.8 Regulatory

3.8.1

All patients and/or their parents or legal guardians must sign a written informed consent.

3.8.2

All institutional, FDA, and NCI requirements for human studies must be met.

3.9 Study Enrollment

3.9.1 IRB Approval

Upon receipt of local IRB approval for a COG study, fax the officially signed copy to the Group Operations Center (GOC) at: (626) 445-6715. The *COG IRB Approval Fax Cover Sheet* is required to be faxed with the official approval. A copy of this cover memo can be obtained from the protocol links area of the Protocol Section on the COG website. After this approval is recorded by GOC staff, the institution will have access to the RDE enrollment screens.

3.9.2 Patient Registration

Prior to study enrollment, all patients must have been registered via the RDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. Please use this number as part of the labeling information on all banking and biology specimens sent to the Biopathology Center or a COG Reference Laboratory. If you have a question about a patient's BPC Number, please call the Biopathology Center at (800) 347-2486.

4.0 TREATMENT PLAN

4.1 Treatment Plan Overview

All patients must begin therapy within 42 days of surgery (for HGG) or within 42 days of diagnosis (for DIPG). Radiation will be given in standard fractions (total dose 59.4 Gy). (See Section 10.0). During radiation, patients will receive Temozolomide daily for 42 days. Patients will begin Maintenance therapy with Temozolomide 4 weeks after the completion of the 42 day course of Temozolomide.

Different Temozolomide doses and schedules will be used during the Chemoradiotherapy and Maintenance Phases.

There have been multiple episodes of PCP reported in patients receiving Temozolomide, particularly when taking corticosteroids. For this reason, patients should receive *Pneumocystis carinii* pneumonia prophylaxis during treatment. However, there have been three reports of prolonged myelosuppression and death in older adults receiving chemoradiotherapy with temozolomide at low-dose along with TMP/SMX prophylaxis. For this reason, TMP/SMX may not be utilized as PCP prophylaxis during chemoradiotherapy. Monthly inhaled or IV pentamidine or an appropriate alternative must be administered during chemoradiotherapy.

TMP/SMX may be substituted during adjuvant, 5-day temozolomide. PCP prophylaxis should be discontinued 3 months after chemotherapy has discontinued.

4.2 Chemoradiotherapy

4.2.1 Radiation Therapy

The goal of treatment planning and dose prescription is that dose to the ICRU reference point shall be 54.0 Gy given over 6 weeks. The boost volume, when present, will receive an additional 5.4 Gy for a total of 59.4 Gy.

4.2.2 Temozolomide

Temozolomide 90mg/m²/day PO daily for 42 days during radiation therapy. Temozolomide must begin by Day 5 of irradiation. See Appendix II and Appendix III for dosing requirements. The 42 days of Temozolomide should be given, regardless of end date of XRT and accounting for interruption. It is recommended that Temozolomide be given at bedtime with antiemetics given 30 minutes prior to the Temozolomide dose.

4.3 Maintenance

Maintenance consists of ten cycles of chemotherapy. Maintenance will commence four weeks after the completion of radiation. Cycles will be repeated every 28 days provided the patient has met the following criteria:

- Peripheral absolute neutrophil count (ANC) $\geq 750/\mu\text{l}$
- Platelet Count $> 75,000/\mu\text{l}$ (transfusion independent)
- Serum creatinine $\leq 1.5 \times$ normal for age
- Total bilirubin $\leq 1.5 \times$ normal for age, and SGPT (ALT) or SGOT (AST) $< 2.5 \times$ normal for age.

4.3.1 Temozolomide

Temozolomide 200mg/m²/day PO Days 1-5 of each 28 day cycle. Maintenance consists of 10 cycles. See Appendix II and Appendix IV for dosing and administration.

4.4 Dose Modifications Based on Toxicity

4.4.1 Dose Reduction During Chemoradiotherapy

4.4.1.1 Non-Hematologic

All grade 4 non-hematologic toxicities should be reported to the study chair.

If grade 3 or 4 non-hematologic toxicity occurs, interrupt temozolomide for 7 days and restart at the prescribed dose provided toxicity is no greater than Grade I. If this criteria has not been met following 7 days of drug interruption, contact the Study Chair.

4.4.1.2

Hold Temozolomide for Grade 3 or 4 vomiting in the presence of appropriate anti-emetic support. If unable to restart temozolomide within 7 days at the prescribed dose, contact the Study Chair.

4.4.1.3 Hematologic

Grade 4 hematologic toxicity requires an interruption of temozolomide for 7 days. Temozolomide can be restarted at the prescribed dose provided the following count criteria are met after a 7 day interruption:

Peripheral absolute neutrophil count (ANC) $\geq 750/\mu\text{L}$

Platelet count $\geq 75,000/\mu\text{L}$ (transfusion independent)

Hemoglobin $\geq 8 \text{ gm/dL}$ (transfusion independent).

If blood counts are not adequate after a 7 day interruption, check counts on Day 10 and if required Day 14. If count criteria has not been met by Day 14 contact the Study Chair.

4.4.2 Dose Reduction During Maintenance

Patients with Grade 3 or 4 hematologic toxicity resulting in delays beyond day 35 from their prior cycle of treatment, will have their subsequent dose decreased to 150 mg/m². Further dose reductions will be done only with the approval of the Study Chair.

If grade 3 or 4 non-hematologic toxicity occurs, delay the start of the next maintenance cycle for 7 days and restart at the prescribed dose provided toxicity is no greater than Grade 1. If this criteria has not been met following a 7 day delay, contact the study chair.

5.0 SUPPORTIVE CARE

5.1 Venous Access

An indwelling central venous access catheter is recommended but optional to facilitate the use of sedation/anesthesia in young children in addition to obtaining blood samples.

5.2 Antiemetics

Appropriate antiemetics should be administered prophylactically and as needed. Corticosteroids should not be used as an antiemetic.

5.3 Cytokine Support

No cytokine support is to be routinely administered to children on this protocol. Participants experiencing neutropenia may receive filgrastim (G-CSF) following approval by the study chair.

5.4 **Fever and Neutropenia**

Patients who develop a fever should be evaluated for neutropenia and infection. Antibiotics should be administered based on institutional policy.

5.5 **Prophylactic Antibiotics**

There have been multiple episodes of PCP reported in patients receiving Temozolomide, particularly when taking corticosteroids. For this reason, patients should receive *Pneumocystis carinii* pneumonia prophylaxis during treatment. However, there have been three reports of prolonged myelosuppression and death in older adults receiving chemoradiotherapy with temozolomide at low-dose along with TMP/SMX prophylaxis. For this reason, TMP/SMX may not be utilized as PCP prophylaxis during chemoradiotherapy. Monthly inhaled or IV pentamidine or an appropriate alternative must be administered during chemoradiotherapy.

TMP/SMX may be substituted during adjuvant, 5-day temozolomide. PCP prophylaxis should be discontinued 3 months after chemotherapy has discontinued.

5.6 **Blood Products**

Packed red blood cells should be given for symptomatic anemia. Platelets should be transfused as required to reduce the possibility of hemorrhage. All blood products should be irradiated to prevent GVHD.

5.7 **Steroids**

Corticosteroid therapy is permissible only for treatment of increased intracranial pressure in patients with CNS tumors.

6.0 REQUIRED OBSERVATIONS

6.1 Required Observations Before and During Protocol Therapy

Observation	Prior to Study Entry	During ChemoRT	Prior to each Maintenance Cycle	At Completion of Therapy
History	X	Week 7	X	
Physical Exam including Ht, Wt, BSA, VS	X	Week 7	X	
Performance Status	X	Week 7	X	
CBC, differential, platelets	X	Weekly	X	X ¹
BUN, Creatinine	X	Weeks 3 and 7	X	X ¹
SGPT, SGOT, bilirubin	X	Weeks 3 and 7	X	X ¹
MRI of brain with gadolinium	X	NA	Prior to each odd number cycle	X ²
MRI of spine with gadolinium	X ³			
Pregnancy Test (Urine or Serum)	X ⁴			
Required Specimens for Pathology (see Section 12.2) and Biology Studies (see Section 12.3)	X			

1. - Obtain on Day 28 of maintenance cycle 10. Repeat weekly until results are normal.
2. - Obtain 3-4 weeks following the final temozolomide administration on Cycle 10.
3. - If positive for neuraxis dissemination, then patient is ineligible.
4. - Obtain within 2 weeks of starting treatment.

6.2 Required Observations Following Completion of Protocol Therapy

Observation	3 Months	6 Months	9 Months	1 Year	1.5 Years	2 Years	2.5 Years	3 Years	3.5 Years	Annually
History	X	X	X	X	X	X	X	X	X	X
Physical Exam including Ht, Wt, BSA, VS	X	X	X	X	X	X	X	X	X	X
MRI of Brain with Gadolinium	X	X	X	X	X	X	X	X	X	X

7.0 DRUG INFORMATION

7.1 Temozolomide (Temodar™) NSC # 362856

Source and Pharmacology: An orally administered alkylating agent, a second generation imadazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. Exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the O⁶-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13hr (intraperitoneally) and 1.29hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100ml/min/m² and plasma elimination half-life is ~100 minutes.

Toxicity:

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Anorexia, nausea, vomiting, abdominal pain, diarrhea, constipation, headache, rash, itching, urinary frequency and/or infection	Convulsions, hemiparesis, dizziness, ataxia, confusion, dysphagia, anxiety, thrombo-embolism (L)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression	Mucositis, lethargy, peripheral edema	Myelosuppression for prolonged periods with increased risk of infection or death, amnesia, insomnia, depression, myalgia, diplopia, visual changes
Delayed: Anytime later during therapy, excluding the above conditions		Alopecia, hepatotoxicity	
Late: Anytime after completion of therapy			Secondary tumors or cancer

¹ Only with high doses (L) Toxicity may also occur later.

Formulation and Stability: 5mg, 20mg, 100mg, 250mg capsules, stored at room temperature.

Guidelines for Administration: Dose should be rounded to the nearest 5mg. See Appendix II and III.

Supplier: Capsules are commercially available. See package insert for further information.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal From Protocol Therapy

- a) Progressive disease as defined in Section 13.4
- b) Parent/patient request
- c) Completion of Chemoradiotherapy and Maintenance therapy
- d) Any patient who develops hypersensitivity to temozolomide
- e) Non-compliance with study medication
- f) Patient withdrawn from protocol therapy due to physician's choice

Patients who are off protocol therapy are to be followed until they meet the criteria for off study (see below). Follow-up data will be required.

