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CHILDREN'S ONCOLOGY GROUP

ACNS0822

A Randomized Phase II/III Study of Vorinostat ([redacted]) and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab ([redacted]) and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children with Newly Diagnosed High-Grade Gliomas

NCI Supplied Agents: Vorinostat ([redacted], NSC# 701852) and Bevacizumab ([redacted], NSC# 704865)

A Groupwide Phase II/III Study

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AGENT NSC# AND IND#'s

Bevacizumab	NSC#704865	[redacted]
Vorinostat	NSC#701852	
Temozolomide	NSC#362856	

SEE SECTIONS 15.0 AND 16.0 FOR SPECIMEN SHIPPING ADDRESSES

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ABSTRACT

The outcome for children with high grade gliomas (HGG) remains poor despite the use of multi-modal therapy with surgery, radiation therapy (RT) and chemotherapy. Although RT does prolong survival slightly, adjuvant chemotherapy has had little impact on survival in children with high grade gliomas. CCG 945 showed no improvement in survival for patients treated with the 8-in-1drug regimen compared to the CCNU/vincristine/prednisone regimen. Five year progression-free survival (PFS) was 19% ± 3%, while those who did not have a GTR had a 5 year PFS of 11% ± 4%.[1] Novel therapies are required to improve the outcome for children with newly diagnosed HGG. Synergistic effects of bevacizumab with other chemotherapeutic agents including camptothecins have been seen in preclinical studies, and the combination of bevacizumab and temozolomide has shown promising results in adult studies of recurrent HGG. Deregulation of histone acetylation has been implicated in the development of several types of cancer, and findings from preclinical studies suggest a potential role for HDAC inhibitors in the treatment of children with hematological and solid tumor malignancies. The use of temozolomide in preclinical models also suggest that temozolomide has at least additive activity with radiation in human glioblastoma cells.[2-6] Hence, the current proposal will study these three agents' roles as radiosensitizers. This study will be done in three parts: an initial feasibility study within the phase II part which will determine the dose of vorinostat that is safe and tolerable in combination with radiation therapy for patients less than 22 years of age; a phase II part that will employ a randomized "pick the winner" approach to determine if either of 2 experimental treatment arms (bevacizumab or vorinostat during chemoradiotherapy), have a higher nominal 1-year event-free survival (EFS) than the de facto standard treatment arm (temozolomide during chemoradiotherapy); and a randomized phase III part where patients will be randomized to either the chosen experimental arm or the temozolomide arm for a formal efficacy (EFS) comparison. EFS, PFS, and overall survival (OS) on each treatment arm will be estimated using Kaplan-Meier curves. All phases of this study, including the feasibility phase, will be available to all COG institutions. Vorinostat will be administered at a starting dose of 230 mg/m^2/dose and, if proved to be safe, will be the dose used in subsequent phases of the study. Descriptive statistics will be used to investigate molecular and biologic markers and their associations with treatment outcome.

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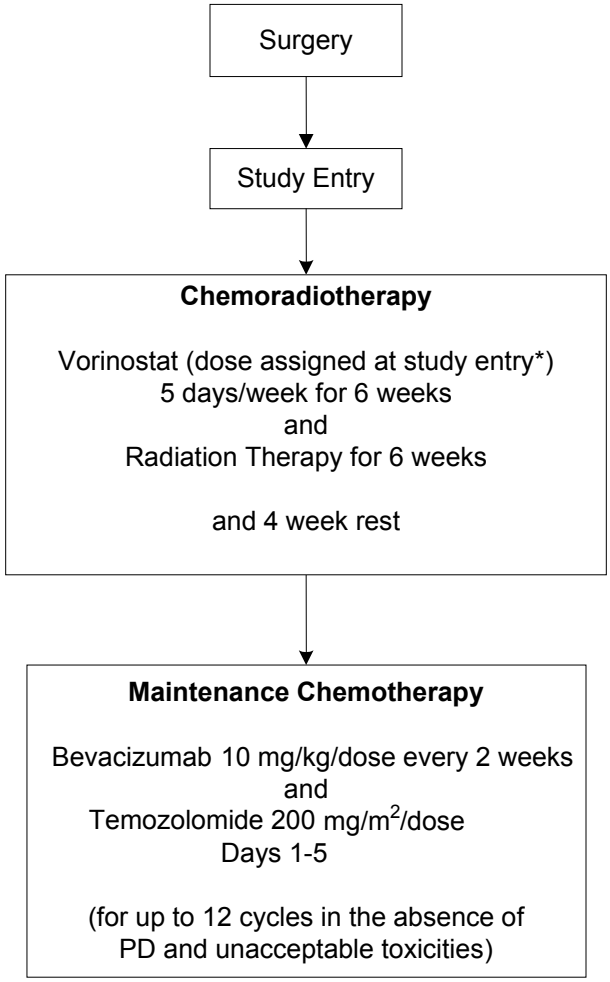
EXPERIMENTAL DESIGN SCHEMA: FEASIBILITY STUDY - VORINOSTAT WITH RADIATION THERAPY

As of Amendment #1, the Feasibility Study was completed.



*Dose assigned at entry is either 230 mg/m^2/dose or 180 mg/m^2/dose
PD = Progressive Disease

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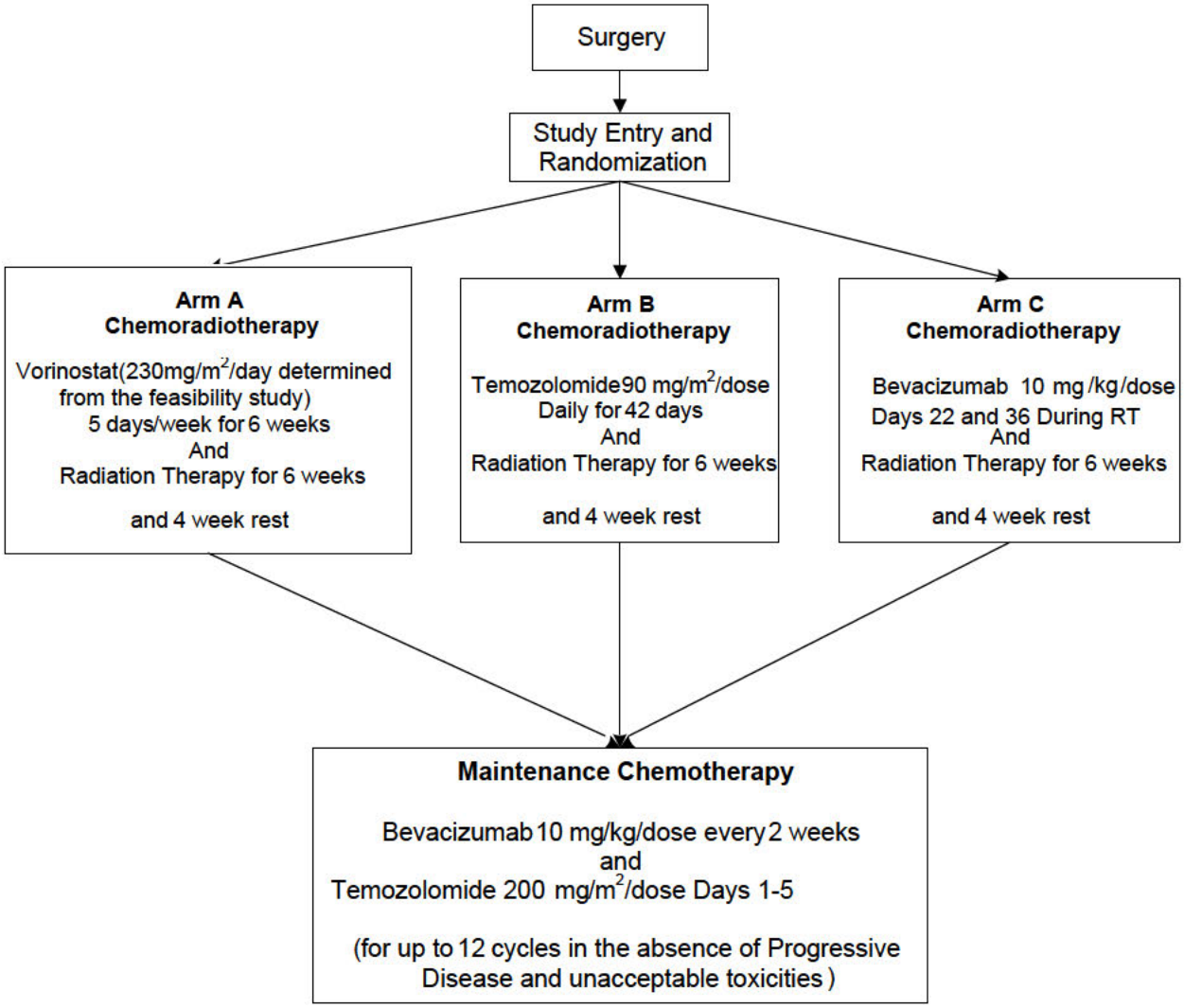
EXPERIMENTAL DESIGN SCHEMA: PHASE II



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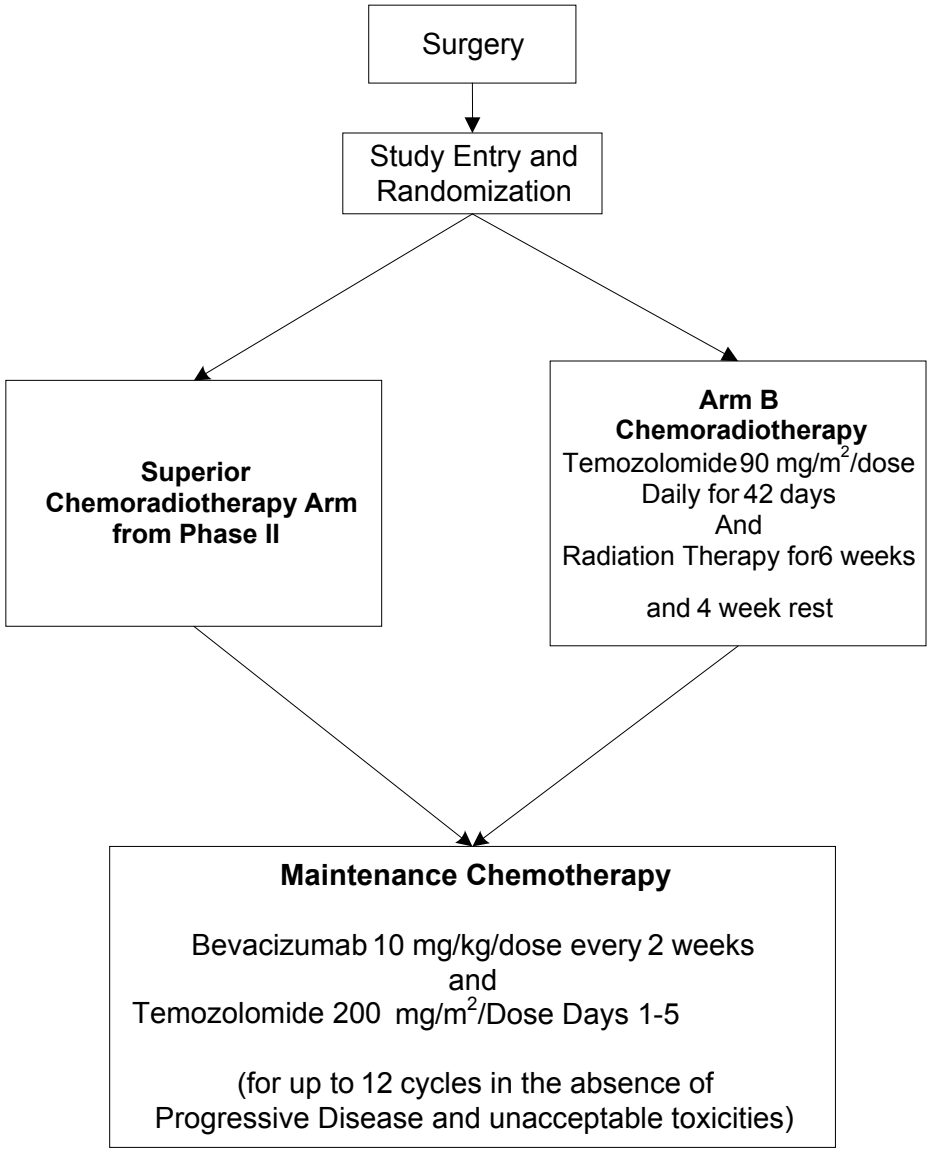

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1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1
To identify the dose of vorinostat that is feasible when given in combination with radiotherapy (RT) in patients with newly diagnosed high-grade gliomas (HGG).

1.1.2
Phase II: To evaluate if either vorinostat (using MTD from feasibility phase) or bevacizumab gives a more promising outcome compared to temozolomide, as measured by one-year event-free survival (EFS), when given in combination with radiotherapy (RT) followed by maintenance chemotherapy with bevacizumab and temozolomide in patients with newly diagnosed high-grade gliomas (HGG).

1.1.3
Phase III: To determine if the agent that has a more promising outcome than temozolomide in the Phase II portion, or the agent with the higher outcome between vorinostat and bevacizumab if both are more promising than temozolomide in the Phase II portion, results in superior event-free survival (EFS) compared to temozolomide, when given in combination with radiotherapy (RT) followed by maintenance chemotherapy with bevacizumab and temozolomide in patients with newly diagnosed high-grade gliomas (HGG).

1.2 Secondary Objectives

1.2.1
Phase II/III: To evaluate the anti-tumor activity as measured by event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) of treatment with either vorinostat, bevacizumab, or temozolomide, when given in combination with radiotherapy followed by maintenance chemotherapy with bevacizumab and temozolomide in patients with newly diagnosed HGG.

1.2.2
To define and evaluate the toxicities of each of the treatment arms of the study.

1.2.3
To conduct gene expression profiling and SNP arrays in patients with newly diagnosed HGG.

1.2.4
To assess telomerase activity, hTert expression, and telomere length in patients with newly diagnosed HGG.

1.2.5
To document changes in MR perfusion and diffusion using MR imaging obtained at baseline, prior to initiation of maintenance therapy with bevacizumab and temozolomide, prior to cycle 3 of maintenance therapy, and subsequent to completion of maintenance therapy.

1.2.6
To correlate functional changes in tumor with responses to bevacizumab treatment using MR diffusion/perfusion imaging.

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1.2.7
To correlate the results of the bevacizumab biology studies in serum or tumor with EFS.

1.2.8
To explore the prognostic significance of MGMT status for patients newly diagnosed with HGG treated with combined surgery, radiation, chemotherapy, and anti-angiogenic therapy.

2.0 BACKGROUND

2.1 High Grade Gliomas

The outcome for children with high grade gliomas remains poor despite the use of multi-modal therapy with surgery, radiation therapy (RT) and chemotherapy. Although RT does prolong time to progression slightly, adjuvant chemotherapy has had little impact on survival in children with high grade gliomas.

The first prospective, randomized study in pediatrics was conducted by the Children's Cancer Group (CCG) in 58 patients with high-grade astrocytoma who were randomized to study the effectiveness of chemotherapy as an adjuvant to standard surgical treatment and radiotherapy. Following surgical therapy, patients were assigned randomly to radiotherapy with or without chemotherapy consisting of chloroethyl-cyclohexyl nitrosourea (CCNU), vincristine (VCR), and prednisone. In this initial study (CCG 943), 5-year event-free survival (EFS) was 46% for patients in the radiotherapy and chemotherapy group, and 18% for patients in the radiotherapy only group. Five-year survival was similarly improved. In patients with glioblastoma multiforme (GBM) and at least a partial resection, the benefit from chemotherapy was clear with a 5-year progression free survival (PFS) of 42% for patients in the radiotherapy and chemotherapy group and 6% for patients in the radiotherapy only group (P=0.001). Five-year overall survival (OS) in this same subgroup was 36% for patients in the radiotherapy and chemotherapy group vs 5% for patients in the radiotherapy only group. Patients whose initial surgery was limited to biopsy and patients with basal ganglia lesions also had significantly worse outcome.[7]

Based on the CCG 943 trial, CCG 945 randomized patients to receive an 8-in-1 drug regimen or the CCNU/vincristine/prednisone regimen (control arm). Between 1985 and 1990, 85 patients were randomly assigned to the control arm and 87 patients were assigned to the experimental (8-in-1 drug) regimen. CCG 945 showed no improvement in survival for patients treated with the 8-in-1 drug regimen compared to the CCNU/vincristine/prednisone regimen. Five year PFS was 33% and 5-year OS was 39% in the experimental group (8-in-1) compared to a PFS of 26% and OS of 29% in the control group. Those who did not have a GTR had a 5-year PFS of 11% (± 4%)[1].

Five-year PFS for patients with anaplastic astrocytomas (AA) was 28% (SE=7%) and for patients with GBM was 16% (SE=17%). A stepwise Cox life-table regression analysis identified independent predictors of improved PFS as a 90% or greater resection of tumor (P<0.02), AA histology (P<0.01) and female sex (P<0.01).

Patients with centrally reviewed AA and a 90% or greater resection had a median time to progression of 31 months, compared with a median time to progression of 12 months in those with less than a 90% resection. For the GBM group, the extent of resection only conferred a modest advantage in terms of survival with a median time to progression of 12 months vs 8 months.

Interestingly, the patients in the control arm in CCG 945, who were treated with prednisone, lomustine, and vincristine (PCV), did not demonstrate the same PFS advantage as those treated with adjuvant PCV chemotherapy in the CCG 943 study. Five-year PFS in CCG 943 for the chemotherapy arm was 46% vs

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26 (±8%) for the CCG 945 control arm. An updated centralized review of the pathology based on the WHO criteria conducted retrospectively confirmed the benefit of the addition of chemotherapy in patients with confirmed GBM treated on CCG 943.

CCG 9933 (1993-1998) evaluated the efficacy of 3 different chemotherapy regimens prior to radiotherapy. Seventy six evaluable patients were randomized to receive 4 courses of high-dose chemotherapy (HDCT) prior to RT. The chemotherapy regimens included etoposide with carboplatin OR ifosfamide OR cyclophosphamide. Patients then went onto receive RT followed by CCNU and VCR. Objective responses to the chemotherapy regimens ranged from 8%-27%. Five-year EFS was 8% (±3%) with an OS of 24% (±5%). There was no difference among the response rates of the HDCT regimens; the relapse rate during HDCT was 30%. Twenty nine percent experienced severe non-hematological toxicities.[8]

POG 9135 was a phase III study that randomized patients between pre-irradiation cisplatin and BCNU or vincristine and cyclophosphamide. The 5-year survival of 20% for the cisplatin/BCNU arm was better than the 5% 5-year survival rate for those treated with vincristine and cyclophosphamide ($P<0.05$).[9]

Based on the adult study by Stupp et al,[10] ACNS0126 treated newly diagnosed children with involved field irradiation with concurrent temozolomide followed by temozolomide 200 mg/m^2 daily for 5 days every 28 days for 10 cycles. [11] (Please see full results in section 2.2.2)

2.2 Rationale for Bevacizumab and Temozolomide post RT in all arms

Malignant gliomas are highly vascularized and infiltrative tumors. They are dependent on endothelial cell proliferation regulated by proangiogenic cytokines, such as vascular endothelial growth factor (VEGF), which is the dominant angiogenic mediator in high grade gliomas.[12,13] In fact, VEGF expression has been shown to correlate with worse prognosis in patients with high grade gliomas[14,15] and antibodies to VEGF have inhibited the growth of GBM in a xenograft model.[16]

2.2.1 Bevacizumab

Bevacizumab (Avastin; Genentech, San Francisco, CA) is a vascular endothelial growth factor (VEGF)-specific recombinant, humanized monoclonal antibody. The antibody was generated by engineering the VEGF binding residues of a murine neutralizing antibody (A4.6.1) into the framework of normal human immunoglobulin G (IgG1). Bevacizumab binds directly to all four VEGF isoforms ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$) with high affinity and specificity and inhibits VEGF from binding to its receptors.

In preclinical studies and clinical studies in adults, bevacizumab has induced stabilization and in some cases regression of tumors including glioblastoma multiforme (GBM).[17-20] Bevacizumab has also been shown to potentiate the cytotoxic effects of chemotherapy and radiation in a number of different adult tumor types, including colorectal cancer and non-small cell lung cancer.[21] Bevacizumab has been approved by Food and Drug Administration (FDA) for usage for first- or second-line treatment in combination with chemotherapy in adults with colorectal carcinoma.

The safety of bevacizumab has been evaluated in a number of adult clinical trials. The most significant adverse events include hypertension, proteinuria, thrombosis and bleeding. Hypertension is the most common Grade 3/4 toxicity reported. Grade 3 hypertension (requiring more than one drug or more intensive therapy than previously) occurs in approximately 10%-20% of study subjects. Reports of Grade 4 hypertension (hypertensive crisis) have been uncommon. Asymptomatic proteinuria, across all grades, is frequently reported with a rare incidence of Grade 4 proteinuria (nephrotic syndrome). Venous thrombotic events have been described in association with bevacizumab therapy; however, in large randomized studies with and without bevacizumab there does not appear to be a statistically significant

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increase in venous thrombotic events. A small but significant increase in arterial thrombotic events has also been observed in patients receiving bevacizumab. At-risk groups include those with a history of atherosclerosis and those over the age of 65.[19,22,23]

Manageable Grade 1/2 bleeding events are commonly observed with bevacizumab therapy. The incidence of more significant bleeding (Grade 3/4) was not significantly increased in a large randomized trial for patients with metastatic colorectal cancer treated with bevacizumab.[22] However, in a phase II trial in patients with non-small-cell lung cancer, life-threatening hemoptysis or pulmonary hemorrhage was observed in 6 of 67 patients who received bevacizumab in combination with paclitaxel and carboplatin.[24] The bleeding in these patients seemed to be linked to the central location, proximity to major blood vessels and tumor cavitation, features common in squamous cell carcinoma. In the follow-up phase III trial, patients with this histology as well as patients with a significant history of gross hemoptysis were excluded and the preliminary results suggest a decreased incidence of fatal bleeding in patients receiving bevacizumab.[25]

Neovascularization is an important process in surgical wound healing. Inhibition of angiogenesis theoretically may impair or delay wound healing. Preclinical models to assess the impact of anti-angiogenic agents in wound repair have been inconsistent, and clinical studies in humans have been limited. Recently, the effect of bevacizumab on postoperative wound healing was assessed in patients with colorectal cancer enrolled in 2 randomized trials. No increased risk of wound healing was noted in patients who began bevacizumab therapy 28-60 days after primary cancer surgery compared to chemotherapy alone. Patients who required major surgery during bevacizumab therapy tended to have more wound healing complications (13% versus 3%), but the difference was not statistically significant.[26]

Schedule and dose of bevacizumab in adult trials has varied between 5 to 15 mg/kg every 2 to 3 weeks. Recent analysis of pharmacokinetic data from 2 phase II adults trials (AVF0780 in colorectal carcinoma and AVF0757 in non-small cell lung cancer) using 2 dosing schedules, 5 mg/kg every 2 weeks and 7.5 mg/kg every 3 weeks, respectively, determined that the overall exposure to bevacizumab was similar.

Recently, the Children's Oncology Group (COG) completed a pediatric phase I study of bevacizumab in patients with refractory solid tumors. Three dose levels (5 mg/kg, 10 mg/kg and 15 mg/kg every 2 weeks intravenously) were studied in a total of 18 evaluable patients. No dose-limiting toxicities were observed at the highest dose level. Only one Grade 3 toxicity, lymphopenia, was observed. In a limited number of patients, pharmacokinetic studies revealed increased serum exposure with dose. The median clearance of bevacizumab was 4.1 ml/day/kg (range 3.5-15.9), and the median half-life was 11.8 days. No objective responses were observed. Five patients had disease stabilization for greater than 3 months.[27]

Bevacizumab has demonstrated synergy with several chemotherapeutic agents including cisplatin, camptothecins and cyclophosphamide in preclinical xenograft models, and has decreased vascular permeability and increased cellular apoptosis in glioblastoma xenograft models.[28]

2.2.2 Temozolomide

Temozolomide is an orally administered alkylating agent, a second generation imadazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. It exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the O^6-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.

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Stupp et al reported the results of a study in which adults with newly-diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone or radiotherapy plus continuous daily temozolomide, followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle), The primary end point was overall survival. A total of 573 patients underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7 percent of patients. Thus, the authors concluded that the addition of temozolomide to radiotherapy for adults with newly diagnosed glioblastoma resulted in a statistically significant survival benefit with minimal additional toxicity. This regimen has become the standard of care for adults with this disease.[10]

The results of RTOG 0625: A Randomized Phase II Trial of Bevacizumab with either Irinotecan (CPT) or Dose-Dense Temozolomide (TMZ) in Recurrent Glioblastoma (GBM) TMZ 75-100 mg/m^2 d 1-21 of 28 d cycle have recently been analyzed. Sixty patients were enrolled on TMZ arm and 57 pts on CPT arm. All had prior radiation and temozolomide. For the TMZ arm, 6m-PFS rate was 40% (95% CI: 27-53%); for the CPT arm, the 6m-PFS rate was 39% (95% CI: 26-52%). Objective responses: TMZ arm with 1 (2%) CR, 11 (19%) PR; CPT arm with 2 (4%) CR, 13(24%) PR. Moderate toxicity was noted: TMZ arm with 30 (50%) grade 3, 10 (17%) grade 4, and 3 (5%) grade 5 (fatal) toxicities; CPT arm had 22(39%) grade 3, 7 (12%) grade 4, and 3 (5%) grade 5 (fatal) toxicities. The 6m-PFS surpassed the predetermined efficacy threshold for both arms, corroborating the efficacy of bevacizumab and CPT and confirming activity for bevacizumab and protracted TMZ for recurrent/progressive GBM, even after prior temozolomide exposure. Toxicities were within anticipated frequencies with a moderately high rate of venous thrombosis, moderate hypertension and one intracranial hemorrhage. Studies to determine the efficacy of bevacizumab in newly diagnosed GBM are underway. (Gilbert et al, Personal Communication)

The combination of TMZ and bevacizumab with or without the addition of irinotecan is currently being tested nationally in several studies for adults with newly diagnosed HGG. Recently, Vrendenburg et al reported the preliminary results of a study using bevacizumab in combination with temozolomide (TMZ) and radiation therapy (XRT) followed by BEV, TMZ, and irinotecan for newly diagnosed glioblastoma multiforme (GBM). 125 patients received radiation therapy and TMZ at 75 mg/m^2/d beginning between 2-6 weeks post-craniotomy. Bevacizumab at 10 mg/kg every 14 days was added a minimum of 4 weeks post- op. Following radiation therapy, patients received 6-12 monthly cycles of TMZ at 200 mg/m^2/d days 1-5, bevacizumab at 10 mg/kg and irinotecan on days 1 and 15. The dose of irinotecan was 340 mg/m^2 for patients on enzyme inducing anti-epileptic drugs (EIAED) and 125 mg/m^2 for patients not on EIAED. Efficacy analysis is based on the first 75 patients and the toxicity analysis includes all 125 patients. The median PFS doubled on this current protocol, 14 months vs. 6.9 months historically. The median overall survival has not been reached, but 56% of the patients are alive at a minimum follow-up of 18 months. In addition, 28% remain progression-free at a median follow- up of 23 months. The regimen was tolerable; 122 of 125 patients completed radiation therapy and 78 completed 6 cycles of post-radiation bevacizumab, TMZ, and irinotecan. There were 4 toxic deaths, MI, PE, PCP, and sepsis. The authors concluded that the addition of bevacizumab to TMZ and radiation followed by TMZ, bevacizumab, and irinotecan is tolerable. The median progression-free survival is improved and the overall survival is prolonged. [29]

Lai, Cloughesy et al recently presented the updated results of a phase II trial of bevacizumab in combination with temozolomide and regional radiation therapy for upfront treatment of adults with newly diagnosed GBM. This was an open label multicenter phase II trial with 70 patients in which bevacizumab was combined with the standard backbone of RT/TMZ. Bavacizumab was also given concurrently with

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radiation. The primary objective was overall survival and progression-free survival. Treatment was tolerated well among the 70 patients. Treatment delivery characteristics were similar to the historical control group.[30] PFS was increased from 6.9 to 14.1 months, while OS increased from 14.6 to 20.3 months. The authors concluded that this bevacizumab-based regimen had promising activity for PFS compared to the historical control data. The treatment appeared tolerable with a toxicity profile consistent with prior bevacizumab studies.[31]

The current RTOG study 0825 is a Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant temozolomide plus bevacizumab versus conventional concurrent chemoradiation and adjuvant temozolomide in patients with newly diagnosed glioblastoma, Preliminary results demonstrate that the combination is well-tolerated, ([redacted], personal communication).

Temozolomide is well-tolerated in children. Nicholson et al reported the results of a phase II trial of temozolomide in children with recurrent CNS malignancies. When temozolomide was administered orally every day for 5-day of each 28-day cycle at doses of 200 mg/m^2/d (patients with no prior craniospinal irradiation [CSI]) or 180 mg/m^2/d (prior CSI), 5 PRs and 1 CR were observed among 104 evaluable patients. PRs occurred in 1 of 23 evaluable patients with high-grade astrocytoma, 1 of 21 with low-grade astrocytoma, and 3 of 25 with medulloblastoma/primitive neuroectodermal tumor (PNET). The CR occurred in an additional patient with medulloblastoma/PNET. The most frequent toxicities were grade 3 or 4 neutropenia (19%) and thrombocytopenia (25%); nonhematologic toxicity was infrequent.[32]

Similar to Stupp et al's study, ACNS0126 study used TMZ as a radiosensitizer followed by 10 cycles of temozolomide 200 mg/m^2/day x 5 days of every 28 day cycle. 107 patients with a diagnosis of anaplastic astrocytoma (AA), glioblastoma multiforme (GBM) or gliosarcoma were enrolled. Outcome was compared to the results for children treated on Children's Cancer Group (CCG) study CCG-945. Ninety patients were eligible (31 AA, 55 GBM and 4 other). The three-year EFS and OS were 11 ± 3% and 22 ± 5%, respectively. The results with temozolomide given during radiation therapy and as adjuvant therapy were similar to CCG 945 (p=0.98). The three-year EFS for AA was 13 ± 6% for ACNS0126 compared to 22 ± 5.5% for CCG-945 (p= 0.95). The three-year EFS for GBM was 7 ± 4% for ACNS0126 compared to 15 ± 5% for CCG-945 (p=0.77). The two-year EFS rate was 17±5% among patients without overexpression of *MGMT* and 5±4% among those with overexpression of MGMT (p=0.045). Interestingly, 1-year PFS for adults receiving TMZ chemoradiotherapy on the Stupp trial was 26.9% as compared to 38% for children on this study, suggesting that the initial response and outcome for children with HGG treated with TMZ chemoradiotherapy is not inferior to that in adults. (Ken Cohen, PI, personal communication). Although ACNS0126 did not demonstrate an improved survival for children with newly diagnosed HGG who were treated with temozolomide, the study did demonstrate comparable survival with less toxicity than in studies utilizing prior nitrosourea-based regimens. TMZ was well-tolerated. Hematologic toxicity was the most common adverse event and was self-limited. No life-threatening acute toxic events occurred. (Ken Cohen, PI, personal communication)

Although ACNS0126 did not demonstrate an improved survival for children with newly diagnosed HGG who were treated with temozolomide, the study did demonstrate comparable survival with less toxicity than in studies utilizing prior nitrosourea-based regimens. TMZ was well-tolerated. Hematologic toxicity was the most common adverse event and was self-limited. No life-threatening acute toxic events occurred, based on its better tolerability and similar efficacy to prior nitrosurea regimens, temozolomide is reasonable backbone to build on for the current proposed study.

Finally, preliminary results are available in 6 children and young adults with newly diagnosed HGG < 30 years of age who have been treated with bevacizumab and TMZ during RT, followed by bevacizumab, temozolomide and irinotecan in a study at Cincinnati Children's Hospital Medical Center. Only one

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patient experienced a dose-modifying toxicity (grade 4 thrombocytopenia/neutropenia) attributable to temozolomide during chemoradiotherapy; prolonged thrombocytopenia prompted discontinuation of therapy. Grade 3 toxicities at least possibly attributable to therapy included neutropenia (1) and hypertension (1). The regimen was well-tolerated both during the chemo-RT and maintenance in children and young adults with newly diagnosed HGG. ([redacted], personal communication)

Thus, based on temozolomide's better tolerability and similar efficacy to prior nitrosurea regimens in children with newly diagnosed HGG, its tolerability and efficacy in combination with bevacizumab in both recurrent and newly diagnosed adults with HGG, and preliminary data about the combination's feasibility in children with newly diagnosed HGG, we believe that the combination of temozolomide and bevacizumab is a reasonable backbone for the currently proposed study.

2.2.3 Adult Studies of the Use of Bevacizumab Combinations in HGG

Vredenburgh et al evaluated the combination of bevacizumab and irinotecan in patients with recurrent advanced malignant gliomas in a phase II trial. Bevacizumab was administered at 10 mg/kg IV every 14 days. The irinotecan dose for patients on EIACD was 340 mg/m^2, compared to 125 mg/m^2 for those not on EIACD. OR were noted in 63%, with a median progression free survival (PFS) of 23 weeks. The 6 month PFS was 38% (34% if including only patients who had received RT more than 12 weeks prior to study entry. Three patients developed a DVT or pulmonary emboli and one patient had an arterial ischemic stroke.[33]

Kang et al reported that, among 27 patients with recurrent HGG treated with irinotecan and bevacizumab, 6 month PFS was 46%, with a median PFS of 5.1 months. Median overall survival (OS) was 12.6 months.[34]

Raval et al reported that 22 patients with recurrent gliomas were treated with bevacizumab 5 mg/kg IV and irinotecan 125 mg/m^2 IV every 2 weeks. All but two patients had a radiographic response (2 CR +, 14 PR +, 4 MR), with a median time to progression (TTP) of 3 months and a median OS of 4.6 months.[35]

Goli et al reported a phase II trial of irinotecan 125 mg/m^2 (for patients not on EIACD) or 350 mg/m^2 (for patients on EIACD) and bevacizumab 10 mg/kg in 68 patients with recurrent high grade glioma. The last 36 patients were treated with irinotecan weekly and bevacizumab 15 mg/kg on Days 1 and 22. The 6 month PFS for GBM was 43% with a median PFS of 23 weeks. For Grade 3 astrocytomas, the 6 month PFS was 61% with a median PFS of 42 weeks. Toxicities included Grade 2 proteinuria, thromboembolic events (n=8) and CNS hemorrhage (n=1).[36]

Cloughesy et al reported the interim results of a randomized phase II trial using bevacizumab versus bevacizumab/irinotecan in patients with recurrent high grade glioma, in which 167 patients were randomized to receive bevacizumab 10 mg/kg (n=85) or bevacizumab 10 mg/kg + irinotecan 125 mg/m^2 over 90 minutes (n=82), (or irinotecan 340 mg/m^2 in patients receiving EIACD) every 2 weeks. The median number of months of therapy was 16.1 months for bevacizumab alone versus 22.2 months for the bevacizumab/irinotecan combination. Six month PFS was 35.6% for bevacizumab (ORR=21.2%) and 51% for bevacizumab/irinotecan (ORR=34.1%), based on independent radiological review.[37]

Friedman et al [29]reported the results of a study that evaluated the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with recurrent glioblastoma in a phase II, multicenter, open-label, noncomparative trial. One hundred sixty-seven patients were randomly assigned to receive bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m^2 or 125 mg/m^2 (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) once every 2 weeks. Primary end points were 6-month progression-free survival and objective response rate, as determined by independent radiology review.

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Secondary end points included safety and overall survival. In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month progression-free survival rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively; and median overall survival times were 9.2 months and 8.7 months, respectively. There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. Of the patients treated with bevacizumab alone or bevacizumab plus irinotecan, 46.4% and 65.8%, respectively, experienced ≥ 3 adverse events, the most common of which were hypertension (8.3%) and convulsion (6.0%) in the bevacizumab-alone group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the bevacizumab-plus-irinotecan group. Intracranial hemorrhage was noted in two patients (2.4%) in the bevacizumab-alone group (Grade 1) and in three patients (3.8%) patients in the bevacizumab-plus-irinotecan group (Grades 1, 2, and 4, respectively). The authors concluded that bevacizumab, alone or in combination with irinotecan, was well tolerated and active in recurrent glioblastoma.

Based on data from adults with recurrent high-grade gliomas, summarized above, the Food and Drug Administration recently approved the use of bevacizumab in patients with recurrent GBM.

2.2.4 Pediatric Studies of the Use of Bevacizumab Combinations in HGG

Recently Gururangan et al completed a phase II study of bevacizumab and irinotecan in patients with recurrent high grade glioma and diffuse intrinsic pontine gliomas (DIPG) through the Pediatric Brain Tumor Consortium. Thirty four eligible patients were enrolled on study; 31 were evaluable. These 31 patients received a median of two courses of bevacizumab plus irinotecan (range, 1 to 19). There were no sustained responses in either stratum. Median time to progression for all 34 eligible patients enrolled was 127 days for MG and 71 days for BSG. Progression-free survival rates at 6 months were 41.8% and 9.7% for MG and BSG, respectively. Toxicities related to bevacizumab included grade 1 to 3 fatigue in seven patients, grade 1 to 2 hypertension in seven patients, grade 1 CNS hemorrhage in four patients, and grade 4 CNS ischemia in two patients. The mean diffusion ratio decreased after two doses of bevacizumab in patients with MG only. Vascular permeability parameters did not change significantly after therapy in either stratum. Inhibition of VEGFR-2 phosphorylation in PBMC was detected in eight of 11 patients after bevacizumab exposure. The authors concluded that although the regimen was well-tolerated, the combination of bevacizumab and irinotecan lacked efficacy in patients with recurrent HGG or DIPG.[149]

Preliminary results are available in 6 children and young adults < 30 years of age with newly diagnosed HGG treated with bevacizumab and TMZ during RT, followed by bevacizumab, temozolomide and irinotecan in a study at Cincinnati Children's Hospital Medical Center. Results are summarized in Section 2.2.2.

2.3 Rationale for Randomization during Initial Chemoradiotherapy

2.3.1 Rationale for Arm A: Vorinostat (SAHA) During Radiation Therapy

Chinnaiyan et al[39] showed that pre-treating U373, a malignant glioma cell line, with 0.75-1 μM of vorinostat for 48-72 hours, and continuing vorinostat with radiation significantly increased its radiosensitivity. This report and another related study of vorinostat in a melanoma cell line[7] identified that vorinostat treatment and radiation significantly reduced DNA repair proteins in the non-homologous end-joining (NHEJ; Ku70, Ku80, DNA-PK) and homologous recombination repair (HRR; Rad51) pathways. Since radiation is thought to exert its anti-tumor effect by inducing double-stranded DNA (dsDNA) breaks, and dsDNA breaks are repaired by the NHEJ and HRR pathways, it has been hypothesized that radiation-enhancement by vorinostat and other HDAC inhibitors is partly mediated by decreased DNA repair proteins. In all the pre-clinical studies, optimal radiation enhancement was observed when HDAC inhibition preceded radiation by 24-72 hours and was continued concurrently with radiation.[39-44]

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Rationale for HDAC Inhibitors as Radiosensitizers

The basal unit of chromatin is the nucleosome. Nucleosomes are composed of 146 BP of DNA wrapped around a protein core formed with histones (H2A, H2B, H3, and H4), which have a lysine-rich amino-terminal tail.[45] The amino terminal tail contains half of the positively charged residues and most of the post translational modification sites of the core histones. The positive charge helps histones bind tightly to the negatively charged DNA. The acetylation status of histones alters the net charge and chromatin structure, thus affecting gene expression.[46]

Two classes of enzymes are involved in determining the acetylation of histones: histone acetyltransferases (HATs) and histone deacetylases (HDACs).[47] Acetylation of histones is associated with transcriptional activation, whereas histone deacetylation is associated with transcriptional repression.[48]

Deregulated Acetylation in Cancer

Deregulation of histone acetylation has been implicated in the development of several types of cancer. Genes that encode HAT enzymes are translocated, amplified, overexpressed and/or mutated in various cancers.[46] The breast cancer susceptibility genes BRCA1 and BRCA2 have been linked to histone acetylation.[49] The carboxy-terminal domain (BCRT) of BRCA1 is associated with histone deacetylases HDAC1 and HDAC2. Thus, mutated BCRA1 may compromise HDAC recruitment and lead to hereditary breast cancer.[50] Several leukemogenic transcription factors repress the expression of specific genes because of aberrant recruitment of HDACs.[45] This repression of gene expression is an important step in the leukemogenic action of these transcription factors.[51-54] Acute myeloid leukemia (AML) M2 disease is associated with an (8,21) translocation that leads to the formation of a potent dominant transcription repressor, AML1-Eto fusion protein, via HDAC recruitment leading to lymphoid oncogenic transformation.[55,56]

These findings indicate that deregulated acetylation of histones plays a role in the pathogenesis of hematological as well as solid tumors by changing the chromatin structure and transcription of genes involved in cell cycle control, differentiation or apoptosis. Thus, there is considerable interest in histone deacetylase inhibition as a potential therapeutic modality in the treatment of hematological and solid tumor malignancies.

HDAC inhibitors have been shown to inhibit proliferation of a variety of pediatric transformed cell lines, including neuroblastoma, rhabdomyosarcoma, osteosarcoma and malignant rhabdoid tumors.[57,58] HDAC inhibitors have also been shown to markedly suppress the growth of a range of pediatric solid tumor xenograft models including neuroblastoma,[59] Ewing's and undifferentiated sarcoma.[58] These agents lead to histone acetylation in vivo and induce tumor cell differentiation or apoptosis, depending on the cell type. These preclinical data have generated significant interest in the clinical evaluation of HDAC inhibitors, such as vorinostat, for the treatment of children with cancer.

HDAC Inhibitors and High Grade Gliomas

Ugur et al examined the antiproliferative effect of vorinostat in six glioblastoma and one endothelial cell lines in vitro. In addition, one glioblastoma cell line (U87MG) was used in in vivo short term (14 days) and survival studies in an orthotopic human glioma athymic mice model. Tumor volume, apoptosis rate, microvessel density, and proliferation index were determined by immunohistochemistry. Vorinostat treatment inhibited the growth of all cell lines in concentrations ranging from 1 μM to 30 μM. For short-term studies, histological analysis showed an 80% reduction of tumor volume in the treatment group ($P < 0.001$). This reduction in tumor volume was associated with a significant increase in the apoptosis rate (31.9%, $P < 0.001$), a significant decrease in both the proliferation rate (36.8%, $P < 0.001$) and angiogenesis rate (30%, $P < 0.05$). For survival studies, the mean survival time was 22 days in the control group compared to 42 days in the treatment group.[60]

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Yin et al measured the effect of vorinostat on growth of GBM cell lines and explants by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. Changes of the cell cycle and relative gene expression were detected by fluorescence-activated cell sorting, real-time reverse transcription-PCR, and Western blotting. After glioma cells were implanted in the brains of mice, the ability of vorinostat to decrease tumor growth was studied. Proliferation of GBM cell lines and explants were inhibited in vitro by vorinostat (ED50, 2 to 20 μM, with 5-day exposure). Vorinostat exposure of human U87 and T98G glioma cell lines, DA66 and JM94 GBM explants, as well as a murine GL26 GBM cell line resulted in an increased accumulation of cells in G2-M of the cell cycle. Many proapoptotic, antiproliferative genes increased in their expression (DR5, TNFalpha, p21WAF1, p27KIP1), and many antiapoptotic, progrowth genes decreased in their levels (CDK2, CDK4, cyclin D1, cyclin D2) as measured by real-time reverse transcription-PCR and/or Western blot after these GBM cells were cultured with vorinostat (2.5 μM, 1 day). Chromatin immunoprecipitation assay found that acetylation of histone 3 on the p21(WAF1) promoter was markedly increased by vorinostat. In vivo murine experiments suggested that vorinostat (10 mg/kg IV, or 100 mg/kg IP) could cross the blood-brain barrier as shown by prominent increased levels of acetyl-H3 and acetyl-H4 in the brain tissue. Furthermore, the drug significantly ($P < 0.05$) inhibited the proliferation of the GL26 glioma cells growing in the brains of mice and increased their survival. Studies of the activity of the HDAC inhibitor, vorinostat, in combination with other therapies have shown additive (imatynib mesylate, all-trans retinoic acid) or synergistic (radiation therapy, flavopiridol) activity in transformed cell lines.[61]

Eyupoglu et al demonstrated that treatment of four glioma cell lines (U87MG, C6, F98, and SMA-560) with MS-275 significantly reduced cell growth in a concentration-dependent manner (IC(90), 3.75 μM). Its antiproliferative effect was corroborated using a bromodeoxyuridine proliferation assay and was mediated by G(0)-G(1) cell cycle arrest (i.e., up-regulation of p21/WAF) and apoptotic cell death. Implantation of enhanced green fluorescent protein-transfected F98 glioma cells into slice cultures of rat brain confirmed the cytostatic effect of MS-275 in a dose escalation up to 20 μM.[62]

Finally, Hockly et al showed that vorinostat can cross the blood brain barrier in an R6/2Hd mouse model of Huntingdon's chorea and increases histone acetylation in the brain.[63]

HDAC Inhibitors as Radiosensitizers

Histone modification has emerged as a promising approach to cancer therapy.[64] Numerous preclinical and clinical studies have been evaluating several HDAC inhibitors including a prodrug of butyric acid [pivaloylomethyl butyrate, AN-9[65,66], hydroxamic acids [suberoylanilide hydroxamic acid (SAHA) (vorinostat), TSA],[67] benzamide derivatives [MS-275 and CI-994],[68,69] cyclic peptides [trapoxin, apicidin, and depsipeptide],[70] valproic acid,[71] and phenylbutyrate derivatives.[72] Recent studies have revealed radiosensitizing capacities of various HDAC inhibitors, including MS-275[73], vorinostat,[70,74,75]; valproic acid,[76] TSA [77], and butyric acid (BA)[41,72], the parental form of AN-9[78]. These data, as well as data derived from other combination studies,[79,80] highlight the potential for incorporating HDAC inhibitors into the multimodality treatment of gliomas. Vorinostat, in particular, has shown promising clinical results,[10,81,82] and has the added key benefit of enhancing radiation-induced cytotoxicity in human malignancies.[39,75]

Several studies have explored the mechanisms of radiosensitization by HDAC inhibitors and indicate that HDAC inhibitors interfere with DNA damage repair.[83,84] Recent publications report that HDAC inhibitors suppress repair of DNA double-strand breaks [39,44,69,73,75,76,85] primarily by affecting non-homologous-end joining (NHEJ) pathways[39,44,75,85] in some reports homologous recombination (HR) is effected as well.[39,44] For example, vorinostat and butyric acid reduce expression of both NHEJ (Ku70, Ku80 and DNA-PKcs) and HR (Rad 50, Rad 51) repair-related genes in several human tumor cell lines.[39,44] The ability of HDAC inhibitors to impede DNA repair following radiation is reflected in several studies that explore the expression of phospho-γ-H2AX, a hallmark of DNA damage. Vorinostat, MS-275, valproic acid, and depsipeptide[44,73,75,76] all prolong expression of phospho-γ-H2AX reflecting enhanced DNA damage following

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HDAC inhibition. Entin-Meer et al specifically examined the effects of combined radiation and HDAC inhibitor treatment on gliomas in vitro and in vivo. They found that AN-9-mediated radiosensitization is associated with increased expression of phospho-γ-H2AX within glioma xenografts, further supporting the conclusion that enhanced radiation-induced DNA damage plays a role in the combined effects of AN-9 and radiation.

In all the pre-clinical studies examining the radiosensitizing properties of HDAC inhibitors, optimal radiation enhancement was observed when HDAC inhibition preceded radiation by 24-72 hours and was continued concurrently with radiation.

Vorinostat: Adult Studies
In two phase II trials, vorinostat 400 mg/day was safe and effective with an overall response rate of 24-30% in refractory advanced patients with CTCL including large cell transformation and Sézary syndrome, leading to FDA approval recently for use in patients with CTCL.[86,87]

The recommended phase II dose, based on multiple phase I studies using several different doses and schedules, is 400 mg PO daily. Observed C_{max} in the 400 mg daily regimen averaged 658 +/- 439 μg/ml (2.67 +/- 1.78 μM), and these values exceeded the IC_{50} (0.5 to 2 μM) required in pre-clinical studies against malignant gliomas. Dose limiting toxicities have included anorexia, fatigue, dehydration, diarrhea and thrombocytopenia.

Galanis et al [88] reported the preliminary results of a phase II trial of 68 patients with recurrent GBM who received vorinostat 200 mg bid x 14 days every 3 weeks. Grade 3+ non-hematologic toxicity consisting mainly of fatigue, diarrhea and dehydration occurred in 23% of patients; Grade 3+ hematologic toxicity consisting mainly of thrombocytopenia occurred in 25% of patients. Patients receiving EIACD had significantly less Grade 3+ non-hematologic toxicity (*P*=0.01) and Grade 3/4 thrombocytopenia (*P*=0.04). Pharmacokinetic analysis showed lower vorninostat C-max and AUC (0-24h) values and higher vorinostat-glucuronide C-max and AUC (0-24h) values in patients receiving EIACD. The trial met the prospectively defined primary efficacy endpoint at the planned interim analysis with 5 of the first 22 patients (23%) being progression-free at 6 months. RNA array analysis, performed in paired baseline and post-vorinostat treatment samples in a subgroup of 5 surgical recurrent GBM patients who received vorinostat for 6 doses prior to surgery, showed upregulation of E-cadherin (*P*=0.02), thus indicating a biologic effect of the HDAC inhibitor on the glioblastoma tumors. Thus, vorinostat was well tolerated in patients with recurrent GBM. Patients on EIACD have less toxicity, which is likely due to increased vorinostat metabolism via glucuronidation. Interim efficacy analysis is indicative of antitumor activity.

Recently, Ree at al reported the results of a study in which patients with gastrointestinal carcinoma scheduled to receive pelvis irradiation (30 Gy in 3 Gy daily fractions) received escalating doses of vorinostat 3 hours before each daily fraction. Among 16 evaluable patients, grade 3 adverse events included grade 3 adverse events included fatigue (n=5), anorexia (n=3), diarrhoea (n=2), hyponatraemia (n=1), hypokalaemia (n=1), and acneiform rash (n=1). Of these, treatment-related grade 3 events (ie, dose-limiting toxicities) were observed in one of six patients at vorinostat 300 mg once daily (fatigue and anorexia), and in two of six patients at vorinostat 400 mg once daily (two events of diarrhea and one each of fatigue, anorexia, hyponatraemia, and hypokalaemia). The maximum-tolerated dose of vorinostat in combination with palliative radiotherapy was thus determined to be 300 mg once daily. Histone hyperacetylation was detected, indicating biological activity of vorinostat.[150]

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Vorinostat: Pediatric Phase 1 Studies

The pediatric single agent MTD has been established as 230 mg/m^2 daily. Dose limiting toxicities have included thrombocytopenia, and fatigue.

2.3.2 Rationale for Arm B: Temozolomide as a Radiosensitizer

Temozolomide is an imidazotetrazine prodrug that undergoes spontaneous hydrolysis to the active metabolite MTIC, which methylates DNA at O^6-guanine and other sites. This drug has excellent oral bioavailability and crosses the blood-brain barrier.[89] Temozolomide can be given concurrent with cranial radiotherapy, with adults tolerating 75 mg/m^2/day for up to 42 consecutive days,[10,81] and children tolerating 90 mg/m^2/day.[82] Advantages of protracted temozolomide include exposure to a greater cumulative amount of drug, depletion of the resistance protein methylguainine-DNA methyltransferase, and anti-angiogenic effects.[90] A large phase III trial showed that protracted temozolomide given concurrently with radiotherapy, followed by maintenance temozolomide (5 days every 4 weeks), was superior to radiotherapy alone (2 year OS: 26% versus 10%).[10] This new standard of care for adults with GBM has been investigated in the COG trial ACNS0126. Preliminary results of ACNS0126 are comparable to those of the historical control group (CCG 945) that has had the best survival outcome to date among children with malignant gliomas. Despite that, the results are still suboptimal, which highlights the need to build upon the temozolomide regimen in an effort to improve outcome.

Preclinical data also suggest that temozolomide has at least additive activity with radiation in human glioblastoma cells.[2-6] Van Nifterik et al recently reported that, in temozolomide-sensitive GBM cell lines, temozolomide can act as a radiosensitizer and is at least additive to gamma-irradiation. Enhancement of the radiation response by temozolomide seemed to be independent of the epigenetically silenced MGMT. They exposed 3 genetically characterized human GBM cell lines (AMC-3046, VU-109, and VU-122) to various single (0-6 Gy) and daily fractionated doses (2 Gy per fraction) of gamma-irradiation. Repeated temozolomide doses were given before and concurrent with irradiation treatment. Immediately plated clonogenic cell-survival curves were determined for both the single-dose and the fractionated irradiation experiments. To establish the net effect on clonogenic cell survival and cell proliferation, growth curves were determined, expressed as the number of surviving cells. All 3 cell lines showed MGMT promoter methylation, lacked MGMT protein expression, and were sensitive to temozolomide. The isotoxic temozolomide concentrations used were in a clinically feasible range. Temozolomide was able to radiosensitize 2 cell lines (AMC 3046 and VU-122) using single-dose irradiation. A reduction in the number of surviving cells after treatment with the combination of temozolomide and fractionated irradiation was seen in all 3 cell lines.[91]

2.3.3 Rationale for Arm C: Bevacizumab as a Radiosensitizer

Gorski et al demonstrated that irradiation of tumor cells induced increased VEGF expression. Pre-treatment of various tumor xenografts in vivo with anti-VEGF therapy, including U87 glioblastoma, had a greater than additive effect when combined with subsequent radiation.[92] Using the same model, Lee et al demonstrated that anti-VEGF mAB exposure induced reduction of tumor vascular density and a reduction of tumor interstitial fluid pressure by 74%. Simultaneously, pO_2 significantly increased. Combined treatment with radiation yielded greater than additive tumor growth delay, independent of experimentally induced normoxic or hypoxic conditions, suggesting that anti-VEGF therapy mitigated the impact of hypoxic conditions in this glioblastoma model in vivo.[93] More recently, the kinetics of vascular changes and 'window of normoxia' was investigated in orthotopically placed U87 glioblastoma in mouse brain following DC101 anti-VEGR2 therapy. Maximum tumor oxygenation occurred by Day 5 following DC101 exposure, and decreased again by Day 8. Radiation exposure Days 4-6 following DC101 exposure yielded synergistic effects, whereas alternative schedules had no more than additive effects.[94] Such findings have been confirmed by independent investigators in melanoma and various carcinoma xenograft models.[92,95]

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Batchelor et al reported that anti-VEGF therapy normalized the tumor vasculature and alleviates edema in glioblastoma patients. In their report of 16 glioblastoma patients treated with the anti-VEGF agent AZD2171, the onset of vascular normalization was rapid and sustainable, but reversible by 28 days following cessation of drug therapy.[96] Gonzalez et al similarly reported the MD Anderson experience with 15 patients with malignant glioma, 8 of who were diagnosed with radiation necrosis. Bevacizumab anti-VEGF therapy, either alone or in combination with chemotherapy, reduced radiation necrosis by decreasing capillary leak and associated brain edema in all 8 patients demonstrated by MRI performed 8 weeks following therapy initiation.[97]

Such attenuation of the effects of radiation necrosis and brain edema may improve quality of life for patients, and may decrease the diagnosis of pseudo progression (radiation-induced tumor inflammation) frequently noted in the first months following chemoradiotherapy in approximately 15% of patients.[98,99]

Mohile et al conducted a study in patients with recurrent high-grade glioma, who received bevacizumab 10 mg/kg IV q 2 weeks and stereotactic intensity modulated IMRT: 30 Gy in 5 fractions over 15 days. Twelve patients with HGG received a median of 5.5 cycles of therapy. Grade 3 events occurred in 10 patients, including hypertension, headache, neutropenia, seizures, hyponatermia and hypophosphatemia. There were no Grade 4 or 5 events, no DLTs and no intracranial hemorrhage. Seven out of twelve patients had objective responses (3 CR, 4 PR). Estimated 6 month PFS was 76%. MR perfusion imaging demonstrated a decrease in mean perfusion values after 1 cycle of bevacizumab.[100]

Narayana et al reported the results of a feasibility study in which 15 patients with high-grade glioma were treated with involved field radiation therapy to a dose of 59.4 Gy at 1.8 Gy/fraction with bevacizumab 10 mg/kg on Days 14 and 28 and temozolomide 75 mg/m^2.[101] Subsequently, bevacizumab 10 mg/kg was continued every 2 weeks with temozolomide 150 mg/m^2 for 12 months. Changes in relative cerebral blood volume, perfusion-permeability index, and tumor volume measurement were measured to assess the therapeutic response. Thirteen patients (86.6%) completed the planned bevacizumab and chemoradiation therapy. Four Grade III/IV non-hematologic toxicities were seen. Radiographic responses were noted in 13 of 14 assessable patients (92.8%). Six patients have experienced relapse, 3 at the primary site and 3 as diffuse disease. One-year progression-free survival and overall survival rates were 59.3% and 86.7%, respectively. The authors concluded that the use of bevacizumab with radiation and temozolomide in the management of newly-diagnosed high-grade glioma patients is feasible.

Desjardins et al presented preliminary results of the Duke study in which adults with newly diagnosed GBM or gliosarcoma received radiation therapy with bevacizumab 10 mg/kg weeks 3 and 5 of RT as well as temozolomide 75 mg/m^2 days 1-42 of RT, followed by a post RT maintenance regimen consisting of irinotecan, avastin q 2 weeks with temozolomide given days 1-5 of each 28 day course.[102] One hundred and twenty five were enrolled, 119 completed RT and 6 did not. Toxicities during radiotherapy included: 3 grade 4 thrombocytopenias (attributable to temozolomide), 1 grade 4 neutropenia. Non hematological toxicities $\geq$ grade 3 during RT included 2 DVT/PE, 1 stitch abscess,1 wound dehiscence, 2 seizures and 1 CNS hemorrhage (grade 2), sudden death secondary to MI (n=1). Hematological toxicities during the maintenance phase included 3 grade 3 thrombocytopenias, 10 grade 4 thrombocytopenia, 14 grade 3 neutropenia, 6 grade 4 neutropenia. (Please note that the myelosuppression was most likely due to temozolomide given during maintenance therapy, which will not be given in ACNS0822). Grade 3 or 4 non-hematological toxicities during maintenance therapy included: 3 DVT/PE, 3 GI toxicities, 1 rectal abscess, 1 sepsis, 1 wound dehiscence, 1 optic neuritis, 2 PCP, 7 patients were taken off study for decreased Karnofsky score or because of patient choice. Thus, the treatment regimen is feasible and tolerable in adults. One-year progression-free survival was reported to be 60%, with a one-year overall survival of 79%. The updated survival data for this trial will be presented at ASCO 2010. Preliminarily, this regimen has doubled the median progression-free survival to 14 months from 6.9 months historically. ([redacted], personal communication).

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Vredenburgh et al reported the preliminary results of the study of Bevacizumab in combination with temozolomide and radiation therapy followed by BEV, TMZ, and irinotecan for newly diagnosed glioblastoma multiforme (GBM). 125 newly diagnosed GBM patients were enrolled between 8/07 and 3/09. Patients received radiation therapy and TMZ at 75 mg/m^2/d beginning between 2-6 weeks post-craniotomy. BEV at 10 mg/kg every 14 days was added a minimum of 4 weeks post- op. Following radiation therapy, patients received 6-12 monthly cycles of TMZ at 200 mg/m^2/d days 1-5, BEV at 10 mg/kg and irinotecan on days 1 and 15. The dose of irinotecan was 340 mg/m^2 for patients on enzyme inducing anti-epileptic drugs (EIAED) and 125 mg/m^2 for patients not on EIAED. The addition of BEV and irinotecan to standard therapy doubled the median PFS, 14 months vs. 6.9 months. The median overall survival has not been reached, but 56% of the patients are alive at a minimum follow-up of 18 months. In addition, 28% remain progression-free at a median follow- up of 23 months. The regimen was tolerable, 122 of 125 patients completed radiation therapy and 78 completed 6 cycles of post-radiation BEV, TMZ, and irinotecan. There were 4 toxic deaths, from a myocardial infaction, pulmonary embolus, PCP and sepsis. The addition of BEV to TMZ and radiation followed by TMZ, BEV, and irinotecan is tolerable. The median progression-free survival is improved and the overall survival is prolonged.[29]

In addition, preliminary data are available from a study in 7 patients with newly diagnosed high-grade gliomas or diffuse intrinsic pontine gliomas < 30 years of age (4 of whom are less than 21 years of age) in a study at Cincinnati Children's Hospital Medical Center. ([redacted], personal communication). In this protocol, patients with HGG receive bevacizumab and temozolomide during RT followed by 12 courses of bevacizumab, temozolomide and irinotecan post RT, and patients with DIPG receive the same therapy without temozolomide. Among the 4 patients less than 21 years of age treated on this protocol, the following non-hematological toxicities attributable to therapy have been observed during the RT-chemotherapy period: grade 1 PTT (n=1), grade 3 infection with normal ANC (n=1), grade 1 anorexia (n=1), grade 1 dermatitis associated with radiation, (n=1). In addition, the following hematological toxicities attributable to therapy have been observed: grade 1 thrombocytopenia (n=1), grade 2 lymphopenia (n=1), grade 1 low WBC (n=1).

2.3.4 Summary of Feasibility Study in ACNS0822 with Vorinostat and Radiation Therapy

Six patients with high grade gliomas were enrolled on the feasibility study. All patients were evaluable for toxicity and received vorinostat 230 mg/m^2/day 5 days per week for 6 weeks during RT. No dose limiting toxicities were reported at this dose level of vorinostat and patients tolerated the combination of RT and vorinostat well. There were no grade 3 or higher non-hematologic toxicities reported during the DLT observation period. All patients' pathology specimens were centrally reviewed. There were three patients with GBM and three with AA.

As part of Amendment #1, the study will re-open to the Phase II portion of the study and all future patients on Arm A will receive vorinostat 230 mg/m^2/day, Monday through Friday, during the chemo-radiation phase.

2.4 Rationale for Biology Studies

2.4.1 Gene expression profiling, miRNA analysis, and SNP arrays

Faury et al recently published data on 32 pediatric GBM (pGBM) and 7 adult GBM (aGBM) samples which they investigated using biochemical and transcriptional profiling. Ras and Akt pathway activation was assessed through the phosphorylation of downstream effectors, and gene expression profiles were generated using the University Health Network Human 19K cDNA arrays. Results were validated using real-time polymerase chain reaction and immunohistochemistry and compared with existing data sets on aGBM. There are at least two subsets of pGBM. One subset, associated with Ras and Akt pathway activation, has very poor

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prognosis and exhibits increased expression of genes related to proliferation and to a neural stem-cell phenotype, similar to findings in aggressive aGBM. This subset was still molecularly distinguishable from aGBM after unsupervised and supervised analysis of expression profiles. A second subset, with better prognosis, is not associated with activation of Akt and Ras pathways, may originate from astroglial progenitors, and does not express gene signatures and markers shown to be associated with long-term survival in aGBM. This small study of gene expression profiles in pGBM, provides valuable insight into active pathways and targets in a cancer with minimal survival,suggests that pediatric malignant gliomas cannot be understood exclusively through studies of adult GBM, and provides a strong rationale for examination of Akt signaling pathway activation, and its relationship to prognosis in the planned cohort, as well as a broad-based assessment of gene expression and genomic alternations as defined by whole genome SNP array profiling in these tumors.[103]

The Cancer Genome Atlas (TCGA) pilot project recently reported the interim integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas and nucleotide sequence[104] aberrations in 91 of the 206 glioblastomas. This analysis provided insights into the roles of ERBB2, NF1 and TP53, demonstrated frequent mutations of the phosphatidylinositol-3-OH kinase regulatory subunit gene PIK3R1, and provided a network view of the pathways altered in the development of glioblastoma. Integration of mutation, DNA methylation and clinical treatment data revealed a link between MGMT promoter methylation and a hypermutator phenotype consequent to mismatch repair deficiency in treated glioblastomas.

Since their initial identification in lower organisms around 15 years ago, several hundred[105-108] microRNAs (miRNAs) are now known to exist within the human genome.[109] These small, non-protein-encoding RNAs play a fundamental role in regulating gene expression which in turn influences many biological processes. Not surprisingly, their role in many types of cancer is now beginning to be appreciated.[110] No comprehensive analysis of miRNA expression changes has been published in pediatric gliomas and only two small studies have been published in adult GBMs to date.[111,112] Ciafrè and colleagues reported that miR-221 expression was frequently upregulated in a small group of nine primary glioblastoma samples while miR-128, miR-181a, miR-181b and miR-181c were downregulated. [111] In contrast, Malzkorn and colleagues investigated the expression changes occurring in miRNAs in a cohort of four secondary glioblastoma patients. They found that increased expression of miR-9, miR-15a, miR-16, miR-17, miR-9a, miR-20a, miR-21, miR-25, miR-28, miR-130b, miR-140 and miR-210 and reduced expression of miR184 and miR 328 were associated with malignant progression in these patients' tumors.[112]

2.4.2 Telomerase activity, *hTert* expression, *hTERC*, and telomere length

Telomerase is a ribonucleoprotein complex that elongates telomeric DNA and appears to play an important role in cellular immortalization and cancers. Because telomerase is expressed in the vast majority of malignant gliomas but not in normal brain tissues, it is a logical target for glioma-specific therapy. Telomerase adds hexameric repeats of 5'-TTAGGG-3' to the ends of telomeres to compensate for the progressive loss with each cell division.[109,110,111] Telomerase activity, which is generally undetectable in normal somatic cells, is expressed in approximately 90% of tumors.[112-114] In malignant gliomas, telomerase activity is very often detected.[115-128] In Grade I and II gliomas, telomerase activity is detected in 0% and 0% to 33%, respectively. In malignant gliomas, telomerase is positive in 10% to 100% of anaplastic astrocytomas and in 26% to 100% of GBM. Although the ratio of telomerase-positive cells in gliomas varies, most of the reports show that the incidence of telomerase expression is closely correlated with the malignancy, and telomerase is detected in the vast majority of malignant gliomas. By contrast, normal brain tissues do not express telomerase activity,[116,122,126,128] while telomerase is detectable only in human embryonic neural precursor cells at low levels.[129]

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Boldrini et al examined telomerase activity by the telomeric repeat amplification protocol (TRAP) assay in 42 gliomas, (32 glioblastomas, 4 anaplastic astrocytomas, 4 differentiated astrocytomas, 1 oligoastrocytoma and 1 oligosarcoma). Telomerase messenger expression (*hTERT* mRNA) was evaluated by reverse transcription-PCR analysis in the same group of tumors. High telomerase activity was detected in 21 of 42 gliomas (50%). The levels of telomerase in terms of its messenger level expression overlapped the activity; in fact, a significant association between telomerase activity and *hTERT* mRNA expression was found ($P<0.0001$). At univariate analysis, advanced age as well as high telomerase activity and *hTERT* mRNA levels were significant predictors of worse prognosis regarding both overall survival ($P=0.007$, $P=0.007$, and $P=0.04$, respectively) and disease-free interval ($P=0.008$, $P=0.008$, and $P=0.04$, respectively). All these variables maintained a significant independent prognostic role in multivariate analyses. Therefore, telomerase is expected to represent a good candidate not only for a useful prognostic and diagnostic marker of malignant gliomas, but in the future may constitute a target for malignant gliomas.[130] However, the generalizability of expression and prognostic relevance of this target in pediatric malignant gliomas remains to be established, and the current study will address this issue.

2.4.3 Assessment of MGMT Promoter Methylation Status in Plasma and Tumor and MGMT Protein Expression in Tumor

O^6-methyl-guanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that promotes resistance of tumor cells to the cytolytic effects of alkylating agents such as temozolomide[20,103,109,110] and possibly incompletely to TMZ/IRI synergy.[32] This enzyme removes methyl adducts at the O^6 position of guanine, an important biologically active target of TMZ and nitrosureas. Expression of MGMT protein and activity is under epigenetic control via MGMT promoter CpG island methylation. Methylation of the MGMT promoter leads to gene silencing, diminished MGMT protein expression, and increased susceptibility to TMZ-based therapy.[103]

Variability in MGMT activity has been correlated with the methylation status of CpG islands within the MGMT promoter.[131] MGMT promoter hypermethylation is associated with a loss of transcription and decreased expression of MGMT.[132] Tumor MGMT promoter hypermethylation is quite variable among pediatric malignancies; although the frequency of MGMT promotor hypermethylation in pediatric patients with primary brain tumors is unknown, there is clear evidence from the CCG-945 study and the ACNS0126 cohort that patients whose tumors had MGMT overexpression has a significantly worse response to alkylator-based therapies with lomustine and temozolomide, respectively.[133,134]

In this study, we plan to compare EFS between patients with MGMT overexpression and those without, and those with MGMT promoter methylation and those without. Given that some of treatment arms will involve use of nonalkylator-based therapy, this would allow a determination of whether patients with MGMT overexpression have an adverse prognosis specifically in the context of alkylator-based therapy, or whether such children have an adverse outcome independent of therapeutic approach.

Because MGMT status has been analyzed by several techniques in previous studies, the tumor MGMT protein status will be assessed directly via protein expression analyses performed via immunohistochemical techniques as well as indirectly by assessing the methylation status of the MGMT promoter via methylation-specific polymerase chain reaction (PCR) assays performed on tumor DNA.[103]

2.5 Rationale for MR Perfusion and Diffusion Imaging Studies

Using magnetic resonance imaging (MRI) techniques, Batchelor et al showed that normalization of tumor vessels in recurrent glioblastoma patients by daily administration of AZD2171 (an oral tyrosine kinase inhibitor of VEGF receptors) has rapid onset, is prolonged but reversible, and has the significant clinical benefit of alleviating edema. Reversal of normalization began by 28 days, though some features persisted for

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as long as four months. Basic FGF, SDF1alpha, and viable circulating endothelial cells (CECs) increased when tumors escaped treatment, and circulating progenitor cells (CPCs) increased when tumors progressed after drug interruption. This study suggests that the timing of combination therapy may be critical for optimizing activity against this tumor.[96]

T2*-weighted perfusion MRI, a method based on the rapid intravenous administration of Gd-DTPA, has been used for the assessment of treatment response to antiangiogenic agents in adults with recurrent high-grade gliomas.[135,136]

In the referenced studies, the variations observed during therapy using this sequence seemed to correlate with the clinical response experienced by the patients. A third study used this sequence in adults with newly diagnosed high-grade glioma and demonstrated its usefulness to assess angiogenesis and microvascular leakage, two characteristics associated with the malignant potential of these tumors.[137] The latter study also demonstrated considerable heterogeneity of the measured parameters within regions of WHO grade III and IV gliomas.

Hamstra et al assessed the role of diffusion magnetic resonance imaging (MRI) using a functional diffusion map (fDM) in providing an earlier measure to predict patient survival. Sixty patients with high-grade glioma were enrolled onto a study of intratreatment MRI at 1, 3, and 10 weeks. Receiver operating characteristic curve analysis was used to evaluate imaging parameters as a function of patient survival at 1 year. Both log-rank and Cox proportional hazards models were utilized to assess overall survival. Greater increases in diffusion in response to therapy over time were observed in those patients alive at 1 year compared with those who died as a result of disease. The volume of tumor with increased diffusion by fDM at 3 weeks was the strongest predictor of patient survival at 1 year, with larger fDM predicting longer median survival (52.6 vs 10.9 months, $P < .003$); hazard ratio [HR] = 2.7; (95% CI, 1.5 to 5.9). Radiologic response (RR) at 10 weeks had similar prognostic value (median survival, 31.6 v 10.9 months; log-rank $P<.001$; HR = 2.9; (95% CI, 1.7 to 7.2). Radiologic response and fDM differed in 25% of cases. A composite index of response including fDM and RR provided a robust predictor of patient survival and may identify patients in whom RR does not correlate with clinical outcome. The authors concluded that with conventional neuroimaging, fDM provided an earlier assessment of equal predictive value, and the combination of fDM and RR provided a more accurate prediction of patient survival than either metric alone.[138]

For imaging assessment, conventional MR imaging techniques will be utilized as well as more advanced MRI techniques for characterization of the tumor at baseline and to assess treatment response in a multiparametric fashion. Advanced techniques will include optional MR perfusion imaging using dynamic susceptibility weighted contrast enhanced –MRI (DSC-MRI) and diffusion tensor imaging (DTI). These techniques will allow assessment of tumor size (Anatomic MRI) and estimate cellularity (DTI) and vascularity (perfusion).[139] Imaging techniques will be performed at a level common to many different scanners likely to be encountered in clinical practice.

MR perfusion:
T2*-weighted perfusion MRI using the rapid intravenous administration of Gd-DTPA (dynamic susceptibility weighted contrast enhanced –MRI or DSC-MRI) is an imaging method that can assess tumor microvascularity and has been shown to correlate with tumor grade in astrocytomas[140,141] and treatment response to antiangiogenic agents in adults with high-grade gliomas.[136] In addition, a recent study has demonstrated that cerebral blood volume (CBV) measurements by DSC-MRI can predict time to progression and survival in patients with gliomas, independent of pathologic findings.[140] Sadeghi et al,[141] found significant correlations between CBV measurements and microvessel density in stereotactically obtained biopsies in patients with brain gliomas.

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The perfusion protocol will be performed using a dynamic, contrast enhanced T2* weighted perfusion technique. Evaluation of cerebral perfusion dynamics will include cerebral blood volume (rCBV), cerebral blood flow (CBF), and mean transit time (MTT) of contrast through the vasculature of the tumor and brain parenchyma.

Diffusion Tensor Imaging:
Imaging of water diffusion (DTI) is an elegant technique to probe brain and tumor microstructure. To completely define the tensor at least six non co-linear diffusion directions are needed. Typical metrics defined are mean diffusivity (MD), apparent diffusion coefficient (ADC), and fractional anisotropy (FA). Although diffusion imaging has been investigated and shown to be effective as a tool to differentiate some intracranial tumor types, results in this regard have been mixed and overlap exists.[142] Changes in water diffusion have been documented occurring in the first few weeks after initiation of treatment and may be useful to predict response to therapy. In a study of patients with glioma treated with radiation and chemotherapy, those with stable disease showed higher ADC in tumor relative to normal appearing white matter at 1 month than in those with tumor progression.[142] Similar findings have been noted in metastatic brain lesions.[143] A more advanced metric involves the calculation of a functional diffusion map.[138,144] This metric utilizes fusion of pre- and post treatment MR imaging and analyzes the change in ADC values in common voxels between the two studies, resulting in a metric that relates to the volume of tumor exhibiting a change in ADC. Volume of tumor exhibiting an increase in ADC correlates well with initial response rate and patient survival.[138]

3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration
Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

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. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2 IRB Approval
Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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IRB/REB approval documents may be faxed (1-215-569-0206), emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 31 days after definitive surgery and no later than 14 calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will not be entered on study**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.6 Mandatory Submission of Tissue for Central Pathology Review (see Section 15.0)

All patients must have tissue submitted for central pathology review, prior to the start of maintenance.

3.1.7 Randomization

The first 6 to 12 patients (depending on toxicities experienced) will be enrolled onto the feasibility part of the study and will not be randomized to treatment. These patients will be assigned to the vorinostat with RT treatment arm, with the dose of vorinostat assigned at time of study entry (either 230 mg/m^2/day or 180/mg/m^2/day). The vorinostat MTD determined upon completion of the feasibility part will be the vorinostat dose used during the remainder of the study.

Following the feasibility study, randomization will take place at the time a patient is enrolled on Study via RDE. In Phase II, patients will be randomized to one of the following arms of chemoradiotherapy: Arm A (vorinostat with RT), Arm B (temozolomide with RT), or Arm C (bevacizumab with RT). In Phase III, patients will be randomized to one of two arms: the superior chemoradiotherapy arm from Phase II (either Arm A or Arm C) or Arm B (temozolomide with RT). Randomization will be stratified by extent of resection (near total resection or gross total resection vs. other) and histology (glioblastoma multiforme vs. other).

3.2 Patient Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

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INCLUSION CRITERIA

3.2.1 Age
Patients must be greater than or equal to 3 years and less than 22 years at the time of enrollment.

3.2.2 Diagnosis

3.2.2.1
Patients must have a newly diagnosed high-grade glioma such as: anaplastic astrocytoma, glioblastoma multiforme, or gliosarcoma. Patients with primary spinal cord malignant gliomas are eligible. Patients with primary brainstem tumors are not eligible. **Patients with a diagnosis of oligodendroglioma or oligoastrocytoma are NOT eligible.**

3.2.2.2
Patients must have histologic verification of diagnosis. **Patients with M+ disease (defined as evidence of neuraxis dissemination) are not eligible**. CSF cytology must be done if clinically indicated prior to study enrollment. **If cytology proves positive, the patient would be considered to have metastatic disease and would, therefore, be ineligible.**

Note: False positive cytology can occur within 10 days of surgery.

3.2.2.3
For patients with intracranial tumors, a pre-operative and post-operative brain MRI with and without gadolinium and a spine MRI if clinically indicated must be obtained. For patients with spinal cord primaries, only a pre and post-operative spine MRI with gadolinium must be obtained. The post-operative MRIs must be obtained within 4 weeks prior to enrollment onto study. The requirement for a post-operative MRI is waived for patients who undergo biopsy only (see Section 7.1).

3.2.3 Performance Level (See https://members.childrensoncologygroup.org/prot/reference_materials.asp)
Patients must have a Lansky or Karnofsky performance status score of ≥ 50%, corresponding to ECOG categories of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.

3.2.4 Prior Therapy

3.2.4.1
Patients must not have received any prior chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant.

3.2.5 Cardiac Disease or Hypertension

- Hypertension must be well controlled (≤ 95th percentile for age and height if patient is ≤ 17 years) on stable doses of medication. (See Appendices I and II for tables of blood pressure based on age and gender. If a patient falls between percentiles for height and age, then the average value should be considered the appropriate one.) If patient is > 17 years, adult normal values should be used (ie, patients must have a SBP ≤ 150 mmHg and/or DBP ≤100 mmHg.)

Please see additional exclusion criteria in 3.2.8 – 3.2.11.

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3.2.6 Concomitant Medications Restrictions (Please see Section 4.2 for the concomitant therapy restrictions for patients during the study).

a. Study Specific:

1) Patients must not be currently receiving other anti-cancer agents.
2) Patients must not be receiving nonsteroidal anti-inflammatory medications known to inhibit platelet function or known to selectively inhibit cyclooxygenase activity. Medicines in this class are excluded.
3) Patients must not be currently receiving enzyme inducing anticonvulsants. (Please see Appendix VII for a list of enzyme inducing and non-enzyme inducing anticonvulsants)
4) Patients must not be receiving other HDAC inhibitors (e.g., valproic acid), as severe thrombocytopenia and gastrointestinal bleeding have been reported with concurrent administration with vorinostat.
5) Patients must not be receiving anticoagulants including systemic thrombolytic agents, heparin, low molecular weight heparins, or warfarin except as required to maintain patency of preexisting permanent vascular catheters or for prevention of thrombosis in the post-operative period.

3.2.7 Surgical Procedures

Patients with a major surgical procedure within 7 days prior to planned start of therapy should be excluded. Patients must have recovered from any surgical procedure before enrolling on this study (see Table below for examples of major, intermediate, and minor surgical procedures).

Please note: For patients receiving bevacizumab, those who have had surgical procedures should not receive bevacizumab within 28 days of a major procedure, 14 days of an intermediate procedure and 7 days of a minor procedure. (Please see below for definitions of types of procedure).