8.2 Off Study Criteria

- a) Death
- b) Lost to follow-up
- c) Entry into another COG therapeutic study
- d) Failure to submit specimens for pathology review and biology studies (HGG patients only)

9.0 NEUROSURGICAL GUIDELINES (FOR PATIENTS WITH HGG ONLY)

9.1 Neurosurgical Procedures

There are no standard neurosurgical procedures for high-grade astrocytomas. The extent of surgical resection will depend upon the location of the tumor within the brain, and its vascularity. Patients potentially eligible for this study will undergo a neurosurgical procedure in which the diagnosis will be pathologically confirmed. When feasible, an attempt will be made to carry out a "gross total" tumor removal; if not feasible, an attempt will be made to remove as much tumor as possible without jeopardizing the patient. If even a subtotal or partial resection is considered hazardous to the patient, then a biopsy procedure must be performed in order to make a pathologic diagnosis. **No patient will be eligible for this study without a pathologic diagnosis and sufficient specimens for the biologic studies.**

9.2 Definitions of Extent of Resection

9.2.1 Biopsy Only

An open surgical removal or closed (e.g. needle) removal of tissue for the sole purpose of making a pathologic diagnosis. If tumor removal is less than 10% of the total tumor mass, this will be considered a biopsy only.

9.2.2 Partial Resection

The surgical removal of greater than 10%, but less than 50%, of the tumor mass.

9.2.3 Subtotal Resection

The surgical removal of greater than or equal to 50%, but less than 90%, of the tumor mass.

9.2.4 Extensive Subtotal Resection

Resection of greater than or equal to 90% of the tumor mass, but residual disease apparent on inspection.

9.2.5

An attempt should be made to estimate the volume of the residual tumor in cm³.

9.3 MRI Scan Confirmation of Extent of Resection

All patients must have confirmation of the neurosurgical opinion of the extent of resection by a post-operative enhanced MRI scan. This scan should be carried out within the first three post-operative days (72 hours), if possible, preferably within 24 hours of surgery.

9.4 Peri-operative Corticosteroids

Some patients with large tumors may require initiation of corticosteroid therapy pre-operatively to reduce associated brain edema.

Usual corticosteroid dosage is 0.25 to 0.5 mg/kg/day of Decadron, in divided doses every 4-6 hours.

Corticosteroids may be continued during the peri-operative period; however, every attempt should be made to taper and discontinue corticosteroid therapy as soon as clinically feasible.

10.0 RADIATION THERAPY GUIDELINES FOR HIGH GRADE GLIOMA

Radiation Therapy is to start within 6 weeks of the operative procedure. Standard and conformal techniques will be allowed in this study. A total dose of 59.4 Gy in 33 fractions over 7 weeks will be delivered with the combination of the initial and boost field techniques. If a Gross Total Resection has been performed, there will be no boost. The final dose for these patients with no gross residual tumor is 54 Gy. For the rare patient with a spinal cord malignant glioma primary, the radiation oncologist, Robert Lavey, M.D., must be contacted for treatment guidelines. Institutions using volume based treatment planning must have an approved 3D benchmark on file at QARC. If IMRT is used, the IMRT Questionnaire and Benchmark must be submitted and approved before the case can be evaluated. Contact QARC or see www.QARC.org for the benchmark materials.

10.1 Equipment

Modality: X-rays with nominal energy of 4 MV or greater. Co-60 is not allowed on this study.

Calibration: The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

10.2 High Grade Glioma Patients

10.2.1 Target Volumes

Evaluation of the tumor volume is made with contrast-enhanced MRI at two intervals, each one used to define a specific clinical target volume.

Clinical Target Volume	Image based CTV definition	Planning Target	PTV definition	Timing
CTV-1	T1-enhanced MRI + 2 cm	PTV-1	CTV-1 plus 3 - 5 mm	Pre-operative
CTV-2	Residual tumor (enhancing lesion) + 1 cm	PTV-2	CTV-2 plus 3 - 5 mm	Post-operative

Pre and post-operative MRI are used to define the GTV. However, for CT based treatment planning purposes, administration of IV contrast at the time of CT acquisition is encouraged. This will facilitate identification of MRI based target volume on planning CT. Use of fusion image registration software is encouraged, if available.

10.2.2 Clinical Target Volume 1

The pre-operative MRI is used to define the large clinical target volume (CTV-1) treated in all patients. The clinical target volume 1 (CTV-1) is based upon MRI taken prior to surgery

The clinical target volume shall include all enhancing areas of brain tissue on a T1 enhanced MRI study with a 2 cm margin in all directions. The definition of the clinical target volume should consider the possible movement of brain tissue into a resection cavity.

Planning target volume (PTV1) shall include the CTV-1 with a 0.3 to .5 cm margin dependent on immobilization techniques. Exact margins will be left up to the discretion of the treating Radiation Oncologist and may not be uniform in all dimensions. The clinician should consider the effects of the beam penumbra when designing the treatment apertures.

10.2.3 Clinical Target Volume 2 (CTV-2)(External Beam Boost)

This boost is delivered only to those patients with gross residual tumor. The post-operative T1 enhanced MRI is used to evaluate the extent of residual tumor. This post-op MRI should be performed within 72 hours, if possible.

The clinical target volume 2 (CTV-2) is the residual tumor (enhancing lesion) with a 1 cm margin.

The planning target volume 2 (PTV-2) shall include the CTV-2 with a .3 to .5 cm margin dependent on immobilization techniques. Exact margins will be left up to the discretion of the treating Radiation Oncologist and may not be uniform in all dimensions. The clinician should consider the effects of the beam penumbra when designing the treatment apertures.

10.3 **Target Dose**

10.3.1 Prescription Point

The prescription point is at or near the isocenter.

If IMRT is used, dose may be prescribed to an isodose surface that encompasses the PTV provided that the dose uniformity requirements in Section 10.3.5 are satisfied.

10.3.2 Dose Definition

Dose is specified in Gy to muscle.

10.3.3 Tissue Heterogeneity

Density corrections are not required, however, inhomogeneity correction may be applied. This is optional and would typically be in the setting of CT-based treatment planning where radiation dose distributions and treatment calculations are automatically generated based upon the CT densities of the treatment-planning scan.

10.3.4 Prescription Point and Fractionation

Planning Target Volume 1 (PTV-1)

Initial Volume (PTV-1): The total dose to the prescription point will be 54.0 Gy given in 30 fractions. The patient will be treated with one fraction per day with all fields treated per day. 1.80 Gy will be delivered to the isocenter.

Planning Target Volume 2 (PTV-2): **This boost is delivered only to those patients with gross residual disease.** The total dose to the prescription point will be 59.4 Gy, i.e., 3 fractions of 1.8 Gy to a total additional 5.4 Gy.

Spinal Cord Malignant Glioma Primary: This above prescription is not to be used for the rare patient with a spinal cord malignant glioma primary. The radiation oncologist, Robert Lavey, M.D., must be contacted for treatment guidelines.

10.3.5 Dose Uniformity

The dose variation in the PTV will be within +10% and -5% of the prescribed dose.

10.3.6 Treatment Interruptions

No treatment breaks in the radiation therapy component of this combined modality treatment are anticipated. Skin reactions should be treated supportively. Low blood counts are generally related to systemic therapy and are not caused or worsened by local field brain RT. In the case of severe or unusual toxicities, Dr. Robert Lavey, rlavey@chla.usc.edu should be consulted before interrupting treatment. The reason for any interruptions greater than three treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation.

10.4 **Treatment Technique**

10.4.1

Two-dimensional or conformal (three dimensional) planning may be used in this study.

10.4.2 Patient Position and Immobilization

Reproducible setups are critical and the use of immobilization devices such as thermoplast mask, bite-block, etc. is strongly recommended.

10.4.3 Field Shaping

Field shaping can be done with blocks or multi-leaf collimation.

10.5 Normal Tissue Sparing

10.5.1 Lenses of the Eyes

The lenses of the eyes must be excluded from the primary beam by the use of shielding blocks that are at least 5 HVL thick.

10.5.2 Optic Nerve and Chiasm

Whenever possible without shielding gross tumor, the dose to the optic nerves and chiasm should not exceed 54.0 Gy and the dose to the retinas of the eyes should not exceed 45.0 Gy, including the dose from the boost.

10.5.3 Spinal Cord

The dose to the spinal cord shall not exceed 46.0 Gy.

10.6 Dose Calculation and Reporting

10.6.1 Prescribed Dose

The monitor units required to deliver the prescribed dose shall be calculated and submitted using the RT-1 or IMRT Dosimetry Summary Form.

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

10.6.2 Dose Uniformity

The maximum and minimum doses in the PTV shall be calculated and reported on the RT-1 or IMRT Dosimetry Summary Form and on the RT-2 (Radiotherapy Total Dose Record Form). These may be extracted from isodose distributions, calculated separately or derived from DVH's.

10.6.3 Dose Specification Points

The daily dose reference point calculated on this study is the isocenter. The total dose to this point shall be calculated and reported on RT-2.

The daily dose to the critical organs indicated in section 10.5 shall be calculated whenever they are included in the radiation therapy treatment field. These doses must be recorded in the treatment records and submitted with the QA documentation. For patients treated with volume-based techniques, the appropriate dose volume histograms shall be submitted.

10.6.4 Isodose Distribution

An isodose plot of the dose distribution in the central transverse plane through the target volume shall be submitted. The prescription point and the outlines of the planning target volume and critical organs shall be shown. Isodose values must be clearly labeled. The effects of shielding blocks shall be included and corrections for heterogeneity shall be shown.

For volume based treatment planning, a hard copy isodose distribution for the total dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume (PTV) must be submitted. If sagittal and coronal planes are not available, then five axial distributions may be submitted (central axis, two superior and two inferior planes). These dose distributions must include the following:

A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT or MR images. However, if such hard copy presents difficulty, similar plots without the gray scale image are acceptable if enough critical contours are identifiable to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

10.7 QA Documentation

If conformal techniques are used to treat patients on this study, a three-dimensional benchmark needs to be completed and submitted to QARC. The benchmark material is available on the QARC website www.QARC.org

Note: Black and white copies of color documentation are not acceptable.

10.7.1 On-Treatment Review

Within three days of the start of radiotherapy, the following data shall be submitted for on-treatment review for patients using **standard planning techniques**:

- Copies of the pre-operative and post-operative MRI utilized in defining the gross target volume.
- Copies of the corresponding MRI and operative reports.
- Copies of simulator films and /or digitally reconstructed radiographs (DRRs) for each field. It is strongly encouraged that the GTV, CTV and PTV1 and PTV2 be drawn on the simulator films.
- Copies of verification (portal) films for each field.
- Pictures of the patient in the treatment position.
- Prescription sheet for the entire treatment course.
- RT-1 Dosimetry Summary Form
- Copies of worksheets and /or printouts used for calculations of monitor settings to give the prescribed dose, and doses to all normal structures.
- Copies of isodose distributions to demonstrate that the dose variation is within specification. The target volumes and the prescription point must be clearly shown.