Examples of Major, Intermediate, or Minor Surgical Procedures

Major Procedures	Intermediate Procedures	Minor Procedures
Major craniotomy for tumor resection	VP-shunt placement	Incision and drainage of superficial skin abscesses
Organ resection	Stereotactic brain biopsy	Punch biopsy of skin lesions
Bowel wall anastomosis		Superficial skin wound suturing
Arteriovenous grafts		Bone marrow aspirate and/or biopsy
Exploratory Laparotomy		Fine needle aspirations
Thoracotomy		Broviac line or infusaport placement
		Paracentesis or thoracocentesis

Please note: Lumbar punctures or placement of PICC lines are not considered minor procedures and may occur at any time prior to or during therapy.

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3.2.8 Organ Function Requirements
All patients must have:

3.2.8.1 Adequate Bone Marrow Function Defined As

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 gm/dL (transfusion independent)

3.2.8.2 Adequate Renal Function Defined As

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.2.8.3 Urine protein should be screened by urine analysis. If protein ≥ 2+ on urinalysis, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg for patient enrollment.

Note: UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formulae:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.2.8.4 Adequate Liver Function Defined As

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age, and
- Serum albumin ≥ 2 g/dL.

3.2.8.5 Central Nervous System Function Defined As

- Patients with a seizure disorder may be enrolled if well-controlled and on nonenzyme-inducing anticonvulsants. If on nonenzyme-inducing anticonvulsants, patient must not be taking valproic acid.

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3.2.8.6 Adequate Coagulation Defined As

- PT INR ≤ 1.5 x upper limit of normal

EXCLUSION CRITERIA

3.2.9
Patients must not have a history of myocardial infarction, severe or unstable angina, clinically significant peripheral vascular disease, Grade 2 or greater heart failure, or serious and inadequately controlled cardiac arrythmia.

3.2.10
Patients must not have a known bleeding diathesis or coagulopathy

3.2.11
Patients who have experienced arterial thromboembolic events, including transient ischemic attacks or cerebrovascular accidents are excluded from participation.

3.2.12
Patients must not have been previously diagnosed with a deep venous thrombosis (including pulmonary embolism), and must not have a known thrombophilic condition (e.g., protein S, protein C, antithrombin III deficiency, Factor V Leiden or Factor II G202`0A mutation, homocysteinemia, or antiphospholipid antibody syndrome).

3.2.13
Patients must not have a history of an abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the last 6 months prior to study entry.

3.2.14
Patients with a serious or non-healing wound, ulcer, or bone fracture are not eligible for this study.

3.2.15
Patients must not have evidence of significant postoperative intracranial hemorrhage, defined as > 1 cm of blood on postoperative MRI scan (potentially in addition to the postoperative scan) obtained within 14 days prior to study entry.

3.2.16
Patients with a history of allergic reaction to Chinese hamster ovary cell products, or other recombinant human antibodies are ineligible.

3.2.17
Pregnant female patients are not eligible for this study. Pregnancy tests with a negative result must be obtained in all post-menarchal females.

3.2.18
Lactating females must agree they will not breastfeed a child while on this study.

3.2.19
Males and females of reproductive potential may not participate unless they agree to use an effective contraceptive method and continue to do so for at least 6 months after the completion of bevacizumab therapy.

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REGULATORY

3.2.20
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.21
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

This is a 2 phase study. The first phase of the study will include a feasibility study component to assess for dose-limiting toxicities (DLTs) and define the maximum tolerable dose (MTD) of vorinostat when given concurrently with radiation therapy (see Experimental Schema). The feasibility study is open to all COG institutions. The MTD found in the feasibility study component will be used in all subsequent phases of the study. The phase II component of the study will compare 2 experimental treatments to a commonly used chemoradiotherapy arm (Arm B with temozolomide). Upon completion of the phase II part of the study, a comparison of 1 year EFS will be made between the experimental arms and the temozolomide chemoradiotherapy arm. If one or both of the experimental arms has a superior 1 year EFS to that of the temozolomide chemoradiotherapy arm, the study will enter the phase III part of the study. If none of the experimental arms is superior to the temozolomide chemoradiotherapy arm, the study will not proceed to Phase III. In Phase III of this study, patients will continue to be accrued and randomly assigned to either the superior experimental arm identified in Phase II or to the temozolomide chemoradiotherapy arm.

All patients must begin therapy within 31 days after definitive surgery. Radiation will be given in standard fractions (total dose 59.4 Gy) over 6 weeks (see Section 14.0 for details). During radiation, patients will receive chemotherapy per one of the three arms described in Section 4.4. All patients will begin Maintenance therapy with bevacizumab and temozolomide commencing 4 weeks after completion of RT for up to a total of 12 cycles.

Growth plate evaluation: Patients who have not yet obtained full adult height will have a plain AP radiograph of a single tibial growth plate obtained prior to initial treatment. If a patient is found to have a closed tibial growth plate, no further radiographs will be required for that patient. If the patient is found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained every 12 weeks during Maintenance therapy.

Patients with evidence of growth plate thickening or other changes or abnormalities should have MRI scans of both knees performed to further assess the degree of physeal pathology and a consultation with an orthopedic surgeon is recommended. However, no dose modifications will be made for bevacizumab.

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4.2 Concomitant Therapy Restrictions

4.2.1 General Restrictions for All Patients on Therapy

4.2.1.1
Patients must not be receiving nonsteroidal anti-inflammatory medications known to inhibit platelet function or known to selectively inhibit cyclooxygenase activity.

4.2.1.2
Patients should not receive coumarin-derivative anticoagulants (eg, warfarin), as prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed in patients receiving vorinostat with coumarin-derivative anticoagulants (eg, warfarin). In general, since all patients will receive bevacizumab during maintenance therapy, patients must not be treated with anticoagulants including systemic thrombolytic agents, heparin, low molecular weight heparins, or warfarin while on protocol therapy, except as required to maintain patency of preexisting permanent vascular catheters.

4.2.1.3
Filgrastim (G-CSF) may be used at the treating physician's discretion to enhance neutrophil recovery when clinically indicated (eg, for culture proven bacteremia or invasive fungal infection). Routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

4.2.1.4
Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

4.2.1.5
Corticosteroid therapy is permissible only for treatment of increased intracranial pressure. The lowest dose consistent with good medical management should be used. Corticosteroids should NOT be used as an antiemetic due to their effect on the blood brain barrier. Use of corticosteroids must be documented on the appropriate case report form.

4.2.2 Concomitant Therapy Restrictions for Patients Receiving Temozolomide

There have been multiple episodes of pneumocystis carinii pneumonia (also called *Pneumocystis jiroveci pneumonia*) (PCP) reported in patients receiving temozolomide, particularly when taking corticosteroids. For this reason, patients should receive PCP 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 trimethoprim/sulfamethoxazole (also called TMP/SMX, cotrimoxazole, Bactrim, Septra) prophylaxis. For this reason, trimethoprim/sulfamethoxazole may not be utilized as PCP prophylaxis during chemoradiotherapy in patients receiving temozolomide as a radiosensitizer. **Monthly inhaled or IV pentamidine or an appropriate alternative must be administered during chemoradiotherapy if patients are receiving temozolomide as a radiosensitizer.** TMP/SMX may be used during adjuvant 5-day temozolomide. PCP prophylaxis should be discontinued 3 months after chemotherapy has discontinued.

For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

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4.3 Definitions of Dose Limiting Toxicities, Maximum Tolerated Dose, and Dose De-Escalation Criteria for Feasibility Study

This information applies to the feasibility study only. For dose modifications based on toxicities during Phase II and Phase III of the study, refer to Section 5.0.

4.3.1 Definition of Dose Limiting Toxicities

Dose-limiting toxicity is assessed during chemoradiotherapy with vorinostat (ie, starting with the first dose of vorinostat and concluding at 2 weeks after the completion of chemoradiotherapy) for each patient treated in the feasibility portion of this study. Dose-limiting toxicities are based on Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Dose-limiting toxicities are defined as:

4.3.1.1 Hematological DLT:

a) Grade 3 decreased platelet count that requires transfusion therapy on greater than 2 occasions during radiation therapy
b) Grade 4 decreased neutrophil count or decreased platelet count

4.3.1.2 Non Hematological DLT

a) Any grade 4 non-hematological toxicity
b) Any grade 3 non-hematological toxicity with the specific exception of
    i. Grade 3 nausea and vomiting of less < 5 days duration responsive to antiemetic therapy;
    ii. Grade 3 increased alanine aminotransferase (ALT or SGPT) that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur upon study re-challenge with study drug
    iii. Grade 3 fever or infection < 5 days duration.
    iv. Grade 3 hypokalemia, hypophosphatemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation
c) Any grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption
d) Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered dose-limiting.
e) Any Grade 2 or higher adverse event requiring interruption of study drug for > 7 days or which recurs upon drug rechallenge.

4.3.1.3 Any Grade 2 or higher toxicity requiring interruption of radiation therapy for > 5 consecutive days or 10 days total.

4.3.2 Definition of Maximum Tolerated Dose

The dose level that has 0 or 1 DLT among the 6 patients will be chosen as the MTD.

4.3.3 Rules for Dose De-Escalation During Feasibility Portion of the Study

The following rules will be applied during the feasibility portion of the study. Six patients will be enrolled at vorinostat 230 mg/m^2/dose with daily RT. If there are fewer than 2 patients with DLTs, this dose will be declared the recommended phase II dose. If there are 2 or more DLTs in this cohort of 6 patients, the

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dose will be de-escalated to 180 mg/m^2/dose, at which level 3 additional patients will be enrolled. If 0 or 1 of the 3 patients has a DLT, an additional 3 patients will be enrolled onto this cohort. If fewer than 2 of the 6 patients have a DLT, the 180 mg/m^2/dose will be declared the recommended phase II dose. If 2 or more of the 6 patients at 180 mg/m^2/dose have a DLT, the study will be amended.

Upon completion of the feasibility study, the study will be amended for the MTD to be used in the remainder of the study. Patients currently on study will continue with maintenance therapy after completion of chemoradiotherapy (see Section 4.9).

4.4 Description of Treatment Arms

4.4.1 Treatment Arm During Feasibility Study

As of Amendment #1, the Feasibility Study was completed.
There will be one treatment arm during this part of the study. Patients will receive chemoradiotherapy with vorinostat at the dose assigned at study enrollment (see Section 3.1.7).

4.4.2 Treatment Arms During Phase II of the Study

Patients will be randomized at study enrollment to one of the three following arms for chemoradiotherapy:

Arm A: Vorinostat at 230 mg/m^2/day, orally, Monday through Friday starting on the first day of radiotherapy as determined in the feasibility study. Vorinostat should be administered 1 to 2 hours prior to each radiation dose. If the first day of RT is not on a Monday, then the patient should receive the first week doses starting on the weekday that radiation therapy starts until Friday of that week.

Arm B: Temozolomide at 90 mg/m^2/dose orally, started in the first week of initiation of RT on a daily basis continuously throughout RT (ie, 7 days a week). The 42 days of temozolomide should be given regardless of the end date of RT.

Arm C: Bevacizumab at 10 mg/kg/dose IV over 90 minutes, Day 22 (± 2 day) and Day 36 (± 2 day) of RT. Bevacizumab should be given at least 2 hours prior to RT. There must be at least 14 days between bevacizumab doses.

4.4.3 Treatment Arms During Phase III of the Study

If the one-year EFS of either treatment Arm A or treatment Arm C is superior to that of the treatment arm B with temozolomide, the study will continue to the phase III portion. In the phase III portion, patients will be randomized at study enrollment to one of the two following arms for chemoradiotherapy:

Arm B: Temozolomide at 90 mg/m^2/dose orally, started in the first week of initiation of RT on a daily basis continuously throughout RT and should continue until the last dose of RT. The 42 days of temozolomide should be given regardless of the end date of RT.

Superior Arm from Phase II of the Study: The treatment arm from Phase II that has a one-year EFS that is superior to temozolomide (either Arm A or Arm C). If neither Arm A nor Arm C is superior to temozolomide, the study will not continue to the phase III portion.

See Section 7.1 for baseline studies to be obtained prior to starting chemoradiotherapy. See Section 7.2 for optional biology studies and optional imaging studies for patients who have provided consent. See Section 16.0 for details of specimen collection, handling, and shipping for optional biology studies, and Section 16.8 for details of optional imaging studies to be obtained.

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See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

4.5 Arm A Chemoradiotherapy with Vorinostat (Feasibility Study Only)

As of Amendment #1, the Feasibility Study was completed.

For the feasibility study only, the dose of vorinostat will be assigned at time of study entry, and will be one of two doses (either 230 mg/m^2/day or 180 mg/m^2/day). The Arm A chemoradiotherapy course lasts 70 days, and is comprised of 6 weeks of concurrent chemotherapy and radiation therapy and a 4 week rest period.

Radiation Therapy

Radiation therapy will be given over 6 weeks during this course. The goal of treatment planning and dose prescription is that the dose to the ICRU reference point shall be 54 Gy given over 6 weeks. The boost volume, when present, will receive an additional 5.4 Gy for a total dose of 59.4 Gy. Radiation will be given in standard fractions. Radiation treatments should not be interrupted or delayed, except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. See Section 14.0 for Radiation Therapy Guidelines.

Dosing should be based on actual BSA. The maximum daily dose of vorinostat is 400 mg.

The therapy map described below assumes Day 1 of RT occurs on a Monday; thus Days 1-5, 8-12, etc. are Monday through Friday.

Vorinostat: PO

Dose: Assigned dose at enrollment (**maximum dose 400 mg**).

Days: 1-5, 8-12, 15-19, 22-26, 29-33, 36-40, daily (Monday through Friday) concomitantly with radiation therapy.

NOTE: **Give 1 to 2 hours prior to daily RT dose.** Please see Appendix III for dosing guidelines based on BSA. For patients who cannot swallow capsules, see Section 6.3 for guidelines for preparing vorinostat suspension. Patients with BSA < 1 m^2 or patients who cannot swallow capsules will receive the vorinostat suspension rounded to the nearest 5 mg (See section 6.3 for preparation guidelines.) If a dose of vorinostat is given and radiation therapy is NOT administered due to sedation or technical issues, the vorinostat dose should not be made up (ie, no more than 30 doses of vorinostat should be given).

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Arm A chemoradiotherapy during the feasibility study is on the next 2 pages.

Following completion of Arm A chemoradiotherapy, Maintenance chemotherapy (see Section 4.9) starts on Day 71 (29 days after the end of chemoradiotherapy) or when criteria to begin Maintenance are met (whichever occurs later).

See Section 15.3 for required pathology materials that must be received by the COG Biopathology Center prior to the start of Maintenance therapy.

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4.5.1a **Chemoradiotherapy for Arm A (Feasibility Study ONLY)** Arm A chemoradiotherapy is for patients receiving vorinostat. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Details are in Section 4.0 (Treatment Overview). Radiation therapy is to be given for six (6) weeks and vorinostat should be given daily (Monday through Friday) throughout RT. (See Section 14.0 for details of radiation therapy).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vorinostat (VORIN) [redacted]	PO	Assigned dose at enrollment	1-5, 8-12, 15-19, 22-26, 29-33, 36-40	**Give 1 to 2 hours prior to daily RT dose.** **Maximum dose: 400 mg.**	a) History, PE (Ht, Wt, BSA, VS), Performance Status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	VORIN ____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		1	____mg	a, b, c, d, e	
		2	____mg		
		3	____mg		
		4	____mg		
		5	____mg		
		8	____mg	b, c, d	
		9	____mg		
		10	____mg		
		11	____mg		
		12	____mg		
		15	____mg	b, c, d	
		16	____mg		
		17	____mg		
		18	____mg		
		19	____mg		
		22	____mg	b, c, d	
		23	____mg		
		24	____mg		
		25	____mg		
		26	____mg		

Course continues on overleaf (Days 29-70).

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4.5.1b **Chemoradiotherapy for Arm A (Feasibility Study ONLY)** - Continued Arm A chemoradiotherapy is for patients receiving vorinostat. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/µL and platelets ≥ 100,000/µL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Details are in Section 4.0 (Treatment Overview). Radiation therapy is to be given for six (6) weeks and vorinostat should be given daily (Monday through Friday) throughout RT. (See Section 14.0 for details of radiation therapy).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vorinostat (VORIN) [redacted]	PO	Assigned dose at enrollment	1-5, 8-12, 15-19, 22-26, 29-33, 36-40	**Give 1 to 2 hours prior to daily RT dose.** **Maximum dose: 400 mg.**	a) History & PE (Ht, Wt, BSA, VS), Performance status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	VORIN ____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		29	____mg	b, c, d	
		30	____mg		
		31	____mg		
		32	____mg		
		33	____mg		
		36	____mg	b, c, d	
		37	____mg		
		38	____mg		
		39	____mg		
		40	____mg		
		43		(a, b, c, d) #	
		71	Start Maintenance chemotherapy (see Section 4.9) on Day 71 or when Maintenance starting criteria are met (whichever occurs later).		

Observation Note:

Obtain during Week 7.

See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see **https://members.childrensoncologygroup.org/prot/reference_materials.asp** under Standard Sections for Protocols.

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4.6 Arm A Chemoradiotherapy with Vorinostat (Phases II and III)

For Phases II and III of this study, the dose of vorinostat used in Arm A will be 230 mg/m^2/day Monday through Friday, the MTD determined in the feasibility study. The Arm A chemoradiotherapy course lasts 70 days, and is comprised of 6 weeks of concurrent chemotherapy and radiation therapy and a 4 week rest period.

Radiation Therapy

Radiation therapy will be given over 6 weeks during this course. The goal of treatment planning and dose prescription is that the dose to the ICRU reference point shall be 54 Gy given over 6 weeks. The boost volume, when present, will receive an additional 5.4 Gy for a total dose of 59.4 Gy. Radiation will be given in standard fractions. Radiation treatments should not be interrupted or delayed, except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. See Section 14.0 for Radiation Therapy Guidelines.

The therapy map described below assumes Day 1 of RT occurs on a Monday; thus Days 1-5, 8-12, etc. are Monday through Friday.

Dosing should be based on actual BSA. The maximum daily dose of vorinostat is 400 mg.

Vorinostat: PO
Dose: 230 mg/m^2/day (**maximum dose 400 mg**).
Days: 1-5, 8-12, 15-19, 22-26, 29-33, 36-40, daily (Monday through Friday) concomitantly with radiation therapy.
NOTE: **Give 1 to 2 hours prior to daily RT dose.** Please see Appendix III for dosing guidelines based on BSA. For patients who cannot swallow capsules, see Section 6.4 for guidelines for preparing vorinostat suspension. Patients with BSA < 1 m^2 or patients who cannot swallow capsules will receive the vorinostat suspension rounded to the nearest 5 mg (See Section 6.4 for preparation guidelines.) If a dose of vorinostat is given and radiation therapy is NOT administered due to sedation or technical issues, the vorinostat dose should not be made up (ie, no more than 30 doses of vorinostat should be given).

If a patient vomits within 30 minutes after the dose of vorinostat is administered and the pill is visible that dose should be repeated. If a patient vomits after 30 minutes, the dose will not be repeated. Patients receiving liquid preparation should not be redosed.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Arm A chemoradiotherapy during phases II and III is on the next 2 pages.

Following completion of Arm A chemoradiotherapy, Maintenance chemotherapy (see Section 4.9) starts on Day 71 (29 days after the end of chemoradiotherapy) or when criteria to begin Maintenance are met (whichever occurs later).

See Section 15.3 for required pathology materials that must be received by the COG Biopathology Center prior to the start of Maintenance therapy.

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4.6.1a **Chemoradiotherapy for Arm A (Phases II and III)** Arm A chemoradiotherapy is for patients receiving vorinostat. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Details are in Section 4.0 (Treatment Overview). Radiation therapy is to be given for six (6) weeks and vorinostat should be given daily (Monday through Friday) throughout RT. (See Section 14.0 for details of radiation therapy.)

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vorinostat (VORIN) [redacted]	PO	230 mg/m^2/day	1-5, 8-12, 15-19, 22-26, 29-33, 36-40	**Give 1 to 2 hours prior to daily RT dose.** **Maximum dose: 400 mg.**	a) History, PE (Ht, Wt, BSA, VS), Performance Status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	VORIN ____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		1	____mg	a, b, c, d, e,	
		2	____mg		
		3	____mg		
		4	____mg		
		5	____mg		
		8	____mg	b, c, d	
		9	____mg		
		10	____mg		
		11	____mg		
		12	____mg		
		15	____mg	b, c, d	
		16	____mg		
		17	____mg		
		18	____mg		
		19	____mg		
		22	____mg	b, c, d	
		23	____mg		
		24	____mg		
		25	____mg		
		26	____mg		

Course continues on overleaf (Days 29-70).

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4.6.1b **Chemoradiotherapy for Arm A (Phases II and III)** Continued Arm A chemoradiotherapy is for patients receiving vorinostat. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Details are in Section 4.0 (Treatment Overview). Radiation therapy is to be given for six (6) weeks and vorinostat should be given daily (Monday through Friday) throughout RT. (See Section 14.0 for details of radiation therapy.)

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vorinostat (VORIN) [redacted]	PO	230 mg/m^2/day	1-5, 8-12, 15-19, 22-26, 29-33, 36-40	**Give 1 to 2 hours prior to daily RT dose.** **Maximum dose: 400 mg.**	a) History & PE (Ht, Wt, BSA, VS), Performance status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging Studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	VORIN ____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		29	____mg	b, c, d	
		30	____mg		
		31	____mg		
		32	____mg		
		33	____mg		
		36	____mg	b, c, d	
		37	____mg		
		38	____mg		
		39	____mg		
		40	____mg		
		43		(a, b, c, d) #	
		71	Start Maintenance chemotherapy (see Section 4.9) on Day 71 or when Maintenance starting criteria are met (whichever occurs later).		

Observation Note:

Obtain during Week 7.

See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see **https://members.childrensoncologygroup.org/prot/reference_materials.asp** under Standard Sections for Protocols.

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4.7 Arm B Chemoradiotherapy with Temozolomide

Phases II and III of this study will include treatment Arm B chemoradiotherapy with temozolomide. The Arm B chemoradiotherapy course lasts 70 days, and is comprised of concurrent chemotherapy and radiation therapy for 42 days and a 4 week rest period.

Radiation Therapy

Radiation therapy will be given over 6 weeks during this course. The goal of treatment planning and dose prescription is that the dose to the ICRU reference point shall be 54 Gy given over 6 weeks. The boost volume, when present, will receive an additional 5.4 Gy for a total dose of 59.4 Gy. Radiation will be given in standard fractions. Radiation treatments should not be interrupted or delayed, except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. See Section 14.0 for Radiation Therapy Guidelines.

Dosing should be based on actual BSA. There is no maximum dosing.

Temozolomide: PO
Dose: 90 mg/m^2/dose.
Days: 1 - 42. Must be given by Day 5 of radiation therapy, and continue throughout radiation therapy.

NOTE: Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer at bedtime on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day.

The temozolomide dose should be rounded off to the nearest 5 mg (round 2.5 mg down [see Appendix IV]). It is recommended that antiemetics be given 30 minutes prior to each temozolomide dose. If emesis occurs within 20 minutes of taking a given dose, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Guidelines for administration of temozolomide capsules to patients who are unable to swallow capsules are provided in Appendix VI or an oral suspension may be compounded (see drug monograph in Section 6.2).

The 42 days of temozolomide should be given regardless of the end date of RT. If a dose of temozolomide is given and radiation therapy is NOT administered due to sedation or technical issues, the temozolomide dose should not be made up (ie, no more than 42 doses of temozolomide should be given).

Trimethoprim/sulfamethoxazole (also called TMP/SMX, cotrimoxazole, Bactrim, Septra) should not be utilized as PCP prophylaxis during chemoradiotherapy. Monthly inhaled or IV pentamidine or an appropriate alternative should be administered during chemoradiotherapy (see Section 4.2.2 above).

Pharmacy note: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See drug monograph for additional details and examples.

See Section 5.0 for Dose Modifications based on Toxicities.

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The therapy delivery map (TDM) for Arm B Chemoradiotherapy is on the next page.

Following completion of Arm B chemoradiotherapy, Maintenance chemotherapy (see Section 4.9) starts on Day 71 (29 days after the end of chemoradiotherapy) or when criteria to begin Maintenance are met (whichever occurs later).

See Section 15.3 for required pathology materials that must be received by the COG Biopathology Center prior to the start of Maintenance therapy.

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4.7.1a **Chemoradiotherapy for Arm B**

Arm B chemoradiotherapy is for patients receiving temozolomide.
This course lasts 70 days (10 weeks).

_____
Patient name or initials

_____
DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Details are in Section 4.0. Radiation therapy is to be given for 6 weeks and temozolomide should be given continuously throughout RT. (See Section 14.0 for details of radiation therapy.)

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Temozolomide (TEMO)	PO	90 mg/m^2/dose	1* through 42	***Must begin by Day 5 of RT, and continue for 42 consecutive days.** Round dose to nearest 5 mg. See admin. guidelines in Section 4.7.	a) History & PE (Ht, Wt, BSA, VS), Performance Status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging Studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	TEMO ____mg	Studies	Comments (Include any held doses, or dose modifications)
	The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.				
			Enter calculated dose above and actual dose administered dose below.		
		1	____mg	a, b, c, d, e	
		2	____mg		
		3	____mg		
		4	____mg		
		5	____mg		
		6	____mg		
		7	____mg		
		8	____mg	b, c, d	
		9	____mg		
		10	____mg		
		11	____mg		
		12	____mg		
		13	____mg		
		14	____mg		
		15	____mg	b, c, d	
		16	____mg		
		17	____mg		
		18	____mg		
		19	____mg		
		20	____mg		
		21	____mg		
		22	____mg	b, c, d	
		23	____mg		
		24	____mg		
		25	____mg		
		26	____mg		
		27	____mg		
		28	____mg		

Course continues on overleaf (Days 29-70).

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4.7.1b **Chemoradiotherapy for Arm B** - Continued Arm B chemoradiotherapy is for patients receiving temozolomide. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **2 pages**. Radiation therapy is to be given for 6 weeks and temozolomide should be given continuously throughout RT. (See Section 14.0 for details of radiation therapy.)

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Temozolomide (TEMO)	PO	90 mg/m^2/dose	1* through 42	***Must begin by Day 5 of RT, and continue for 42 consecutive days.** Round dose to nearest 5 mg. See admin. guidelines in Section 4.7.	a) History & PE (Ht, Wt, BSA, VS), Performance Status b) CBC (differential, platelets) c) BUN, Creatinine, AST, ALT, bilirubin d) Electrolytes (Ca^{++}, PO_4, Mg^{++}) e) Optional Imaging Studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	TEMO ____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		29	____mg	b, c, d	
		30	____mg		
		31	____mg		
		32	____mg		
		33	____mg		
		34	____mg		
		35	____mg		
		36	____mg	b, c, d	
		37	____mg		
		38	____mg		
		39	____mg		
		40	____mg		
		41	____mg		
		42	____mg		
		43		(a, b, c, d) #	
		71	Start Maintenance chemotherapy (see Section 4.9) on Day 71 or when Maintenance starting criteria are met (whichever occurs later).		

Observation Note:

Obtain during Week 7.

See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see **https://members.childrensoncologygroup.org/prot/reference_materials.asp** under Standard Sections for Protocols.

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4.8 Arm C Chemoradiotherapy with Bevacizumab

Phase II of this study will include treatment Arm C chemoradiotherapy with bevacizumab. Pending the results from Phase II, Phase III of the study may also include treatment arm C. The Arm C chemoradiotherapy course lasts 70 days, and is comprised of 6 weeks of concurrent chemotherapy and radiation therapy and a 4 week rest period.

Radiation Therapy

Radiation therapy will be given over six (6) weeks during this course. The goal of treatment planning and dose prescription is that the dose to the ICRU reference point shall be 54 Gy given over 6 weeks. The boost volume, when present, will receive an additional 5.4 Gy for a total dose of 59.4 Gy. Radiation will be given in standard fractions. Radiation treatments should not be interrupted or delayed, except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. See Section 14.0 for Radiation Therapy Guidelines.

Dosing should be based on weight. There is no maximum dosing.

The therapy map described below assumes Day 1 of RT occurs on a Monday; thus Days 1-5, 8-12, etc. are Monday through Friday.

Bevacizumab: IV Over 90 Minutes

Dose: 10 mg/kg/dose

Days: Day 22 (± 2 days) and Day 36 (± 2 days) of RT. Bevacizumab should be given at least 2 hours prior to RT. There must be at least 14 days between Bevacizumab doses. A platelet count of 75,000/μL, with or without platelet transfusion, is required to administer bevacizumab.

Note: Infuse first dose over 90 minutes. If tolerated without infusion-related side effects, the second dose may be given over 60 minutes. Check vital signs prior to infusion and monitor for infusion-related reactions every 30 minutes and at the end of the infusion. Monitor every 15 minutes while the infusion rate is being adjusted. Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.) Anaphylactic precautions should be observed during bevacizumab administration. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well-tolerated. Bevacizumab is incompatible with D_5W (the drug is inactivated).

Special precautions: Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery (eg, organ resection, exploratory laparotomy, thoractomy) or 14 days after intermediate surgical procedure (eg, paracentesis or thoracocentesis) and until the surgical wound is fully healed. Minor surgical procedures (eg, biopsies, infusaport, or Broviac line placement) need to have fully healed and occurred > 7 days prior to initiation of bevacizumab.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Arm C chemoradiotherapy is on the next page.

Following completion of Arm C chemoradiotherapy, Maintenance chemotherapy (see Section 4.9) starts on Day 71 (29 days after the end of chemoradiotherapy) or when criteria to begin Maintenance are met (whichever occurs later).

See Section 15.3 for required pathology materials that must be received by the COG Biopathology Center prior to the start of Maintenance therapy.

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4.8.1a **Chemoradiotherapy for Arm C** Arm C chemoradiotherapy is for patients receiving bevacizumab. This course lasts 70 days (10 weeks).	_____ Patient name or initials _____ DOB

Criteria to start this course: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). This course lasts 70 days and this Therapy Delivery Map is on **1 page**. Radiation therapy is to be given for six (6) weeks and bevacizumab should be given prior to RT on Days 22 and 36. (See Section 14.0 for details of radiation therapy.)

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bevacizumab (BEVA) [redacted]	IV over 90 minutes*	10 mg/kg/dose	Days 22 and 36 (± 2 days)	Bevacizumab should be given at least 2 hours prior to RT. There must be at least 14 days between Bevacizumab doses. A platelet count of 75,000/μL, with or without platelet transfusion, is required to administer bevacizumab. *Second infusion may be given over shorter duration if well-tolerated. See admin. guidelines in Section 4.8.	a) History, Ht, Wt, BSA Performance Status b) PE (VS, inc BP), CBC (differential, platelets) Electrolytes (Ca^{++}, PO_4, Mg^{++}) c) BUN, Creatinine, AST, ALT, bilirubin, d) Urinalysis for Protein (urine dipstick or UPC ratio) e) Optional Imaging Studies (see section 16.8) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt____kg

Date Due	Date Given	Day	BEVA____mg	Studies	Comments (Include any held doses, or dose modifications)
		The day numbering below is provided for your convenience, and assumes Day 1 of RT is on a Monday. The timing (days) of chemoradiotherapy will vary, depending on which day of the week is Day 1 of RT therapy.			
			Enter calculated dose above and actual dose administered dose below.		
		1		a, b, c, d, e	
		8		b, c, d	
		15		b, c, d	
		22	mg	b$, c, d,	
		29		b, c, d	
		36	____mg	b$, c, d,	
		43		(a, b, c, d) #	
		71	Start Maintenance chemotherapy (see Section 4.9) on Day 71 or when Maintenance starting criteria are met (whichever occurs later).		

Observation Note:
Obtain during Week 7.
$ Obtain BP only.

See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

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4.9 Maintenance Therapy

All patients will receive maintenance therapy upon completion of chemoradiotherapy and tumor evaluation, in the absence of disease progression and unacceptable toxicities (See Section 5.0).

Maintenance consists of 12 cycles of chemotherapy. Maintenance will commence 4 weeks after the completion of radiation therapy. Criteria to start the first cycle of maintenance chemotherapy include:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/µl
- Platelet Count > 100,000/µl (without transfusion within the last 7 days)
- Serum creatinine ≤ 1.5 x normal for age (see Section 3.2.8.2)
- Total bilirubin ≤ 1.5 x normal for age, and SGPT (ALT) < 2.5 x normal for age
- The patient has no evidence of progressive disease (see Section 10.4) as assessed clinically and/or by imaging studies

Cycles will be repeated every 28 days. Criteria to start the second and subsequent cycles of maintenance chemotherapy include:

- Peripheral absolute neutrophil count (ANC) ≥ 750/µl
- Platelet Count > 75,000/µl (without transfusion within the last 7 days)
- Serum creatinine ≤ 1.5 x normal for age (see Section 3.2.8.2)
- Total bilirubin ≤ 1.5 x normal for age, and SGPT (ALT) < 2.5 x normal for age
- The patient has no evidence of progressive disease (see Section 10.4) as assessed clinically and/or by imaging studies
- The patient did not experience a bevacizumab-related targeted toxicity that requires discontinuation or withholding of bevacizumab as listed in Section 5.3.

Prior to beginning Maintenance therapy, obtain optional biology samples and imaging studies for patients who have provided consent. See Section 16.0 for details of biology specimen collection, handling, and shipping and Section 16.8 for details of optional imaging studies to be obtained.

Disease evaluations should occur prior to every odd number maintenance cycle and growth plate evaluations should occur every 12 weeks during maintenance therapy (see Section 7.1 for details).

See Section 15.3 for required pathology materials that must be received by the COG Biopathology Center prior to the start of Maintenance therapy.

See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

The administration schedule below describes one 4-week cycle of Maintenance therapy.

Dosing for bevacizumab is to be calculated by weight.

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Bevacizumab: IV over 90 minutes*
Dose: 10 mg/kg/dose.
Days: 1 and 15. A platelet count of >75,000/µL, with or without platelet transfusion, is required to administer bevacizumab.
Note: *Infuse first dose over 90 minutes. If tolerated without infusion-related side effects, the second dose may be given over 60 minutes. Again, if tolerated, the third dose and all subsequent doses may be given over 30 minutes. Check vital signs prior to infusion and monitor for infusion-related reactions every 30 minutes (during 60 and 90 minute infusions) and at the end of the infusion. Monitor every 15 minutes while the infusion rate is being adjusted. Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.) Anaphylactic precautions should be observed during bevacizumab administration. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well-tolerated. Bevacizumab is incompatible with D_5W (the drug is inactivated).

Special precautions: Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery (eg, organ resection, exploratory laparotomy, thoractomy) or 14 days after intermediate surgical procedure (eg, paracentesis or thoracocentesis) **and** until the surgical wound is fully healed. Minor surgical procedures (eg, biopsies, infusaport, or Broviac line placement) need to have fully healed **and** occurred > 7 days prior to initiation of bevacizumab.

Temozolomide: PO
Dose: 200 mg/m^2/dose.
Days: 1 – 5 of each cycle.

NOTE: Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer at bedtime on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day.

The temozolomide dose should be rounded off to the nearest 5 mg (round 2.5 mg down). See Appendix V. It is recommended that antiemetics be given 30 minutes prior to each temozolomide dose. If emesis occurs within 20 minutes of taking a given dose, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Guidelines for administration of temozolomide capsules to patients who are unable to swallow capsules are provided in Appendix VI or an oral suspension may be compounded (see drug monograph in Section 6.2).

Pharmacy note: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See drug monograph for additional details and examples.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Maintenance is on the next page.

Following completion of the first Maintenance cycle, the Maintenance cycle is repeated for up to 12 cycles, as tolerated and in the absence of disease progression (see Section 10.4 for Response Evaluation). Subsequent Maintenance cycles should begin on Day 29 or when starting criteria (see above) are met (whichever occurs later).

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4.9.1 **Maintenance – All Patients** Maintenance is given in 12 cycles. Each cycle lasts 28 days. This course lasts 336 days. Use a copy of this page once for each cycle. *(Please note cycle number below.)*	_____ Patient name or initials _____ DOB

Criteria to start cycle 1: ANC ≥ 1000/µl, platelets > 100,000/µl (transfusion independent), serum creatinine ≤ 1.5 x normal for age (see Section 3.2.8.2) , total bilirubin ≤ 1.5 x normal for age, and SGPT (ALT) < 2.5 x normal for age. Criteria to start cycles 2 through 12: ANC ≥ 750/µl, platelets > 75,000/µl (transfusion independent), serum creatinine ≤ 1.5 x normal for age, total bilirubin ≤ 1.5 x normal for age, SGPT (ALT) < 2.5 x normal for age, bevacizumab-related targeted toxicity that requires discontinuation or withholding of bevacizumab as listed in Section 5.3, and no progressive disease. This Therapy Delivery Map relates to one cycle, and this Therapy Delivery Map is on **1 page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bevacizumab (BEVA) [redacted]	IV over 90 minutes*	10 mg/kg/dose	1 and 15	*May be given over shorter duration if well-tolerated. See admin. guidelines in Section 4.9.	a) History & Performance Status b) PE (Ht, Wt, BSA, VS, inc BP), c) CBC (differential, platelets) d) BUN, creatinine, AST, ALT, bilirubin, Electrolytes (Ca++, PO^4, Mg++) e) MRI of the Head with and without gadolinium (with echo) f) MRI of the Spine with gadolinium g) X-ray of right knee h) Urinalysis for protein (urine dipstick or UPC ratio) i) Optional imaging studies (see Sections 16.8 for details) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Temozolomide (TEMO)	PO	200 mg/m^2/dose	1 through 5	Round dose to nearest 5 mg. See admin. guidelines in Section 4.9.	

Please enter Cycle # _____ Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Day	BEVA ____mg	TEMO ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered dose below.			
		1	____mg	____mg	a, b, c, d, e*, f^ , h^+, $i^\#$	
		2		____mg		
		3		____mg		
		4		____mg		
		5		____mg		
		15	____mg		$b^\$$, c	
		28			$c^@$, $g^\&$, $i^\#$	
		29	Begin next cycle on Day 29 or when criteria to begin cycle are met (whichever occurs later). Repeat for a total of 12 cycles. See Section 7.1 for end of therapy evaluations.			

Observation Notes:

* Obtain prior to every odd number maintenance cycle.

^ Obtain prior to every odd number maintenance cycle only if patient has spinal primary or if clinically indicated.

& Obtain tibial x-ray (AP and lateral views) of the right knee in patients who have not yet obtained full adult height at the completion of cycles 3, 6, 9, and 12. If abnormalities are detected on routine X-rays following treatment, MRI scan of both knees should be performed

+ If urine dipstick is 2+ or greater from protein, hold bevacizumab and obtain UPC ratio within 3 days of Day 1 dose of bevacizumab. See bevacizumab dose modifications for proteinuria (Section 5.3). If UPC ratio is > 1, collection of 24 hour urine for measurement of urine protein level is recommended but not required.

Obtain prior to starting Maintenance, prior to Cycle 3 and at the end of Maintenance.

$ Obtain BP only.

@ Obtain on Day 28 of maintenance cycle 12. Repeat weekly until results are normal.

See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

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5.0 DOSE MODIFICATIONS FOR TOXICITIES

The following dose modifications for toxicities are for use during phase II and phase III of the study. Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity.

5.1 Dose Modifications During Chemoradiotherapy

Doses reduced due to vorinostat, temozolomide, related-toxicity will not be re-escalated, even if there is minimal or no toxicity with the subsequent reduction in dose. For patients receiving vorinostat or temozolomide during RT, one dose reduction is allowed. Patients who again experience dose modifying toxicity after a single dose reduction will no longer receive vorinostat or temozolomide, but will continue protocol-defined therapy as planned (continue with radiation therapy and maintenance therapy).

Thus, if, in the feasibility component of the study, the dose of 230 mg/m^2 of vorinostat is deemed to be intolerable, and a cohort of patients are enrolled at the 180 mg/m^2 dose level, patients receiving 180 mg/m^2/dose will be allowed one dose reduction (to 130 mg/m^2/dose) if they experience dose limiting hematological or non-hematological toxicities.

There will be no dose reductions made for toxicity related to bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described in section 5.3.For patients receiving bevacizumab during RT, see Section 5.3 for dose modifications. If bevacizumab is stopped, patients should contine protocol-defined therapy as planned.

5.1.1 Hematological Toxicities

5.1.1.1

If Grade 3 decreased platelet count that requires transfusion therapy on greater than 2 occasions during radiation therapy occurs, reduce the dose of the respective study arm-specific agent as follows:

- Reduce the temozolomide dose to 60 mg/m^2/dose (see Dosing Table in Appendix IV)
- Reduce the vorinostat dose to 180 mg/m^2/dose (or 130 mg/m^2/dose if starting at the dose of 180 mg/m^2/dose [see section 5.1, above])
- Hold the dose of bevacizumab

5.1.1.2

If Grade 4 decreased neutrophil count or Grade 4 decreased platelet count occurs, discontinue vorinostat, temozolomide, or bevacizumab. CBCs should be checked twice weekly until:

- ANC > 750/µL
- Platelet count > 75,000/µL (transfusion independent)

If the counts recover to above criteria within 14 days of drug discontinuation, resume vorinostat, temozolomide at the reduced doses discussed in section 5.1.1.1. Resume Bevacizumab at the same dose of 10 mg/kg.

Please notify the Study Chair if counts have not recovered to the above criteria within 14 days of discontinuing vorinostat, temozolomide, or bevacizumab. If Grade 4 toxicity recurs, despite these dose reductions, vorinostat, temozolomide, or bevacizumab should be discontinued and not restarted, the patient should complete remaining radiation therapy and should receive temozolomide and bevacizumab as maintenance therapy.

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5.1.2 Non-Hematological Toxicities

5. 1. 2. 1
If platelets do not recover to > 75,000/μL or ANC does not recover to ≥ 750/μL by 14 days after the planned start of the next treatment cycle, temozolomide and bevacizumab should be held. Bevacizumab and temozolomide may be given if platelets have recovered to > 75,000/μL and ANC has recovered to ≥ 750/μL. Temozolomide doses should be reduced by 25% to150 mg/m^2/day x 5 days for the next course, at the time of recovery. Bevacizumab should be resumed at the same dose.

5.1.2.2
If, despite the dose reduction for subsequent courses, the ANC does not recover to ≥ 750/μL and the platelets to >75,000/μL by 14 days after the planned start of the next treatment course, no further temozolomide should be given and the patient may continue to receive bevacizumab in subsequent courses as soon as the criteria required for subsequent courses of therapy (see Section 4.9) are met.

5.1.2.3
Chemotherapy will be held for the remainder of the cycle if Grade 4 decreased neutrophil count (<500/ μL) or Grade 4 decreased platelet count (<25,000/ μL) is observed. CBCs should be checked twice weekly until count recovery has occurred. Chemotherapy with bevacizumab and temozolomide may be restarted if platelets have recovered to >75,000/μL and if ANC has recovered to ≥ 750/μL. Temozolomide doses should be reduced by 25% to150 mg/m^2/day x 5 days for the next course when the criteria required for subsequent courses of therapy are met. Bevacizumab should be resumed at the same dose.

5.2 **Dose Modifications during Maintenance Therapy**

5.2.1 Hematological Toxicities

5. 2. 1. 1
If platelets do not recover to > 75,000/μL or ANC does not recover to ≥ 750/μL by 14 days after the planned start of the next treatment cycle, temozolomide and bevacizumab should be held. Bevacizumab and temozolomide may be given if platelets have recovered to ≥ 75,000/μL.

5.2.1.2
Chemotherapy will be held for the remainder of the cycle if Grade 4 decreased neutrophil count for greater than 7 days or Grade 4 decreased platelet count on 2 separate days in a 7 day period is observed. CBCs should be checked twice weekly until count recovery has occurred. Bevacizumab and temozolomide may be given if platelets have recovered to ≥ 75,000/μL.

5.2.2 Non-Hematological Toxicities

5.2.2.1
Patients who experience bevacizumab-related toxicities listed in Section 5.3 should follow guidelines delineated in this section.

5.2.2.2
Patients with toxicity attributed to bevacizumab but not listed in Section 5.3 may continue on study provided the toxicity is reversible to eligibility requirements within 14 days after the planned start of the next treatment course.

5.2.2.3

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Patients who have any Grade 3 or 4 non-hematologic toxicity that does not resolve to meet starting criteria by 14 days after the planned start of the next cycle must be removed from protocol therapy. **Please note that patients who experience bevacizumab-related Grade 3 or Grade 4 non-hematological toxicities should follow guidelines delineated in Section 5.3.**

5.3 Bevacizumab Dose Modifications

There will be no dose reductions made for toxicity related to bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described in the table below. If bevacizumab is held and a patient cannot resume treatment before the stipulated time for the particular toxicity, the patient will be taken off protocol therapy.

Table 5.3 Treatment Modification for Bevacizumab-Related Adverse Events

DOSE MODIFICATIONS FOR BEVACIZUMAB RELATED ADVERSE EVENTS

Event	CTCAE v 4.0 Grade	Action to be Taken
Allergic reactions, **Or** **Infusion-related reactions** **OR** **Anaphylaxis**	Grade 1-2	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.) Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab.
Thromboembolic Event (Arterial); arterial ischemia – Cardiac ischemia – Myocardial infarction – CNS ischemia (TIA, CVA) – Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab.

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Event	CTCAE v 4.0 Grade	Action to be Taken
Thromboembolic Event (Venous)	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met: – The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions). – The subject must not have had hemorrhagic events while on study. – The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
	Grade 4 (symptomatic)	Discontinue bevacizumab.
Hypertension* **Use age and height appropriate normal values > 95th percentile ULN for pediatric patients (see Appendices I and II)**	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.]	
	Grade 1 If age ≤ 17 years: Asymptomatic, transient (< 24 hrs) BP increase >ULN; intervention not indicated. If age > 17 years: (SBP 120-139 mmHg or DBP 80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic: If age ≤ 17 years: Recurrent or persistent (≥ 24 hrs) BP > ULN; If age > 17 years: (SBP 140-159 mmHg or DBP 90-99 mm Hg)	If age ≤ 17 years: monotherapy indicated continue bevacizumab. If age > 17 years: Begin anti-hypertensive therapy and continue bevacizumab.
	Grade 2 symptomatic: **OR** Grade 3: (>17 years: SBP >160mmHg or DBP >100mmHg) requiring more than one drug or more intensive therapy than previously (all ages)	• Start or adjust anti-hypertensive therapy • Hold bevacizumab until symptoms resolve **AND** BP < 95th percentile ULN for age and height, if age ≤ 17 years; or BP < 160/90mmHg if age > 17 years.
	Grade 4: (all ages) life threatening (e.g. hypertensive crisis or malignant hypertension)	Discontinue bevacizumab.
Heart Failure or LV dysfunction	Heart failure ≥ grade 2 LV dysfunction ≥ grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis	If 24-h urine protein < 2.0gm	Continue bevacizumab

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Event	CTCAE v 4.0 Grade	Action to be Taken
for urine protein creatinine (UPC) ratio, or dipstick If Dipstick ≥ 2+ proteinuria or UPC ratio ≥ 1, 24 hour urine protein should be obtained	If 24-h urine protein ≥ 2 gm	• Hold bevacizumab until 24-h urine protein < 2 gm. • Discontinue bevacizumab if urine protein does not recover to < 2 after 8 weeks of bevacizumab interruption
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: – the bleeding has resolved and Hb is stable; – there is no bleeding diathesis that would increase the risk of therapy; – there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.
	Grade 2-4	Discontinue bevacizumab.
Hemorrhage (any other organ systems)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: – the bleeding has resolved and Hb is stable; – there is no bleeding diathesis that would increase the risk of therapy; – there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of Grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab.
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN. • Discontinue bevacizumab upon diagnosis of RPLS.
Wound dehiscence requiring medical or surgical intervention or wound complications	Grade 2 Grade 3-4	Hold bevacizumab until healing Discontinue bevacizumab.
Perforation (GI or any other organ)		Discontinue bevacizumab.
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab.

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Event	CTCAE v 4.0 Grade	Action to be Taken
Obstruction of GI tract	Grade 2 requiring medical intervention	• Hold bevacizumab until complete resolution.
	Grade 3-4	• Hold bevacizumab until complete resolution. • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab.

5.3.1 Guidelines for CNS hemorrhage (punctuate lesions)

Definition of punctate hemorrhage identified by neuroimaging:

Punctate hemorrhage on neuroimaging refers to:

1. Small (< 2mm) foci of presumed hemorrhagic signal within the lesion often demonstrated by GRE techniques, without associated mass effect.

2. Curvilinear areas of hemorrhagic signal (< 2 mm thickness) surrounding the lesion, often seen with high grade glial tumors. This would include areas identified only on GRE sequences (presumably related to hemosiderin deposition.

Patients with punctate hemorrhage will be allowed to continue bevacizumab therapy but will be closely monitored for signs and symptoms of worsening hemorrhage. In such an event, repeat neuroimaging studies should be obtained including CT scan of head followed by MRI scan of brain with GRE sequences. Patients with worsening hemorrhage should be taken off bevacizumab. This action would also apply to those who are asymptomatic and are found to have worsening hemorrhage on a subsequent routine MRI scan of the brain.

5.3.2 Surgical procedures

Patients may not have had a planned major surgical procedure (such as resection of recurrent disease) within 28 days of initiating bevacizumab. If major surgery for local control is planned during study therapy for a patient on bevacizumab, then the bevacizumab should be held for one cycle prior and for 28 days post definitive resection, unless the patient has had a significant post-operative wound complication that, in the opinion of the investigator, would preclude bevacizumab administration. In this clinical situation post-operative bevacizumab should be withheld for longer. These restrictions are due to concerns of delayed wound healing and hemorrhage. Minor surgical procedures (e.g., biopsies, vascular catheter placement, G-tube) need to have fully healed and occurred > 7 days prior to initiating bevacizumab.

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6.0 DRUG INFORMATION

Drugs are listed in alphabetical order.

6.1 Bevacizumab

(rhuMAb VEGF, Avastin®) NSC# 704865 [redacted] (11/08/11)

Source and Pharmacology:

Bevacizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab approximate molecular weight is 149,000 daltons. Bevacizumab blocks the binding of VEGF to its receptors resulting in inhibition of angiogenesis.

The estimated half-life of bevacizumab is approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days in 491 patients who received 1 to 20 mg/kg weekly, every 2 weeks, or every 3 weeks. The clearance and the central volume of distribution are higher in males than females. Clearance was higher in those patients with a higher tumor volume.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

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Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr. 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr. 3)***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***
	Colitis		***Colitis (Gr. 3)***
	Constipation		***Constipation (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Dyspepsia		***Dyspepsia (Gr. 2)***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3] (Gr. 2)***
	Gastrointestinal obstruction[4]		
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr. 3)***
	Nausea		***Nausea (Gr. 3)***
	Vomiting		***Vomiting (Gr. 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr. 3)***
	Infusion related reaction		***Infusion related reaction (Gr. 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr. 3)***
	Pain		***Pain (Gr. 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr. 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[7]		***Infection[7] (Gr. 3)***
	Infections and infestations - Other (peri-rectal abscess)		

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INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		***Wound dehiscence (Gr. 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr. 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr. 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr. 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr. 2)***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr. 3)***
	Weight loss		***Weight loss (Gr. 3)***
	White blood cell decreased		***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[8]		
	Myalgia		***Myalgia (Gr. 3)***
	Osteonecrosis of jaw[9]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr. 2)***
	Headache		***Headache (Gr. 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[10]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr. 3)***
	Proteinuria		***Proteinuria (Gr. 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[11]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr. 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr. 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	

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	Cough		***Cough (Gr. 3)***
	Dyspnea		***Dyspnea (Gr. 2)***
	Epistaxis		***Epistaxis (Gr. 3)***
	Hoarseness		***Hoarseness (Gr. 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr. 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr. 2)***
	Urticaria		***Urticaria (Gr. 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr. 3)***
	Thromboembolic event		***Thromboembolic event (Gr. 3)***
		Vascular disorders - Other (arterial thromboembolic event)[12]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[8]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[9]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[10]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

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[11]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.
[12]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

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

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Effect in Pregnancy and Lactation:
Bevacizumab has been shown to be teratogenic in rabbits when administered in doses that are two-fold greater than the recommended human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorption, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Bevacizumab is likely to result in adverse effects on pregnancy. It is not known whether Bevacizumab is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown.

Effect on Growth and Development:
Studies of bevacizumab in animals showed a decrease in ovarian function and abnormal bone growth. These and other effects of bevacizumab may potentially impair growth and development. Abnormal changes in the bones after treatment with bevacizumab have been observed in young children with growing bones. This side effect appeared to be reversible after the treatment was stopped, but has not been assessed with long-term use of the drug.

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Formulation and Stability: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400 mg (25mg/mL, 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Upon receipt, refrigerate the intact bevacizumab vials at 2-8°C (36-46°F). Store in the outer carton to protect bevacizumab vials from light. Do not freeze. Do not shake.

Bevacizumab vials contain no antibacterial preservatives and are labeled for single use. Discard any unused portion left in the vial immediately after use.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
Do not administer as an intravenous (IV) push or bolus. Prior to administration, dilute the dose in 0.9% sodium chloride for injection to a final concentration of 1.4-16.5 mg/mL. Inspecte visually for particulate matter and discoloration prior to administration.

The chemical and physical stability of the diluted solution in 0.9% sodium chloride is 48 hours at 2°C-30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Bevacizumab is incompatible with D5W.

To ensure complete delivery of bevacizumab IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the line:

1. When the bevacizumab infusion is complete, while maintaining a closed system, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.
   Please note: the flush is not included in the total recommended infusion times.

Supplier: Supplied by Genentech and distributed by the NCI DTCD. **Do not use commercially available drug.**

Agent Ordering
NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612. The form can be obtained at http://ctep.cancer.gov/forms/default.htm. For questions about drug orders, transfers, returns, or accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

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Agent Accountability
Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and http://ctep.cancer.gov/forms/default.htm to obtain a copy of the DARF and Clinical Drug Request form.)

Agent Returns
Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/default.htm.

6.2 TEMOZOLOMIDE

(Temodar®, Temodal®) NSC# 362856 (05/10/11)

Source and Pharmacology:
An orally administered alkylating agent, a second generation imidazotetrazine. 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 O^6-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 1.13 hr (intraperitoneally) and 1.29 hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100 mL/min/m^2 and plasma elimination half-life is ~ 100 minutes.

Toxicity:

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

Formulation and Stability: Temozolomide capsules are available in six different strengths (5, 20, 100,

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140, 180, 250 mg). The capsules vary in size, color, and imprint according to strength. In the US, capsules are packaged in 5-count and 14-count bottles. In other countries temozolomide may be packaged in 5-count, 14-count or 20-count bottles. Temozolomide capsules are stored at controlled room temperature.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

There is a potential for medication errors involving temozolomide capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule.

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

Each strength of temozolomide must be dispensed in a separate vial or in its original glass bottle. Based on the dose prescribed, determine the number of each strength of temozolomide capsules needed for the full course as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250-mg capsules, five 20-mg capsules, and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each bottle or vial to equal the total daily dose prescribed by the physician. Institutions that have the capability to dispense temozolomide as daily doses in a blister pack may do so, taking specific precautions to ensure that the appropriate dose is provided and that the patient is educated to understand the daily dosing regimen.

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10mg/mL suspension triturate the contents of ten 100mg capsules (1000mg), 500mg povidone K-30 and 25mg anhydrous citric acid dissolved in 1.5mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension is stable for 7 days at room temperature or 60 days in the refrigerator. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Trissel LA, Yanping Z, Koontz SE. Temozolomide stability in extemporaneously compounded oral suspensions. *Int J Pharm Compounding* 10:396-9, 2006).

Alternatively, the capsules can be opened and mixed with apple sauce or juice (see Appendix VI in the protocol).

Supplier: Commercially available. See package insert for further information.

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6.3 **VORINOSTAT**
(Zolinza®, suberoylanilide hydroxamic acid, SAHA) NSC# 701852, [redacted] (11/02/11)

Source and Pharmacology: Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA), is a histone deacetylase (HDAC) inhibitor. Its chemical name is N-hydroxy-N'-phenyl-octane-1, 8-diotic acid diamide, N-hydroxy-N'-phenyl (9CI) octanediamide. The HDAC enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, such as histones and transcription factors. In some cancer cells, there is an overexpression of HDACs or an abnormal recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription.

Vorinostat inhibits HDAC by binding directly to the catalytic pocket of HDAC1, HDAC2, and HDAC3 (Class I) and HDAC6 (Class II) enzymes. Inhibition of HDAC activity allows for the accumulation of acetylated histones. This accumulation influences the regulation of gene expression. In vitro, exposure of cultured transformed cell to vorinostat led to G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation and demonstrated synergistic and additive activity in combination with other cancer therapies (including radiation, kinase inhibitors, cytotoxic agents, and differentiating agents). The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

After oral administration, vorinostat is rapidly absorbed, however, administration with a high-fat meal resulted in a 33% increase in the extent of absorption and a 2.5-hour delay in the rate of absorption compared to the fasted state. Vorinostat is approximately 71% bound to human plasma protein. It is extensively metabolized to inactive metabolites, primarily by glucuronidation and hydrolysis followed by beta-oxidation. The two metabolites, O-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid are pharmacologically inactive. In vitro studies indicate that vorinostat is not metabolized by and does not inhibit the activity of cytochrome P-450 enzymes. Less than 1% of an administered dose is excreted unchanged in the urine. Approximately 35-52% of an oral dose of vorinostat is excreted in the urine as the two major metabolites. The mean terminal half-life of vorinostat and the O-glucuronide metabolite is approximately 2 hours, while that of the 4-anilino-4-oxobutanoic acid metabolite it is 11 hours.

Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed in patients receiving vorinostat with coumarin-derivative anticoagulants (eg, warfarin). Therefore PT and INR should be monitored when coumarin-dervative anticoagulants are started or discontinued. When vorinostat was administered with other HDAC inhibitors (eg, valproic acid), severe thrombocytopenia and gastrointestinal bleeding have been reported.

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Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Vorinostat (SAHA, NSC 701852)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 702 patients.* Below is the CAEPR for vorinostat (SAHA).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, October 18, 2011[1]

Adverse Events with Possible Relationship to Vorinostat (SAHA) (CTCAE 4.0 Term) [n= 702]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea Vomiting			***Nausea (Gr 2)*** ***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***

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	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypoalbuminemia		
	Hypocalcemia		
	Hypokalemia		
	Hyponatremia		
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Muscle weakness[3]		***Muscle weakness[3] (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Skin and subcutaneous tissue disorders - Other (skin necrosis)	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

[4]Prolongation of prothrombin time and International Normalized Ratio have been observed in patients using vorinostat concomitantly with coumarin-derivative anticoagulants.

Also reported on vorinostat (SAHA) trials but with the relationship to vorinostat (SAHA) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular fibrillation
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis;

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Gingival pain; Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (angioedema); General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Herpes zoster)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Vascular access complication; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged[4]; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased[4]; Investigations - Other (elevated LDH); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypoglycemia; Hypomagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Chest wall pain; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysphasia; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (head injury); Nervous system disorders - Other (polyneuropathy); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Uterine hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Nasal congestion; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (arterial thrombosis); Vasculitis

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

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to vorinostat is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Effect in pregnancy: Vorinostat is **Pregnancy Category D**. It may cause fetal harm when administered to a pregnant woman. Adequate contraception must be used by all patients (both male and female) and their partners during therapy with vorinostat and for 30 days after the completion of study drug administration.

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Formulation and Stability: Vorinostat is supplied as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat. The inactive ingredients in each capsule include microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Vorinostat 100 mg capsules are supplied in bottles containing 120 capsules.

Store vorinostat capsules at room temperature, 15 to 30ºC (59 to 86ºF). Do not store above 30ºC and avoid exposure to excessive moisture.

A formulation for compounding vorinostat suspension by the pharmacy is provided below:

Ingredients:

Vorinostat 100 mg capsules	20 capsules
OraPlus or Suspensol S	20 mL
OraSweet	20 mL

Instructions:
Add 20 mL of Suspensol S or OraPlus into an amber or clear glass 4 ounce bottle. Place the contents of 20 capsules of vorinostat 100 mg into the same bottle and shake to disperse. Shaking may take up to 3 minutes. Once dispersed, add 20 mL of OraSweet to achieve a total volume of 40 mL. Shake again to disperse. The final concentration is 50 mg/mL. Store at room temperature. The suspension is stable for 2 weeks.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
Vorinostat should be taken with food. The capsules should not be opened or crushed. A suspension can be prepared by the pharmacy for patients that cannot swallow (see Formulation and Stability section above).

If a patient needs less than 120 capsules for a treatment cycle, the exact number of capsules needed for treatment can be counted into a prescription bottle.

Direct contact of the powder in vorinostat capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. Clean powder spills from broken or damaged vorinostat capsules carefully minimizing inhalation. Wash spill area at least 3 times with ethyl alcohol, followed by water.

Supplier: Supplied by Merck Research Laboratories and distributed by the NCI DTCD. **Do not use commercially available drug.**

Agent Ordering
NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612. The form can be obtained at http://ctep.cancer.gov/forms/default.htm. For questions about drug orders, transfers, returns, or

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accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

Agent Returns

Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/forms/returns-03.pdf. The appropriate forms may be obtained at: http://ctep.cancer.org

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7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

7.1 Required Clinical, Laboratory and Disease Evaluations

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Obtain prior to start of phase unless otherwise indicated.

Observation	Baseline	During ChemoRT	During Maintenance Therapy	At Time of Progression	At Completion of Therapy
History	X	Weeks 1 and 7	Prior to each cycle	X	
Physical Exam (Ht, Wt, BSA, VS[including BP])	X	Weeks 1 and 7 BP prior to each dose of bevacizumab	Prior to each cycle; BP prior to each dose of bevacizumab	X	
Performance Status	X	Weeks 1 and 7	Prior to each cycle		
CBC (differential, platelets)	X	Weekly	Prior to each bevacizumab dose		X[1]
PT INR	X				
Electrolytes (including Ca++, PO_4, Mg++)	X	Weekly	Prior to each cycle		
BUN, Creatinine	X	Weekly	Prior to each cycle		X[1]
AST, ALT, bilirubin	X	Weekly	Prior to each cycle		X[1]
Urinalysis for dipstick or protein and urine protein creatinine (UPC) ratio	X[10]	Weekly Arm C	Prior to each cycle[7]		
Total protein/albumin	X				
MRI of brain with and without gadolinium[8]	X[5]		Prior to each odd number cycle	X[4]	X[2]
MRI of spine with gadolinium[8]	X[3]		Prior to each odd number cycle[3]	X[3]	
Pregnancy Test (for females of childbearing potential)	X				
Required Specimens for Pathology Central Review (see Section 15.0)			Prior to first cycle		
Growth Plate Evaluation X-ray of right knee[6]	X		End of Cycles 3, 6, 9, 12		
Optional Biology and Imaging (See Section 16.0)	X		X[9]		X

1. Obtain on Day 28 of maintenance cycle 12. Repeat weekly until results are normal.
2. Obtain 3-4 weeks following the final bevacizumab+temozolomide administration on Cycle 12.
3. Obtain if patient has spinal primary or if clinically indicated. If positive for neuraxis dissemination (development of metastatic disease), then patient is ineligible.
4. Because of the high incidence of disseminated disease at the time of relapse, spinal MRIs are encouraged.
5. Obtain brain pre-op MRI and baseline post-op MRI both with and without gadolinium. Post-op MRI must be done within 4 weeks prior to starting treatment. Post-op MRI is not required if the patient underwent biopsy only.
6. Obtain pre-treatment tibial x-ray (AP and lateral views) of the right knee in patients who have not yet obtained full adult height and to be repeated every 12 weeks during Maintenance. If abnormalities are detected on routine X-rays following treatment, MRI scan of both knees should be performed and a consultation with an orthopedic surgeon is recommended. However, no dose modifications will be made for bevacizumab.

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7. If urine dipstick is 2+ or greater from protein, hold bevacizumab and obtain UPC ratio within 3 days of Day 1 dose of bevacizumab. See bevacizumab dose modifications for proteinuria (Section 5.3). If UPC ratio is ≥ 1, 24 hour urine protein should be obtained.
8 Gradient echo imaging by MRI must be used to further assess and follow-up any occurrence of symptomatic ITH initially detected by MRI. Any positive gradient echo imaging should be repeated weekly until demonstration of stable or decreasing signal abnormalities consistent with hemorrhage is achieved.
9. Obtain prior to starting Maintenance and prior to Cycle 3.
10. Urine protein should be screened by urine analysis. If 2+ on urinalysis, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg for patient enrollment. See note above regarding calculation of UPC ratio.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 Optional Biology and Imaging Studies

The following optional biology and imaging studies are to be obtained from patients providing consent for these studies.

STUDIES TO BE OBTAINED	Baseline	Prior to Maintenance Therapy	Prior to Cycle 3 of Maintenance Therapy	Upon Completion of Maintenance therapy
Biology				
Telomerase activity, *hTERT* expression, *hTERC* and telomere length	X			
Gene expression and miRNA profiling	X			
Genome Allelotype and SNP Arrays	X			
MGMT and other markers	X			
Imaging				
MR perfusion and diffusion imaging[1]	X	X	X	X

1. Optional imaging studies will be performed only in patients with evidence of residual tumor on the MRI performed to determine extent of resection prior to start of therapy.

See Section 16.0 for details of optional biology specimen collection and shipping. See Section 16.8 for details of optional imaging studies to be obtained.

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7.3 **Follow-up**

See COG Late Effects Guidelines for recommended post treatment follow-up at http://www.childrensoncologygroup.org/disc/LE/default.htm.

The following studies are recommended until the patient is off study as defined in Section 8.2.

7.3.1 Recommended 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	4 Years	Annually 5 to 10 Years	At Relapse
History, Physical Exam incl. Ht, Wt, BSA, VS (inc. BP)	X	X	X	X	X	X	X	X	X	X	X	X
MRI of Brain with and without gadolinium	X	X	X	X	X	X	X	X	X	X	X	X
MRI of the Spine with gadolinium	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X*

[1] Obtain if patient has spinal primary or if clinically indicated.
* Spinal MRIs with gadolinium performed due to the high incidence of disseminated disease at the time of relapse.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

See COG Late Effects Guidelines for recommended post treatment follow-up http://www.childrensoncologygroup.org/disc/LE/default.htm

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 **Criteria for Removal From Protocol Therapy**

a) Progressive disease (see Section 10.4).
b) Development of unacceptable toxicity as outlined in Section 4.3 for the feasibility phase of study and as outlined in Section 5.0 for phases II and III of study.
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of planned therapy.
e) Physician determines it is in patient's best interest.
g) Development of a second malignancy.
h) Patient becomes pregnant/breatfeeding while on study.

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 unless consent was withdrawn.

8.2 **Off Study Criteria**

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) The tenth anniversary the date the patient was enrolled on this study.

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9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

This is a study for patients with newly diagnosed high-grade gliomas. Patients will be treated with local irradiation with a particular radiosensitizer, followed by maintenance chemotherapy with bevacizumab and temozolomide. The study has a feasibility part to obtain the MTD of vorinostat when given concurrently with RT. Upon its successful completion, the study will open to the Phase II part where patients will be randomized to receive concurrent radiation with 1 of the 3 radiosensitizers: vorinostat, bevacizumab, or temozolomide, and maintenance chemotherapy with bevacizumab and temozolomide. In the Phase II part, temozolomide is considered the control treatment; vorinostat and bevacizumab are considered experimental treatments. If at least one of the experimental treatments has a higher 1-year EFS than temozolomide in the Phase II part, the Phase III part of the study will open and the experimental treatment with a higher 1-year EFS between the 2 experimental treatments will be chosen for Phase III. Phase III of the study will formally compare the experimental treatment identified in Phase II to treatment with temozolomide. For the Phase II/III parts, randomization will be stratified by extent of resection (near total resection or gross total resection vs. other) and histology (glioblastoma multiforme vs. other). More details on each part of the study are discussed below.

The feasibility part will enroll 6 patients at 230 mg/m^2/dose with daily RT. If there are fewer than 2 patients with DLTs, we will declare this dose of vorinostat as the recommended Phase II dose to be used with RT. If we have 2 or more DLT in this cohort of 6 patients, we would then dose de-escalate to 180 mg/m^2 and open the cohort to 3 patients at this dose level. If 0 or 1 of the 3 patients has a DLT, we will expand this cohort by adding 3 additional patients. If fewer than 2 of the 6 patients have a DLT, this dose level (180 mg/m^2) will be declared as the recommended Phase II dose. If 2 or more of the 6 patients at 180 mg/m^2 have a DLT, the study will be amended. The probability that a dose level will be considered tolerable (ie, 0 or 1 DLT among 6 patients) is 0.89, 0.66, 0.42, or 0.23 if the true rate of DLT at that dose level is 10%, 20%, 30%, or 40%, respectively.

Upon successful completion of the feasibility part, the study will open for the Phase II part, with 108 patients randomized to one of the three treatments (36 patients per arm): vorinostat, bevacizumab, or temozolomide. At the end of the Phase II part, if neither of the 2 experimental arms has a 1-year EFS rate that is higher than that of the temozolomide arm, the study will be closed. If 1 of the 2 experimental arms has a 1-year EFS rate that is higher than that of the temozolomide arm, the study will continue to the Phase III part and this experimental arm will be chosen for comparison with temozolomide in the Phase III part of the study. If both experimental arms have a higher 1-year EFS rate than that of the temozolomide arm, the experimental treatment with the higher 1-year EFS rate will be chosen for further comparison with temozolomide. If the study continues to the Phase III part, patients will be randomized between 2 arms: one control arm (temozolomide) and one experimental arm. In the Phase III part, accrual will continue until 64 additional patients are randomized to each of the 2 arms. The final Phase III comparison will include patients randomized to the 2 arms in both the Phase II part and Phase III part of the study.

9.2 Patient Accrual and Expected Duration of Trial

Recent COG studies of patients with newly diagnosed high-grade gliomas (HGG) include ACNS0126 and ACNS0423. ACNS0126 accrued 99 eligible HGG patients between December 2002 and October 2004, with an average accrual rate of 54 patients per year. ACNS0423 accrued 107 eligible HGG patients between March 2005 and August 2007; the average accrual rate after the first 6 months was also about 54 patients per year. Therefore, the estimated annual accrual for the current study is 54 patients.

The feasibility part of the study will accrue 6-12 eligible patients. Given the overall annual accrual rate estimate of 54 patients, accruing 6-12 patients should take less than 6 months. Consider the 8 weeks

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evaluation period after the first 6 patients, or also after the first 9 and 12 patients, the complete duration for the feasibility part is expected to be about 12 months. The Phase II part of the study will accrue 108 eligible patients which is expected to take about 2 years. One year of additional follow-up will be needed to evaluate the Phase II outcome. If the study opens to the Phase III part, we will accrue an additional 128 eligible patients, which is expected to take about 2.4 years. Therefore, the total accrual duration (only the time when the study is open to accrual), if the study continues to the Phase III part, will be about 5 years. The total study duration from study activation until the end of accrual (including evaluation periods for the feasibility/II parts), is expected to be about 6.5 years. A minimal 1-year of additional follow-up is planned before the final Phase III analysis can be performed.

Of the 118 patients enrolled on the previous HGG study ACNS0423, 12 (10%) were deemed ineligible. As of Amendment #1, the accrual for the feasibility part of the study was 6 patients and all were eligible. Considering a 10% rate of ineligible enrollment on this study, the total accrual for Phase II may be up to 120 patients and the total accrual for Phase III may be up to 142 patients.

9.3 Statistical Analysis Methods

9.3.1 Endpoints

Safety and feasibility endpoints:

- Feasibility part: DLT for vorinostat, when given concurrently with RT.
- Phase II: toxic death, individual toxicities especially Grade 3 or 4 hemorrhage, significant delay (> 2 weeks) in the completion of RT, and significant delay (> 2 weeks) in the start of any course of maintenance therapy.
- Phase III: toxic death, individual toxicities especially Grade 3 or 4 hemorrhage

Efficacy endpoints for Phase II/III:

- Event-free survival (EFS), defined as time to the first occurrence of any of the following events: disease progression, relapse, second malignant neoplasm, or death from any cause.
- Overall survival (OS), defined as time to death from any cause.
- Progression-free survival (PFS), defined as time to the occurrence of disease progression or recurrence.

9.3.2 Power Considerations for Phase II/III

In the Phase II part of the study, patients are randomized to 1 of the 3 arms: 1 control arm (temozolomide) and 2 experimental arms (vorinostat, bevacizumab). At the end of the Phase II part, the experimental treatment with a higher 1-year EFS rate among the 2 experimental arms, if its 1-year EFS is also higher than that of the temozolomide arm, will be chosen for further comparison with temozolomide in the Phase III part. If temozolomide arm has the highest 1-year EFS among the 3 arms, the study will be closed. We use 1-year EFS as the main endpoint for the Phase II part because, in this study, tumor response and shorter-term EFS are not considered good indicators of treatment effect.

ACNS0126 and ACNS0423 both used temozolomide and concurrent radiation therapy to treat patients with newly diagnosed high-grade gliomas. The maintenance therapies used in these 2 studies and in the current study are all different. Based on November 2008 data, the observed 1-year EFS (±SE) on ACNS0126 is 39% ± 5%; the observed 1-year EFS (±SE) on ACNS0423 is 49% ± 5%. Given these data, for power considerations we assume a 1-year EFS rate of 45% for the temozolomide arm (control arm) on this study. For the Phase III part of the study which will compare the overall EFS curves for the 2 arms, we assume a long-term EFS rate of 15% for the temozolomide arm, based on limited long-term data on ACNS0126 and long-term outcome data on an earlier high-grade glioma protocol CCG 945.

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Between the 2 experimental arms, we use arm 1 to denote the arm with the better EFS in truth and arm 2 to denote the other. Below we discuss the probability of selecting arm 1 after the Phase II part and the probability of establishing its superiority in EFS over temozolomide at the end of the Phase III part. Obviously such probabilities depend on the true EFS of arm 1 and that of temozolomide arm. However, since the design only picks the better performer of the 2 experimental arms from the Phase II part, 1-year EFS for arm 2 will also influence the probability of selecting arm 1 after the Phase II part, and in term affect the probability of establishing the superiority of arm 1 over temozolomide at the end of the Phase III part.

In the table below, the selection probabilities for arm 1 and arm 2 after the Phase II part are presented in columns 2 and 3. For example, if the 1-year EFS rates for arm 1 and arm 2 are 60% and 40% respectively, the probability that the study will continue to the Phase III part with arm 1 is 0.85. On the other hand, if the 1-year EFS rate for arm 1 is 60% but the 1-year EFS rate for arm 2 is 55%, the probability of selecting arm 1 is reduced to 0.63, because under this scenario the chance of selecting arm 2 increases even though arm 1 is still better than arm 2 in truth. The probability of the study not continuing on to the Phase III part, meaning that neither of the 2 experimental arms has a 1-year EFS rate that is higher than that of the temozolomide arm, is one minus the probabilities in column 2 and column 3. In these scenarios, the 1-year EFS of arm 1 needs to be at least 60% compared to 45% in temozolomide arm for arm 1 to have a decent probability of being selected for the Phase III part. The probability of selecting arm 1 decreases with increasing 1-year EFS in arm 2.

Table 1: Probability of selection (after Phase II) and that of establishing superiority to temozolomide (after Phase III) for each experimental arm

Scenarios	Phase II** Selection Probability		Overall Phase III*** Success Probability	
	arm 1	arm 2	arm 1	arm 2
arm 1 = 65%*				
arm 2 = 60%	0.66	0.32	0.65	0.30
arm 2 = 55%	0.78	0.18	0.77	0.13
arm 2 = 50%	0.88	0.09	0.86	0.03
arm 2 = 45%	0.91	0.04	0.90	0.01
arm 2 = 40%	0.94	0.01	0.92	<0.01
arm 1 = 60%*				
arm 2 = 55%	0.63	0.31	0.57	0.21
arm 2 = 50%	0.74	0.17	0.66	0.07
arm 2 = 45%	0.81	0.08	0.73	0.01
arm 2 = 40%	0.85	0.03	0.76	<0.01
arm 1 = 45%*				
arm 2 = 45%	0.31	0.31	0.03	0.03
arm 2 = 40%	0.38	0.17	0.04	<0.01

*Temozolomide arm is the control arm, with 45% 1-year EFS.
**36 patients in each of the 3 arms.
***100 patients in each of the 2 arms including the 36 patients from the Phase II part.

Note that an experimental arm is only chosen for further study in the Phase III part if its 1-year EFS rate is higher than that of the temozolomide arm; if its outcome equals that of the temozolomide arm, it will

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not be chosen. In these calculations, for the rare situation where the 1-year EFS is the same for the 2 experimental arms and better than that of the temozolomide arm, half of that probability is added to the selection probability of arm 1 and half to that of arm 2. This simple approach means that, in the event of such a "tie", we will randomly pick one experimental arm for further study. However, we will most likely consider other factors, such as toxicity profiles, for tie-breaking if such a tie occurs. The probabilities of such a tie are so rare that they have little impact on the results presented above.

For the Phase III part, a log rank test will be performed to compare the EFS between the 2 arms (100 patients each) after a minimal of 1 year of additional follow-up at a 1-sided alpha level of 0.05. However, for this study, the traditional power and size for this test between the chosen experimental arm and the temozolomide arm cannot be easily defined. This is because the occurrence of the Phase III part depends on the outcomes in the Phase II part which also involves the non-chosen experimental arm. In addition, the Phase II patients are included in the Phase III comparison; their early outcomes (1-year EFS) are already observed and have to occur in a particular direction (experimental arm higher than temozolomide) for the Phase III part to happen.

In column 4 and 5 of Table 1, we illustrate the overall probability of establishing a significantly better outcome for arm 1 (or arm 2) at the end of the Phase III with the specified log rank test in the current study design. For example, the success rate for arm 1 (with 60% 1-year EFS) ranges from 0.57- 0.76 if arm 2 has a 1-year EFS that is between 55% and 40%. The probability presented is the overall probability for a particular arm before the inception of the Phase II/III part, so is not conditional on the arm being chosen for Phase III. Note that if this is a standard Phase III comparison with the same sample size and other parameters, the power for the comparison between arm 1 and the temozolomide arm will be about 0.84. Here, the reduction in "power" is because arm 1, though the best of the 3 in truth, is not always chosen after the Phase II part, which reduces its overall success probability. Comparing column 2 and column 4, one can see that if arm 1 is truly the best of the 3 and "wins" in the Phase II part, the conditional probability of its overall success given the Phase II success and Phase II outcome will be quite high. In Table 1, selection probabilities for the Phase II part are computed by exact binomial probabilities. The overall success rates for the final Phase III comparison are estimated from simulation studies because the log rank test compares the entire EFS curve rather than just 1-year EFS. To carry out the simulations, additional assumptions need to be made on the failure patterns of the patients. Event-free survival curves are approximated by cure models where a proportion of the patients become long-term survivors and failures for the remaining patients follow an exponential pattern. The temozolomide arm is assumed to have 45% 1-year EFS and 15% long-term EFS. The whole EFS curve under the cure model with exponential failure is fully specified by EFS rates at these 2 time points. The differences in event free survival between the temozolomide arm and the experimental arm are assumed to be the same at 1 year and at long term, which then specify the whole EFS curves for the experimental arms.