10.7.2 On-Treatment Review for 3D Conformal Treatment Planning

If **3D-conformal treatment planning** is utilized, submit the following for on-treatment review:

- Copies of the pre-operative and post-operative MRI utilized in defining the gross target volume.
- Copies of the corresponding MRI and operative reports.
- Copies of the planning CT or MRI with target volumes and critical structures (see 10.5.2) delineated.
- First day portal films (or hard copy of real time portal images) if achievable, simulator films if used as part of the planning process, and digitally reconstructed radiographs of each treatment portal.
- Simulator films if used as part of the planning process, and digitally reconstructed radiographs of each treatment portal.
- One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
- Pictures of the patient in the treatment position.
- Prescription sheet for the entire treatment course.
- RT-1 or IMRT Dosimetry Summary Form, whichever is applicable.

- BEV's of portals showing collimator, beam aperture, target volume and critical structures.
- A rooms eye view (REV), i.e., a composite illustration of all the fields and their angles, if available from your planning system. Otherwise submit an overview diagram or illustration of the patient with all beams and their orientation indicated.
- Copies of worksheets and /or printouts used for calculations of monitor settings to give the prescribed dose, and doses to all normal structures.
- Copies of the isodose distributions for the total dose plan in the axial, sagittal and coronal planes, which includes the isocenter of the planning target volume. The target volumes and the prescription point must be clearly shown.
- Dose volume histograms for the entire treatment course or total prescribed dose for PTV1 (and PTV2, if treated) and any critical structures (see 10.5.2). If IMRT is used, a DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Documentation of an independent check of the calculated dose if IMRT is used.

10.7.3 Post-Treatment Review

Within one week of the completion of radiotherapy, the following data shall be submitted.

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas and specified dose points.
- RT-2 Radiotherapy Total Dose Record
- Copies of additional simulation and verification (portal) films for any field modifications made subsequent to the initial reporting of data for on-treatment review.
- Copies of revised RT-1 or IMRT forms, when modifications have been made subsequent to the initial reporting.
- Copies of calculations and isodoses performed subsequent to the submission of the on-treatment data.

10.7.4 Address

These data should be forwarded to:

Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rhode Island 02903-1025
Telephone (401) 454-4301
FAX (401) 454-4683

10.7.5 Questions

Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rhode Island 02903-1025

Questions regarding the radiotherapy section of this protocol should be directed to:

Robert Lavey, M.D.
Childrens Hospital Los Angeles
Radiation Oncology MS-54
4650 Sunset Blvd.
Los Angeles, CA 90027
Phone: (323) 669-2417
Fax: (323) 668-7978
E-mail: rlavey@chla.usc.edu

10.8 Definitions of Deviations in Protocol Performance

10.8.1 Prescription Dose

Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.

Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

10.8.2 Dose Uniformity

Minor Deviation: The variation of dose in one of the target volumes exceeds +10% and -5% of the dose to the planning target volume.

10.8.3 Volume

Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.

Major Deviation: Transection of tumor (GTV) or potentially tumor bearing area (CTV).

11.0 RADIATION THERAPY GUIDELINES FOR DIFFUSE INTRINSIC PONTINE GLIOMAS

3D conformal therapy is required for this protocol. Intensity modulated radiation therapy (IMRT) may be used. Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark. Those treating with IMRT must complete the IMRT Questionnaire and Benchmark. The benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) and must be submitted before patients on this protocol can be evaluated.

11.1 Equipment

11.1.1 Modality

Accelerator x-ray beams with nominal energy of at least 4 MV shall be used. Use of Cobalt-60 is not permitted.

11.1.2 Conformal Therapy

Conformal Therapy is mandatory for this study. Intensity Modulated Radiation Therapy (IMRT) may be used.

11.1.3 Calibration

All therapy units used for this protocol shall have their calibrations verified by the Radiological Physics Center (RPC).

11.2 **Target Volume Definitions**

11.2.1 Localization

A treatment planning CT scan obtained in the treatment immobilization device is required. MRI fusion is encouraged.

11.2.2 GTV

The gross tumor volume is defined as the tumor best demonstrated on MRI. The MRI sequence that best defines the extent of disease should be used.

11.2.3 CTV

The clinical target volume shall include the GTV with a 1cm margin in all directions.

11.2.4 PTV

Planning target volume (PTV) shall include the CTV with a 0.3 cm to 0.5 cm margin dependent on immobilization techniques. Exact margins will be left up to the discretion of the treating Radiation Oncologist and may not be uniform in all dimensions. The clinician should consider the effects of the beam penumbra when designing the treatment apertures.

11.2.5 Organs at Risk

Where possible normal structures such as optic chiasm, spinal cord, cochlea, optic nerves, globes, pituitary gland, brainstem, etc. should be outlined.

11.3 **Target Dose**

11.3.1 Prescription Volume

Dose is to be prescribed to an isodose surface that encompasses the PTV and that satisfies the dose uniformity requirements in Section 11.4.5.

11.3.2 Dose Definition

The absorbed dose is specified as Gy-to-muscle.

11.3.3 Tissue Heterogeneity

Density corrections shall be used.

11.3.4 Prescribed Dose and Fractionation

The dose to the PTV shall be 59.4 Gy given at 1.8 Gy/fraction in 33 fractions, one fraction per day.

No treatment breaks in the radiation therapy component of this combined modality treatment are anticipated. The reason for any interruptions greater than three treatment days should be recorded in the patient treatment chart and submitted with the QA documentation. Treatment interruptions greater than 1 week should be discussed with the study chair.

11.3.5 Dose Uniformity

The entire PTV should be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive greater than 110% of the prescription dose, as evaluated by dose-volume histogram (DVH).

11.4 **Treatment Technique**

11.5.1 Treatment Planning

Volume-based (CT scan) treatment planning is mandatory in this protocol. Techniques which shield normal tissue are essential providing that they do not compromise treatment of the PTV.

11.4.2 Field Shaping

Field shaping shall be performed. Multi-leaf collimators are permitted for both 3D conformal and for IMRT treatment.

11.4.3 Beam Modifiers

Compensators may be used.

11.5 **Organs at Risk (Normal Tissue Sparing)**

It is important to protect normal vital structures whenever possible. Where possible normal structures such as optic chiasm, spinal cord, cochlea, optic nerves, globes, pituitary gland, brainstem, etc. should be outlined and DVHs generated. The recommended dose limits for pertinent structures are as shown in Table One below.

Table One: Normal Tissue Dose Limits

Treatment should begin within 5 days of study enrollment. The treatment should be completed within 7 weeks.

Organ / Structure	Dose Limit
Optic Chiasm	50.4 Gy
Spinal Cord	50.4Gy
Cochlea	50.4Gy

11.5.1 Dose Calculation and Reporting

If treating with 3D conformal techniques, the 3D Benchmark must be completed and submitted to QARC.

If treating with IMRT, the IMRT Questionnaire and Benchmark must be completed and submitted to QARC before patients on this protocol can be evaluated. The Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org).

11.5.2 Prescribed Dose

For 3D conformal techniques: The monitor units required to deliver the prescribed dose must be submitted using the RT-1 Dosimetry Summary Form for each field.

For IMRT techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the IMRT Dosimetry Summary Form. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

11.5.3 Dose Uniformity

The maximum and minimum doses in the target volumes shall be calculated and reported on the appropriate (RT-1 or IMRT) Dosimetry Summary Form. These may be extracted from DVH's.

11.5.4 Organs at Risk

DVHs for the following normal tissues shall be submitted: optic chiasm, spinal cord, cochlea, optic nerves, globes, pituitary gland, brainstem

11.5.5 Isodose Distributions

A hard copy isodose distribution for the total dose plan in the axial, sagittal and coronal planes at the center of the planning target volume must be submitted. These dose distributions must include the following:

A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT images. However, if such hard copy presents difficulty, similar plots without gray scale image are acceptable if enough critical contours are identifiable to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

11.6 **Quality Assurance Documentation**

11.6.1 On-Treatment Review

Within three days of the start of radiotherapy, the following data for the radiotherapy fields shall be submitted for on-treatment review:

- a. Copies of all diagnostic materials used in defining the target volume. The initial (pre-study) imaging is required.
- b. Photographs of the patient in the treatment position with the fields marked
- c. Prescription Sheet for the Entire Treatment
- d. Copies of the worksheets and printouts used for calculations of monitor settings to give the prescribed dose.
- e. Color copies of isodose distributions to demonstrate that the dose variation is within protocol guidelines. The target volume must be clearly shown.
- f. Documentation of an independent check of the calculated dose if IMRT is used.
- g. Simulator films (if used as part of the treatment planning process) and digitally reconstructed radiographs of each treatment portal (if possible).
- h. First day portal films (or hard copy of real time portal images) if achievable.
- i. A completed appropriate (RT-1 or IMRT) Dosimetry Summary Form.
- j. One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
- k. Beam's eye views if 3D conformal planning is used.
- l. "A room view display of all fields should be submitted if available from your planning system."
- m. Dose volume histograms for the total treatment for each PTV and the normal tissues specified in section 5.73. If IMRT is used, a DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

11.6.2 Review Following Completion of Radiotherapy

Within one week of the completion of radiotherapy, the following data shall be submitted:

- a. Copies of additional simulation films and verification (portal) films for any major field modifications made subsequent to the initial reporting data.
- b. The RT-1 or IMRT Dosimetry Summary Form if any changes have been made subsequent to submission of previous.
- c. The RT-2 Radiotherapy Total Dose Record form.
- d. A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas, including target volumes and normal tissues.
- e. Copies of calculations performed subsequent to the submission of the previous data.

11.6.3 The data should be sent to:

Quality Assurance Review Center
272 West Exchange Street Suite 101
Providence, RI 02903-1025
Telephone: 401-454-4301
FAX: 401-454-4683

Dosimetry and Physics Questions should be directed to:

QARC Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street Suite 101
Providence, RI 02903-1025
Telephone: 401-454-4301
FAX: 401-454-4683

Radiotherapy Questions should be directed to:

Robert Lavey, M.D.
Childrens Hospital Los Angeles
Radiation Oncology MS-54
4650 Sunset Blvd
Los Angeles, CA 90027
Phone: (323) 669-2417
Fax: (323) 668-7978
Email: rlavey@chla.usc.edu

11.7 **Definitions of Deviation in Protocol Performance**

Minor deviation: The delivered dose to the prescription volume differs from protocol specification by more than 5% but less than 10%.

Major deviation: The delivered dose to the prescription volume differs from protocol specification by more than 10%.

Dose Uniformity: A minor deviation if more than 10% of the PTV receives more than 110% of the prescription dose.

Volume:

Minor deviation: Margins for PTV less than specified, or field(s) excessively large.

Major deviation: GTV not included within 95% dose volume

12.0 NEUROPATHOLOGY GUIDELINES/BIOLOGY SPECIMEN REQUIREMENTS

12.1 Eligible Tumors

The following non-brainstem high-grade gliomas are eligible for biology studies. DIPG patients are exempt from the neuropathology and biology studies.

- a) Anaplastic astrocytoma (Grades 3)
- b) Glioblastoma multiforme, all types and variants (Grade 4)
- c) Gliosarcoma

12.2 Central Review

12.2.1 Required Materials

The following specimens must be received prior to start of maintenance. The neuropathologist at each participating institution, at the completion of review of each case originating at his/her institution, should submit the following to the COG Biopathology Center:

- Tissue blocks from each representative lesion. Blocks will be retained at the Biopathology Center unless return is requested by the institution. If blocks are unavailable, then from each representative block the following are REQUIRED:
 - Two H & E stained sections
 - Four unstained sections prepared for immunohistochemistry.
- Institutional neuropathologist's report
- Transmittal form

Label blocks (or slides), pathology report and transmittal form with the patient's COG Patient ID Number and the corresponding institutional surgical pathology ID number.

12.2.2 Address

All materials should be submitted to:

COG Biopathology Center
Children's Hospital
700 Children's Drive, Room WA1340
Columbus, OH 43205
(614) 722-2894

12.2.3 Central Review Process

The primary review process will be performed by Dr. Peter Burger and a secondary review by Drs. Brat and Rosenblum. All materials submitted from the individual institutions will be reviewed, and if additional material is required, it will be processed from wet formalin-fixed tissue.

Three neuropathologists (Drs. Burger, Brat, and Rosenblum) have agreed to act as central reviewers for this trial. Dr. Burger has agreed to do an initial review of the pathology by the completion date of XRT. Should Dr. Burger's diagnosis differ from that of the institutional pathologist, Drs. Brat and Rosenblum will provide an expedited second opinion prior to the beginning of adjuvant therapy.

12.3 **Biology Studies**

Unstained slides will be submitted prior to start of maintenance to the Biopathology Center who will forward the slides to St. Jude Children's Research Hospital and The Glioma Resource Laboratory at the University of Pittsburgh. The formalin-fixed, paraffin-embedded specimens will be analyzed to determine MGMT expression using immunohistochemical methods. In addition, tumors will be identified in which MGMT expression is silenced by determining promoter CpG methylation in DNA isolated from formalin-fixed, paraffin-embedded tumor samples. Microsatellite instability assays will be used to determine whether a functional MMR system is present in tumor cells by comparing DNA isolated from formalin-fixed paraffin-embedded tumor samples with DNA isolated from the patient's peripheral blood white cells.

MIB-1 expression analysis will be performed using a standardized immunohistochemical protocol, as previously published^{36,38} to identify areas of maximal expression within the tumor sample. p53 mutation analysis will incorporate microdissection-based topographic genotyping and direct sequence analysis, as previously reported.^{36,37}

12.3.1 Required Materials

- A 5ml peripheral blood specimen in a green top tube (sodium heparin) must be shipped overnight on wet ice **prior to the initiation of chemoradiotherapy**.
- If tissue blocks were sent to the Biopathology Center for Pathology Review, then the required materials will be processed from the blocks by the BPC and the institution does not need to send slides or micron sections to meet the biology requirements for this protocol.
- If tissue blocks were not sent for Pathology Review then the following materials are **required** for biology studies and must be received **prior to the start of maintenance**:
 - Ten unstained slides from a representative block for biology studies must be received prior to the start of maintenance.
 - Three 20-micron sections from a formalin-fixed, paraffin-embedded tumor sample must be received prior to the start of maintenance. These three sections should be in a sterile microfuge (Eppendorf type) tube.
- A completed transmittal form must be sent with each shipment of specimens.

Label the peripheral blood with the COG Patient ID Number. Label slides and tumor sections with the Patient's BPC number, specimen type and the collection date.

12.3.2 Addresses

Ship the **peripheral blood** overnight on wet ice for delivery before 11:00 the next morning:

Robert W. Sobol, Ph.D
Hillman Cancer Center
University of Pittsburgh Cancer Institute
Research Pavilion
5117 Centre Avenue, Suite 2.6
Pittsburgh, Pennsylvania, 15213-1863
Phone: (412) 623-7764
Lab Phone: 412) 623-7807

If blood is collected on a Friday, you must call Dr. Robert Sobol before shipping to verify that someone will be available to accept a Saturday delivery.

Ship the slides **and/or tumor sections** to the Biopathology Center:

Biopathology Center
Children's Hospital
700 Childrens Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2810

*Be sure to include the room number. Packages without a room number may be returned to the sender.

13.0 STATISTICAL CONSIDERATIONS

This study represents the first in potentially a larger series of small, non-randomized pilot studies of treatment for high-grade glioma (HGG) in children. In this first trial, the primary objectives of the statistical analysis will be to compare the short and long-term outcome of patients treated with XRT and Temololomide (TMZ) with a mature series of patients treated on previous CCG and POG studies in this disease. A focus of the latter analysis is to determine whether there is compelling early evidence that the two experimental treatments will result in a significant improvement in outcome compared to the historical data. A second objective is to assess the significance of MGMT (i.e., AGT) and of MMR deficiency, as mechanisms of TMZ resistance and hence markers of poor prognosis.

13.1 Design Considerations

This pilot study described herein is viewed as part of a long-term strategy for screening potential treatments for HGG in children. In order to take into consideration the possibility that in the near future other treatment approaches worthy of piloting will become available, the size of the current pilot studies will be limited to a number of patients that is adequate for reasonably precise statistical inference, and that can be enrolled within 1 year to 18 months. Additional pilot segments may be added to this study if other promising treatments become available. In the event that other promising treatments are not available after this time period, the current pilot will continue to accrue patients in order to achieve greater precision in analyses of MGMT and MMR relationship to prognosis.

13.2 Patient Accrual

From past experience, it is reasonable to expect that accrual of eligible HGG patients will be at least 50 per year from COG institutions, with higher accrual rates possible.

13.3 Study Duration

This first pilot study in the series will accrue 50 eligible patients with assessable tumor tissue and with minimum follow-up of six months after the end of radiation therapy. Accrual will continue until there is reasonable assurance that this goal has been achieved. Ineligibility and drop-out rates are unlikely to exceed 20%, and probably will be much less than this, so that at most 60 patients will likely be required to achieve this goal. Accrual will therefore require 12 to 14 months, although the rapidity with which the study is activated in different COG institutions will lengthen the time for completion of the first pilot study.

In the event that a successor pilot therapy is not available, this study will continue accrual until at most 100 eligible patients with assessable tumor tissue and adequate follow-up is reasonably assured.

13.4 Study Endpoints

13.4.1 Efficacy Endpoints

The primary endpoint for the evaluation of treatment efficacy will be event-free survival, defined as the time to disease progression, disease relapse, occurrence of a second malignant neoplasm, or death from any cause. The secondary endpoints include survival, which is defined as the time to death from any cause.

13.4.2 Safety and Toxicity Endpoints

The primary endpoint for patient safety monitoring is toxic death, which is a death primarily attributable to complications of treatment.

13.5 Comparison of Short-Term EFS Rate With Historical Baseline

13.5.1 Parametric Model of the Event-Free Survival Function

The main study analysis will be based on a non-mixture parametric cure model (PCM) of the form

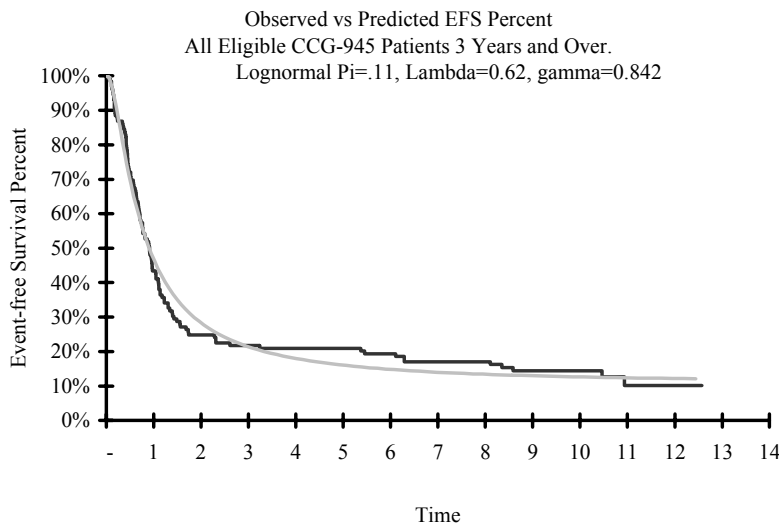
$$S(t) = e^{F(t) \ln \pi}$$

where $S(t)$ is the event-free survival function, π is the long-term EFS (cure) rate, and

$$F(t) = \Phi\left(\ln\left[(\lambda t)^\gamma\right]\right)$$

is a lognormal distribution function with shape parameter γ and scale parameter λ [47].

This PCM describes outcome in a series of 129 eligible randomized HGG patients (based on review histopathological diagnosis) aged 3 and over who were treated on CCG-945, with maximum likelihood estimates $\hat{\pi}=0.11$ (95% CI: 0.05, 0.17), $\hat{\lambda}=0.61/\text{year}$ (0.44, 0.88), $\hat{\gamma}=0.84$ (0.71,1.0). The product limit estimate and parametric model fit are shown in the figure.



The PCM will serve as an historical baseline of comparison with the pilot series. (Note that the historical series will be augmented with data from POG-9135 for the final protocol.) The primary early comparison will be for 1-year EFS. The comparison of 1-year EFS in the pilot study compared to the historical control percent at that time will be based on a lower, one-sided, 95% confidence bound on the differences in EFS percent estimated from the non-mixture PCM.

13.5.2 Precision of Estimate of Short-Term EFS as a Function of Pilot Cohort Maturity

Based on the cohort size of 50, at any given time T from the start of the enrollment of a pilot series, the estimate of T-0.5 year EFS percent will have a standard error of 8% to 8.5%. Hence, 6 months from the time that patient enrollment ends at 1 year, the precision of 1-year EFS will be approximately that specified, so that in comparison to the 1-year EFS of approximately 45% in the historical series, an observed 1-year EFS of approximately 59% will be significant at the one-sided $p=0.05$ level, and there will be 80% power against an improvement to about 66%. Based on a cohort size of 100, the standard errors and detectable differences will decrease by a factor of approximately 1/1.414. The analysis will be adjusted for extent of resection and histology.