9.4 Interim Monitoring

9.4.1 Monitoring for Toxic Death and Grade 3 or 4 Hemorrhage

During the Phase II part of the study, we will monitor the rate of toxic death and that of Grade 3 or 4 hemorrhage separately for each arm during RT. In ACNS0126, among 99 patients there were 2 deaths within 1 month on study, which are considered slightly attributable to the treatment. In ACNS0423, all 7 deaths which occurred during treatment or within 31 days after treatment are considered due to disease progression. Two incidences of Grade 3 or 4 hemorrhage were reported among 105 patients during chemoradiotherapy on ACNS0423. Based on these data, for the current study we consider 2% the maximum tolerable rate for both toxic death and for Grade 3 or 4 hemorrhage. For each arm, we will accept at most 2 toxic deaths or 2 incidences of Grade 3 or 4 hemorrhage among the 36 patients. The monitoring rule will be triggered 3.5%, 37%, 56%, or 82% of the time if the true incidence is 2%, 6%, 8%, or 12%, respectively. We will also monitor toxic death rate and Grade 3 or higher hemorrhage rate

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separately during maintenance therapy for patients from all 3 arms combined, since they all receive the same maintenance therapy. The rule for maintenance therapy will be triggered if at least 4/54, 6/108 patients experience toxic death/hemorrhage; it is satisfied 4% of the time if the true incidence is 2%, and 80% of the time when the true incidence is 7%.

If the study opens to the Phase III part, the rate for toxic death and that for Grade 3 or 4 hemorrhage during chemoradiotherapy will be also examined for each arm. Among the 100 patients on each arm (temozolomide arm and the chosen experimental arm), we can accept at most 4 incidences for toxic deaths or for Grade 3 or 4 hemorrhage. The chance that the combined rule for Phase II/III (≥3/36, ≥5/100) will be satisfied is 7% if the true incidence is 2%, and is 85% if the true incidence is 7%. The rate of toxic death and that for Grade 3 or 4 hemorrhage during the common maintenance will also be examined by including all patients treated on Phase II or Phase III parts. We will consider the rate for toxic death or that for Grade 3 or 4 hemorrhage unacceptable if we observe 9 or more incidences among the 236 Phase II/III patients. The combined rule (≥4/54, ≥ 6/108, ≥ 9/236) will be satisfied 7% of the time if the true incidence is 2%; it will be met 85% of the time when the true incidence is 5%.

When a safety monitoring rule is met, the study accrual will be temporarily suspended. The study committee will perform a careful review of the toxicity incidences, and report the results and study committee recommendation such as accrual suspension or therapy modification for the involved arm to the DSMC. DSMC also may make other recommendations based on their review of the toxicity and safety data at any time.

9.4.2 Monitoring for Feasibility of Each Radiosensitizer and Common Maintenance Chemotherapy

During the Phase II part of the study, the feasibility of each radiosensitizer and the common maintenance therapy will be examined via the incidence of significant delay (> 2 weeks) in the completion of RT and the incidence of significant delay (> 2 weeks) in the start of any course of maintenance (among total courses combining all 3 arms). A review of treatment feasibility and patient safety will be undertaken when we observe > 10% significant delays in the completion of RT specifically if we observe at least 5/18 or 8/36 significant delays. The rule will be met about 4% of the time if the true incidence of delay is 10%, and 90% of the time if the true incidence is 30%. Because the number of total maintenance courses cannot be easily estimated (as patients may not all complete 12 courses), it is not feasible to specify the set of statistics-based boundaries for monitoring delays in maintenance therapy. The monitoring will be based on the marginal incidence of significant delay in the start of any course of maintenance observed at each interim report. Similar review will be undertaken if the rate of delays during maintenance exceeds 10%.

9.4.3 Efficacy monitoring

At the end of the Phase II part, interim comparisons of EFS by log rank test will be performed to evaluate whether there is early compelling evidence of improvement in EFS in either experimental arm compared to the control arm. The monitoring boundary will be based on Lan-Demet's method with spending function αt^2. If there is significant evidence of efficacy for either experimental arm compared to the control arm, the study will be referred to DSMC for consideration of early closure after the Phase II part due to efficacy. If the study continues to the Phase III part, an interim comparison of EFS by log rank test between the chosen experimental arm and the control arm will be performed approximately halfway through the Phase III enrollments and will be based on Lan-Demet's method with spending function αt^2. In addition, during Phase II/III, for each interim Data and Safety Monitoring Committee (DSMC) report, outcome of the current study participants will be compared to historical data on ACNS0126 and ACNS0423. This informal monitoring aims to compare outcome of patients who received maintenance therapy with bevacizumab to patients who did not receive maintenance therapy with bevacizumab. Since such comparison is not an aim of the study, we will not employ any formal monitoring rules; if, in an

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interim analysis, the outcome of the current study is significantly worse than those of the prior studies (with a p value of < 0.05), the issue will be brought to the DSMC for their attention and evaluation.

9.5 Analysis Plans

9.5.1 Analysis plans for the primary aims of Phase II/III

We will estimate event-free survival (EFS) for patients on each arm by Kaplan-Meier product-limit method. After the Phase II part, the experimental arm with a higher nominal 1-year EFS will be chosen for further study in the phase III part if its 1-year EFS rate is also higher than that of the temozolomide arm. If the study opens to the Phase III part, Kaplan-Meier curves will be used to estimate EFS of the 2 arms combining all patients randomized to the regimen during the Phase II and the Phase III parts. The primary analysis will be based on a log rank test that compares the EFS between the chosen experimental arm and the temozolomide arm; the cutoff value for the Z-statistics will be 1.64.

9.5.2 Analysis plans for Phase II/III secondary aim

Event-free survival (EFS), overall survival (OS), and progression-free survival (PFS) will be calculated for patients treated with each radiosensitizer by Kaplan-Meier estimates. Log rank tests will be used to compare these survival outcomes between different treatment groups on the current study. Similar log rank analyses will be performed to compare outcomes for patients treated on the current study to those for HGG patients treated on previous COG protocols (ACNS0126 and ACNS0423); in particular, outcomes for patients on Arm B (temozolomide) will be compared to that for HGG patients on ACNS0126 and ACNS0423 to isolate contribution of bevacizumab plus temozolomide maintenance therapy versus single agent temozolomide maintenance therapy and temozolomide plus lomustine maintenance therapy, respectively. Incidence of individual toxicities will be estimated for each chemoradiotherapy arm and for maintenance chemotherapy.

9.5.3 Analysis plans for laboratory and imaging aims

Descriptive statistics will be used to summarize the biological/laboratory/imaging measures for the study, including telomerase activity, hTert expression, telomere length, MGMT promoter methylation status, MGMT protein expression, and various measures in MR perfusion and diffusion from MR imaging. Changes in these measures across time-points (baseline, prior to maintenance therapy, prior to cycle 3 and after maintenance therapy) will be summarized similarly, using descriptive statistics on the measures that are collected at multiple time points. Mean and standard deviation will be used to summarize continuous measures; log transformation of a continuous measure may be considered when appropriate. Categorical measures will be described by percentage distribution of the categories; in the case of binary measures a 95% CI will be estimated. SNP analysis and gene expression and microRNA analysis will be carried out using Affymetrix software, and dChip or GCOS software respectively. Exploratory analyses to correlate a particular biological/laboratory/imaging characteristic with survival outcomes might be performed. Log rank tests will be used to explore the prognostic significance of a categorical factor on EFS, OS or PFS. Cox proportional hazards models will be used to explore the effect of a continuous marker on survival outcomes, and will be used for exploratory multivariate analysis examining the effect of the characteristic of interest with adjustments for other patient or treatment characteristics. The power of such exploratory analyses examining the association of a laboratory or imaging characteristics with survival outcomes depend on many factors: 1) total sample size of the study (whether the study goes to Phase III); 2) the portion of patients that participate in the particular optional study; 3) the proportion of patients possessing the high risk characteristics (assuming a simple comparison based on a binary risk factor); 4) the survival outcomes in the high-risk group and in the low-risk group. Therefore, it is difficult to prospectively estimate the power characteristics for individual biology analysis and these analyses are exploratory in nature.

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9.6 Gender and Ethnicity Considerations

Review of outcome data from previous COG 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.

9.7 Gender and Minority Accrual Estimates

The target for the feasibility part of the study was 6-12 eligible patients. As of Amendment #1, the accrual for the feasibility part of the study has been completed and was 6 patients and all were eligible. The expected accrual for the Phase II and Phase III parts of the study are 108 eligible patients and 128 eligible patients, respectively. The accrual target on the study, therefore, is 242 eligible patients. Considering a 10% ineligibility rate for Phase II and Phase III, the maximum enrollment for this study may be up to 268 patients in order to assure that the required number of eligible patients are enrolled.

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	11	9	20
Not Hispanic or Latino	111	137	248
Ethnic Category: Total of all subjects	122	146	268
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	6	5	11
Black or African American	16	9	25
Native Hawaiian or other Pacific Islander	2	0	2
White	98	132	230
Racial Category: Total of all subjects	122	146	268

This distribution was derived from the recent COG study ACNS0423 for patients with newly diagnosed high-grade gliomas.

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10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

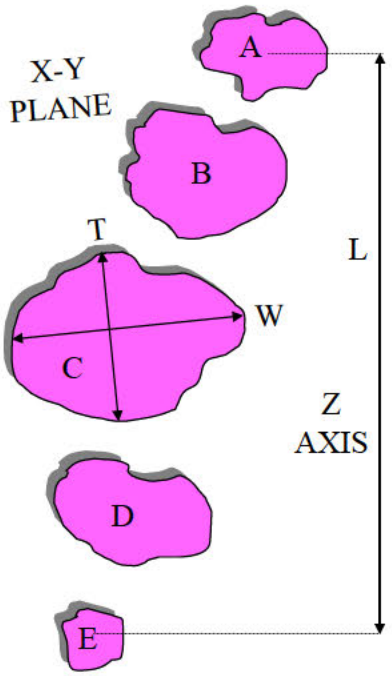
This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Additionally, toxicities are to be reported on the appropriate data collection forms.

10.2 Methodology to Determine Tumor Measurement

Tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular for each target lesion. Regarding MRI imaging, the radiologist may select whatever sequence best highlights the tumor (T1 enhanced or T2 weighted or FLAIR images) and the same sequence should be used for serial measurements. Response determination will be based on a comparison of an area (W x T – see below) between the baseline assessment and the study date designated in the follow-up Report Form. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described.

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. Either T1 or T2 weighted images are used - 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. This longest measurement of the tumor is referred to as the width (W).
2. The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in 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

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RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST) AND PRODUCT OF TWO DIAMETERS (WHO)
(Modified from Appendix II, Table 2, JNCI 92:213, 2000)

Response	Diameter, 2R Decrease	Product, $(2R)^2$ Decrease
	30%	50%
	50%	75%
Disease Progression	**Increase**	**Increase**
	12%	25%
	20%	44%
	25%	56%
	30%	69%

3. The cystic or necrotic components of a tumor are <u>not</u> 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 and T 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
4. 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 and change in extent/thickness assessed on follow up studies. **Note that patients with leptomeningeal disease are not eligible for enrollment on this study.**
5. 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	CR, IR/SD	No	**PR**
SD	CR, IR/SD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease
IR – Incomplete Response

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

10.3 **Selection of Target and Non-Target Lesions**

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. **Note that patients with M+ disease are not eligible for enrollment on this study.**
2. If multiple measurable lesions are present, up to 3 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions (including CSF positive for tumor cells).
3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).
4. Any change in size of non-target lesions should be noted, though does not need to be measured.

10.4 **Response Criteria for Target Lesions**

1. Response criteria are assessed in 2 dimensions – the product of W x T.
2. To assess response/progression, the ratio is calculated:
   $\frac{W \times T \text{ (current scan)}}{W \times T \text{ (reference scan)}}$
3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence.
4. Response Criteria for target lesions:

Complete Response (CR): Disappearance of all target lesions.
Partial response (PR): ≥ 50% decrease in the sum of the products of the two perpendicular diameters of target lesions, compared to baseline measurement.
Stable Disease (SD): Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): ≥ 25% increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment (see exception below); OR the appearance of one or more new lesions, OR worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, presumed post-therapy swelling etc) PLUS any increase in tumor cross-sectional area (or tumor volume).

However, because radiotherapy may be associated with transient, reversible swelling during or within the first 3 months after completion of RT, there may be a lag time between the initiation of therapy and maximal anti-tumor effect. Removing a patient from protocol therapy as soon as tumor area increases by 25% may result in the treatment being terminated prematurely. It is quite possible that if these patients were maintained on protocol therapy, their disease might eventually stabilize and even regress.

Therefore, patients will not be considered to have progressive disease and will not be removed from protocol therapy for radiographic worsening secondary to local tumor enlargement (LTE), defined as increase in maximal bi-dimensional tumor area of 25% or more but less than 50%, and with no

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new lesions on any MRI performed within 3 months from completion of RT (i.e. on the required MRI 4 weeks after completing RT, or the scan performed prior to cycle 3 of the maintenance). Thus, during and for 3 months after completion of RT, patients should only be removed from protocol therapy for progressive disease if there is 50% or more increase in tumor area (with or without neurological worsening), OR if there is the appearance of one or more new lesions on the MRI **outside** the radiation port.

The criteria for progressive disease as defined above will commence with the required brain MRI scans done more than 3 months after completion of RT (i.e. prior to cycle 5 of therapy, or scans done for suspected progression more that 3 months after completion of RT). Patients whose tumors meet these criteria will be removed from protocol therapy.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

10.5 Response Criteria for Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions.
Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.
Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

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Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the CTEP Version 4.0 of the NCI Common Terminology Criteria (CTCAE).* The CTEP version of the CTCAE v4.0 provides descriptive terminology and a grading scale for each adverse event listed. The CTEP version of the CTCAE version 4.0 is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm**).** All appropriate treatment locations should have access to a copy of the CTEP CTCAE v4.0.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.*

Expected **events for a CTEP IND agent are defined as those listed in the ASAEL** (Agent Specific Adverse Event List), a subset of the CAEPR (Comprehensive Adverse Event and Potential Risks). For investigational agents that are not commercially available and are being studied under a company's IND, expected AEs are usually based on the Investigator's Brochure.

Unexpected **events for a CTEP IND agent are defined as those NOT listed in the ASAEL.**

Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

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11.4 **Reporting method**

- Use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov.

An AdEERS report must be submitted by the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm,

- Fax supporting documentation **for AEs related to investigational agents** to:
  - The NCI for agents supplied under a CTEP IND **only** (fax # 301-230-0159).
  - and to COG for **all** IND studies (fax # 626-241-1795; attention: COG AE Coordinator).

- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI.** Fax this material to COG (fax # 626-241-1795; attention: COG AE Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.5 **When to report an event in an expedited manner**

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web based application **and/or by telephone call to the Study Chair.**

  In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497. In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic AdEERS system by the original submitter of the report at the site.

- Submit the report **within 5 calendar days** of learning of the event.

11.6 **Other recipients of adverse event reports**

COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

11.7 **Reporting of Adverse Events for investigational agents – AdEERS 24-hour notifications, and complete report requirements.**

Reporting requirements are provided in Table A. **The investigational agents used in this study are bevacizumab [redacted] and vorinostat [redacted]**

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Table A

Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3[3]		Grades 4 & 5[2]	Grades 4[3] & 5[2]
	Unexpected and Expected	Unex-pected	Expected	Unexpected with Hospitali-zation	Unexpected without Hospitali-zation	Expected with Hospitali-zation	Expected without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	**24-Hour**; 5 Calendar Days	5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in Non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

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

3 Please see exceptions below under section entitled "Additional Instructions or Exceptions."

March 2005

Note: **All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.**

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete AdEERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

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- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the AdEERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:

- **Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via AdEERS for an agent under a CTEP IND [and via AdEERS for non-CTEP IND agent] per the timelines outlined in the table above.**

- **Grades 1- 4 myelosuppression do not require expedited reporting unless unexpected.**

- As of August 25, 2010 all secondary malignancies should be reported via AdEERS

- **The following SAEs will be exempted from expedited reporting through AdEERS**
  - G3-4 Decreased neutrophil count/febrile neutropenia, regardless of hospitalization
  - G3-4 Diarrhea, Nausea, Vomiting, or Dehydration, regardless of hospitalization

11.8 Reporting of Adverse Events for commercial agents – AdEERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via AdEERS.

As of August 25, 2010 all secondary malignancies should be reported via AdEERS

11.9 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for AdEERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all AdEERS reportable events and Grade 3 and higher Adverse Events. Dose Limiting Toxicities will also be reported during chemoradiotherapy on the Feasibility phase of the study.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*".

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). 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.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

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Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 CRADA/CTA

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA), hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@mail.nih.gov

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

13.0 NEUROSURGICAL GUIDELINES

13.1 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.**

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13.2 Definitions of Extent of Resection

13.2.1 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.

13.2.2 Partial Resection
The surgical removal of greater than 10% but less than 50% of the tumor mass.

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

13.2.4 Near Total Resection (Extensive Subtotal Resection)
Resection of greater than or equal to 90% of the tumor mass, but residual disease apparent on inspection.

13.2.5 Gross Total Resection
Resection of all visible tumor.

13.2.6
An attempt should be made to estimate the volume of the residual tumor in cm^2.

13.3 Imaging Confirmation of Extent of Resection
See Section 18.0 for Neuroimaging Guidelines. All patients must have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI with and without contrast. Post-operative imaging of the brain should be done within 72 hours of surgery if possible (preferably within 24 hours of surgery), and prior to the onset of edema or gliosis which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time or is difficult to interpret, the scan should be repeated 10 or more days after surgery.

13.4 Peri-operative Corticosteroids
Some patients with large tumors may require initiation of corticosteroid therapy pre-operatively to reduce associated cerebral edema or improve neurologic function.

Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of, dexamethasone 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 (7 days).

13.5 Special Precautions for Bevacizumab
Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery (eg, organ resection, exploratory laparotomy, thoractomy) or 14 days after intermediate surgical procedure (eg, paracentesis or thoracocentesis) **and** until the surgical wound is fully healed. Minor surgical procedures (eg, biopsies, infusaport, or Broviac line placement) need to have fully healed **and** occurred > 7 days prior to initiation of bevacizumab.

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14.0 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities (per COG Administrative Policy 3.9).

General Guidelines
Radiation therapy will be given concurrently with chemotherapy (vorinostat, temozolomide, or bevacizumab) in newly diagnosed patients with localized high-grade glioma. The primary site will be irradiated even if gross-total resection was achieved. This study mandates the use of conformal or intensity-modulated radiation therapy; the use of CT-MR registration to define the target volumes, and electronic data submission. Given the infiltrative nature of high-grade glioma, patients presenting with extensive disease and large tumor volumes may be treated with simple beam arrangements.

Required Benchmark and Questionnaires:
3D-conformal radiotherapy (3D-CRT) or intensity modulated radiation therapy (IMRT) using photons are required for this study. **Patients may not receive proton therapy on this protocol.** Centers participating in this protocol using 3D-CRT are required to complete the 3D Benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom (see Section 14.8). All centers participating in this protocol must complete the QARC CT/MR image fusion benchmark. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. Contact the RPC (http://rpc.mdanderson.org/rpc) for information regarding their IMRT phantoms.

Guidelines and Requirements for the Use of IMRT
Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored cooperative group trials. These guidelines are available through www.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

14.1 Indications for Radiation Therapy

14.1.1 Treatment
All patients will be irradiated and volumetric targeting for radiation therapy planning is required.

14.1.2 Timing of Radiation Therapy
Radiation therapy must start within 31 days of the definitive surgical procedure.

14.1.3 Criteria to Start Radiation Therapy
There are no contraindications to radiation therapy. Patients taking phenytoin should be weaned and/or switched to a different anticonvulsant as soon as feasible.

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14.2 Emergency Irradiation

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol. Patients who require urgent irradiation after protocol enrollment may initiate treatment using a simple beam's eye view treatment approach. The treatment may then be modified to improve conformity or normal tissue sparing as soon as feasible.

14.3 Equipment

Modality: X-rays with a nominal energy of ≥ 4MV. In the unusual circumstance of a superficial lesion, electron fields may be used. Conformal and IMRT techniques are allowed in this study. **Patients may not receive proton beam therapy on this protocol.**

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

CT treatment planning: All patients will undergo CT treatment planning for this protocol. Image section thickness ≤ 3mm should be taken throughout the extent of the irradiated volume.

14.4 Target Volumes

The International Commission on Radiation Units and Measurements (ICRU-50 and 62)[145,146] www.icru.org prescription methods and nomenclature shall be utilized for this study. Although the MRI obtained immediately prior to radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after surgical resection or biopsy. Most patients with high-grade glioma require a combination of pre- and post-operative MR sequences to delineate the full extent of disease. MR pre- and post-gadolinium contrast T1, T2, and FLAIR sequences should be reviewed. The sequence that best defines the extent of initial disease should be used to determine GTV1 and registered to the treatment planning CT. The GTV, CTV and PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

14.4.1 Gross Tumor Volume 1 (GTV1)

GTV1 will include all the tissues initially involved with disease and the entirety of residual tumor defined by the pre-operative and post-operative MRI. GTV1 will include both enhancing and non-enhancing areas of the tumor, MR T2-weighted imaging abnormality, and the resection bed. The GTV1 will take into account changes in brain anatomy resulting from tumor resection or CSF shunting.

- GTV1 is the volume of tissue containing the highest concentration of tumor cells.
- GTV1 includes disease defined by neuroimaging before and after surgery.
- GTV1 is corrected volumetrically after surgical resection.
- GTV1 includes the pre and post-contrast MR T1 and T2 abnormality.
-

Special Circumstances (GTV1)

- The surgical corridor should not be included in the delineation of the GTV unless suspected to contain tumor.
- In cases where there is discrepancy between imaging studies or intra-operative findings, the larger volume will define GTV1.

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14.4.2 Gross Tumor Volume 2 (GTV2)
There are several options to define GTV2. GTV2 may be determined based on extent of resection prior to radiation therapy, residual enhancing or non-enhancing residual tumor by T1-weighted MRI or may be the same as GTV1 when the resultant PTV2 is considered by the treating radiation oncologist to be tolerable for treatment to 5940cGy.

GTV2 Option 1
GTV2 = post-operative tumor bed after gross-total resection.

GTV2 Option 2
GTV2 = residual tumor as determined by pre- and post-contrast T1-weighted MRI.

GTV2 Option 3
GTV2 = GTV1 when the resultant PTV2 is considered relatively small and the treating radiation oncologist determines that the patient will tolerate 5940cGy to this volume.

14.4.3 Clinical Target Volume 1 (CTV1)
- CTV1 is defined as the volume of tissue containing subclinical microscopic disease.
- CTV1 for this protocol is the GTV1 with an anatomically confined margin of 2cm.
- CTV1 should be tailored at tissue interfaces where invasion/infiltration is not likely.
- The CTV may be manually moved inward to the inner table of the bony calvarium.

14.4.4 Clinical Target Volume 2 (CTV2)
- The CTV2 margin should be an expansion of the GTV2 to encompass microscopic disease.
- The CTV2 for this protocol is the GTV2 with an anatomically confined margin of 1 cm.
- The CTV2 should be tailored at tissue interfaces where invasion/infiltration is not likely.
- The CTV may be manually moved inward to the inner table of the bony calvarium.

14.4.5 Planning Target Volume 1 (PTV1)

The PTV includes the CTV with an added margin that is intended to account for patient movement and set-up variability. The treating radiation oncologist will select a margin between 3 and 5mm that reflects the appropriate set-up uncertainty and internal margin for the individual patient and treatment facility.

The PTV-1 will include the CTV-1 plus a 3-5 mm margin in all dimensions. The PTV may extend beyond bone margins, and may extend beyond the skin surface.

The PTV-2 will include the CTV-2 plus a 3-5 mm margin in all dimensions. The PTV may extend beyond bone margins, and may extend beyond the skin surface.

Motion Management and Margins to Account for Target Volume and Organ Motion
Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the IM component of the PTV and is meant to account for potential motion of the CTV. The planning organ at risk volume (PRV) includes the corresponding organ at risk (OAR) volume surrounded by a margin to compensate for motion or physiologic change in the tissue volume. If adequate clinical data do not exist to define the IM component of the PTV or the PRV margin, the following suggestions are provided:

- A margin matching the PTV margin may be added to any OAR to form the PRV.

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- Brain tumors susceptible to cyst expansion should be monitored closely.

14.5 Target Dose

Table 14.5 Prescribed Doses and Fractionation

Nominal Dose by Site	Target Volume	Dose/fraction	Number of Fractions
Primary Site 5400cGy	PTV1	180cGy	30
Primary Site Boost 540cGy	PTV2	180cGy	3

Prescribed dose: Dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied as noted below.

Dose Definition: Dose is to be specified in centigray (cGy)-to-muscle.

Tissue Heterogeneity: Heterogeneity corrections are required and shall be applied for conformal radiation therapy and IMRT in compliance with current guidelines for the use of IMRT in clinical trials. The heterogeneity correction algorithm must be approved by QARC. For questions about heterogeneity corrections or approved algorithms, please contact QARC (www.QARC.org).

14.5.1 Prescription Point and Fractionation

Planning Target Volume 1 (PTV1)
The total dose to the PTV1 prescription isodose surface will be 5400cGy given in 30 fractions of 180cGy. The patient should be treated with one fraction per day. All fields should be treated each day.

Planning Target Volume 2 (PTV2)
The total boost dose to the PTV2 prescription isodose surface will be 540cGy given in 3 fractions. The cumulative dose to the prescription point will be 5940cGy. The patient should be treated with one fraction per day. All fields should be treated each day. Simultaneous integrated boost is not allowed.

14.5.2 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 DVH. Wedges, compensators, and other methods of generating uniform dose distributions are encouraged.

14.5.3 Interruptions, Delays and Dose Modifications: There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

14.6 Treatment Technique

Beam Configuration: Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar), or IMRT is required to minimize dose to normal surrounding structures. In situations with

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clinical target volumes occupying significant proportions of whole brain volume, opposed lateral beam approaches may be offered when more complex approaches and beam arrangements demonstrate limited benefit.

Patient Position: Reproducible setups are critical and the use of immobilization devices is strongly encouraged. Use of anesthesia is permitted if necessary for proper positioning.

Field Shaping: Field shaping shall be done with either customized cerrobend blocking or multileaf collimation.

14.7 Organs at Risk

The organs at risk (OAR) guidelines in this section are recommendations. If the recommended doses to a particular OAR are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, IMRT may be preferred to meet these recommendations and the required target volume coverage guidelines.

14.7.1 Cochleae

- D50% ≤ 3500cGy – Goal (single cochlea)
- Comment – There is no dose limit for the cochleae.
- Structure definition - Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

14.7.2 Optic Globes

- D50% ≤ 1000cGy and D10% ≤ 3500cGy – Goal
- D50% ≤ 2000cGy and D10% ≤ 5400cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the anterior chamber of the eye and minimize dose to the entire eye without compromising target volume coverage during treatment of PTV1. In the event that the recommended constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition - Each eye should be separately contoured on the treatment planning CT or MR as a circular structure from the most superior to inferior aspect.

14.7.3 Optic Nerves and Chiasm

- D50% ≤ 5400cGy and D10% ≤ 5600cGy – Goal
- D50% ≤ 5600cGy and D10% ≤ 5800cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage during treatment of PTV1. In the event that the recommended constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition – The optic nerve may be contoured on CT or MR. The contour should appear on at least two successive CT or MR images.

14.7.4 Spinal Cord[147]

- D50% ≤ 2600cGy and D10% ≤ 5700cGy - Goal
- D50% ≤ 5000cGy and D10% ≤ 5900cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage during treatment of PTV1. If any portion of the spinal cord receives the prescription dose during the treatment of PTV1, it is preferable to allow that portion of the spinal

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cord to receive 5400cGy during the first 30 fractions of treatment. During treatment of PTV2; however, the entire spinal cord volume should receive no more than 70% or 126cGy per fraction during each of the last three treatments to achieve the recommended constraints provided in this section.

- Structure Definition - For the purposes of this study, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For purposes of comparison and consistency with dose volume data, the spinal cord should be contoured on a number of images to be determined by the image section thickness (CT section thickness, n=number of images; 2mm, n=30; 2.5 mm, n=24; 3 mm, n=20).

14.7.5 Brainstem[148]

- D50% $\leq$ 6100cGy and D10% $\leq$ 6300cGy - Goal
- D50% $\leq$ 6200cGy and D10% $\leq$ 6400cGy – Maximum
- Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage during treatment of PTV1. In the event that the recommended constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure Definition - The brainstem may be contoured on the treatment planning CT or MR and will include the midbrain, pons and medulla. The cranial extent will be inferior to the IIIrd ventricle and optic tracts. The caudal extent will end at the foramen Magnum.

14.8 Dose Calculations and Reporting

Prescribed Dose

The dose prescription and fractionation hsall be reported on the RT-1/IMRT Dosimetry Summary Form. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be reported on the RT-2 Radiotherapy Total Dose Record.

Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record form. The appropriate dose-volume histograms should be submitted. If IMRT is used, a DVH must 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. In addition, a DVH for "Body" shall be submitted in all cases to enable calculation of the required volumes in Table 14.8b.

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Table 14.8a Required DVH data regardless of primary treatment site

Required DVH
Right Eye
Left Eye
Right Optic Nerve
Left Optic Nerve
Optic Chiasm
Brainstem
Spinal Cord
Right Cochlea
Left Cochlea
Body
Unspecified Tissue

Treated Volume, Irradiated Volume and Conformity Index

The treated volume (TV) is the tissue volume that receives therapeutic dose. For the purpose of this protocol this would include the prescribed total dose of 59.4Gy and 95% of the prescribed dose or 56.4Gy. This information may be used by the investigators, along with the absolute volume of the PTV, to calculate the conformity indexes (CI) $CI_{100\%}$ and $CI_{95\%}$, respectively. The irradiated volume (IV) is the tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance. The descriptive statistics for these and other tissue volumes maybe used for correlation with unusual side effects or to develop practical guidelines for future high-grade brain tumor protocols.

Table 14.8b Required Absolute (mL) Volumetric Information

Required Volumes (ml)
TV=V56.4Gy
TV=V59.4Gy
IV=V35Gy
IV=V45Gy
IV=V54Gy
PTV
CTV
GTV
Entire Brain
Unspecified Tissue

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14.9 Quality Assurance Documentation

On-treatment review is NOT required for this study. Within one week of the completion of radiation therapy, detailed treatment data shall be submitted.

Digital Submission:

Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the QARC web site at www.qarc.org under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Treatment Planning System Output:

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field. . Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. This shall include GTV1, CTV1, PTV1, and GTV2, CTV2 and PTV2, when indicated. A DVH shall be submitted for the organs at risk specified in section 14.8. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data:

- All diagnostic imaging, corresponding radiology reports, and operative report used to plan the target volume. This includes CT and MRI scans PRIOR to attempted surgical resection of the primary tumor. Digital format is preferred.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- Documentation of an independent check of the calculated dose when IMRT is used.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.
- If emergency RT is administered, documentation should be provided in the form of the RT-2 Total Dose Record Form and the radiotherapy record (treatment chart).

Forms:

- RT-1/IMRT Dosimetry Summary Form.
- The RT-2 Radiotherapy Total Dose Record Form.

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These data should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

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

COG Protocol Dosimetrist
Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

14.10 Definitions of Deviations in Protocol Performance

	DEVIATION	
	Minor	**Major**
Prescription Dose		
	Difference in prescribed or computed dose is 6-10% of protocol specified dose	Difference in prescribed or computed dose is > 10% of protocol specified dose
Dose Uniformity		
	>10% PTV received > 110% of the protocol dose *or* 95% isodose covers < 100% of CTV	90% isodose covers < 100% of CTV
Volume		
	CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	GTV does not encompass MR-visible residual tumor
Organs at Risk		
	Will be assessed at time of data review	Will be assessed at time of data review

15.0 NEUROPATHOLOGY GUIDELINES AND CENTRAL PATHOLOGY REVIEW SPECIMEN REQUIREMENTS

15.1 Central Review

A retrospective central pathology review will be performed for all patients. The review outcome will not alter the patient's status on the study. The aim of the central pathology review is to provide confirmation of the diagnosis and to ensure accuracy and fidelity of the data. The classification and grading of the tumors will be performed according to the WHO criteria. The submission of pathology material shall be made directly from the participating institutions. The review pathologist may utilize unstained sections for a variety of supplemental tests. The remaining slides shall be kept as back-up material, or shall be used to perform additional staining as needed.

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15.2 Specimen Handling

Optimal and standardized evaluation of each case necessitates handling according to the below guidelines, as possible:

The treating institution should perform a panel of immunohistochemical (IHC) stains on the best /most representative block to aid in diagnostic work up. It is highly recommended that this panel include: GFAP (also S100, if GFAP-is weak, focal or negative appearing) Synaptophysin, Neurofilament protein, EMA, MIB-1 (Ki-67) and p53: Ideally, these institutional IHC stained slides could/ should be made available for central review. In the event all IHC stains are negative or IHC stain results are equivocal, electron microscopy, performed by the institution, may be of benefit if a sample was fixed for this at the time of surgery. A copy of any electron microscopy report should be included with the institution's pathology report sent for central review, as described in 15.3. Ideally, the institutional IHC stained slides could/should be made available for central review and would be returned upon completion of review.

Solid tumor cytogenetic study results (i.e. karyotyping) may also be of benefit, if sufficient sample is available, to be performed by the referring institution; if a report of these results is available, it should also be included with the institution's pathology report sent for central review. All tissue received by institutional pathology and *not* utilized for recommended special studies, should be prepared for light microscopy sections.

15.3 Required Pathology Review Material

The following specimens must be received prior to the start of maintenance.

- Representative paraffin-embedded 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. (Also include any outside consultant's report.)
- Operative Report(s)
- Institutional Neuropathology Worksheet
  - Any history of pre-operative (pre-biopsy or pre-resection) medical therapy (i.e. corticosteroids, radiation or other) should be noted; some may impact and alter histopathology
  - Cytogenetics report, if done
  - Any CSF cytology reports, if applicable
  - Electron Microscopy Report, if done
- **ACNS0822 Specimen Transmittal Form** to accompany each shipment.

15.4 Specimen Shipping

All pathology review materials must be labeled with the patient's COG Patient ID Number and the Surgical Path ID (SPID Number) from the corresponding pathology report. Cases for Standard Central Review are shipped by regular mail or using your institution's courier prior to the start of Maintenance:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2894
Fax: (614) 722-2865

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

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16.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

Participation in optional biology studies is strongly encouraged. In addition, institutions are strongly encouraged to enroll and submit specimens for ACNS02B3. If enough material is available to meet the biology requirements of this protocol and still have enough material left to meet minimal banking requirement for ACNS02B3, then the institution could receive credit for both this therapeutic trial and ACNS02B3.

All specimens will be banked and processed at the COG Biopathology Center (BPC) and distributed from there as well.

16.1 Overview of Biology Specimen Requirements

Study	Blood (all blood to be sent to BPC)	Tumor tissue (all tumor to be sent to BPC)
Telomerase activity, *hTert* and *hTR* expression, and telomere length	Send blood only if frozen tumor tissue sent: 4 ml in purple top (EDTA) tube prior to start of protocol therapy	Snap frozen
Gene expression and miRNA profiling	n/a	Snap frozen
Genome Allelotype and SNP Analyses	Send blood only if tumor tissue sent: 5 ml in a green top tube (sodium heparin) and 5 mL in a purple top tube (EDTA) prior to start of protocol therapy	Snap frozen; or If frozen tumor not available but block sent for pathology, no extra samples need be sent. If frozen tumor or block not sent for pathology, send 1) formalin-fixed block or 3-10 50 µm scrolls and 10 unstained slides and 2) ten 20 µm paraffin sections mounted on plain slides (not PLUS) unbaked AND ten 4 µm paraffin sections mounted on PLUS slides
MGMT and other markers	5 ml in purple top (EDTA) tube prior to start of protocol therapy	Tissue blocks (if sent for pathology); otherwise: -Ten 4 micron sections (unstained slides) from a representative block -Three 20-micron scrolls in a sterile microfuge (Eppendorf type) tube from a formalin-fixed, paraffin-embedded tumor sample.
TOTAL of SPECIMENS	**4 mL purple top (not sent if no tumor sent)** **5 mL purple top (not sent if no tumor sent)** **5 mL green top (not sent if no tumor sent)** **5 mL purple top**	**Snap frozen (as much as possible)** **Block** **If no block, then:** **a) 3-10 50 µm scrolls and 10 unstained slides;** **b) Ten 20 µm paraffin sections mounted on plain slides (not PLUS) unbaked AND ten 4 µm paraffin sections mounted on PLUS slides;** **c) Ten unstained slides and three 20-micron scrolls**

16.2 Snap Frozen Tumor Specimens

Process tumor specimens from first and any subsequent surgery according to the guidelines below. Send snap frozen tumor specimens to the Biopathology Center (BPC) in Columbus, Ohio. Portions of the tissue will be used for the correlative biology studies according to the priority list of biology studies in Section 16.2.2.

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As many 100 mg pieces of tissue as possible should be frozen in foil in liquid nitrogen within 10 minutes after tumor removal. Frozen tissue should be sent on dry ice to the BPC. A minimum tumor tissue of > 0.5 cm^3 is preferred.

Note: It is recommended that the pathologist bring a liquid N2 container up to the frozen section room, so that if adequate tissue is available at the time of frozen section, some is immediately snap frozen at that time for possible COG studies and/ or tumor banking. The neurosurgeon(s) OR personnel, and Pathology lab personnel may well need to be informed/ educated regarding the importance of rapid receipt and snap freezing of tumor once removed from the patient. If there is *insufficient* tumor received for rapid processing/ snap freezing during frozen section evaluation, as described above, then any subsequent parts of tumor removed for this purpose should still be snap frozen within 20 minutes of removal/ resection from the patient.

Frozen tumor specimens should only be dispatched on Monday through Thursday for delivery Tuesday through Friday to the BPC (see Section 16.2.1 for shipping address).

All tumor samples will be banked and processed by the COG Biopathology Center (BPC) and distributed from there.

16.2.1 Specimen Shipment

When frozen and room temperature specimens are shipped together, they can be shipped to the BPC in a Specimen Procurement Kit. This dual chambered kit allows for the shipment of either cold or room temperature specimens AND frozen specimens in the same container. Dry ice may be placed in either compartment of the kit, but should not be put in both. This kit contains most of the supplies necessary for shipping specimens to the BPC. The Specimen Procurement Kit should only be used when frozen tissue is included in the shipment. Blood with a cold pack will need to be submitted separately in your own packaging. To request a Specimen Procurement Kit, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. For packing and shipping instructions please see **Shipping Specimens in a Dual Chambered Kit** at https://members.childrensoncologygroup.org/prot/biology.asp. Ship to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

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

16.2.2 Priority List of Biology Studies

In the event of limited snap frozen tumor sample availability, sample studies will be prioritized as follows:

1) Assessment of telomerase activity, *hTert* and *hTR* expression, and telomere length analyses
2) Gene expression profiling and miRNA analyses
3) Genome Allelotype and SNP Array analyses

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16.3 **Telomerase activity, hTert expression, and telomere length studies**

Tumor tissue and peripheral blood will be obtained from all consenting patients, and will be analyzed for telomerase activity, *hTert* and *hTR* expression, and telomere length. The blood sample should only be sent if frozen tumor tissue was sent.

Snap Frozen Tumor Tissue: Snap frozen tissue will be distributed by the BPC, according to the priority list of biology studies (see Section 16.2.2). A minimum of 100 mg tumor tissue is preferred.

Peripheral Blood: Four (4) mL of peripheral blood will be collected in a purple top tube (EDTA) prior to the start of protocol therapy.

Label the specimens with the patient's BPC number, the specimen type and collection date. The blood specimen must be sent the same day it was drawn with a completed ACNS0822 Specimen Transmittal Form. Blood may be shipped Monday through Friday for delivery Tuesday through Saturday. Frozen tumor tissue must be shipped Monday through Thursday for delivery Tuesday through Friday. Ship specimens to the BPC at the address listed in 16.2.1.

16.4 **Gene expression and miRNA profiling**

Tumor tissue from all consenting patients will be analyzed for gene expression and miRNA profiling.

Snap Frozen Tumor Tissue: Snap frozen tissue will be distributed by the BPC, according to the priority list of biology studies (see Section 16.2.2). A minimum of 100 mg tumor tissue is preferred.

16.5 **Genome Allelotype and SNP Array Analyses**

Frozen tumor tissue, paraffin embedded and peripheral mononuclear cells (PBMCs) will be obtained from all consenting patients prior to starting treatment for studies of angiogenic gene expression. The blood sample should only be sent if tumor tissue was sent.

- **Snap Frozen Tumor Tissue**: Frozen tumor tissue will be distributed by the BPC, according to priority list of biology studies (see Section 16.2.2). A minimum tumor tissue > 0.5 cm^3 is preferred. Paraffin-embedded material should be submitted in addition to the frozen tissue sample.
  -If frozen tumor was not sent to the BPC but formalin-fixed blocks were sent, then the materials will be processed from the blocks by the BPC and the institution does not need to send slides, scrolls, or micron sections.
  -If neither frozen tumor nor blocks were sent to the BPC, formalin-fixed block with > 80% tumor should be sent although this will compromise the studies being performed. (Paraffin blocks will be returned upon request only.)
  -If neither frozen tumor nor blocks were sent to the BPC and the institution cannot release blocks, three to ten 50 µm scrolls should be sent and 10 unstained slides (Please indicate percent tumor represented.)
- **Paraffin Sections**: **These sections will be prepared by the BPC if blocks were sent to the BPC.**
  Ten 20 µm paraffin sections mounted on plain slides (not PLUS) unbaked should be submitted for laser capture microdissection and ten 4 µm paraffin sections mounted on PLUS slides should be submitted for possible FISH confirmation of gene copy number changes. These sections will be prepared by the BPC if blocks were sent to the BPC.
- **Peripheral Blood**: 5 mL of peripheral blood in a green top tube (sodium heparin) and 5 mL of blood in a purple top tube (EDTA) will be collected any time before the initiation of therapy. Do

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not send if the patient has had a whole blood transfusion. Do not send if a tumor specimen is not sent. If tumor is submitted, it is strongly encouraged that the peripheral blood be sent as well.

Label all specimens and the accompanying paperwork with the patient's BPC number, the collection date and specimen type. An ACNS0822 Specimen Transmittal Form must accompany each shipment. Blood samples should be stored and shipped AT ROOM TEMPERATURE. Ship specimens to the BPC via Federal Express, Priority Overnight to the address listed in Section 16.2.1. Blood may be shipped Monday through Friday for delivery Tuesday through Saturday. All other specimens must be shipped Monday through Thursday for delivery Tuesday through Friday.

16.6 MGMT status and immmunohistochemical marker studies

Tumor tissue and peripheral blood will be obtained prior to starting treatment from consenting patients enrolled on this study to evaluate a series of immunohistochemical markers associated with outcome in previous pediatric high-grade glioma studies.

Tumor Tissue:

- If tissue blocks were sent to the Biopathology Center for Pathology Review, then the materials will be processed from the blocks by the BPC and the institution does not need to send slides or micron sections.
- If tissue blocks were not sent for Pathology Review then the following materials for the MGMT biology study must be received:
  - Ten unstained slides from a representative block
  - Three 20-micron sections from a formalin-fixed, paraffin-embedded tumor sample. These three sections should be in a sterile microfuge (Eppendorf type) tube.

Peripheral Blood: 5 mL of blood will be collected into a purple top tube (EDTA) prior to the start of protocol therapy.

Label all specimens with the patient's BPC number, specimen type and collection date. A completed ACNS0822 Specimen Transmittal Form must accompany each shipment. Ship slides and sections in padded envelopes via Federal Express Priority Overnight. Ship blood via Federal Express Priority Overnight at ROOM TEMPERATURE any time before the initiation of therapy. Ship all specimens to the BPC using the address listed in Section 16.2.1. Blood may be shipped Monday through Friday for delivery Tuesday through Saturday. All other specimens must be shipped Monday through Thursday for delivery Tuesday through Friday.

16.7 Description of Biology Studies

16.7.1 Assessment of telomerase activity, *hTert* and *hTR* expression, and telomere length

Tumor tissue will be obtained from all consenting patients enrolled on all treatment arms of this study prior to starting treatment. Tumor samples will be analyzed for *TERT* and *hTR* subunits expression using quantitative real time PCR. Telomerase enzyme activity will be assessed using the TRAP assay. Telomere length will be assessed by Southern blot and/or flow cytometry.

16.7.2 Gene expression profiling and SNP Arrays

SNP Array Analysis

With the availability of normal blood DNA as a reference, LOH in the corresponding tumor sample can be measured very precisely at a single SNP locus. One of the advantages of using SNP array for whole genome scanning is that it not only provides locus-specific genotypes but also accurately quantify the copy number of each allele. Genomic DNA will be obtained from fresh tumor tissue biopsies frozen in

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liquid nitrogen and stored at -80°C using TRIzol Reagent (Life Technologies, GibcoBRL) according to the manufacturer's recommendations. Where frozen tissue is not available, DNA extraction will be obtained from formalin-fixed, paraffin-embedded tissue scrolls. For normal DNA, genomic DNA will extracted from matched peripheral blood leukocytes using Wizard Genomic DNA Purification Kit (Promega) according to the manufacturer's recommendations. Isolated DNA is then loaded on Affymetrix arrays and scanned as per the manufacturer's protocol. All data analysis will be carried out using Affymetrix software.

Expression Array Analysis
Total RNA will be isolated from fresh frozen tumor tissue using TRIzol Reagent (Life Technologies). RNA integrity will be confirmed with the Agilent 2100 Bioanalyzer (Agilent Technologies). We will use HG_U133plus2 or Genechip® Human Gene 1.0 ST array (Affymetrix, Santa Clara, CA) for expression analysis. Preparation of cRNA, hybridization, scanning, and image analysis of the arrays will be performed according to manufacturer's protocols. Briefly, five μg of total RNA will be used to generate cRNA probes and combined with a mixture of control cRNAs (made from bacterial genes BioB, BioC, BioDN and CreX) before hybridization. The U133plus2 arrays consist of more than 47,000 gene probe sets, each representing a transcript. Each probe set consists of 16 perfectly complementary 25 base long probes (PMs) as well as 16 mismatch probes (MMs) that are identical except for an altered central base. All GeneChip images will be visually inspected for irregularities and analyzed by dChip or GCOS software.

MicroRNA analysis
Total RNA from expression array analysis (see above) will also be used for this study. The presence of an intact miRNA population will be confirmed with the Bioanalyzer (Agilent Technologies). After labeling, samples will be hybridized to the Human miRNA Microarray v3 (Agilent Technologies, Santa Clara, CA) or superior version depending on what is available at the time of sample processing. The v3 chip contains probes for 866 human miRNAs and 89 human viral miRNAs identified from the Sanger database v12.0.

16.7.3 Exploration of the prognostic significance of MGMT and other markers of potential treatment resistance
Tumor tissue will be obtained prior to starting treatment from consenting patients enrolled on this study to evaluate a series of immunohistochemical markers associated with outcome in previous pediatric high-grade glioma studies. Particular emphasis will be placed on examining MGMT expression, which has been associated with response to alkylator-based therapy in the CCG-945 and ACNS0126 cohort. Additional markers to be examined include p53, MIB1 (a marker of proliferation status), and pAkt and pMAPK, growth signaling intermediates that have been associated with an adverse prognosis in recent studies.[103] Tumor samples (unstained slides) will be analyzed using immunoperoxidase labeling techniques, as previously applied in ACNS0126 and ACNS0423. In addition to assessment of MGMT expression using immunohistochemical methods, 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.

16.8 Optional Imaging Studies (MR Perfusion and MR Diffusion Tensor Imaging)

Optional imaging studies will be performed only in patients with evidence of residual tumor on the MRI performed to determine extent of resection prior to start of therapy.

For subjects who provide consent, MR perfusion and diffusion studies will be obtained at the following timepoints:

1) Prior to the start of protocol therapy
2) Prior to the start of maintenance therapy

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3) Prior to cycle 3 of maintenance therapy
4) Subsequent to completion of maintenance therapy

16.8.1 Perfusion Studies:
The EPI-GRE imaging sets will be analyzed at the centralized reading location with an automated method which uses the global arterial input function with deconvolution techniques to yield parametric maps of cerebral blood volume (CBV), flow (CBF) and mean transit times (MTT) or equivalent measures using standard clinical software and in-house software for perfusion analysis. ROI assessment of regions of highest tumoral CBV compared with contralateral hemispheric white matter will be used to establish rCBV ratios for baseline and follow-up purposes.

Perfusion:

GRE- EPI Perfusion sequence. EPI GRE sequence, FA: 35 degrees, 128 x 128 matrix, FOV = 26, TR: 1500 ms or less, TE: minimum. ASSET (SENSE) use if possible. Contrast injection optimally by power injector (1-3ml/sec) or by hand injection if not possible. Slice number as allowable by scanner to at least cover the tumor. At least 50 phases are acquired.

16.8.2 Diffusion Studies:
Diffusion weighted imaging will be performed using diffusion tensor imaging. This will allow for quantitative analysis of tumor diffusion in areas in close proximity to normal looking brain in order to better estimate tumor invasiveness into adjacent white matter as well as to assess diffusion characteristics of tumor tissue before and during treatment. Standard maps produced are Mean diffusivity, Fractional anisotropy, and Trace diffusion. Imaging processing will be performed at the centralized reading location using standard clinical software and in-house software for diffusion analysis. Region-of-interest analysis of tumor and peritumoral regions will be performed. Primary assessment will be by ROI analysis of diffusivity within the solid components of the tumor.

Diffusion Tensor Imaging:

DTI Imaging sequence: 12 – 25 direction (depending upon scanner) 3mm slice thickness, gap:0, b=1000, 128 x 128 matrix, FOV 38.4 cm. (isotropic dataset), ASSET (SENSE) use if possible.

The optional perfusion and diffusion MR imaging will be reviewed by the study neuroradiologist, Dr. James Leach.

Address Information
Copies of scans and the corresponding radiology reports of the optional studies for central review should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is

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acceptable via Dicommunicator. Contact QARC at Dicommunicator@QARC.org for further information. Alternative electronic methods, e.g., sFTP are possible. Contact QARC for more information.

17.0 NEUROIMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

17.1 Timing of MRIs

To document the degree of residual tumor, standard whole brain MRI with and without contrast (gadolinium) and spine MRI with and without contrast (gadolinium) must be performed at the following time points:

- within 4 weeks preceding enrollment into the study
- prior to each odd numbered cycle of maintenance therapy
- when patient is removed from protocol therapy (upon completion of therapy or at progression)

17.2 Whole Brain MRI With and Without Contrast

Preoperative brain MRI with and without contrast (gadolinium) is required. To document the degree of residual tumor, postoperative brain MRI with and without contrast must be done.

Postoperative brain MRI (with and without contrast) preferably within 48 hours of surgery is encouraged, but if unable to be done at that time (or postoperative changes obscure potential residual tumor) postoperative imaging should be done within 28 days of surgery.

Required sequences:

1. Sagittal T1 localizer; 4 mm skip 0.4 mm
2. Axial FSE T2; 4 mm, skip 0.4 mm
3. Axial T2 FLAIR; 4 mm skip 0.4
4. Axial diffusion; 4-5 mm skip 0 (single shot, matrix 128 x 128 or 128 x 192, B=1000)
5. Axial T1; 4 mm skip 0.4 mm
6. Axial gradient echo (susceptibility sequence); 4-5 mm skip 1-2 mm. TE=20, flip angle =20.
7. Axial T1 with contrast; 4 mm skip 0.4 mm
8. Sagittal T1 with contrast; 4 mm skip 0.4 mm
9. Axial T2 FLAIR with contrast; 4 mm skip 0.4

Optional sequences (depending on tumor)
Precontrast :

1. Sagittal or coronal FSET2; 4 mm skip 0.4 mm, depending on tumor configuration/orientation
2. Axial diffusion tensor (see optional sequences, Section 16.8)

Post contrast :

1. Coronal T1 : 4mm skip 0.4
2. T1-weighted gradient echo volume sequence (SPGR or equivalent)
3. Axial Perfusion (see optional sequences, Section 16.8)

NOTES:

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1. DO NOT INTERLEAVE T1 weighted sequences
2. Flow compensation should not be used / not on all T1 enhanced sequences
3. Fat Saturation not necessary

For patients who have provided consent, see details for optional perfusion and diffusion imaging in Section 16.8.

17.3 Spinal MRI With and Without Contrast

The MRI scan must be performed of the entire spine with and without contrast, and must be performed in at least two planes. Exception: The spine imaging can be performed with contrast only, if it immediately follows the enhanced brain MRI. If there is significant motion artifact and/or hemorrhage, then the scan is not evaluable and must be repeated or the patient is not eligible for study.

1. Whole spine sagittal T1; 3 mm skip 0 – 0.3 mm.

Technical notes:

- Phase direction AP, frequency direction SI
- Acquire 2 separate acquisitions (one cervical and upper thoracic, the second lower thoracic and lumbosacral) to optimize placement of presaturation pulse.
- Place anterior saturation pulse close to the anterior margin of the spinal column - to minimize motion artifacts from chest/abdomen.
- Pixel size 1 mm^2 or less (example: for 26 cm FOV, use 256 x 256 matrix)
- Keep TE to minimum (<15 msecs)
- Do not use fat saturation

2. Axial T1 images through the entire spine; 4-5 mm thick, skip 1-2mm.

Technical notes:

- Phase direction RL, frequency direction AP
- Keep TE to minimum (< 15 msecs)
- DO NOT INTERLEAVE

For primary tumors of the spinal cord, add:

1. Whole spine sagittal T2; 3 mm skip 0mm.

Technical notes:

- Can keep Phase direction AP, frequency direction SI, with anterior saturation pulses; or switch phase direction SI, frequency direction AP, with inferior and superior saturation pulses if that produces better images (less CSF pulsation artefacts)
- Pixel size 1 mm^2 or less (example: for 26 cm FOV, use 256 x 256 matrix)

2. Axial FSE T2, 4-5mm skip 0-1 mm, through tumor

NOTE:
In the routine evaluation for subarachnoid metastatic dissemination from brain tumors to the spine:

1. High quality T1 images are essential - without artefacts from physiologic motion (cardiac, respiratory) or from CSF pulsation.
2. T2 weighted sequences (sagittal or axial) are not needed. They are optional.

17.4 Tumor Response Assessment

For the response assessment, MRI scans obtained prior to each odd numbered maintenance cycle will be compared to the baseline MRI scan. **Exception:** In cases of progressive disease, the reference scan should be the MRI with the smallest product observed since the start of treatment (not necessarily at week 8).

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17.5 Central Review for Phase II and III

Central review will be performed for all patients with reported responses of CR or PR. Submit the following studies with their corresponding reports to the address below.

If Brain Measurable Disease:

- Brain MRI with and without contrast performed within 4 weeks prior to enrollment
- Brain MRI with and without contrast to document best response (subsequent evaluations do not need to be submitted if no change from earliest best response).

If Spine Measurable Disease:

- Spine MRI with and without contrast performed within 4 weeks prior to enrollment
- Spine MRI with and without contrast to document best response (subsequent evaluations do not need to be submitted if no change from earliest best response).

17.6 Address Information

Copies of scans of the required studies for central review should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicommunicator. Contact QARC at Dicommunicator@QARC.org for further information. Alternative electronic methods, e.g., sFTP are possible. Contact QARC for more information.

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APPENDIX I: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN GIRLS AGE 1-17 YEARS

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

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APPENDIX II: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN BOYS AGE 1-17 YEARS

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

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APPENDIX III: DOSING GUIDELINES FOR VORINOSTAT CAPSULE FORMULATION

BSA ranges (m^2) for doses of Vorinostat			
Vorinostat Dose Level	**Vorinostat dose (mg) to be administered***		
	200	**300**	**400**
230 mg/m^2/dose	≥1 – 1.08	1.09 – 1.52	≥1.53
(If dose modification due to toxicity) 180 mg/m^2/dose	≥1 – 1.38	1.39 – 1.94	≥ 1.95

***The absolute daily dose of vorinostat should not exceed 400 mg.**

*Patients with BSA < 1 m^2 or patients who cannot swallow capsules will receive the vorinostat suspension rounded to the nearest 5 mg (See Section 6.4 for preparation guidelines.)

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APPENDIX IV: TEMOZOLOMIDE DOSING DURING CHEMORADIOTHERAPY

TEMOZOLOMIDE DOSING TABLE for STARTING DOSE - 90 mg/m^2

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.48-0.52	43-47	45
0.53-0.58	48-52	50
0.59-0.63	53-57	55
0.64-0.69	58-62	60
0.70-0.75	63-67	65
0.76-0.80	68-72	70
0.81-0.86	73-77	75
0.87-0.91	78-82	80
0.92-0.97	83-87	85
0.98-1.02	88-92	90
1.03-1.08	93-97	95
1.09-1.13	98-102	100
1.14-1.19	103-107	105
1.20-1.25	108-112	110
1.26-1.30	113-117	115
1.31-1.36	118-122	120
1.37-1.41	123-127	125
1.42-1.47	128-132	130
1.48-1.52	133-137	135
1.53-1.58	138-142	140
1.59-1.63	143-147	145
1.64-1.69	148-152	150
1.70-1.75	153-157	155
1.76-1.80	158-162	160
1.81-1.86	163-167	165
1.87-1.91	168-172	170
1.92-1.97	173-177	175
1.98-2.02	178-182	180
2.03-2.08	183-187	185
2.09-2.13	188-192	190
2.14-2.19	193-197	195
2.20-2.25	198-202	200
2.26-2.30	203-207	205
2.31-2.36	208-212	210
2.37-2.40	213-217	215

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TEMOZOLOMIDE DOSING TABLE for REDUCED DOSE= 60 mg/m^2

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.46-0.54	28-32	30
0.55-0.62	33-37	35
0.63-0.70	38-42	40
0.71-0.79	43-47	45
0.80-0.87	48-52	50
0.88-0.95	53-57	55
0.96-1.04	58-62	60
1.05-1.12	63-67	65
1.13-1.20	68-72	70
1.21-1.29	73-77	75
1.30-1.37	78-82	80
1.38-1.45	83-87	85
1.46-1.54	88-92	90
1.55-1.62	93-97	95
1.63-1.70	98-102	100
1.71-1.79	103-107	105
1.80-1.87	108-112	110
1.88-1.95	113-117	115
1.96-2.04	118-122	120
2.05-2.12	123-127	125
2.13-2.20	128-132	130
2.21-2.29	133-137	135
2.30-2.37	138-142	140
2.38-2.40	143-147	145

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APPENDIX V: TEMOZOLOMIDE DOSING DURING MAINTENANCE

TEMOZOLOMIDE DOSING TABLE for MAINTENANCE STARTING DOSE= 200 mg/m^2

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.49-0.51	98-102	100
0.52-0.53	104-106	105
0.54-0.56	108-112	110
0.57-0.58	114-116	115
0.59-0.61	118-122	120
0.62-0.63	124-126	125
0.64-0.66	128-132	130
0.67-0.68	134-136	135
0.69-0.71	138-142	140
0.72-0.73	144-146	145
0.74-0.76	148-152	150
0.77-0.78	154-156	155
0.79-0.81	158-162	160
0.82-0.83	164-166	165
0.84-0.86	168-172	170
0.87-0.88	174-176	175
0.89-0.91	178-182	180
0.92-0.93	184-186	185
0.94-0.96	188-192	190
0.97-0.98	194-196	195
0.99-1.01	198-202	200
1.02-1.03	204-206	205
1.04-1.06	208-212	210
1.07-1.08	214-216	215
1.09-1.11	218-222	220
1.12-1.13	224-226	225
1.14-1.16	228-232	230
1.17-1.18	234-236	235
1.19-1.21	238-242	240
1.22-1.23	244-246	245
1.24-1.26	248-252	250
1.27-1.28	254-256	255
1.29-1.31	258-262	260
1.32-1.33	264-266	265
1.34-1.36	268-272	270
1.37-1.38	274-276	275
1.39-1.41	278-282	280
1.42-1.43	284-286	285
1.44-1.46	288-292	290
1.47-1.48	294-296	295
1.49-1.51	298-302	300
1.52-1.53	304-306	305
1.54-1.56	308-312	310
1.57-1.58	314-316	315

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1.59-1.61	318-322	320
1.62-1.63	324-326	325
1.64-1.66	328-332	330
1.67-1.68	334-336	335
1.69-1.71	338-342	340
1.72-1.73	344-346	345
1.74-1.76	348-352	350
1.77-1.78	354-356	355
1.79-1.81	358-362	360
1.82-1.83	364-366	365
1.84-1.86	368-372	370
1.87-1.88	374-376	375
1.89-1.91	378-382	380
1.92-1.93	384-386	385
1.94-1.96	388-392	390
1.97-1.98	394-396	395
1.99-2.01	398-402	400
2.02-2.03	404-406	405
2.04-2.06	408-412	410
2.07-2.08	414-416	415
2.09-2.11	418-422	420
2.12-2.13	424-426	425
2.14-2.16	428-432	430
2.17-2.18	434-436	435
2.19-2.21	438-442	440
2.22-2.23	444-446	445
2.24-2.26	448-452	450
2.27-2.28	454-456	455
2.29-2.31	458-462	460
2.32-2.33	464-466	465
2.34-2.36	468-472	470
2.37-2.38	474-476	475
2.39-2.40	478-480	480

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TEMOZOLOMIDE DOSING TABLE for MAINTENANCE STARTING DOSE= 150 mg/m^2

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.50-0.51	75-76	75
0.52-0.55	78-82	80
0.56-0.58	84-87	85
0.59-0.61	88-91	90
0.62-0.65	93-97	95
0.66-0.68	99-102	100
0.69-0.71	103-106	105
0.72-0.75	108-112	110
0.76-0.78	114-117	115
0.79-0.81	118-121	120
0.82-0.85	123-127	125
0.86-0.88	129-132	130
0.89-0.91	133-136	135
0.92-0.95	138-142	140
0.96-0.98	144-147	145
0.99-1.01	148-151	150
1.02-1.05	153-157	155
1.06-1.08	159-162	160
1.09-1.11	163-166	165
1.12-1.15	168-172	170
1.16-1.18	174-177	175
1.19-1.21	178-181	180
1.22-1.25	183-187	185
1.26-1.28	189-192	190
1.29-1.31	193-196	195
1.32-1.35	198-202	200
1.36-1.38	204-207	205
1.39-1.41	208-211	210
1.42-1.45	213-217	215
1.46-1.48	219-222	220
1.49-1.51	223-226	225
1.52-1.55	228-232	230
1.56-1.58	234-237	235
1.59-1.61	238-241	240
1.62-1.65	243-247	245
1.66-1.68	249-252	250
1.69-1.71	253-256	255
1.72-1.75	258-262	260
1.76-1.78	264-267	265
1.79-1.81	268-271	270
1.82-1.85	273-277	275
1.86-1.88	279-282	280
1.89-1.91	283-286	285
1.92-1.95	288-292	290
1.96-1.98	294-297	295
1.99-2.01	298-301	300

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2.02-2.05	303-307	305
2.06-2.08	309-312	310
2.09-2.11	313-316	315
2.12-2.15	318-322	320
2.16-2.18	324-327	325
2.19-2.21	328-331	330
2.22-2.25	333-337	335
2.26-2.28	339-342	340
2.29-2.31	343-346	345
2.32-2.35	348-352	350
2.36-2.38	354-357	355
2.39-2.40	358-360	360

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APPENDIX VI: INSTRUCTIONS FOR ADMINISTRATION OF TEMOZOLOMIDE (PATIENTS UNABLE TO SWALLOW CAPSULES AND CANNOT OBTAIN A SUSPENSION)

- If the person giving this medicine is pregnant or thinks she may be pregnant, she should not touch this medicine.

Temozolomide is an anti-cancer medicine, and special precautions must be taken when handling it. There is potential hazard to anyone who handles these medicines once the protective capsule is opened. If your child cannot swallow the capsule you will be required to open the capsules and mix the contents of the capsule into apple sauce or apple juice. This process must be done according to the following guidelines to make sure the medicine is given safely.

- Find a place to work that is free from drafts or wind and is not a place where food is stored or prepared.
- Cover the area with foil with a paper towel over it.
- Temozolomide can be mixed into apple sauce or apple juice.
- Put the apple sauce or apple juice into a container (or cup) that you can throw away.
- Put on gloves and mask.
- Open each capsule and put the powder in the apple sauce or apple juice and give IMMEDIATELY. The medicine may not dissolve completely if mixing in apple juice so make sure you have extra apple juice to add if you need to.
- If you need to add more juice or apple sauce, remove your gloves before touching the main food container, then place new gloves on before adding the extra juice or apple sauce to the medicine. (You do not want any medicine that may be on your gloves to get into the main food container of juice or apple sauce.).
- You must be able to throw away anything that the medicine touches, such as the spoon used for mixing or eating the apple sauce or the cup used for juice.
- Once all of the medicine is taken, throw away the following in a plastic bag: medicine cup, the container the medicine was mixed in, the cover you used for the work area, mask, gloves and anything else that the medicine has touched.

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APPENDIX VII: ENZYME INDUCING AND NON-ENZYME INDUCING ANTICONVULSANTS

Non-enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Zonisamide	Zonegran
Enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxycarbazepine	Trilepta

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APPENDIX VIII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Feasibility study)
(for children from 7 through 12 years of age)

A Study of Adding a Drug to Treatment for Newly Diagnosed Brain Tumors that Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in your brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you were just diagnosed with a type of brain tumor that is more likely to grow fast. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to shrink or get rid of the tumor than other treatment often used.

3. There is no "normal" treatment for glioma tumors that grow fast. But, often an operation to take out the tumor is done. Then, high-energy x-rays are used to kill any cancer cells left in the brain. Many children also get anti-cancer medicines to kill the cancer cells. These treatments do not work very well at getting rid of the tumor. Study doctors want to see if giving a drug during the x-ray treatments will help get rid of cancer cells. Study doctors also want to see if giving 2 drugs after x-ray treatment can help get rid of the tumor. Study doctors hope this new treatment will work better to kill cancer cells than a treatment that is often used.

   Children who are part of this study will be given an anti-cancer medicine called vorinostat. Vorinostat is a medicine that you will swallow. You will take vorinostat during the time you are having the x-ray treatments. Because we are not sure how much vorinostat is best to give during x-ray treatment, you may get more or less of the drug than another child on the study. At the end of the x-ray treatment you will have a rest for 4 weeks where no treatment is given. Then you will be given 2 more anti-cancer medicines for about 11 more months. You will have about 8 scans done during these 11 months to see how the tumor reacts to the treatment. You will also have x-rays taken of your knees every 12 weeks to check how you are growing. Then you will be finished with the treatments.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new medicine during radiation treatment will work better to make your tumor get smaller or go away. Because the 2 anti-cancer medicines you will get after radiation treatment is a new treatment, we hope a benefit is that this part of treatment will work better to make your tumor shrink or go away. But, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may get a treatment that is not as good at shrinking or getting rid of the tumor as the commonly used treatment and you may have bad health problems from the new medicine. Because the 2 anti-cancer medicines you will get after radiation treatment is a new treatment, there is a risk that you may have more bad health problems from the new combination of medicines. Other things may happen to you that we do not yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

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7. We are asking your "okay" to collect some extra blood and pieces of tumor, and to do some special scans. We want to see if there are ways to tell how the tumor will react to treatment. The blood would be collected when other standard blood tests are being done, so there would not be any extra needle sticks. The tumor samples would be taken at the time you have any operation. We will not do an operation just to get pieces of tumor. The special scans will be done when regular scans are done. You can still take part in this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Feasibility study)
(for teens from 13 through 17 years of age)

A Study of Adding a Drug to Treatment for Newly Diagnosed Brain Tumors that Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a "high-grade" glioma. This means the tumor is more likely to grow quickly and to spread. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to shrink or get rid of high-grade glioma than a commonly used treatment for this disease.

   Most children and teens with gliomas have surgery to take out the tumor and then get radiation therapy (powerful x-rays directed at the tumor location). Many children and teens also get chemotherapy drugs (anti-cancer medicines). Treatments for gliomas do not work very well at shrinking or getting rid of the tumor. Study doctors want to see if giving chemotherapy during radiation therapy will work better than radiation therapy alone to get rid of the tumor. They also want to see if giving two chemotherapy drugs after radiation therapy will help get rid of the tumor for as long as possible.

3. Children and teens who are part of this study will be treated with a drug called vorinostat during the time radiation treatments are given, for 6 weeks. Because we are not sure how much vorinostat is best to give during x-ray treatment, you may get more or less of the drug than another child or teen on the study. Then you will have a rest for 4 weeks where no treatment is given. Then you will be given more chemotherapy with a combination of 2 drugs for about 11 more months. This combination of drugs is experimental. You will have about 8 scans done during these 11 months to see how the tumor is reacting to the treatment. If you have not yet stopped growing, every 12 weeks during treatment you will also have x-rays taken of your knees to check how you are growing.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new drug given during radiation treatment will be better at shrinking or getting rid of the tumor than the commonly used treatment. We hope that the new combination of drugs given after radiation treatment will work better to shrink or get rid of the tumor than the commonly used treatment. However, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that you may have side effects from the combination of radiation therapy with the vorinostat. Some possible side effects include things like being very tired, an upset stomach, and not being able to keep food down. Another risk to you is that you may have more side effects from the 2 drug combination that is given after radiation therapy. Some of these side effects may include high blood pressure, bleeding problems, and feeling sick to your stomach. Other things may happen to you that we do not yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

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7. We are asking your permission to collect additional blood and tumor samples, and to do special scans. We want to see if there are ways to tell how the cancer will respond to treatment. The blood samples would be taken when other standard blood tests are being performed, so there would be no extra needle sticks. The tumor samples would be taken during surgeries you had. We would not do a surgery just to get these samples. The special scans would be done when other normal scans are done. You can still be treated on this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Phase II)
(for children from 7 through 12 years of age)

A Study Comparing 3 Treatments for Newly Diagnosed Brain Tumors That Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in your brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a tumor that is more likely to grow fast. A research study is when doctors work together to try out new ways to help people who are sick. Most children with gliomas have an operation to take out the tumor and then get radiation therapy (powerful x-rays directed at the tumor location). Many children also get anti-cancer medicines. Treatments for gliomas do not work very well at shrinking or getting rid of the tumor. Study doctors want to try two new treatments to see if they will work better than a commonly used treatment.

3. Children who are part of this study will be given an anti-cancer medicine and have radiation treatments for 6 weeks. Some children will get one of two new medicines during radiation treatment. Some children will get a commonly used medicine during radiation treatment. Then you will have a rest for 4 weeks where no treatment is given. Then you will be given 2 more anti-cancer medicines for about 11 more months. You will have about 8 scans done during these 11 months to see how the tumor reacts to the treatment. You will also have x-rays taken of your knees every 12 weeks to check how you are growing. Then you will be finished with the treatments.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." If you get one of the new medicines during radiation treatment, we hope that a benefit to you of being part of this study is that you will get a treatment that works better to make your tumor get smaller or go away. If you get the medicine that is not new, we hope a benefit to you is helping study doctors learn more about how to treat brain tumors. Because the 2 anti-cancer medicines you will get after radiation treatment is a new treatment, we hope a benefit is that this part of the treatment will work better to make your tumor shrink or go away. However, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." Another risk to you is that you may have more side effects from the 2 drug combination that is given after radiation therapy. Some of these side effects may include high blood pressure, bleeding problems, and feeling sick to your stomach. Other things may happen to you that we do not yet know about. Other things may happen to you that we do not yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your "okay" to collect some extra blood and pieces of tumor, and to do some special scans. We want to see if there are ways to tell how the tumor will react to treatment. The tumor samples would be taken at the time you would normally have any operation, so there would be no extra operations. The blood would be collected when other regular blood tests are done, so there would be no extra needle sticks. The special scans would be done when other regular scans are done. You can still take part in this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Phase II)
(for teens from 13 through 17 years of age)

A Study Comparing 3 Treatments for Newly Diagnosed Brain Tumors that Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a "high-grade" glioma. This means the tumor is more likely to grow quickly and to spread. A research study is when doctors work together to try out new ways to help people who are sick. Most children and teens with gliomas have surgery to take out the tumor and then get radiation therapy (powerful x-rays directed at the tumor location). Many children and teens also get chemotherapy drugs (anti-cancer medicines). Treatments for gliomas do not work very well at shrinking or getting rid of the tumor. Study doctors want to try two new treatments to see if they will work better than a commonly used treatment.

3. Children and teens who are part of this study will be given chemotherapy and have radiation treatments for 6 weeks. Some children and teens will receive 1 of 2 new drugs during radiation treatment, while others will receive a commonly used drug. You have a 1 in 3 chance of getting each drug. Then you will have a rest for 4 weeks where no treatment is given. Then you will be given more chemotherapy with a combination of 2 drugs for about 11 more months. This combination is experimental. Then you will be given more chemotherapy with 2 different drugs for about 11 more months. (These 2 drugs will be new for everyone). You will have about 8 scans done during these 11 months to see how the tumor is reacting to the treatment. If you have not yet stopped growing, every 12 weeks during treatment you will also have x-rays taken of your knees to check how you are growing.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study if you get one of the new drugs during radiation treatment is that the new treatment will be better at shrinking or getting rid of the tumor than the commonly used treatment. If you receive the commonly used treatment, we hope that a benefit to you is knowing that you will help doctors learn more about how to treat gliomas. For all children and teens in this study, we hope that the new combination of drugs given after radiation treatment will work better to shrink or get rid of the tumor than the commonly used treatment. However, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." If you receive one of the 2 new drugs during radiation treatment, one risk to you from this study is that you may receive a treatment that is not as good as the common treatment in shrinking or getting rid of the tumor. Another risk is that you may have more side effects from the new treatment than the common treatment. These side effects include headaches, high blood pressure, tiredness, diarrhea, vomiting and loss of appetite. If you receive the commonly used drug during radiation treatment, the risk to you is that you may receive a treatment that is not as good as the new treatment at shrinking or getting rid of your tumor. There is the risk that the new treatment given after radiation treatment will not work as well as the common treatment to shrink or get rid of the tumor, and you may have more side effects from the 2 drugs used. Some of these side effects are high blood pressure, bleeding problems, and feeling sick to your stomach. Other things may happen to you that we do not yet know about.

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6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

7. We are asking your permission to collect additional blood and tumor samples, and to do special scans. We want to see if there are ways to tell how the cancer will respond to treatment. The blood samples would be taken when other standard blood tests are being performed, so there would be no extra needle sticks. The tumor samples would be taken during any surgeries you had, so you would have no extra surgeries. The special scans would be done when other regular scans are done. You can still be treated on this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Phase III)
(for children from 7 through 12 years of age)

A Study Comparing 2 Treatments for Newly Diagnosed Brain Tumors That Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in your brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a tumor that is more likely to grow fast. A research study is when doctors work together to try out new ways to help people who are sick. Most children with gliomas have an operation to take out the tumor and then get radiation therapy (powerful x-rays directed at the tumor location). Many children also get anti-cancer medicines. Treatments for gliomas do not work very well at getting rid of the tumor. Study doctors want to try a new treatment to see if it will work better than a commonly used treatment.

3. Children who are part of this study will be given an anti-cancer medicine and have radiation treatments for 6 weeks. Some children will get one new medicine during radiation treatment. Some children will get a commonly used medicine during radiation treatment. Then you will have a rest for 4 weeks where no treatment is given. Then you will be given 2 more anti-cancer medicines for about 11 more months. You will have about 8 scans done during these 11 months to see how the tumor reacts to the treatment. You will also have x-rays taken of your knees every 12 weeks to make sure you are growing normally. Then you will be finished with the treatments.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." If you get the new medicine during radiation treatment, we hope that a benefit to you of being part of this study is that you will get a treatment that works better to make your tumor get smaller or go away. If you get the medicine that is not new, we hope a benefit to you is helping study doctors learn more about how to treat brain tumors. Because the anti-cancer medicines you will get after radiation treatment is a new treatment, we hope a benefit is that this part of the treatment will work better to make your tumor shrink or go away. However, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." If you get the new medicine during radiation treatment, the risks to you from this study are that you may get a treatment that is not as good at shrinking or getting rid of the tumor as the commonly used treatment, and you may have more health problems from the new medicine. If you do not get the new medicine during radiation treatment, the risk to you is that you may not get a treatment that works better to make your tumor shrink or go away. Because the 2 anti-cancer medicines you will get after radiation treatment is a new treatment, there is a risk that that you may have bad health problems from the new combination of medicines. Other things may happen to you that we do not yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your "okay" to collect extra blood and pieces of tumor, and to do some special scans. We want to see if there are ways to tell how the tumor will react to treatment. The tumor samples would be taken at the time you have any operation, so there would be no extra operations. The blood would be collected when other regular blood tests are being done, so there would be no extra needle sticks. The special scans would be done when other regular scans are done. You can still take part in this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0822 (Phase III)
(for teens from 13 through 17 years of age)

A Study Comparing 2 Treatments for Newly Diagnosed Brain Tumors that Grow Quickly

1. We have been talking with you about your glioma. A glioma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a "high-grade" glioma. This means the tumor is more likely to grow quickly and to spread. A research study is when doctors work together to try out new ways to help people who are sick. Most children and teens with gliomas have surgery to take out the tumor and then get radiation therapy (powerful x-rays directed at the tumor location). Many children and teens also get chemotherapy drugs (anti-cancer medicines). Treatments for gliomas do not work very well at shrinking or getting rid of the tumor. Study doctors want to try a new treatment to see if it will work better than a commonly used treatment.

3. Children and teens who are part of this study will be given chemotherapy and have radiation treatments for 6 weeks. Some children and teens will receive a new drug during radiation treatment, while others will receive a commonly used drug. You have a 50-50 chance of getting either drug. Then you will have a rest for 4 weeks where no treatment is given. Then you will be given more chemotherapy with a combination of 2 drugs for about 11 more months. This combination is experimental. You will have about 8 scans done during these 11 months to see how the tumor is reacting to the treatment. If you have not yet stopped growing, every 12 weeks during treatment you will also have x-rays taken of your knees to check how you are growing.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study if you get the new drug during radiation treatment is that the new treatment will be better at shrinking or getting rid of the tumor than the commonly used treatment. If you receive the commonly used treatment, we hope that a benefit to you is knowing that you will help doctors learn more about how to treat gliomas. For all children and teens in this study, we hope that the new combination of drugs given after radiation treatment will work better to shrink or get rid of the tumor than the commonly used treatment. However, we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." If you receive the new drug during radiation treatment, one risk to you from this study is that you may receive a treatment that is not as good as the common treatment in shrinking or getting rid of your tumor. Another risk is that you may have more side effects from the new treatment than the common treatment. These side effects include headaches, high blood pressure, tiredness, vomiting and loss of appetite. If you receive the commonly used drug during radiation treatment, the risk to you is that you may receive a treatment that is not as good as the new treatment at shrinking or getting rid of your tumor. There is the risk that the new treatment given after radiation treatment will not work as well as the common treatment to shrink or get rid of the tumor, and you may have more side effects from the 2 drugs used. Some of these side effects are high blood pressure, bleeding problems, and feeling sick to your stomach. Other things may happen to you that we do not yet know about.

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6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

7. We are asking your permission to collect additional blood and tumor samples, and to do special scans. We want to see if there are ways to tell how the cancer will respond to treatment. The blood samples would be taken when other standard blood tests are being performed, so there would be no extra needle sticks. The tumor samples would be taken during any surgeries you had, so you would have no extra surgeries. The special scans would be done when other regular scans are done. You can still be treated on this study even if you do not allow us to collect the extra blood or tumor samples for research or to do the special scans.

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SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH – FEASIBILITY STUDY

As of Amendment #1 the feasibility study was completed.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the 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 local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACNS0822, *A Randomized Phase II/III Study of Vorinostat and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children with Newly Diagnosed High-Grade Gliomas*

PART 1 – Feasibility Study of Vorinostat with Radiation Therapy

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to take part in this research study because you have been diagnosed with a type of brain tumor called a high-grade glioma. A "high-grade" glioma is a tumor that grows fast and is more likely to spread.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for high-grade gliomas and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

Standard treatment for high-grade gliomas includes surgery to remove as much tumor as possible followed by radiation therapy (treatment with high-dose x-rays). Treatment may also include chemotherapy (anti-cancer drugs) during and after radiation treatment. Temozolomide is

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one of the chemotherapy drugs often used during radiation therapy to treat newly diagnosed high-grade glioma. Anti-cancer drugs, such as temozolomide, are also commonly used in Maintenance therapy for newly diagnosed high-grade glioma. Maintenance therapy is therapy given after radiation therapy.