Since pilot studies in this series will have differing levels of maturity, and the final decision about the efficacy of these treatments compared to historical baseline or other future pilot groups in this series will depend on the timing of these comparisons and whether other pilot studies are performed in this series, no formal statistical framework for selection will be proposed. In addition to the 1-year EFS comparison described above, a number of PCM-based comparisons between pilot series and historical baseline may be possible depending on the maturity of the data.⁶³

13.6 **Interim Monitoring**

13.6.1 Monitoring for Efficacy

There will be no monitoring for efficacy for either series in this study before the 50th evaluable patient has been enrolled, since this accrual goal will have been completed before sufficient information to allow such monitoring is available. In the event that this study will proceed to an accrual goal of 100 patients, an interim analysis will be performed when the 50th evaluable patient has been enrolled. A one-sided, one-degree of freedom PCM-based likelihood-ratio test of a proportional-hazards decrease in efficacy from the historical baseline will be performed at the overall 5% Type I level, with adjustment based on the methods of Tsiatis et al.⁶⁴ A significant result will constitute compelling evidence that the outcome is significantly worse than predicted, and will likely result in a decision to discontinue the pilot.

13.6.2 Monitoring for Toxic Death, for Delays in Completion of XRT Due to TMZ-Related Toxicity, and for Delays in the Start of Maintenance Chemotherapy.

No serious problems are expected with toxic death or with significant delays in treatment due to TMZ. We will nevertheless monitor rates of toxic death during XRT and during maintenance. We will also monitor significant delays in completion of XRT or in the start of maintenance courses. Statistical monitoring rules will not be used. Rather, a careful review of treatment and patient safety will be undertaken whenever observed rates nominally exceed the maximum acceptable rate, or when there is a large observed difference in these rates between the treatment groups.

The following measures will be computed:

1. Rate of toxic death prior to maintenance. The maximum acceptable rate is 2%.
2. Cumulative incidence of toxic death during therapy. The maximum acceptable rate is 5%.
3. Incidence of occurrence of significant delays in the completion of XRT. A greater than 2 week delay will be considered significant.
4. Cumulative incidence of occurrence of significant delays in the start of any course of maintenance chemotherapy. A greater than 2-week delay will be considered significant. The maximum acceptable rate is 10%.

13.7 **Analysis of Prognostic Significance of MGMT and MMR**

The analysis of the prognostic significance of MGMT and MMR will be based on all patients in this series who are treated with a TMZ-containing regimen. We will assume that at least 75 patients are

available for analysis of 3-year EFS, either from this pilot or from a combined series of TMZ-containing pilots.

Based on data in adults^{30,65} it is expected that MGMT will be absent in approximately 26% of tumors, and it is expected that these patients will have a better prognosis. Assume 3-year EFS of approximately 25% overall, and using a one-sided, 5% Wald test of difference in 3-year EFS, there will be 80% power to detect a difference of 31% in 3-year EFS (i.e., 49% in MGMT negative vs. 17% in MGMT positive). This is a reasonably-sized difference to expect for a useful distinction in prognosis based on MGMT.

Based on data in adults³⁴ it is expected that MMR will be present in approximately 79% of tumors, and it is expected that these patients will have a better prognosis. Assume as above 3-year EFS of approximately 25% overall, and using a one-sided, 5% Wald test of difference in 3-year EFS, there will be 80% power to detect a difference of 22% in 3-year EFS (i.e., 30% in MMR positive vs. 8% in MMR negative). This also is a reasonably-sized difference to expect for a useful distinction in prognosis based on MMR.

These considerations will depend ultimately on the cutpoint used to distinguish positive vs negative tumors with respect to MGMT and MMR.

13.8 Gender and Ethnicity Considerations

Review of outcome data from previous CCG studies for high-grade glioma indicates that treatment effects are consistent within gender and ethnicity. That is, no one treatment examined has proven superior for one gender or ethnic group. Because of this, the study size will not be adjusted to ensure high power to detect differences in outcome in groups defined by ethnicity or gender.

We will, however, contrast therapeutic outcomes in two situations. First, across subgroups defined by gender, *viz.*, males *v.* females. Second, across subgroups defined by ethnicity, *viz.*, white *v.* black *v.* Hispanic.

Expected Accrual by Sex and Race/Ethnicity (Total N=100)					
SEX/RACE	White	Black	Hispanic	Asian	Other/Mixed
Female	42	6	3	1	1
Male	33	6	4	1	-
Total	75	12	7	2	1

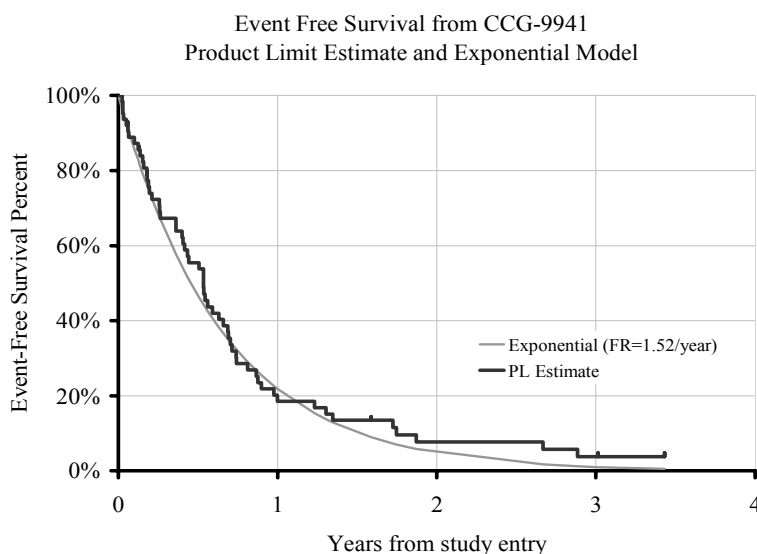
13.9 Statistical Considerations for Diffuse Intrinsic Pontine Glioma Patients

The two most recent group-wide studies of DPG conducted in COG institutions were CCG-9941, which enrolled 63 patients in 35 months, CCG-9882, which enrolled 119 patients in 34 months, and POG-9239, which enrolled 64 patients in 45 months. Clearly, The CCG-9882 represents closer to the actual numbers of patients that will be available, representing an accrual rate of 42 patients per year among former CCG institutions alone, and hence at least 65 patients per year among current COG institutions. From this experience, even with competition from PBTC studies or other group wide studies, the accrual to this study will be at least 20 to 25 per year.

Historical Data

The most recent relevant historical data on the outcome of DPG is derived from CCG-9941. The figure below shows the event-free survival in this cohort of patient, as well as an exponential failure time model of EFS. One observes that the failure time distribution up to one year can be well approximated by an

exponential failure time model with $\lambda=1.52/\text{year}$, and that one-year EFS estimated from this model is 21.9%. This is consistent to within a few percent of other large historical series.



Study Endpoints

Primary Efficacy Endpoint

The primary study endpoint for treatment efficacy is time to treatment failure (TTF), measured from the start of treatment, from which event-free survival (EFS) percent will be computed. Failure events include tumor progression, tumor recurrence, or death from any cause.

Secondary Efficacy Endpoints

The secondary endpoint for treatment efficacy is time to death (TTD) from any cause, from which survival (S) is computed.

Primary Toxicity Endpoints

The primary toxicity endpoints include:

Any Grade 4 hematologic toxicity that persists for more than 7 days or that requires platelet transfusions for a period of time exceeding 7 days during chemoradiotherapy. Any Grade 3 or 4 non-hematologic toxicity, with the exception of Grade 3 nausea and/or vomiting which can be controlled within 7 days, Grade 3 skin reaction, and Grade 3 transaminitis.

Study Duration

This study is designed using a modified sequential design which will determine the actual sample size. A maximum of 60 patients will be enrolled on this study. However, this number would only be enrolled if there is continuing evidence that the outcome in patients on the study is greater than 21.9% EFS at 1 year, which is the historical baseline discussed above.

Analytic plan monitoring and final analysis of treatment efficacy

The primary objective of the statistical analysis is to determine whether the current treatment produces one-year EFS rates higher than the historical baseline of 21.9%, which is the maximum likelihood estimated derived from an exponential model during the first year from study CCG-9941. This determination will be based on a one-sided, one-sample test of proportions,

$$Z = \frac{\hat{p} - p}{\sqrt{\hat{V}(\hat{p})}}$$

where \hat{p} is the estimated proportion of patients who are event-free at 1 year, $p=0.219$, and $\hat{V}(\hat{p})$ is the estimated asymptotic variance of \hat{p} . Censoring in this disease in the first year of follow-up is expected to be minimal or non-existent, in which case the test statistic will be based on the simple estimate of the proportion of patients who are event-free at one year. The estimated variance in this case will be $\hat{p}(1-\hat{p})/n$, when n is the total sample size. If the censoring rate is not negligible, then the product-limit estimate of 1-year EFS will be substituted for \hat{p} , and the Greenwood variance estimate in the denominator term. (Kalbfleisch and Prentice, 1982). The test will be performed after the last enrolled patient has been followed for a minimum of one year. The criteria for significance will be the upper 90th percentile of the standard normal distribution, so that the test is performed at a nominal 10% Type I error level. The power computations contained herein are based on the simple test of proportions.