WHY IS THIS STUDY BEING DONE?

High-grade gliomas are hard to treat successfully. Study doctors want to find treatments that will be better at getting rid of or shrinking high-grade gliomas. One thing they want to do is try using different chemotherapy drugs during radiation therapy. Treatment that combines chemotherapy and radiation therapy at the same time is called "chemoradiotherapy". Two drugs that will be used in this study are vorinostat and bevacizumab.

Early studies have shown that vorinostat and bevacizumab may help radiation therapy work better to get rid of cancer cells. One study of adults with high-grade glioma found that vorinostat helped keep the cancer from getting worse over 6 months. Recently, a study was completed to find the highest dose of vorinostat that can be given safely to children. Another study of adults with high-grade glioma found that bevacizumab combined with radiation therapy helped get rid of or shrink tumors.

Study doctors also want to see if using different drugs during maintenance therapy will be better than treatment with temozolomide in helping to get rid of or shrink high-grade gliomas. Another drug that they want to try together with temozolomide is bevacizumab. Temozolomide is commonly used in maintenance therapy for brain tumors. It is well-tolerated and has fewer side effects than other drugs commonly used in maintenance therapy. Study doctors want to find out if adding bevacizumab to treatment with temozolomide during maintenance therapy will work better than temozolomide alone. Bevacizumab is a drug that works differently than traditional chemotherapy drugs. Cancer cells need to have a blood supply just as normal body cells do. Bevacizumab is an antibody that works to stop the growth of blood vessels in the tumor.

In studies of adults with different types of cancer, patients who had bevacizumab added to their chemotherapy treatments did better than those who did not. Other studies of adults with high-grade gliomas suggest that adding bevacizumab to treatment with other drugs is well-tolerated and works better than either the bevacizumab or the other drugs alone to help keep the cancer from getting worse. Bevacizumab was recently approved for use in adults with recurrent high-grade glioma. Early results are available from an ongoing study of children with newly-diagnosed brain tumors. These children are being treated with the combination of temozolomide, irinotecan and bevacizumab during maintenance therapy and the results to date suggest the combination is well-tolerated. Study doctors think the combination of temozolomide and bevacizumab will be well-tolerated by children who take part in this study, and that the combination may work better than temozolomide alone to get rid of or shrink high-grade gliomas.

This study is being done in 3 parts. Part 1 of this study is to find the dose of vorinostat that can be given safely to children during radiation therapy. Once this dose is known, the study will continue to Part 2. Part 2 of the study will test and compare 3 treatments. Part 3 of this study will compare the 2 best treatments from Part 2. People who are in Part 1 of this study will not be in Part 2 or 3. We are now doing Part 1 of the study. You are being asked to enroll on Part 1 of this study.

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The goals of Part 1 of this study are to:

- **Find out the dose of vorinostat that can be given safely to children while they are receiving radiation therapy. The combination of vorinostat with radiation therapy is experimental.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of people enrolled on this study is expected to be 248. We will enroll between 6 and 12 people on Part 1 of this study.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

This is a 3-part study, and different parts of this study will be done to test different treatments. In Part 1 of this study some subjects may be given a different dose of vorinostat than the subjects treated with vorinostat in Parts 2 and 3 of the study. Subjects are people who agree to be treated on this study.

Part 1
We will try to find out the highest dose of vorinostat that can be given in combination with radiation therapy without causing side effects that are too severe. This dose is called the maximum tolerated dose, or MTD.

From 6 to 12 subjects will take part in Part 1. The dose of vorinostat for the first 6 subjects will be 230 mg/m^2. If that dose doesn't cause too many side effects, then that dose will be the dose used in the rest of the study. But, if the dose of 230 mg/m^2 causes too many side effects, then the next 3 subjects will get vorinostat at a lower dose (180 mg/m^2). If the lower dose does not cause too many side effects, then another 3 subjects will receive the lower dose. If the lower dose doesn't cause too many side effects in these 6 subjects, it will be the dose used in the rest of the study. If the lower dose does cause too many side effects, we will change the study.

In Part 2, we will treat more subjects to find out how effective the MTD of vorinostat found in Part 1 is against newly diagnosed high-grade gliomas, when it is given in combination with radiation therapy. We will compare treatment with vorinostat during radiation therapy to two other treatments each using a different drug during radiation therapy.

In Part 3, we will compare the two treatments found to work the best during Part 2 to see which one is more effective against newly diagnosed high-grade gliomas.

The remainder of this informed consent will discuss what will happen on Part 1 of this study.

Treatment Plan

The treatment plan involves cancer fighting medicine called chemotherapy and radiation therapy. The treatment on this clinical trial takes about 12 to 14 months. It is divided into 2 phases.

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The first phase of treatment is called "chemoradiotherapy". This phase lasts about 70 days, or 10 weeks. During this first phase, you will be given radiation therapy to the brain 5 days a week for 6 weeks. On the days that you receive radiation therapy, you will take vorinostat 1 to 2 hours before the radiation therapy. After you complete radiation therapy and treatment with vorinostat, you will have a 4-week rest, during which no treatment is given.

The second phase of treatment, called Maintenance therapy, begins after the 4-week rest period. During Maintenance therapy, you will not receive any further radiation therapy but you will have more chemotherapy. Maintenance therapy consists of 1 cycle of treatment repeated for up to a total of 12 cycles. Each cycle is 28 days long. During each cycle, you will receive two drugs, called bevacizumab and temozolomide. Temozolomide will be given on 5 days and bevacizumab will be given on 2 days during each cycle. Maintenance therapy lasts about 336 days or 11 months.

There is one treatment arm in Part 1 of this study. It is:

- **Arm A: Chemoradiation with vorinostat followed by maintenance chemotherapy with bevacizumab and temozolomide.**

Diagram of Treatment

A diagram of treatment on Part 1 of this study can be seen below.

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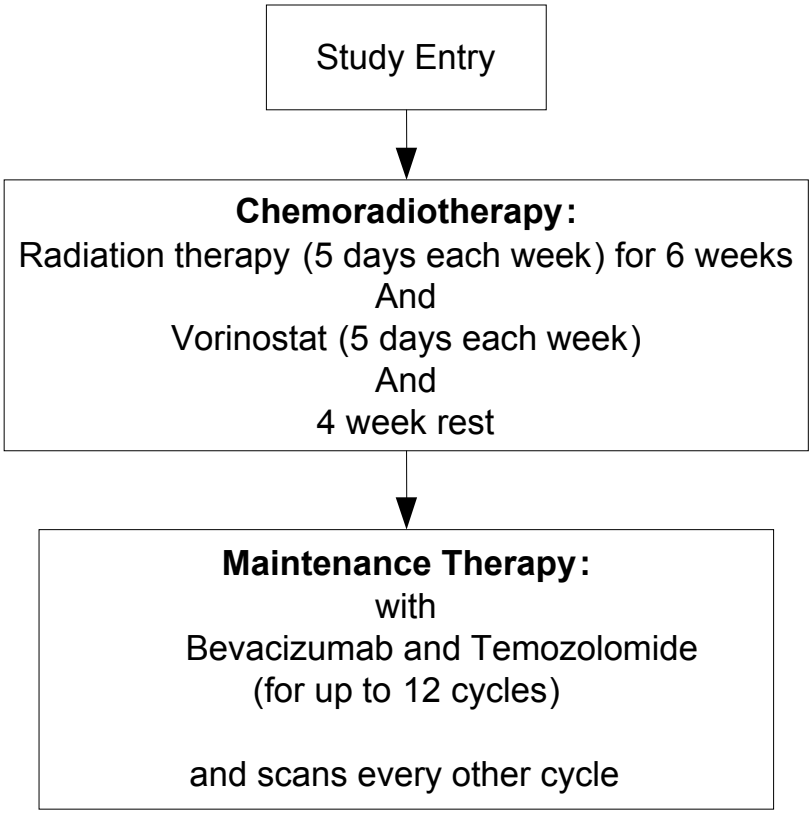

Treatment Plan Tables

Treatment that is commonly used for newly diagnosed high-grade gliomas is described in **Attachment #1**. This includes the standard radiation therapy that all subjects will receive while part of this study and temozolomide commonly used during radiation therapy and during maintenance therapy. The following drug therapies relate to the experimental chemoradiotherapy and maintenance therapy in this study.

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. It can be given by IV push over several minutes or by infusion over minutes or hours.

Most drugs on this study will be given using a needle or tubing inserted into a vein **(IV).**

Chemoradiotherapy Treatment for All Subjects

All subjects will receive vorinostat during the chemoradiotherapy phase of treatment. **The experimental treatment is using vorinostat instead of temozolomide.**

Drug	How the drug will be given	Days
Vorinostat	PO (1 to 2 hours before radiation therapy)	1-5, 8-12, 15-19, 22-26, 29-33, 36-40

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All subjects will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Maintenance Chemotherapy Treatment for All Subjects

All subjects on this study will receive the same chemotherapy drugs during Maintenance chemotherapy. These drugs are bevacizumab and temozolomide. The purpose of Maintenance chemotherapy is to kill any remaining glioma cells that may regrow and cause a relapse (cancer coming back). Each Maintenance cycle lasts about 28 days and the cycle may be repeated for up to a total of 12 cycles. Maintenance lasts about 11 months. **The experimental treatment is using bevacizumab and temozolomide instead of temozolomide alone as maintenance therapy.**

Drug	How the drug will be given	Days
Bevacizumab	IV over 90 minutes*	1 and 15
Temozolomide	PO	1-5

**The first dose will be given over 90 minutes. If you tolerate it well and do not have any bad side effects, the second dose may be given over 60 minutes. Again, if tolerated, each remaining dose may be given over 30 minutes.*

During maintenance chemotherapy, you will have several scans done so the study doctors can see how the tumor is responding to treatment. You will have scans before you begin, and scans after you finish this part of your treatment. You will also have scans after every two cycles of maintenance chemotherapy, to see if the tumor has changed. If the tumor has not gotten larger, you will get more cycles of maintenance chemotherapy, up to a possible total of 12 cycles.

If at any time your disease gets worse or you have serious side effects from the treatment, you will be taken off study therapy. If this happens, your doctor will discuss other treatment options with you at that time.

Research Study Tests and Procedures

The following tests will be done because you are part of this study. These tests are not part of standard care.

Some of the tissue already taken and used to make the diagnosis of your disease and some of the scans used to check your response to treatment will be sent to a central review center as part of COG quality control.

If you have not yet stopped growing, you will have X-rays taken of your right knee every 12 weeks during maintenance chemotherapy to check for normal bone growth. If the study doctors think it is necessary, you may also have MRI scans of both knees done after one or more of these X-rays.

Optional Research Tests

In addition to the treatment goals, we would like to use tumor and blood samples collected on this study to answer some research questions that might benefit future patients. You can choose to be in this clinical trial without taking part in the optional biology research portion. Biology studies will help us find out more about how the study drugs work to destroy cancer cells and help us understand why some people may respond better or worse to the treatments.

Tumor tissue removed during your surgery will be sent to a central lab to document the type of tumor you have. We would like to do some extra tests on your tumor tissue, and take some

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extra blood and do some tests on it. We would also like to do some extra imaging studies, or scans (special MRI scans) to study physical changes in the tumor that happen during treatment.

The goals of the optional research studies are:

- To study DNA from tumor and blood samples to see if certain genetic characteristics (the hereditary information that is passed on from cell to cell and tells the cell how to function) can be used to help identify people who are more likely to have a better treatment response.

- To study tumor tissue and blood to see if the biological characteristics of the tissue and blood relate to how well a subject responds to treatment. We want to look at the amount of certain enzymes (proteins that help with chemical reactions in the body) found in the tumor that help protect it from the effects of chemotherapy. This information will help us to target more effective therapies against high grade glioma in the future.

- To use special MRI scanning techniques that give more information about the blood flow, structure, and functioning of the tumor. These scans are called perfusion MRIs and diffusion MRIs. They will be used together with the standard MRI scans to see if they can help identify people who are more likely to have a better treatment response.

The table below gives information about the samples we would like to use for the optional research studies.

Samples for Optional Research Studies

Who will we ask for a sample?	What Sample(s) are we asking for?	When will we ask for the sample(s)?
All subjects	Blood (about 2 teaspoonfuls if you do not agree to allow us to collect tumor tissue and about 3 teaspoonfuls, if you do allow us to collect tumor tissue)	Before treatment begins
All subjects	Tumor tissue	At the time of surgery
Subjects with tumor visible on post-surgery scan done before treatment begins	Special MRI scans	Before treatment begins, Before maintenance therapy begins, prior to cycle 3 of Maintenance and at the completion of therapy.

Although these studies are very important to understanding more about treatments for high-grade glioma, the results of these studies will not directly affect your treatment. The test results will not be given back to you.

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HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study for about 12 to 14 months. After treatment, subjects will have follow-up examinations and medical tests. We would like to continue to find out about your health for about 10 years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study.

Your doctor or the study doctor may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experiences side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

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WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications.

Common side effects include nausea, vomiting, hair loss, and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. Some chemotherapy may lead to sterility. Sterility is the inability to have children. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy.

The risks of temozolomide, which is commonly given as treatment, and risks of standard radiation therapy are listed in the tables in **Attachment #2**.

Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not cure the cancer or that the cancer can go away after the treatment and then come back at a later date.

For Women:
The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your regular doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid nursing.

For Men:
The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid

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pregnancy that works well or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your regular doctor immediately.

Risks of Study

There is a risk that the experimental chemoradiotherapy treatment with vorinostat may not work as well as the common chemoradiotherapy treatment with temozolomide. There is also a risk that you may have more side effects from the experimental chemoradiotherapy treatment.

There is also a risk that the experimental combination of bevacizumab and temozolomide during maintenance therapy may not be as effective as the commonly used maintenance therapy with temozolomide. There is also the risk that you may have more side effects from the bevacizumab and temozolomide than you would from temozolomide alone. The major concerns with bevacizumab are high blood pressure, protein in the urine that may mean kidney damage, bleeding, blood clots, heart damage and poor healing after surgery. These side effects are usually mild, but they can be life-threatening. Bevacizumab may make the side effects from temozolomide worse.

The risks of the commonly used temozolomide are listed in the table on **Attachment #2**. **The risks and side effects related to the study drugs vorinostat and bevacizumab are shown in the tables below.**

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Risks and side effects related to <u>vorinostat</u> include those which are:

Likely	Less Likely	Rare but serious
• Fewer red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of platelets that may cause you to bruise and bleed more easily • A feeling of extreme tiredness, weakness, sleepiness, or not feeling well that is not relieved by sleep • Loss of appetite • Diarrhea • Nausea • Vomiting	• Low numbers of white blood cells called lymphocytes and / or neutrophils that may make it easier to get infections. The infections may be life threatening • Low number of white blood cells can make it easier to get infections • Fever (high temperature) • Hair loss • Constipation • Excessive loss of water from the body • Dry mouth • Acid or upset stomach (heartburn) • Change in the way things taste • Infection • Abnormally low level of the protein albumin in the blood. Low albumin may result in leaking of fluid from the blood into the tissue • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of sugar in the blood that may require treatment • Abnormally low levels of certain salts (electrolytes) like phosphate and/or calcium and/or sodium, and/or potassium in the body which may require that you take supplements by mouth or vein • An involuntary and abnormal contraction of muscle • Loss of strength in the muscles • Dizziness (or sensation of lightheadedness, giddiness, spinning or rocking) • Abdominal pain • Cough • Feeling short of breath • Weight loss	• Death of skin tissue which could lead to surgical treatment and be life-threatening

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Risks and side effects related to Bevacizumab include those which are:

Likely	Less Likely	Rare But Serious

• Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future
• High blood pressure
	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
	• Fewer white blood cells and red blood cells in the blood
	  ○ a low number of white blood cells can make it easier to get infections*
	  ○ a low number of red blood cells can make you feel tired and weak
	• Fast heart rate usually originating in an area located above the ventricles
	• Vertigo; sensation of a spinning movement
	• General pain, pain in the chest (not heart-related), in the abdomen (belly), in the muscles, or in the joints
	• Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools and abdominal (belly) pain
	• Constipation
	• Diarrhea
	•Acid or upset stomach (heartburn)
	•Bleeding in some organ(s) of the digestive system
	• Blockage in an organ(s)/part(s) of the digestive tract
	• Partial or complete blockage of the small and/or large bowel. The block is a functional rather than actual blockage of the bowel.
	• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)
	• Nausea
	• Vomiting
	• A feeling of weakness and/or tiredness
	• Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing
	• Allergic reaction by your body to the drug product that can occur
		• Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
		• Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal heart electrocardiogram (EKG) and blood tests can confirm damage to the heart.
		• Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
		• Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
		• Heart attack caused by a blockage or decreased blood supply to the heart
		• Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)
		• Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
		• Abnormal hole between an organ of the digestive tract and another organ of tissue
		• A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
		• Development of ulcers (erosion (ulceration) of the lining of the intestines which can result in pain and/or bleeding
		• Allergic reaction which can be life threatening and potentially fatal. This reaction requires immediate medical treatment. It may include fever, chills and skin rash. Less commonly wheezing, shortness of breath, swelling of the throat, drop in blood pressure, and rapid heart rate may occur.

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	immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing • Infection including infection (collection of pus) around the rectum • Premature opening of a wound along surgical stitches after surgery • Delayed or poor wound healing after surgery • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of liver or bone enzyme called alkaline phosphatase indicating bone disease or liver irritation or damage • Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle • Loss of weight • Loss of appetite • Aches and pains in the muscles and joints • Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of this drug. • Destruction or death of jawbone • Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness) • Headache or head pain • Nerve damage that may cause pain, burning, numbness, and tingling in the hands and feet and may affect the ability to perform tasks that require fine movements • Fainting • Blood in the urine • Protein in the urine which may indicate kidney damage • Bleeding in the vagina • Runny or stuffy nose, sneezing	• Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures) • Severe bleeding which can occur in the brain, lungs, and other parts of the body and which may be life threatening • Stroke caused by decreased blood flow to the brain • Damage to the brain which may lead to difficulty thinking, carrying out normal tasks, seizures (convulsions), difficulty seeing, blindness, or other visual changes, which if caught early can be reversed • Sudden decrease in kidney function • Damage to the kidneys that causes protein to be lost from the blood by leaking from the kidneys into the urine and causing swelling usually in the legs and ankles from fluid build-up in body tissues • Severe damage to the kidneys causing then to stop working and resulting in the buildup of waste products, fluids, salts and minerals in the body. The damage may be permanent and can be life-threatening. • Abnormal hole between part of the urinary system and another organ or tissue • Abnormal hole between the vagina and another organ or tissue • Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs • An abnormal hole in the nasal septum, the wall inside the nose that runs down the middle and divides the nose into two sides. The presence of the hole can cause frequent crusting, blockage, bleeding, whistling while breathing, and running nose • An abnormal hole between the tube that connects the mouth with the stomach (esophagus) AND the lining of the windpipe (trachea). This is a rare, life-threatening and potentially fatal complication. • Blood clots in the arteries which can block the blood flow to such areas as the brain leading to strokes, the heart with possible heart attack, the intestines or the legs. The lack of blood flow can damage these organs. These are more common in older people with

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	• **Cough** • **Shortness of breath** • **Nose bleed** • **Hoarseness or other change in voice** • **Itching** • **Skin rash** • **Hives** • **Formation of a blood clot that plugs the blood vessel and can lead to pain and swelling in the area of the clot. Such clots may also break loose and travel to another area. They can cause damage or be life-threatening depending on where they go.**	**pre-existing problems such as heart or blood vessel disease.**

***Neutropenia (decrease in white blood cells) is a common side effect of chemotherapy drugs. The incidence of this event may be increased when bevacizumab is added to chemotherapy; there was also an increase in neutropenia-related fever and infections, including rare incidences of infection with fatal outcomes.**

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. These potential benefits could include getting rid of the cancer for as long as possible. We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in the study. Standard therapy is described on page 1.**
- **Taking part in another study.**

Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

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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. Information about the certificate is included in **Attachment #3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The drug company that makes vorinostat and the drug company that makes bevacizumab.**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

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. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.
You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. You will not be paid for participation in this study.

This study includes providing specimens to the researchers; there are no plans for you to profit from any new products developed from research done on your specimens.

The NCI will supply the vorinostat and bevacizumab at no charge while you take part in this study. The NCI does not cover the cost of getting the vorinostat and bevacizumab ready and giving it to you, so you or your insurance company may have to pay for this.

It is also possible that the manufacturers may not continue to provide vorinostat and/or bevacizumab to the NCI for some reason. If this would occur, other possible options are:

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- You might be able to get the vorinostat and/or bevacizumab from the manufacturers or your pharmacy but you or your insurance company may have to pay for it.

- If there is no vorinostat and/or bevacizumab available at all, no one will be able to get more and the study would close.

If a problem with getting vorinostat and/or bevacizumab occurs, your study doctor will talk to you about these options.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years from now since all of the people on the study need to have completed treatment.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research related problem or you think you have been injured in this study, contact Dr. XXXX or your doctor at XXXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at XXXX.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX.

WHERE CAN I GET MORE INFORMATION?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

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Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.
You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Optional Research Questions

Please note: This section of the informed consent form is about the optional research tests of this study. You may take part in this additional research if you want to. You can still be a part of the treatment study even if you say 'no' to taking part in these additional research tests.

Please read the sentences below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

1. You may have tumor samples from any biopsies or surgeries I may have had. I understand that this tissue will be used to study certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

2. You may take samples of my blood prior to starting treatment for research about certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

3. I agree to have special MRI scans taken for research studies at the time standard MRI scans are taken for my treatment if I have residual tumor on the MRI before starting therapy. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

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SIGNATURE

I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# IRB Approved:

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Attachment #1
Treatment and Procedures Common to all Patients with High-Grade Gliomas

Central Line
For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Methods for Giving Drugs
Drugs will be given by tablet or liquid swallowed through the mouth **(PO)**.

Chemoradiotherapy with Temozolomide
Chemotherapy with temozolomide is commonly used during radiation therapy for newly diagnosed high-grade glioma. The table below shows this chemotherapy treatment.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	Every Day, for 42 days

Maintenance Therapy with Temozolomide
Temozolomide is commonly used during maintenance therapy for newly diagnosed high-grade glioma. Each cycle of maintenance therapy lasts about 28 days. The table below shows this maintenance chemotherapy treatment.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	1 – 5 of each cycle

The risks of temozolomide are shown in **Attachment #2**.

Standard Radiation Therapy for Subjects on All Treatment Arms
All subjects will receive standard radiation therapy while on this study. Standard radiation therapy for high-grade glioma is radiation therapy to the brain 5 days a week for 6 weeks. The amount of radiation you receive on this study will be the standard amount used to treat newly diagnosed high-grade glioma. The risks of standard radiation therapy are shown in **Attachment #2**.

Standard Tests and Procedures
The following tests and procedures are part of regular cancer care and may be done even if you do not join the study:

- Frequent labs to monitor blood counts and blood chemistries.
- Urine tests to measure how your kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.
- MRI scans to monitor your response to treatment.
- Tests to monitor liver functioning.

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Attachment #2
Risks of Chemotherapy Drugs and Radiation Used to Treat High-Grade Gliomas

Risks and side effects related to temozolomide include those which are:

Likely	Less Likely	Rare But Serious

• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Nausea
• Vomiting
• Constipation
• Loss of appetite
	• Diarrhea
	• Headache
	• Tiredness
	• Difficulty swallowing
	• Dizziness
	• Anxiety or depression
	• Difficulty sleeping
	• Rash
	• Itching
	• Increased need to urinate
	• Urinary tract infections
	• Mouth sores
	• Fluid build-up in legs and arms
	• Hair loss
	• Elevation in the blood of certain enzymes found in the liver
	• Visual disturbances that may cause double vision
	• Forgetfulness or confusion
	• Aches and pains in muscles and joints
	• Pain in the abdomen
		• Convulsions
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening
		• Partial paralysis or weakness of one side of the body
		• Blood clots which may be life-threatening
		• A new cancer or leukemia resulting from this treatment

Radiation Risks

All types of radiation therapy have side effects. Some side effects depend on the location of the tumor. Some go away during or soon after treatment (short-term effects), and others may appear later (long-term effects). In addition, the side effects of radiation can be made worse by other treatments that are given (surgery, chemotherapy, or other medicine). There may be side effects that we do not know about yet. The list below gives possible short-term and long-term side effects.

Short-term: **Possible short–term side effects of radiation therapy include nausea and vomiting; fatigue (tiredness) and loss of appetite; irritation or redness of the skin and hair loss corresponding to the entrance and exit points of the radiation beams; rarely there is peeling of the skin at the site of irradiation; if the ear canal or middle ear receives a significant doses there may be an increase in the amount of ear wax (cerumen), there may also be a feeling of fullness that may last for weeks or months although this should be uncommon; in general, blood counts are not reduced by treatment of small volumes of the brain, for those children who have received chemotherapy and G-CSF prior to radiation therapy there may be a transient lowering of counts during treatment although this would most likely be due to the prior chemotherapy. Hospitalization should not be required during radiation therapy. In the event that you require general anesthesia or sedation during**

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radiation therapy, the short term side effects of treatment listed above may be slightly worse, including fatigue and loss of appetite.

Long-term: **The occurrence and severity of long-term side effects of radiation therapy to the brain depend on the age of the patient at the time of treatment, the area of the brain that requires treatment, complications that arise from the tumor or treatments prior to radiation therapy such as surgery and chemotherapy. Growth hormone deficiency after radiation therapy is common. Less common are deficiencies in thyroid hormone, stress (adrenal) hormone, and the hormones required for puberty. Any type of hearing loss after radiation therapy alone occurs only in the minority of cases and many years after treatment. Combined with chemotherapy such as that used in this study, hearing loss maybe seen within one to two years after radiation therapy. Radiation therapy may affect the ability to learn and, generally speaking, overall performance in school. Radiation therapy may also affect growth and development by decreasing the growth of bone and soft tissues that are in the field of treatment. Permanent hair loss occurs rarely. The doses of radiation used in this study are generally accepted as safe, meaning that the chance of breakdown of normal tissue (necrosis) or significant blood vessel damage that would result in stroke or permanent neurologic damage is very rare. With any type of radiation therapy there is always the chance that another tumor may appear years later in tissues that are in the field of radiation.**

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Attachment #3
Certificate of Confidentiality

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.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH – PHASE II STUDY

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the 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 local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACNS0822, *A Randomized Phase II/III Study of Vorinostat and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children with Newly Diagnosed High-Grade Gliomas*

PART 2 – Comparing Three Treatments

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to take part in this research study because you have been diagnosed with a type of brain tumor called a high-grade glioma. A "high-grade" glioma is a tumor that grows fast and is more likely to spread.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for high-grade gliomas and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

Standard treatment for high-grade gliomas includes surgery to remove as much tumor as possible followed by radiation therapy (treatment with high-dose x-rays). Treatment may also include chemotherapy (anti-cancer drugs) during and after radiation treatment. Temozolomide is one of the chemotherapy drugs often used during radiation therapy to treat newly diagnosed high-grade glioma. Anti-cancer drugs, such as temozolomide, are also commonly used in

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Maintenance therapy for newly diagnosed high-grade glioma. Maintenance therapy is therapy given after radiation therapy.

WHY IS THIS STUDY BEING DONE?

High-grade gliomas are hard to treat successfully. Study doctors want to find treatments that will be better at getting rid of or shrinking high-grade gliomas. One thing they want to do is try using different chemotherapy drugs during radiation therapy. Treatment that combines chemotherapy and radiation therapy at the same time is called "chemoradiotherapy". Two drugs that will be used in this study are vorinostat and bevacizumab.

Early studies have shown that vorinostat may help radiation therapy work better to get rid of cancer cells. One study of adults with high-grade glioma found that vorinostat helped keep the cancer from getting worse over 6 months. Recently, a study was completed to find the highest dose of vorinostat that can be given safely to children.

Study doctors also want to see if using different drugs during maintenance therapy will be better than treatment with temozolomide in helping to get rid of or shrink high-grade gliomas. Another drug that they want to try together with temozolomide is bevacizumab. Temozolomide is commonly used in maintenance therapy for brain tumors. It is well-tolerated and has fewer side effects than other drugs commonly used in maintenance therapy. Study doctors want to find out if adding bevacizumab to treatment with temozolomide during maintenance therapy will work better than temozolomide alone. Bevacizumab is a drug that works differently than traditional chemotherapy drugs. Cancer cells need to have a blood supply just as normal body cells do. Bevacizumab is an antibody that works to stop the growth of blood vessels in the tumor.

In studies of adults with different types of cancer, patients who had bevacizumab added to their chemotherapy treatments did better than those who did not. Other studies of adults with high-grade gliomas suggest that adding bevacizumab to treatment with other drugs is well-tolerated and works better than either the bevacizumab or the other drugs alone to help keep the cancer from getting worse. Bevacizumab was recently approved for use in adults with recurrent high-grade glioma. Early results are available from an ongoing study of children with newly-diagnosed brain tumors. These children are being treated with the combination of temozolomide, irinotecan and bevacizumab during maintenance therapy and the results to date suggest the combination is well-tolerated. Study doctors think the combination of temozolomide and bevacizumab will be well-tolerated by children who take part in this study, and that the combination may work better than temozolomide alone to get rid of or shrink high-grade gliomas.

This study is being done in 3 parts. In Part 1 of this study we found the dose of vorinostat that can be given safely to subjects during radiation therapy. This dose will now be used in this part of the study, Part 2. Part 2 of this study will test and compare 3 treatments. Part 3 of this study will compare the 2 best treatments from Part 2. People who are in Part 2 of this study will not be in Part 3. We are now doing Part 2 of the study. You are being asked to enroll on Part 2 of this study.

The goals of Part 2 of this study are to:

- **Find out what effects, good and/or bad, chemoradiotherapy with vorinostat followed by maintenance therapy with bevacizumab and temozolomide has on people with newly diagnosed high-grade gliomas. The combination of vorinostat with radiation therapy is experimental. Maintenance therapy with bevacizumab and temozolomide is experimental.**

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- **Find out what effects, good and/or bad, chemoradiotherapy with bevacizumab followed by maintenance therapy with bevacizumab and temozolomide has on people with newly diagnosed high-grade gliomas. The combination of bevacizumab with radiation therapy is experimental. Maintenance therapy with bevacizumab and temozolomide is experimental.**

- **Find out what effects, good and/or bad, chemoradiotherapy with temozolomide followed by maintenance therapy with bevacizumab and temozolomide has on people with newly diagnosed high-grade gliomas. The combination of temozolomide with radiation therapy is not experimental. Maintenance therapy with bevacizumab and temozolomide is experimental.**

- **Compare the effects of the three treatments above to find out which is better at getting rid of or shrinking tumors and has the least amount of side effects.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of people enrolled on this study is expected to be up to 268. We enrolled 6 patients on Part 1. We will enroll up to 120 people on Part 2 of this study. Later, we will enroll up to 142 more people on Part 3 of this study.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Random Assignment

Subjects (people participating in the study) will receive one of 3 different treatment plans. The treatment plan they receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer to make sure that there are about the same number of people on each treatment plan of the study. The randomization process is described in the COG Family Handbook for Children with Cancer.

Treatment Plan

The treatment plans involve cancer fighting medicine called chemotherapy and radiation therapy. The treatment on this clinical trial takes about 12 to 14 months. It is divided into 2 phases.

The first phase of treatment is called "chemoradiotherapy". This phase lasts about 70 days, or 10 weeks. During this first phase, you will be given radiation therapy to the brain 5 days a week for 6 weeks. Within the first week of starting radiation therapy, you will begin taking one of 3 drugs (bevacizumab, vorinostat, or temozolomide) during this phase. You will continue taking the drug while you receive radiation therapy. After you complete radiation therapy and the treatment with the drug, you will have a 4-week rest, during which no treatment is given.

The second phase of treatment, called Maintenance therapy, begins after the 4-week rest period. During Maintenance therapy, you will not receive any further radiation therapy but you will have more chemotherapy. Maintenance therapy consists of 1 cycle of chemotherapy treatment repeated for up to a total of 12 cycles. Each cycle is 28 days long. During each cycle, you will receive two drugs, called bevacizumab and temozolomide. Temozolomide will be given

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on 5 days and bevacizumab will be given on 2 days during each cycle. Maintenance therapy lasts about 336 days or 11 months.

The 3 treatment plans are the same except for a difference in what drug you will receive during chemoradiotherapy. All treatment plans will use the same radiation therapy. All treatment plans will use the same Maintenance chemotherapy.

The 3 treatment arms are called Arm A, Arm B, and Arm C as follows:

- **Arm A: Chemoradiotherapy with vorinostat followed by maintenance chemotherapy with bevacizumab and temozolomide.**
- **Arm B: Chemoradiotherapy with temozolomide followed by maintenance chemotherapy with bevacizumab and temozolomide.**
- **Arm C: Chemoradiotherapy with bevacizumab followed by maintenance chemotherapy with bevacizumab and temozolomide.**

Randomization

Randomization: Subjects will be randomized to either Arm A with vorinostat, Arm B with temozolomide, or Arm C with bevacizumab. The radiation therapy itself will be the same in all groups of subjects. Maintenance therapy will also be the same in all groups of subjects.

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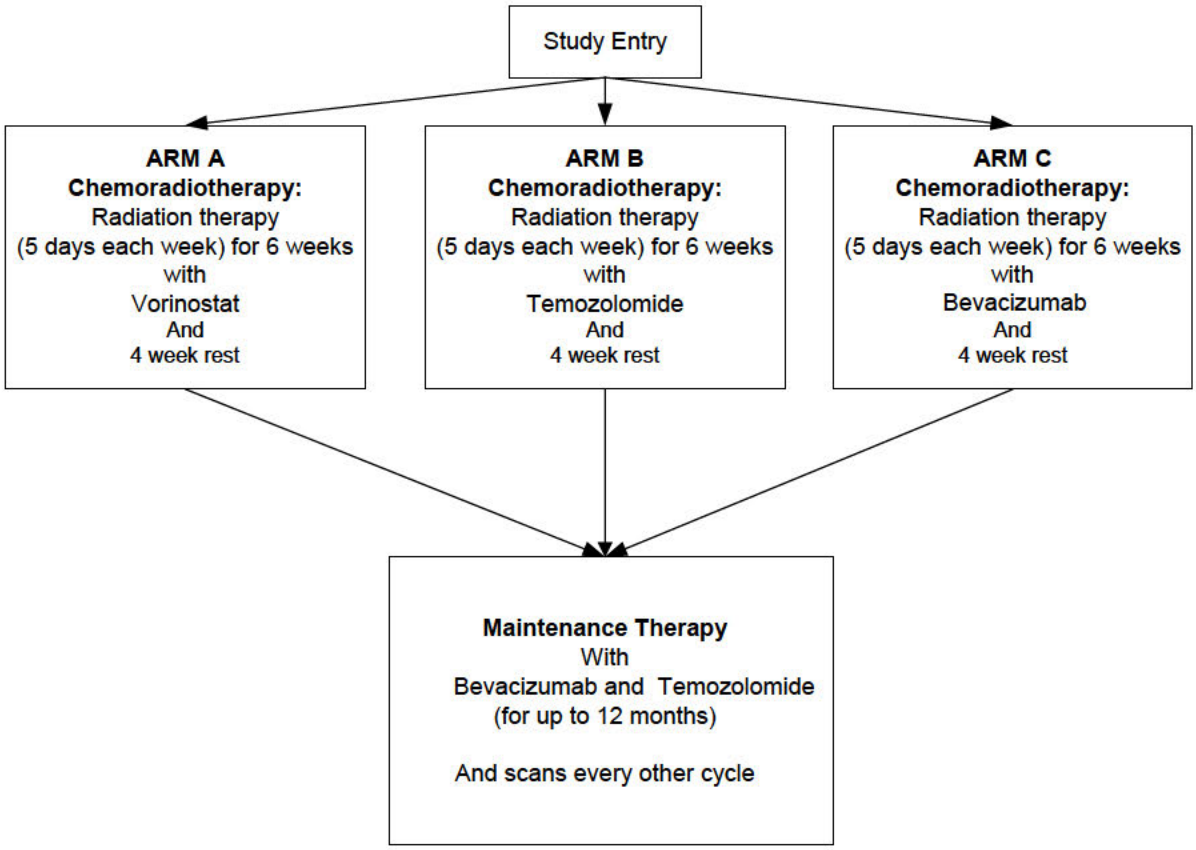
Diagram of Treatment

A diagram of treatment on Part 2 of this study can be seen below.



Treatment Plan Tables

Treatment that is commonly used for newly diagnosed high-grade gliomas is described in **Attachment #1**. This includes the standard radiation therapy that all subjects will receive, and also the commonly used temozolomide chemotherapy that subjects on study treatment Arm B will receive during radiation therapy and that all subjects will receive during maintenance therapy. The following drug therapies relate to the experimental comparison of the treatment groups in this study and to the experimental Maintenance therapy for all subjects.

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. It can be given by IV push over several minutes or by infusion over minutes or hours.

Most drugs on this study will be given using a needle or tubing inserted into a vein **(IV).**

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Chemoradiotherapy Treatment for Subjects who are on Treatment Arm A
Subjects on Arm A will receive vorinostat during the chemoradiotherapy phase of treatment. The experimental treatment is using vorinostat instead of temozolomide.

Drug	How the drug will be given	Days
Vorinostat	PO (1 to 2 hours before radiation therapy is given)	1-5, 8-12, 15-19, 22-26, 29-33, 36-40

If you vomit the dose within 30 minutes and the pill is visible, repeat the same dose. If you vomit 30 minutes after taking the dose or take the liquid dose do not repeat it.

Subjects on Arm A will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Chemoradiotherapy Treatment for Subjects who are on Treatment Arm B
Subjects on Arm B will receive temozolomide during the chemoradiotherapy phase of treatment. See **Attachment #1**.

Subjects on Arm B will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Chemoradiotherapy Treatment for Subjects who are on Treatment Arm C
Subjects on Arm C will receive bevacizumab during the chemoradiotherapy phase of treatment. The experimental treatment is using bevacizumab instead of temozolomide.

Drug	How the drug will be given	Days
Bevacizumab	IV over 90 minutes*, 2 hours before radiation therapy is given	22 and 36

**The first dose will be given over 90 minutes. If you tolerate it well and do not have any bad side effects, the second dose may be given over 60 minutes. Again, if tolerated, each remaining dose may be given over 30 minutes.*

Subjects on Arm C will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Maintenance Chemotherapy Treatment for ALL SUBJECTS on ALL Treatment Arms
All subjects on this study will receive the same chemotherapy drugs during Maintenance chemotherapy. These drugs are bevacizumab and temozolomide. The purpose of Maintenance chemotherapy is to kill any remaining glioma cells that may regrow and cause a relapse (cancer coming back). Each Maintenance cycle lasts about 28 days and the cycle may be repeated for up to a total of 12 cycles. Maintenance lasts about 11 months. The experimental treatment is using bevacizumab and temozolomide instead of temozolomide alone as maintenance therapy.

Drug	How the drug will be given	Days
Bevacizumab	IV over 90 minutes*	1 and 15
Temozolomide	PO	1-5

**The first dose will be given over 90 minutes. If you tolerate it well and do not have any bad side effects, the second dose may be given over 60 minutes. Again, if tolerated, each remaining dose may be given over 30 minutes.*

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During maintenance chemotherapy, you will have several scans done so the study doctors can see how the tumor is responding to treatment. You will have scans before you begin, and scans after you finish this part of your treatment. You will also have scans after every two cycles of maintenance chemotherapy, to see if the tumor has changed. If the tumor has not gotten larger, you will get more cycles of maintenance chemotherapy, up to a possible total of 12 cycles.

If at any time your disease gets worse or you have serious side effects from the treatment, you will be taken off study therapy. If this happens, your doctor will discuss other treatment options with you at that time.

Research Study Tests and Procedures

The following tests will be done because you are part of this study. These tests are not part of standard care.

Some of the tissue already taken and some of the scans used to check your response to treatment will be sent to a central review center as part of COG quality control.