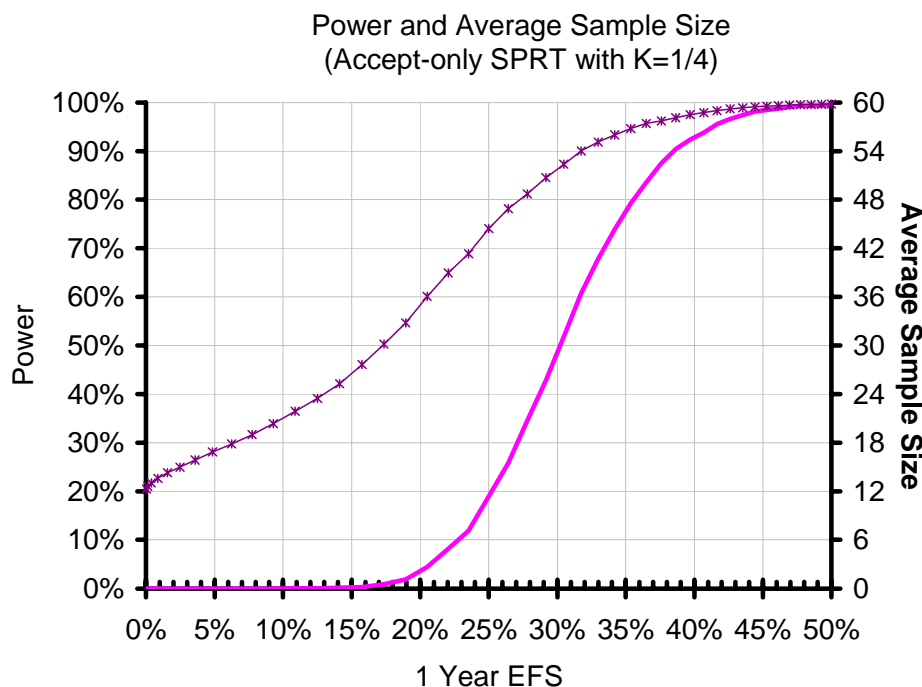
The final study sample will result from a sequential monitoring plan, which will limit the number of patients enrolled on the trial in the event that there is no early evidence of treatment efficacy greater than the historical baseline. The monitoring plan will be based on a modified Sequential Probability Ratio Test (SPRT, Piantadosi, 1997). Only the ‘acceptance’ bound of the SPRT will be used. In formulating this test, the null hypothesis value of the 1-year EFS of 21.9%, and the alternative hypothesis value of 35%, will be used. Under the assumption that time to progression follows an exponential distribution for the first year, these values correspond to exponential failure rates of $\lambda_0=1.521$ and $\lambda_1=1.050$ per year. Hence, the SPRT criterion used for interim monitoring will be

$$\left(\frac{\lambda_1}{\lambda_0}\right)^d e^{-(\lambda_1-\lambda_0)T_g} < K$$

where the left-hand-side is the exponential likelihood ratio, T is the total person-years of follow-up, and $K=1/4$.

The figure below shows the power characteristic and average sample size for the final statistical test in the context of this monitoring rule. The value K was selected to provide an acceptable tradeoff between average sample size and power. The figure was based on a simulation of 10,000 experiments for each point on the X-axis, with an assumed monitoring interval of 3 months, and average annual accrual rates of 24 patients per year (2 per month). The solid line is the power of the final significance test, and the hashed line is the average sample size.

Given that the test is being performed in the context of monitoring that essentially truncates the distribution of the estimated proportion (conditional on sample size), the variance estimate in the denominator of the test statistic will be an overestimate, and hence the actual Type I error rate will be less than the nominal. One can see that the actual Type I error rate of this test is smaller than the nominal 10% rate in the context of the SPRT monitoring rule, and under the null hypothesis 1-year EFS rate of 21.9% this study will enroll on average 39 patients. If 1-year EFS rate with this treatment is only 15%, then on average 26 patients will be enrolled. However, if treatment efficacy has been improved so that 36% of patients are event-free at 1 year, then this will be detected in final analysis with 80% power, with an average sample size in this circumstance of approximately 57 patients.



Monitoring for Toxic Death, for Delays in Completion of XRT Due to TMZ-Related Toxicity, and for Delays in the Start of Maintenance Chemotherapy.

No serious problems are expected with toxic death or with significant delays in treatment due to TMZ. We will nevertheless monitor rates of toxic death during XRT and during maintenance. We will also monitor significant delays in completion of XRT or in the start of maintenance courses. Statistical monitoring rules will not be used. Rather, a careful review of treatment and patient safety will be undertaken whenever observed rates nominally exceed the maximum acceptable rate.

The following measures will be computed:

1. Rate of toxic death prior to maintenance. The maximum acceptable rate is 2%.
2. Cumulative incidence of toxic death during therapy. The maximum acceptable rate is 5%.
3. Incidence of occurrence of significant delays in the completion of XRT. A greater than 2 week delay will be considered significant.
4. Cumulative incidence of occurrence of significant delays in the start of any course of maintenance chemotherapy. A greater than 2-week delay will be considered significant. The maximum acceptable rate is 10%.

14.0 EVALUATION CRITERIA

14.1 Common Terminology Criteria

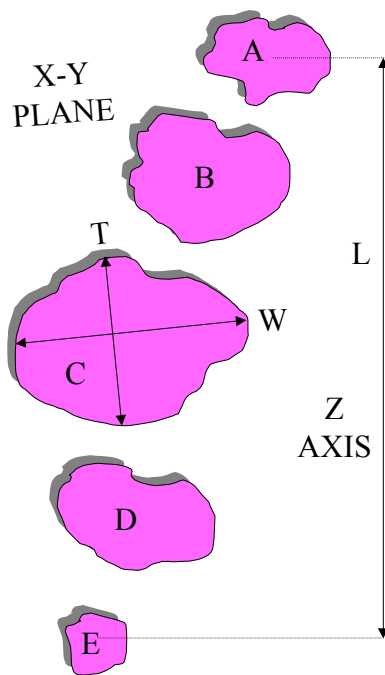
This study will utilize the CTC version 2.0 of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the current version of the CTC Version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). Additionally, toxicities are to be reported on the appropriate data collection forms.

14.2 Methodology to Determine Tumor Measurement For HGG Patients

Tumor response criteria are determined by changes in size using all 3 dimensional measurements: width (W), transverse (T), and length (L) measurements. Thus for all tumors these 3 measurements need to be recorded, using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). The following section describes the methodology.

(See drawing below for illustration)

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) – tumor extent in the plane perpendicular to the selected plane)



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

4. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be “measurable”. Options:
 - if the cyst/necrosis is eccentric, the W, T and L of the solid portion should be measured, the cyst/necrosis excluded from measurement
 - if the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion
 - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured

5. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted, change in extent/thickness assessed on follow up studies.

6. **Overall Response Assessment**

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
CR or PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The sections that follow discuss the selection and evaluation of each of these types of lesions.

14.3 Methodology to Determine Tumor Measurement For DIPG Patients

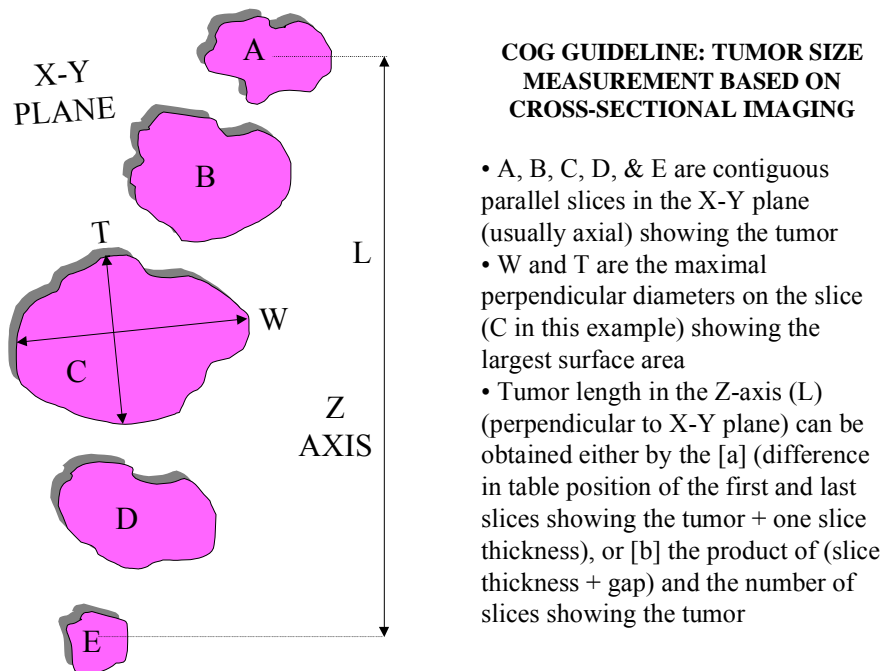
Tumor response criteria for this study are to be determined by changes in size using the maximal 2-dimensional **cross-sectional** tumor measurements, TxW (product of the longest diameter of the tumor [**width (W)**] and its longest perpendicular diameter [**transverse (T)**]), using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). This will allow comparison with historical studies as outlined in the statistical design section, such as CCG-9941 and 9883, which used cross-sectional measurements in their determination of response status.

Tumor length (L), perpendicular to the TxW plane should also be measured and recorded, since this will provide historical data for future studies that will rely exclusively on volumetric response determinations. However, for the current study, 3-dimensional tumor volume change will not be used to determine response status.

The following section describes the methodology.
(See drawing below for illustration)

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.

3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) tumor extent in the plane perpendicular to the selected plane).
4. Leptomeningeal tumor spread is not a target lesion, as its presence at diagnosis would make the patient ineligible for this brainstem glioma study. The presence and location of leptomeningeal tumor spread at relapse should be noted.



Overall Response Assessment

The overall response assessment takes into account response in the target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesion	New Lesions	Overall Response
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD
Any	Yes	PD

The sections that follow discuss the selection and evaluation of each of these types of lesions.

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14.4 Selection of Target and Non-Target Lesions

For intrinsic pontine brainstem gliomas, only one lesion/mass is present at diagnosis, and therefore is considered a “target” for measurement/follow up to assess for tumor progression/response. **(Patients with multiple target lesions at diagnosis are considered to have disseminated disease and would be ineligible for this study).**

If other non-target lesions develop at relapse (including CSF positive for tumor cells), their location should be noted, although they do not need to be measured.

14.5 Response Criteria for Target Lesions

For this study, comparison of maximal 2-dimensional measurements, TxW (product of the longest diameter [width (W)] and its longest perpendicular diameter [transverse (T)]) will be used for Response Criteria for Target Lesions.

Complete Response (CR): The disappearance of all abnormal signal within the brainstem and return to normal size of the brainstem.

Partial response (PR): $\geq 50\%$ decrease in the sum of the products of the two perpendicular diameters of the target lesion, taking as reference the initial baseline measurements

Stable Disease (SD): Neither sufficient decrease in the products of the two perpendicular diameters of the target lesion to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in the target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): 25% or more increase in the cross sectional area of the largest two diameters of the target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

15.0 ADVERSE EVENT REPORTING REQUIREMENTS

15.1 General Guidelines For All Adverse Events

Adverse event collection and reporting is a routine part of every clinical trial. The first step is to identify the event using the Common Toxicity Criteria (CTC).

A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC Version 2.0. The severity of the event should then be graded using the CTC criteria. Next, determine if the adverse event is related to the medical treatment or procedure (attribution). If so, determine whether the adverse event is expected or unexpected. With this information and the adverse event reporting section in each protocol, the investigator can determine whether an adverse event should be reported to the NCI as an expedited report or a routine report.

15.1.1 Persistent Adverse Events

An adverse event that persists from one course (cycle) to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event, which **resolves and then re-occurs** during a different course (cycle) must **be reported** each course (cycle) it re-occurs. For example:

- A patient experiences Grade 3 thrombocytopenia during cycle one. During cycle two the adverse event persists but the severity remains unchanged. During cycle three the adverse event persists but increases in severity to Grade 4. The following should be submitted as expedited reports:

Cycle One – Grade 3 Thrombocytopenia

Cycle Two – No Report

Cycle Three – Grade 4 Thrombocytopenia

15.1.2 Baseline Adverse Events

An adverse event should NOT be reported if a patient is entered on a study with a pre-existing condition (e.g., elevated laboratory value). If the adverse event increases in severity, the investigator should re-assess the event to determine if the event should be reported. No modification in grading should be made to account for abnormalities noted at baseline. For example:

- A patient enters a trial with an AST equivalent to Grade 1. If the AST remains unchanged at the end of cycle one, the adverse event should NOT be reported. If the AST increases to a Grade 3 level, the adverse event should be re-assessed and reported if it fulfills the other adverse event reporting criteria. The AST would be reported at Grade 3 with no adjustment for the baseline AST equivalent to Grade 1.
- A patient enters a study with diarrhea equivalent to Grade 2. The diarrhea resolves during the first cycle of therapy. If, during a subsequent cycle the patient experienced Grade 2 diarrhea, the adverse event should be re-assessed and reported if it fulfills adverse event reporting guidelines.

15.2 **Adverse Event Reporting For Commercial Agents**

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the following procedures should be followed:

15.2.1

What To Report: Any life-threatening (Grade 4) or fatal (Grade 5) adverse event with an attribution of possible, probable or definite to a study drug that is **also unexpected** (not listed in the package label).

15.2.2

When To Report: These events should be reported within ten (10) working days.

15.2.3

Where To Report: These adverse events with commercial agents must be reported to the FDA and a copy provided to the NCI using the MedWatch form. A copy of the MedWatch form can be obtained from the FDA's MedWatch Web site (see below) or the CTEP home page in Appendix 12 of the Investigator's Handbook. The MedWatch report can be sent by the following mechanisms:

To the FDA:	NCI:	COG
On Line: www.fda.gov/medwatch	Copy	Copies
Mail: MedWatch 5600 Fishers Lane Rockville, MD 20852-9787	Mail: Investigational Drug Branch P.O. Box 30012 Bethesda, MD 20824	Operations Center:: Fax: 626-445-4334
Fax: 1-800-332-0178	Fax: 301-230-0159	Data Center: Fax: 626-445-4334

15.3 Reporting Secondary AML/MDS

15.3.1 What To Submit:

Within two weeks of an AML/MDS diagnosis following treatment for cancer on NCI-sponsored trials, submit the following:

- a completed NCI/CTEP Secondary AML/MDS Report Form;
- a copy of the pathology report confirming the AML/MDS; and
- a copy of the cytogenetic report (if available).

Submit instead of the MedWatch Form (FDA #3500)

15.3.2

Where To Send:

NCI	COG (Copies)
Mail: Investigational Drug Branch P.O. Box 30012 Bethesda, MD 20824	Mail: AER Coordinator 440 E. Huntington Dr. Suite 300 P.O. BOX 60012 Arcadia, CA 91066-6012

Submit instead of the MedWatch Form (FDA#3500) for cases of secondary AML/MDS (if sent by fax, please follow with hard copy by mail as soon as possible). The Operations/Statistical Center will fax the form (and accompanying reports) to the Investigational Drug Branch of the NCI.

16.0 RECORDS AND REPORTING

16.1 Categories Of Research Records

Research records for this study can be divided into three categories:

1. Reference Labs, Biopathology Reviews, and QARC data. These data accompany submissions to these centers, who forward their data electronically to the COG. Research Data System.
2. Non-computerized information: Roadmaps, Pathology Narrative Reports, Surgical Reports. These forms are faxed to the Statistics and Data Center at (626) 445-4334.

3. Computerized Information supplied after Registration. All other computerized data will be entered on the C.O.G. Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE Screens) provided in the data form packet.

This is a secure password controlled system. Upon authentication, you will enter the information, with the aid of schedules and worksheets (essentially paper copies of the RDE screens) as provided in the data form packet. See separate Data Form Packet which includes submission schedule.

16.2 **CDUS**

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

July 6, 2004

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA					
Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II: TEMOZOLOMIDE DOSING

Temozolomide Dosing

	Chemoradiotherapy (90 mg/m²/day)	
BSA (m ²)	Calculated Dose (mg)	Administered Dose (mg)
.20-.50	3 MG/KG/Day	3 MG/KG/Day
.51-.58	45.9-52.2	50
.59-.63	53.1-56.7	55
.64-.69	57.6-62.1	60
.70-.75	63.0-67.5	65
.76-.80	68.4-72.0	70
.81-.86	72.9-77.4	75
.87-.91	78.3-81.9	80
.92-.97	82.8-87.3	85
.98-.99	88.2-89.1	90
1.0	90	90
1.1	99	100
1.2	108	110
1.3	117	120
1.4	126	125
1.5	135	135
1.6	144	145
1.7	153	155
1.8	162	160
1.9	171	170
2.0	180	180

	Maintenance (200mg/m²/day)	
BSA (m ²)	Calculated Dose (mg)	Administered Dose (mg)
.20-.50	6.7 MG/KG/Day	6.7 MG/KG/Day
.51	102	100
.52-.53	104-106	105
.54-.56	108-112	110
.57-.58	114-116	115
.59-.61	118-122	120
.62-.63	124-126	125
.64-.66	128-132	130
.67-.68	134-136	135
.69-.71	138-142	140
.72-.73	144-146	145
.74-.76	148-152	150
.77-.78	154-156	155
.79-.81	158-162	160
.82-.83	164-166	165
.84-.86	168-172	170
.87-.88	174-176	175
.89-.91	178-182	180
.92-.93	184-186	185
.94-.96	188-192	190
.97-.98	194-196	195
.99-1.0	198-200	200
1.1	220	220
1.2	240	240
1.3	260	260
1.4	280	280
1.5	300	300
1.6	320	320
1.7	340	340
1.8	360	360
1.9	380	380
2.0	400	400

APPENDIX III: TEMODAR ADMINISTRATION AND MEDICATION DOCUMENTATION FORM FOR CHEMORADIO THERAPY

- Temodar is an oral cancer medicine that your child will be taking for treatment of his brain tumor. Important guidelines for taking this medicine include:
- Temodar must be kept in a dark container
- Temodar should be taken the same time everyday and the capsules must be swallowed whole. It is recommended that Temodar be given at bedtime with antiemetics given 30 minutes prior to the Temodar dose.
- Temodar capsules may not be crushed or chewed
- If the capsules must be opened, please refer to the instruction sheet for administration (see Appendix V)
- If your child requires nausea medicine it should be taken approximately 30 minutes prior to the Temodar dose
- If the dose of Temodar is vomited (which is unusual with this medicine) do not repeat the dose

Medication Record: Please fill in the table each day the medicine is given. Please bring this form to clinic each visit so that your provider can review the information.

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				

Day	Date	Dose	Other Medicines	Problems
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				

APPENDIX IV: TEMODAR ADMINISTRATION AND MEDICATION DOCUMENTATION FORM FOR MAINTENANCE

- Temodar is an oral cancer medicine that your child will be taking for treatment of his brain tumor. Important guidelines for taking this medicine include:
- Temodar must be kept in a dark container
- Temodar should be taken the same time everyday and the capsules must be swallowed whole. It is recommended that Temodar be given at bedtime with antiemetics given 30 minutes prior to the Temodar dose.
- Temodar capsules may not be crushed or chewed
- If the capsules must be opened, please refer to the instruction sheet for administration (See Appendix V)
- If your child requires nausea medicine it should be taken approximately 30 minutes prior to the Temodar dose
- If the dose of Temodar is vomited (which is unusual with this medicine) do not repeat the dose

Medication Record: Please fill in the table each day the medicine is given. Please bring this form to clinic each visit so that your provider can review the information.

Cycle 1

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 2

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 3

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 4

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 5

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 6

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 7

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 8

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 9

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

Cycle 10

Day	Date	Dose	Other Medicines	Problems
1				
2				
3				
4				
5				

APPENDIX V: INSTRUCTIONS FOR ADMINISTRATION OF TEMODAR

(Patients who are unable to swallow capsules)

Temodar is an oral cancer medicine that your child will be taking for treatment of his/her brain tumor. Your child is unable to swallow capsules so the following instructions must be followed for safe administration of this medicine.

- Temodar must be kept in a dark container
- Temodar should be taken the same time everyday
- If your child requires nausea medicine it should be taken prior to the Temodar
- If the dose of Temodar is vomited (which is unusual) do not repeat the dose
- If the person dispensing this medicine is pregnant or suspects she is pregnant she should not dispense this medicine

Temodar is an anti-cancer agent, special precautions must be taken when handling this medicine. There is potential hazard to anyone who handles this medicine once the protective capsule is opened. Since your child is unable to swallow the capsule you will be required to open the capsules and mix the contents of the capsule in apple sauce or apple juice. This process must be done according to the following guidelines to ensure safe administration of this medicine.

- Find a place that is as free of air flow as possible and is not an area where food is stored or prepared.
- The work surface should be covered with an impermeable and disposable mat such as the one a pharmacy uses to reduce exposure to other members of the family.
- Temodar can be mixed in apple sauce or apple juice.
- Place the apple sauce or apple juice in a disposable container.
- Put on gloves, mask and goggles (eye protection).
- Open each capsule and place the powder in a medicine cup.
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup.
- If you need to have additional juice or apple sauce remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves).
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce.
- Once all of the medicine is taken throw away the following in the red bag: medicine cup, the container the medicine was mixed in, the cover for the work surface, mask, gloves and anything else that has been in contact with the medicine.
- Once a course of medicine is completed bring the red bag with you to the clinic so it can be disposed of properly.

SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

ACNS0126, A Phase II Study of Temozolomide in the Treatment of Children with High-grade Glioma or diffuse intrinsic Pontine Gliomas

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be filed with the COG Group Operations Center's Regulatory Compliance Office before a patient may be registered on this study.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial (a research study involving human patients). Clinical trials only include patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

This study is being carried out by the Children's Oncology Group (COG). COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, and Switzerland. It is common medical practice to treat children with cancer on national research studies like this one.

You are being asked (to allow your child) to take part in this study because you have (your child has) a type of brain tumor called a high-grade glioma or diffuse intrinsic pontine gliomas. Standard treatment for high-grade and diffuse intrinsic pontine gliomas includes surgery to remove as much tumor as possible followed by radiation therapy (treatment with high-dose x-rays). Treatment may also include anti-cancer drugs (chemotherapy) during and after radiation treatment. Current standard treatments are not very effective against high-grade and diffuse intrinsic pontine gliomas.

Temozolomide is new anti-cancer drug that is being studied for the treatment of brain tumors. It has been used in other studies and a dose that is safe for children has been determined. This study looks at how well Temozolomide works when given with and after radiation therapy.

WHY IS THIS STUDY BEING DONE?

The goals of this study are:

- **to see if treatment with Temozolomide and radiation works better than other treatments for high-grade and diffuse intrinsic pontine gliomas that we have used in the past**
- **to look at side effects of the treatment (*A side effect is an unintended result of a treatment.*); and**
- **to study surgically removed tumor tissue to see if biological characteristics of the tissue relate to how well a patient responds to treatment.**

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 50 patients participating in this study.

WHAT WILL HAPPEN TO ME (MY CHILD) ON THIS STUDY?

Patients begin treatment on this study no later than 6 weeks following surgery for HGG patients and no later than 6 weeks of diagnosis for DIPG patients. Tumor tissue removed during surgery as well as a small blood sample will be sent to a central lab to see if there is a relationship between tumor biology and how well patients on this study respond to treatment.

TREATMENT

The first phase of treatment is called Chemoradiotherapy. During this first phase, you (your child) will be given radiation therapy to the brain 5 days a week for 6 weeks. Within the first week of starting radiation therapy, you (your child) will begin taking the drug Temozolomide by mouth (90 mg/m²/day), and will continue taking the drug for 42 days (6 weeks). After you (your child) complete radiation therapy and the 6-week treatment with Temozolomide, you will be given a 4-week rest, during which no treatment is given.

The second phase of treatment, called Maintenance, begins at the end of the rest period. During Maintenance, you (your child) will take the drug Temozolomide again, but this time at a higher dose (200 mg/m²/day) and on a different schedule. No further radiation is given. You (your child) will take Temozolomide by mouth for 5 days in a row, followed by 23 days of not taking the drug. This 28-day cycle will be repeated 10 times.

Please see the attached instruction sheet for patients who are unable to swallow the Temozolomide capsules.

STANDARD MEDICAL TESTS

Before treatment on this study begins, and while receiving treatment, you will receive a series of standard medical tests:

- Physical exam
- Blood tests
- Urine tests
- Pregnancy test (before the start of treatment, for females of childbearing potential)
- Tests of liver function
- Magnetic Resonance Imaging (MRI) of the brain and spine (MRI uses magnetic waves to look at soft tissues of the body)

HOW LONG WILL I (MY CHILD) BE ON THIS STUDY?

You (your child) will be treated on this study for about 12-14 months. However, you (your child) will continue to have physical exams, blood tests (until tests are normal) and MRIs every three to six months for four years after treatment so that researchers can continue to observe any effects of treatment. After four years, you (your child) will continue to have a physical exam and MRI every year. In addition, we would like to continue to collect some medical information about how you are (your child is) for as long as you are willing to let us.

The researchers may decide to take you (your child) off the study early if your (your child's) cancer gets worse or you (your child) experiences side effects from the treatment that are considered too severe.

You can leave (remove your child from) the study at any time. However, if you consider leaving (removing your child from) the study, we encourage you to talk to your (your child's) regular physician and to the research physician before making a final decision.

WHAT ARE THE RISKS OF THE STUDY?

Possible side effects of treatment with Temozolomide

The following table presents the kinds of side effects that may be experienced by patients treated with Temozolomide:

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to less than 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Loss of appetite, nausea, vomiting, diarrhea, constipation, headache, rash, itching, increased need to urinate, urinary tract infections	Convulsions, dizziness, difficulty walking, confusion, difficulty swallowing, anxiety, partial paralysis or weakness of one side of the body, blood clots which may be life-threatening (L)
Prompt: Within 2-3 weeks, prior to next course	Decrease in the number of red and white blood cells and platelets made in the bone marrow	Mouth sores, tiredness, fluid buildup in legs and arms	Prolonged decrease in the number of red and white blood cells and platelets made in the bone marrow with an increased risk of infection or death, memory-loss, unable to sleep, depression, muscle aches, blurred or double vision
Delayed: Anytime later during therapy, excluding the above conditions		Hair loss, liver damage	
Late: Anytime after completion of therapy			Cancer

Possible Side-effects of Daily, Oral Temozolomide in Combination with Bactrim

In a separate study using a 42-day continuous schedule of temozolomide plus radiation and Bactrim (a drug given to prevent pneumonia), some adult patients experienced a decrease in the number of platelets, and red and white blood cells made in the bone marrow that lasted an unusually long period of time. This resulted in infections, including a few cases where patients died as a result of these infections.

Reproductive Risks

Because we do not know the effects Temozolomide can have on an unborn baby, you (your child) should not become pregnant or father a baby while on this study. You (your child) should not nurse a baby while on this study. Ask about counseling and more information about preventing pregnancy.

Since this is a new, experimental treatment for children, other presently unknown side effects may be encountered. You (your child) will be watched closely and the drugs will be discontinued if serious side effects develop.

Possible side effects of radiation therapy to the brain

Short-term side effects:

- Hair loss (all hair may not grow back after treatment)
- Irritation or redness of the skin with possible peeling of the skin at the site of radiation.
- Areas of the ear canal exposed to radiation may develop inflammation and irritation weeks or months after treatment that may cause plugging of ears, and balance problems.

Long-term side effects:

- Changes in hormone function
- Growth failure
- Vision problems
- Partial hearing loss
- Memory loss
- Learning difficulties

WILL I (MY CHILD) BENEFIT FROM THIS STUDY?

There may or may not be direct medical benefits to you (your child) from taking part in this study. It is hoped that the information learned from this study may help future patients with brain tumors.

ARE THERE OTHER TREATMENT OPTIONS?

Yes, there are other options.

- **The standard treatment for high-grade glioma which is surgery, radiation therapy, and treatment with standard anticancer drugs.**
- **Another experimental treatment (if available).**
- **No further treatment and comfort care only.**

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

WILL MY (MY CHILD'S) RECORDS BE CONFIDENTIAL?

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

You may read your (your child's) medical record. The records are available to those caring for you (your child) at this hospital.

Organizations that may inspect/or copy your (your child's) medical and research records for quality assurance and data analysis include:

- **The Children's Oncology Group**
- **The National Cancer Institute**
- **The Food and Drug Administration**
- **The Institutional Review Board of this hospital**

Names of participants or material identifying participants (except as described above) will not be released without written permission, unless required by law.

WILL I HAVE TO PAY FOR THIS TREATMENT?

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

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

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

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

WHAT ARE MY (MY CHILD'S) RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose (for your child) not to participate in this study. If you decide not to (let your child) participate, you (your child) will not be penalized and you (your child) will still receive the standard treatment.

If you choose to (allow your child to) participate, you may discontinue your (your child's) participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of you (your child).

You also have the right to know about new information that may affect your (your child's) health, welfare, or your willingness to (let him/her) participate in the study. You will be provided with this information as soon as it becomes available.

Whether you participate or not, you (your child) will continue to get the best medical care this hospital can provide.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or an injury related to the research, please call

NAME at TELEPHONE NUMBER

For questions about your rights as a study participant, please call

NAME OF INSTITUTIONAL REVIEW BOARD REPRESENTATIVE*

at TELEPHONE NUMBER

*The Institutional Review Board is a group of people who review the research study to protect your rights.

WHERE CAN I GET MORE INFORMATION?

- Call the National Cancer Institute's Cancer Information Service:
1-800-4-CANCER (1-800-422-6237) OR
1-800-332-8615 (for the hearing impaired)
- You will be given a copy of this protocol (complete study plan) upon request.
- Visit the National Cancer Institute's Web sites:

CancerTrials: <http://cancertrials.nci.nih.gov>

This site provides comprehensive clinical trials information.

CancerNet™: <http://cancernet.nci.nih.gov>

This site provides accurate cancer information including the Physicians Data Query (PDQ). The PDQ is the National Cancer Institute's comprehensive cancer database. It contains peer-reviewed summaries on cancer treatment, screening, prevention, and supportive care; a registry of about 1,700 open and 10,300 closed cancer clinical trials from around the world; and directories of physicians, genetic counselors, and organizations that provide cancer care.

- You will be given a copy of this consent form.

STATEMENT OF CONSENT

I have already read the above information. I have asked all my questions and I have gotten answers. I agree to enroll (my child) in this study.

A copy of this consent form will be provided to me

PATIENT NAME _____

SIGNATURE OF PATIENT

DATE

SIGNATURE OF PARENT OR GUARDIAN

DATE

SIGNATURE OF PHYSICIAN OR
RESPONSIBLE INVESTIGATOR

DATE

INSTRUCTIONS FOR ADMINISTRATION OF TEMOZOLOMIDE

(Patients who are unable to swallow capsules)

Temodar is an oral cancer medicine that your child will be taking for treatment of his/her brain tumor. Your child is unable to swallow capsules so the following instructions must be followed for safe administration of this medicine.

- Temodar must be kept in a dark container
- Temodar should be taken the same time everyday
- If your child requires nausea medicine it should be taken prior to the Temodar
- If the dose of Temodar is vomited (which is unusual) do not repeat the dose
- If the person dispensing this medicine is pregnant or suspects she is pregnant she should not dispense this medicine

Temodar is an anti-cancer agent, special precautions must be taken when handling this medicine. There is potential hazard to anyone who handles this medicine once the protective capsule is opened. Since your child is unable to swallow the capsule you will be required to open the capsules and mix the contents of the capsule in apple sauce or apple juice. This process must be done according to the following guidelines to ensure safe administration of this medicine.

- Find a place that is as free of air flow as possible and is not an area where food is stored or prepared.
- The work surface should be covered with an impermeable and disposable mat such as the one a pharmacy uses to reduce exposure to other members of the family.
- Temodar can be mixed in apple sauce or apple juice.
- Place the apple sauce or apple juice in a disposable container.
- Put on gloves, mask and goggles (eye protection).
- Open each capsule and place the powder in a medicine cup.
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup.
- If you need to have additional juice or apple sauce remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves)
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce.
- Once all of the medicine is taken throw away the following in the red bag: medicine cup, the container the medicine was mixed in, the cover for the work surface, mask, gloves and anything else that has been in contact with the medicine.

Once a course of medicine is completed bring the red bag with you to the clinic so it can be disposed of properly.