If you have not yet stopped growing, you will have X-rays taken of your right knee every 12 weeks during maintenance chemotherapy to check for normal bone growth. If the study doctors think it is necessary, you may also have MRI scans of both knees done after one or more of these X-rays.

Optional Research Tests

In addition to the treatment goals, we would like to use tumor and blood samples collected on this study to answer some research questions that might benefit future patients. You can choose to be in this clinical trial without taking part in the optional biology research portion. Biology studies will help us find out more about how the study drugs work to destroy cancer cells and help us understand why some people may respond better or worse to the treatments.

Tumor tissue removed during your surgery will be sent to a central lab to document the type of tumor you have. We would like to do some extra tests on your tumor tissue, and take some extra blood and do some tests on it. We would also like to do some extra imaging studies, or scans (special MRI scans) to study physical changes in the tumor that happen during treatment.

The goals of the optional research studies are:

- To study DNA from tumor and blood samples to see if certain genetic characteristics (the hereditary information that is passed on from cell to cell and tells the cell how to function) can be used to help identify people who are more likely to have a better treatment response.

- To study tumor tissue and blood to see if the biological characteristics of the tissue and blood relate to how well a subject responds to treatment. We want to look at the amount of certain enzymes (proteins that help with chemical reactions in the body) found in the tumor that help protect it from the effects of chemotherapy. This information will help us to target more effective therapies against high grade glioma in the future.

- To use special MRI scanning techniques that give more information about the blood flow, structure, and functioning of the tumor. These scans are called perfusion MRIs and diffusion

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MRIs. They will be used together with the standard MRI scans to see if they can help identify people who are more likely to have a better treatment response.

The table below gives information about the samples we would like to use for the optional research studies.

Samples for Optional Research Studies

Who will we ask for a sample?	What Sample(s) are we asking for?	When will we ask for the sample(s)?
All subjects	Blood (about 2 teaspoonfuls if you do not agree to allow us to collect tumor tissue and about 3 teaspoonfuls, if you do allow us to collect tumor tissue)	Before treatment begins
All subjects	Tumor tissue	At the time of surgery
Subjects with tumor visible on post-surgery scan done before treatment begins	Special MRI scans	Before treatment begins, Before maintenance therapy begins, prior to cycle 3 and at the end of treatment.

Although these studies are very important to understanding more about treatments for high-grade glioma, the results of these studies will not directly affect your treatment. The test results will not be given back to you.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study for about 12 to 14 months. After treatment, subjects will have follow-up examinations and medical tests. We would like to continue to find out about your health for about 10 years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study.

Your doctor or the study doctor may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experiences side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

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WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications.

Common side effects include nausea, vomiting, hair loss, and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. Some chemotherapy may lead to sterility. Sterility is the inability to have children. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy.

The risks of temozolomide, which is commonly given as treatment, and risks of standard radiation therapy are listed in the tables in **Attachment #2**.

Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not cure the cancer or that the cancer can go away after the treatment and then come back at a later date.

Reproductive risks
Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Risks of Study
If you are assigned to Arm B with temozolomide, there is a risk that you may not receive a chemoradiotherapy treatment that is better at getting rid of your cancer.

If you are assigned to Arm A with vorinostat or to Arm C with bevacizumab, there is a risk that the experimental chemoradiotherapy treatment may not work as well as the chemoradiotherapy treatment with temozolomide. There is also a risk that you may have more side effects from the experimental chemoradiotherapy treatment.

For all subjects in this study, there is the risk that the experimental combination of bevacizumab and temozolomide during maintenance therapy may not be as effective as the commonly used maintenance therapy with temozolomide alone. There is also the risk

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that you may have more side effects from the bevacizumab and temozolomide than you would from temozolomide alone. The major concerns with bevacizumab are high blood pressure, protein in the urine that may mean kidney damage, bleeding, blood clots, heart damage and poor healing after surgery. These side effects are usually mild, but they can be life-threatening. Bevacizumab may make the side effects from temozolomide worse.

The risks of the commonly used temozolomide are listed in the table on **Attachment #2**. **The risks and side effects related to the study drugs bevacizumab and vorinostat are shown in the tables below.**

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Risks and side effects related to Bevacizumab include those which are:

Likely	Less Likely	Rare But Serious

• Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future
• High blood pressure
	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
	• Fewer white blood cells and red blood cells in the blood
	  ○ a low number of white blood cells can make it easier to get infections*
	  ○ a low number of red blood cells can make you feel tired and weak
	• Fast heart rate usually originating in an area located above the ventricles
	• Vertigo; sensation of a spinning movement
	• General pain, pain in the chest (not heart-related), in the abdomen (belly), in the muscles, or in the joints
	• Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools and abdominal (belly) pain
	• Constipation
	• Diarrhea
	• Acid or upset stomach (heartburn)
	• Bleeding in some organ(s) of the digestive system
	• Blockage in an organ(s)/part(s) of the digestive tract
	• Partial or complete blockage of the small and/or large bowel. The block is a functional rather than actual blockage of the bowel.
	• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)
	• Nausea
	• Vomiting
	• A feeling of weakness and/or tiredness
	• Reaction that can occur during
		• Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
		• Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal heart electrocardiogram (EKG) and blood tests can confirm damage to the heart.
		• Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
		• Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
		• Heart attack caused by a blockage or decreased blood supply to the heart
		• Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)
		• Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
		• Abnormal hole between an organ of the digestive tract and another organ of tissue
		• A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
		• Development of ulcers (erosion (ulceration) of the lining of the intestines which can result in pain and/or bleeding
		• Allergic reaction which can be life threatening and potentially fatal. This

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	or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing • Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing • Infection including infection (collection of pus) around the rectum • Premature opening of a wound along surgical stitches after surgery • Delayed or poor wound healing after surgery • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of liver or bone enzyme called alkaline phosphatase indicating bone disease or liver irritation or damage • Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle • Loss of weight • Loss of appetite • Aches and pains in the muscles and joints • Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of this drug. • Destruction or death of jawbone • Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness) • Headache or head pain • Nerve damage that may cause	reaction requires immediate medical treatment. It may include fever, chills and skin rash. Less commonly wheezing, shortness of breath, swelling of the throat, drop in blood pressure, and rapid heart rate may occur. • Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures) • Severe bleeding which can occur in the brain, lungs, and other parts of the body and which may be life threatening • Stroke caused by decreased blood flow to the brain • Damage to the brain which may lead to difficulty thinking, carrying out normal tasks, seizures (convulsions), difficulty seeing, blindness, or other visual changes, which if caught early can be reversed • Sudden decrease in kidney function • Damage to the kidneys that causes protein to be lost from the blood by leaking from the kidneys into the urine and causing swelling usually in the legs and ankles from fluid build-up in body tissues • Severe damage to the kidneys causing then to stop working and resulting in the buildup of waste products, fluids, salts and minerals in the body. The damage may be permanent and can be life-threatening. • Abnormal hole between part of the urinary system and another organ or tissue • Abnormal hole between the vagina and another organ or tissue • Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs • An abnormal hole in the nasal septum, the wall inside the nose that runs down the middle and divides the nose into two sides. The presence of the hole can cause frequent crusting, blockage, bleeding, whistling while breathing, and running nose • An abnormal hole between the tube that connects the mouth with the

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	pain, burning, numbness, and tingling in the hands and feet and may affect the ability to perform tasks that require fine movements • **Fainting** • **Blood in the urine** • **Protein in the urine which may indicate kidney damage** • **Bleeding in the vagina** • **Runny or stuffy nose, sneezing** • **Cough** • **Shortness of breath** • **Nose bleed** • **Hoarseness or other change in voice** • **Itching** • **Skin rash** • **Hives** • **Formation of a blood clot that plugs the blood vessel and can lead to pain and swelling in the area of the clot. Such clots may also break loose and travel to another area. They can cause damage or be life-threatening depending on where they go.**	**stomach (esophagus) AND the lining of the windpipe (trachea). This is a rare, life-threatening and potentially fatal complication.** • **Blood clots in the arteries which can block the blood flow to such areas as the brain leading to strokes, the heart with possible heart attack, the intestines or the legs. The lack of blood flow can damage these organs. These are more common in older people with pre-existing problems such as heart or blood vessel disease.**

***Neutropenia (decrease in white blood cells) is a common side effect of chemotherapy drugs. The incidence of this event may be increased when bevacizumab is added to chemotherapy; there was also an increase in neutropenia-related fever and infections, including rare incidences of infection with fatal outcomes.**

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Risks and side effects related to <u>vorinostat</u> include those which are:

Likely	Less Likely	Rare but serious
• Fewer red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of platelets that may cause you to bruise and bleed more easily • A feeling of extreme tiredness, weakness, sleepiness, or not feeling well that is not relieved by sleep • Loss of appetite • Diarrhea • Nausea • Vomiting	• Low numbers of white blood cells called lymphocytes and / or neutrophils that may make it easier to get infections. The infections may be life threatening • Low number of white blood cells can make it easier to get infections • Fever (high temperature) • Hair loss • Constipation • Excessive loss of water from the body • Dry mouth • Acid or upset stomach (heartburn) • Change in the way things taste • Infection • Abnormally low level of the protein albumin in the blood. Low albumin may result in leaking of fluid from the blood into the tissue • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of sugar in the blood that may require treatment • Abnormally low levels of certain salts (electrolytes) like phosphate and/or calcium and/or sodium, and/or potassium in the body which may require that you take supplements by mouth or vein • An involuntary and abnormal contraction of muscle • Loss of strength in the muscles • Dizziness (or sensation of lightheadedness, giddiness, spinning or rocking) • Abdominal pain • Cough • Feeling short of breath • Weight loss	• Death of skin tissue which could lead to surgical treatment and be life-threatening

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In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. These potential benefits could include getting rid of the cancer for as long as possible. We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in the study. Standard therapy is described on page 1.**
- **Taking part in another study.**

Please talk to your doctor about these and other options.

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WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

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. Information about the certificate is included in **Attachment #3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The drug company that makes vorinostat and the drug company that makes bevacizumab.**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

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. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. You will not be paid for participation in this study.

This study includes providing specimens to the researchers; there are no plans for you to profit from any new products developed from research done on your specimens.

The NCI will supply the vorinostat and bevacizumab at no charge while you take part in this study. The NCI does not cover the cost of getting the vorinostat and bevacizumab ready and giving it to you, so you or your insurance company may have to pay for this.

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It is also possible that the manufacturers may not continue to provide vorinostat and/or bevacizumab to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get the vorinostat and/or bevacizumab from the manufacturers or your pharmacy but you or your insurance company may have to pay for it.
- If there is no vorinostat and/or bevacizumab available at all, no one will be able to get more and the study would close.

If a problem with getting vorinostat and/or bevacizumab occurs, your study doctor will talk to you about these options.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years from now since all of the people on the study need to have completed treatment.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at XXXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at XXXX

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX

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WHERE CAN I GET MORE INFORMATION?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available at: http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Optional Research Questions
Please note: This section of the informed consent form is about the optional research tests of this study. You may take part in this additional research if you want to. You can still be a part of the treatment study even if you say 'no' to taking part in these additional research tests.

Please read the sentences below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

1. You may have tumor samples from any biopsies or surgeries I may have had. I understand that this tissue will be used to study certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

2. You may take samples of my blood prior to starting treatment for research about certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

3. I agree to have special MRI scans taken for research studies at the time standard MRI scans are taken for my treatment if I have residual tumor on the MRI before starting therapy. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

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SIGNATURE

I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# IRB Approved:

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Attachment #1
Treatment and Procedures Common to all Patients with High-Grade Gliomas

Central Line
For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Methods for Giving Drugs
Drugs will be given by tablet or liquid swallowed through the mouth **(PO)**.

Temozolomide Chemoradiotherapy for Subjects on Treatment Arm B
Subjects on Arm B will receive a commonly used chemotherapy for newly diagnosed high-grade glioma during chemoradiotherapy treatment. The table below shows the chemotherapy that subjects on Arm B will receive.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	Every Day, for 42 days

Maintenance Therapy with Temozolomide
Temozolomide is commonly used during maintenance therapy for newly diagnosed high-grade glioma. Each cycle of maintenance therapy lasts about 28 days. The table below shows this maintenance chemotherapy treatment.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	1 – 5 of each cycle

The risks of temozolomide are shown in **Attachment #2**.

Standard Radiation Therapy for Subjects on All Treatment Arms
All subjects will receive standard radiation therapy while on this study. Standard radiation therapy for high-grade glioma is radiation therapy to the brain 5 days a week for 6 weeks. The amount of radiation you receive on this study will be the standard amount used to treat newly diagnosed high-grade glioma. The risks of standard radiation therapy are shown in **Attachment #2**.

Standard Tests and Procedures
The following tests and procedures are part of regular cancer care and may be done even if you do not join the study:

- Frequent labs to monitor blood counts and blood chemistries.
- Urine tests to measure how your kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.
- MRI scans to monitor your response to treatment.
- Tests to monitor liver functioning.

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Attachment #2
Risks of Chemotherapy Drugs and Radiation Used to Treat High-Grade Gliomas

Risks and side effects related to temozolomide include those which are:

Likely	Less Likely	Rare But Serious

• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Nausea
• Vomiting
• Constipation
• Loss of appetite
	• Diarrhea
	• Headache
	• Tiredness
	• Difficulty swallowing
	• Dizziness
	• Anxiety or depression
	• Difficulty sleeping
	• Rash
	• Itching
	• Increased need to urinate
	• Urinary tract infections
	• Mouth sores
	• Fluid build-up in legs and arms
	• Hair loss
	• Elevation in the blood of certain enzymes found in the liver
	• Visual disturbances that may cause double vision
	• Forgetfulness or confusion
	• Aches and pains in muscles and joints
	• Pain in the abdomen
		• Convulsions
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening
		• Partial paralysis or weakness of one side of the body
		• Blood clots which may be life-threatening
		• A new cancer or leukemia resulting from this treatment

Radiation Risks

All types of radiation therapy have side effects. Some side effects depend on the location of the tumor. Some go away during or soon after treatment (short-term effects), and others may appear later (long-term effects). In addition, the side effects of radiation can be made worse by other treatments that are given (surgery, chemotherapy, or other medicine). There may be side effects that we do not know about yet. The list below gives possible short-term and long-term side effects.

Short-term: **Possible short–term side effects of radiation therapy include nausea and vomiting; fatigue (tiredness) and loss of appetite; irritation or redness of the skin and hair loss corresponding to the entrance and exit points of the radiation beams; rarely there is peeling of the skin at the site of irradiation; if the ear canal or middle ear receives a significant doses there may be an increase in the amount of ear wax (cerumen), there may also be a feeling of fullness that may last for weeks or months although this should be uncommon; in general, blood counts are not reduced by treatment of small volumes of the brain, for those children who have received chemotherapy and G-CSF prior to radiation therapy there may be a transient lowering of counts during treatment although this would most likely be due to the prior chemotherapy. Hospitalization should not be required during radiation therapy. In the event that you require general anesthesia or sedation during**

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radiation therapy, the short term side effects of treatment listed above may be slightly worse, including fatigue and loss of appetite.

Long-term: **The occurrence and severity of long-term side effects of radiation therapy to the brain depend on the age of the patient at the time of treatment, the area of the brain that requires treatment, complications that arise from the tumor or treatments prior to radiation therapy such as surgery and chemotherapy. Growth hormone deficiency after radiation therapy is common. Less common are deficiencies in thyroid hormone, stress (adrenal) hormone, and the hormones required for puberty. Any type of hearing loss after radiation therapy alone occurs only in the minority of cases and many years after treatment. Combined with chemotherapy, such as that used in this study, hearing loss maybe seen within one to two years after radiation therapy. Radiation therapy may affect the ability to learn and, generally speaking, overall performance in school. Radiation therapy may also affect growth and development by decreasing the growth of bone and soft tissues that are in the field of treatment. Permanent hair loss occurs rarely. The doses of radiation used in this study are generally accepted as safe, meaning that the chance of breakdown of normal tissue (necrosis) or significant blood vessel damage that would result in stroke or permanent neurologic damage is very rare. With any type of radiation therapy there is always the chance that another tumor may appear years later in tissues that are in the field of radiation.**

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Attachment #3
Certificate of Confidentiality

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.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH – PHASE III STUDY

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the 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 local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACNS0822, *A Randomized Phase II/III Study of Vorinostat and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children with Newly Diagnosed High-Grade Gliomas*

PART 3 – Comparing Two Treatments

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to take part in this research study because you have been diagnosed with a type of brain tumor called a high-grade glioma. A "high-grade" glioma is a tumor that grows fast and is more likely to spread.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for high-grade gliomas and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

Standard treatment for high-grade gliomas includes surgery to remove as much tumor as possible followed by radiation therapy (treatment with high-dose x-rays). Treatment may also include chemotherapy (anti-cancer drugs) during and after radiation treatment. Temozolomide is one of the chemotherapy drugs often used during radiation therapy to treat newly diagnosed

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high-grade glioma. Anti-cancer drugs, such as temozolomide, are also commonly used in Maintenance therapy for newly diagnosed high-grade glioma. Maintenance therapy is therapy given after radiation therapy.

WHY IS THIS STUDY BEING DONE?

High-grade gliomas are hard to treat successfully. Study doctors want to find treatments that will be better at getting rid of or shrinking high-grade gliomas. One thing they want to do is try using different chemotherapy drugs during radiation therapy. Treatment that combines chemotherapy and radiation therapy at the same time is called "chemoradiotherapy".

Early studies have shown that vorinostat may help radiation therapy work better to get rid of cancer cells. One study of adults with high-grade glioma found that vorinostat helped keep the cancer from getting worse over 6 months. Recently, a study was completed to find the highest dose of vorinostat that can be given safely to children.

Study doctors also want to see if using different drugs during maintenance therapy will be better than treatment with temozolomide in helping to get rid of or shrink high-grade gliomas. Another drug that they want to try together with temozolomide is bevacizumab. Temozolomide is commonly used in maintenance therapy for brain tumors. It is well-tolerated and has fewer side effects than other drugs commonly used in maintenance therapy. Study doctors want to find out if adding bevacizumab to treatment with temozolomide during maintenance therapy will work better than temozolomide alone. Bevacizumab is a drug that works differently than traditional chemotherapy drugs. Cancer cells need to have a blood supply just as normal body cells do. Bevacizumab is an antibody that works to stop the growth of blood vessels in the tumor.

In studies of adults with different types of cancer, patients who had bevacizumab added to their chemotherapy treatments did better than those who did not. Other studies of adults with high-grade gliomas suggest that adding bevacizumab to treatment with other drugs is well-tolerated and works better than either the bevacizumab or the other drugs alone to help keep the cancer from getting worse. Bevacizumab was recently approved for use in adults with recurrent high-grade glioma. Early results are available from an ongoing study of children with newly-diagnosed brain tumors. These children are being treated with the combination of temozolomide, irinotecan and bevacizumab during maintenance therapy and the results to date suggest the combination is well-tolerated. Study doctors think the combination of temozolomide and bevacizumab will be well-tolerated by children who take part in this study, and that the combination may work better than temozolomide alone to get rid of or shrink high-grade gliomas.

This study is being done in 3 parts. Parts 1 and 2 are now finished. In Part 1, we found the dose of vorinostat that can be given safely to subjects during radiation therapy. In Part 2, we tested and compared two experimental treatments (one using vorinostat and one using bevacizumab) with treatment using temozolomide. Results from Part 2 showed that *[insert bevacizumab or vorinostat]* worked better than treatment with temozolomide to help keep the cancer from getting worse over one year. We are now doing Part 3 of the study. In Part 3, study doctors want to test and compare chemoradiotherapy using *[insert bevacizumab or vorinostat]* with chemoradiotherapy using temozolomide. By comparing the two treatments in another group of patients, study doctors hope to confirm the results seen in Part 2. You are being asked to enroll on Part 3 of this study.

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The goals of Part 3 of this study are to:

- **Compare the effects of two treatments to find out which is better at getting rid of or shrinking tumors and has the least amount of side effects. The two treatments are:**
    - **Chemoradiotherapy with *[insert either bevacizumab or vorinostat]* followed by maintenance therapy with bevacizumab and temozolomide has on people with newly diagnosed high-grade gliomas. The combination of *[insert either bevacizumab or vorinostat]* with radiation therapy is experimental. Maintenance therapy with bevacizumab and temozolomide is experimental.**
    - **Chemoradiotherapy with temozolomide followed by maintenance therapy with bevacizumab and temozolomide has on people with newly diagnosed high-grade gliomas. The combination of temozolomide with radiation therapy is not experimental. Maintenance therapy with bevacizumab and temozolomide is experimental.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of people enrolled on this study is expected to be up to 268. We enrolled 6 patients on Part 1 and up to 120 people on Part 2 of this study. Now we are enrolling up to 142 more people on Part 3 of this study.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Random Assignment

Subjects (people participating in the study) will receive one of 2 different treatment plans. The treatment plan they receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer to make sure that there are about the same number of people on each treatment plan of the study. The randomization process is described in the COG Family Handbook for Children with Cancer.

Treatment Plan

The treatment plans involve cancer fighting medicine called chemotherapy and radiation therapy. The treatment on this clinical trial takes about 12 to 14 months. It is divided into 2 phases.

The first phase of treatment is called “chemoradiotherapy”. This phase lasts about 70 days or 10 weeks. During this first phase, you will be given radiation therapy to the brain 5 days a week for 6 weeks. Within the first week of starting radiation therapy, you will begin taking one of the 2 drugs (either [*insert bevacizumab or vorinostat*] or temozolomide) used during this phase. You will continue taking the drug while you receive radiation therapy. After you complete radiation therapy and treatment with the drug, you will have a 4-week rest, during which no treatment is given.

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The second phase of treatment, called Maintenance therapy, begins after the 4-week rest period. During Maintenance therapy, you will not receive any further radiation therapy but you will have more chemotherapy. Maintenance therapy consists of 1 cycle of treatment repeated for up to a total of 12 cycles. Each cycle is 28 days long. During each cycle, you will receive two drugs called bevacizumab and temozolomide. Temozolomide will be given on 5 days and bevacizumab will be given on 2 days during each cycle. Maintenance therapy lasts about 336 days or 11 months.

The 2 treatment plans are the same except for a difference in what drug you will receive during chemoradiotherapy. All treatment plans will use the same radiation therapy. All treatment plans will use the same Maintenance chemotherapy.

The 2 treatment arms are called Arm A and Arm B as follows:

- **Arm A: Chemoradiation with [*insert bevacizumab or vorinostat*] followed by maintenance chemotherapy with bevacizumab and temozolomide.**

- **Arm B: Chemoradiation with temozolomide followed by maintenance chemotherapy with bevacizumab and temozolomide.**

Randomization

Participants will be randomized to receive either [*insert bevacizumab or vorinostat*] or temozolomide during radiation therapy. The radiation therapy itself will be the same in all groups of subjects. Maintenance therapy will also be the same in all groups of subjects.

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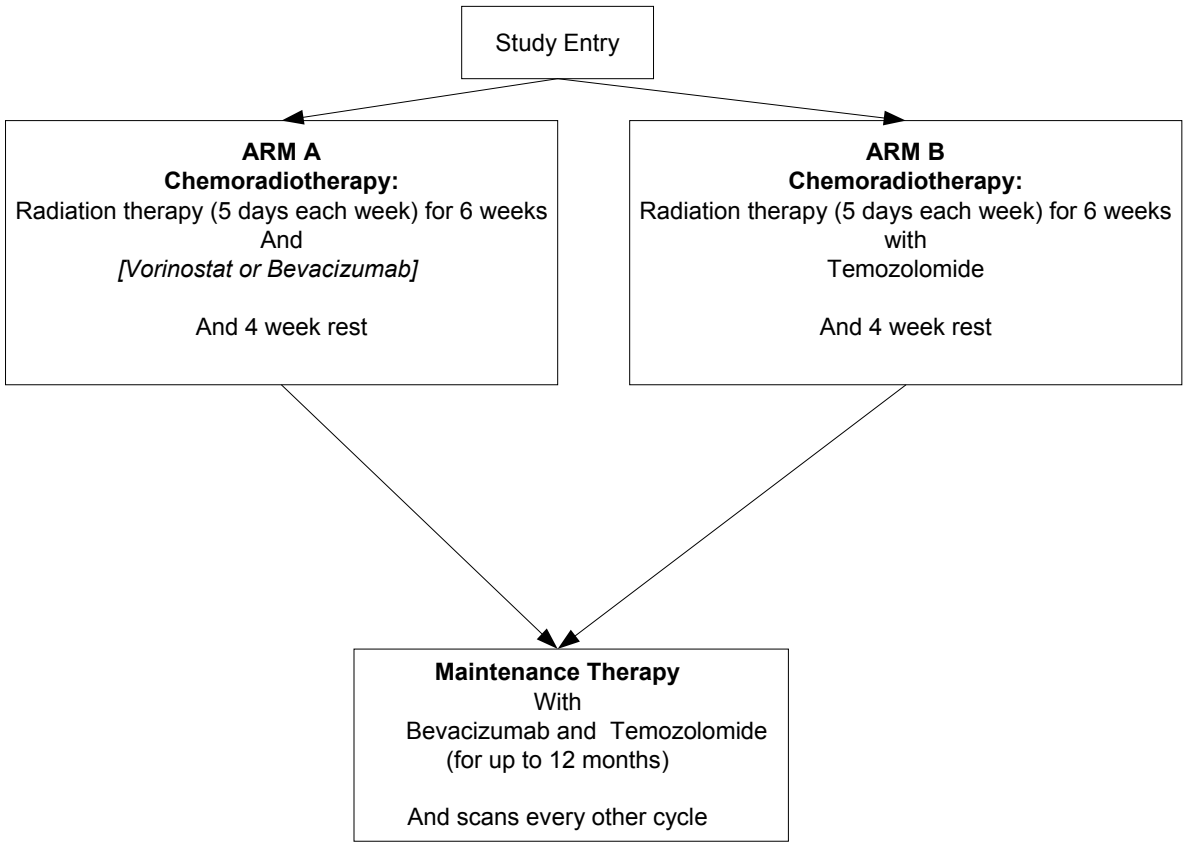
Diagram of Treatment

A diagram of treatment on Part 3 of this study can be seen below.



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Treatment Plan Tables

Treatment that is commonly used for newly diagnosed high-grade gliomas is described in **Attachment #1**. This includes the radiation therapy that all subjects will receive, and also the commonly used temozolomide chemotherapy that subjects on study treatment Arm B will receive during radiation therapy and that all subjects will receive during maintenance therapy. The following drug therapy relates to the experimental comparison of the treatment group in this study, and to the experimental Maintenance therapy for all subjects.

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. It can be given by IV push over several minutes or by infusion over minutes or hours.

Most drugs on this study will be given using a needle or tubing inserted into a vein **(IV).**

Chemoradiotherapy Treatment for Subjects on Treatment Arm A

Subjects on Arm A will receive [*insert bevacizumab or vorinostat*] during the chemoradiotherapy phase of treatment. **The experimental treatment is using [*insert bevacizumab or vorinostat*] instead of temozolomide.**

[insert only the row for bevacizumab or vorinostat]

Drug	How the drug will be given	Days
Vorinostat	PO (1 to 2 hours before radiation therapy is given)	1-5, 8-12, 15-19, 22-26, 29-33, 36-40
Bevacizumab	IV over 90 minutes* 2 hours before radiation therapy is given	22 and 36

**The first dose will be given over 90 minutes. If you tolerate it well and do not have any bad side effects, the second dose may be given over 60 minutes. Again, if tolerated, each remaining dose may be given over 30 minutes.*

Subjects on Arm A will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Chemoradiotherapy Treatment for Subjects who are on Treatment Arm B

Subjects on Arm B will receive temozolomide during the chemoradiotherapy phase of treatment. See Attachment #1.

Subjects on Arm B will receive the standard radiation therapy for high-grade gliomas. Standard radiation therapy is described in **Attachment #1**.

Maintenance Chemotherapy Treatment for ALL SUBJECTS on ALL Treatment Arms

All subjects on this study will receive the same chemotherapy drugs during Maintenance chemotherapy. These drugs are bevacizumab and temozolomide. The purpose of Maintenance chemotherapy is to kill any remaining glioma cells that may regrow and cause a relapse (cancer coming back). Each Maintenance cycle lasts about 28 days and the cycle may be repeated for up to a total of 12 cycles. Maintenance lasts about 11 months. **The experimental treatment is using bevacizumab and temozolomide instead of temozolomide alone as maintenance therapy.**

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Drug	How the drug will be given	Days
Bevacizumab	IV over 90 minutes*	1 and 15
Temozolomide	PO	1-5

**The first dose will be given over 90 minutes. If you tolerate it well and do not have any bad side effects, the second dose may be given over 60 minutes. Again, if tolerated, each remaining dose may be given over 30 minutes.*

During maintenance chemotherapy, you will have several scans done so the study doctors can see how the tumor is responding to treatment. You will have scans before you begin, and scans after you finish this part of your treatment. You will also have scans after every two cycles of maintenance chemotherapy, to see if the tumor has changed. If the tumor has not gotten larger, you will get more cycles of maintenance chemotherapy, up to a possible total of 12 cycles.

If at any time your disease gets worse or you have serious side effects from the treatment, you will be taken off study therapy. If this happens, your doctor will discuss other treatment options with you at that time.

Research Study Tests and Procedures

The following tests will be done because you are part of this study. These tests are not part of standard care.

Some of the tissue already taken and some of the scans used to check your response to treatment will be sent to a central review center as part of COG quality control.

If you have not yet stopped growing, you will have X-rays taken of your right knee every 12 weeks during maintenance chemotherapy to check for normal bone growth. If the study doctors think it is necessary, you may also have MRI scans of both knees done after one or more of these X-rays.

Optional Research Tests

In addition to the treatment goals, we would like to use tumor and blood samples collected on this study to answer some research questions that might benefit future patients. You can choose to be in this clinical trial without taking part in the optional biology research portion. Biology studies will help us find out more about how the study drugs work to destroy cancer cells and help us understand why some people may respond better or worse to the treatments.

Tumor tissue removed during your surgery will be sent to a central lab to document the type of tumor you have. We would like to do some extra tests on your tumor tissue, and take some extra blood and do some tests on it. We would also like to do some extra imaging studies, or scans (special MRI scans), to study physical changes in the tumor that happen during treatment.

The goals of the optional research studies are:

- To study DNA from tumor and blood samples to see if certain genetic characteristics (the hereditary information that is passed on from cell to cell and tells the cell how to function) can be used to help identify people who are more likely to have a better treatment response.

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- To study tumor tissue and blood to see if the biological characteristics of the tissue relate to how well a subject responds to treatment. We want to look at the amount of certain enzymes (proteins that help with chemical reactions in the body) found in the tumor that help protect it from the effects of chemotherapy. This information will help us to target more effective therapies against high grade glioma in the future.

- To use special MRI scanning techniques that give more information about the blood flow, structure, and functioning of the tumor. These scans are called perfusion MRIs and diffusion MRIs. They will be used together with the standard MRI scans to see if they can help identify people who are more likely to have a better treatment response.

The table below gives information about the samples we would like to use for the optional research studies.

Samples for Optional Research Studies

Who will we ask for a sample?	What Sample(s) are we asking for?	When will we ask for the sample(s)?
All subjects	Blood (about 2 teaspoonfuls if you do not agree to allow us to collect tumor tissue and about 3 teaspoonfuls, if you do allow us to collect tumor tissue)	Before treatment begins
All subjects	Tumor tissue	At the time of surgery
Subjects with tumor visible on post-surgery scan done before treatment begins	Special MRI scans	Before treatment begins, Before maintenance therapy begins, prior to cycle 3 and at the end of treatment.

Although these studies are very important to understanding more about treatments for high-grade glioma, the results of these studies will not directly affect your treatment. The test results will not be given back to you.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study for about 12 to 14 months. After treatment, subjects will have follow-up examinations and medical tests. We would like to continue to find out about your health for about 10 years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study.

Your doctor or the study doctor may decide to take you off this study under the following circumstances:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experiences side effects from the treatment that are considered too severe

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- if new information becomes available that shows that another treatment would be better for you

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications.

Common side effects include nausea, vomiting, hair loss, and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. Some chemotherapy may lead to sterility. Sterility is the inability to have children. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy.

The risks of temozolomide, which is commonly given as treatment, and risks of radiation therapy are listed in the tables in **Attachment #2**.

Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not cure the cancer or that the cancer can go away after the treatment and then come back at a later date.

<u>Reproductive risks</u>
Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study

Risks of Study
If you are assigned to Arm B with temozolomide, there is a risk that you may not receive a chemoradiotherapy treatment that is better at getting rid of your cancer.

If you are assigned to Arm A with [*insert bevacizumab or vorinostat*], there is a risk that the experimental chemoradiotherapy treatment may not work as well as the

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chemoradiotherapy treatment with temozolomide. There is also a risk that you may have more side effects from the experimental chemoradiotherapy treatment.

For all subjects in this study, there is the risk that the experimental combination of bevacizumab and temozolomide during maintenance therapy may not be as effective as the commonly used maintenance therapy with temozolomide. There is also the risk that you may have more side effects from the bevacizumab and temozolomide that you would from temozolomide alone. The major concerns with bevacizumab are high blood pressure, protein in the urine that may mean kidney damage, bleeding, blood clots, heart damage and poor healing after surgery. These side effects are usually mild, but they can be life-threatening. Bevacizumab may make the side effects from temozolomide worse.

The risks of the commonly used temozolomide are listed in the table on **Attachment #2**. **The risks and side effects related to the study drugs bevacizumab *[if vorinostat then insert "and vorinostat"]* are shown in the tables below.**

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Risks and side effects related to Bevacizumab include those which are:

• Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future
• High blood pressure
	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
	• Fewer white blood cells and red blood cells in the blood
	  ○ a low number of white blood cells can make it easier to get infections*
	  ○ a low number of red blood cells can make you feel tired and weak
	• Fast heart rate usually originating in an area located above the ventricles
	• Vertigo; sensation of a spinning movement
	• General pain, pain in the chest (not heart-related), in the abdomen (belly), in the muscles, or in the joints
	• Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools and abdominal (belly) pain
	• Constipation
	• Diarrhea
	• Acid or upset stomach (heartburn)
	• Bleeding in some organ(s) of the digestive system
	• Blockage in an organ(s)/part(s) of the digestive tract
	• Partial or complete blockage of the small and/or large bowel. The block is a functional rather than actual blockage of the bowel.
	• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)
	• Nausea
	• Vomiting
	• A feeling of weakness and/or tiredness
	• Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood
		• Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
		• Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal heart electrocardiogram (EKG) and blood tests can confirm damage to the heart.
		• Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
		• Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
		• Heart attack caused by a blockage or decreased blood supply to the heart
		• Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)
		• Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
		• Abnormal hole between an organ of the digestive tract and another organ of tissue
		• A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
		• Development of ulcers (erosion (ulceration) of the lining of the intestines which can result in pain and/or bleeding
		• Allergic reaction which can be life threatening and potentially fatal. This reaction requires immediate medical treatment. It may include fever, chills and skin rash. Less commonly

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	pressure, and difficulty breathing • Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing • Infection including infection (collection of pus) around the rectum • Premature opening of a wound along surgical stitches after surgery • Delayed or poor wound healing after surgery • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of liver or bone enzyme called alkaline phosphatase indicating bone disease or liver irritation or damage • Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle • Loss of weight • Loss of appetite • Aches and pains in the muscles and joints • Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of this drug. • Destruction or death of jawbone • Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness) • Headache or head pain • Nerve damage that may cause pain, burning, numbness, and tingling in the hands and feet and may affect the ability to	wheezing, shortness of breath, swelling of the throat, drop in blood pressure, and rapid heart rate may occur. • Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures) • Severe bleeding which can occur in the brain, lungs, and other parts of the body and which may be life threatening • Stroke caused by decreased blood flow to the brain • Damage to the brain which may lead to difficulty thinking, carrying out normal tasks, seizures (convulsions), difficulty seeing, blindness, or other visual changes, which if caught early can be reversed • Sudden decrease in kidney function • Damage to the kidneys that causes protein to be lost from the blood by leaking from the kidneys into the urine and causing swelling usually in the legs and ankles from fluid build-up in body tissues • Severe damage to the kidneys causing then to stop working and resulting in the buildup of waste products, fluids, salts and minerals in the body. The damage may be permanent and can be life-threatening. • Abnormal hole between part of the urinary system and another organ or tissue • Abnormal hole between the vagina and another organ or tissue • Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs • An abnormal hole in the nasal septum, the wall inside the nose that runs down the middle and divides the nose into two sides. The presence of the hole can cause frequent crusting, blockage, bleeding, whistling while breathing, and running nose • An abnormal hole between the tube that connects the mouth with the stomach (esophagus) AND the lining of the windpipe (trachea). This is a rare, life-threatening and potentially

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	perform tasks that require fine movements • Fainting • Blood in the urine • Protein in the urine which may indicate kidney damage • Bleeding in the vagina • Runny or stuffy nose, sneezing • Cough • Shortness of breath • Nose bleed • Hoarseness or other change in voice • Itching • Skin rash • Hives • Formation of a blood clot that plugs the blood vessel and can lead to pain and swelling in the area of the clot. Such clots may also break loose and travel to another area. They can cause damage or be life-threatening depending on where they go.	fatal complication. • Blood clots in the arteries which can block the blood flow to such areas as the brain leading to strokes, the heart with possible heart attack, the intestines or the legs. The lack of blood flow can damage these organs. These are more common in older people with pre-existing problems such as heart or blood vessel disease.

***Neutropenia (decrease in white blood cells) is a common side effect of chemotherapy drugs. The incidence of this event may be increased when bevacizumab is added to chemotherapy; there was also an increase in neutropenia-related fever and infections, including rare incidences of infection with fatal outcomes.**

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[if vorinostat, then include this table]

Risks and side effects related to vorinostat include those which are:

Likely	Less Likely	Rare but serious
• Fewer red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of platelets that may cause you to bruise and bleed more easily • A feeling of extreme tiredness, weakness, sleepiness, or not feeling well that is not relieved by sleep • Loss of appetite • Diarrhea • Nausea • Vomiting	• Low numbers of white blood cells called lymphocytes and / or neutrophils that may make it easier to get infections. The infections may be life threatening • Low number of white blood cells can make it easier to get infections • Fever (high temperature) • Hair loss • Constipation • Excessive loss of water from the body • Dry mouth • Acid or upset stomach (heartburn) • Change in the way things taste • Infection • Abnormally low level of the protein albumin in the blood. Low albumin may result in leaking of fluid from the blood into the tissue • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Increase in the level of sugar in the blood that may require treatment • Abnormally low levels of certain salts (electrolytes) like phosphate and/or calcium and/or sodium, and/or potassium in the body which may require that you take supplements by mouth or vein • An involuntary and abnormal contraction of muscle • Loss of strength in the muscles • Dizziness (or sensation of lightheadedness, giddiness, spinning or rocking) • Abdominal pain • Cough • Feeling short of breath • Weight loss	• Death of skin tissue which could lead to surgical treatment and be life-threatening

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

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ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. These potential benefits could include getting rid of the cancer for as long as possible. We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in the study. Standard therapy is described on page 1.**
- **Taking part in another study**

Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

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. Information about the certificate is included in **Attachment #3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The drug company that makes *[insert if vorinostat is used:* vorinostat*]* and the drug company that makes bevacizumab.**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

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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. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. You will not be paid for participation in this study.

This study includes providing specimens to the researchers; there are no plans for you to profit from any new products developed from research done on your specimens.

The NCI will supply the *[insert if vorinostat used in phase 3:* vorinostat and] bevacizumab at no charge while you take part in this study. The NCI does not cover the cost of getting the *[If vorinostat:* vorinostat and] bevacizumab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturers may not continue to provide the *[insert if vorinostat used in phase 3*: vorinostat and/or] bevacizumab to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the [*insert if vorinostat used in phase 3*: vorinostat and/or] bevacizumab from the manufacturers or your pharmacy but you or your insurance company may have to pay for it.

- If there is no *[insert if vorinostat used in phase 3:* vorinostat and/or] bevacizumab available at all, no one will be able to get more and the study would close.

If a problem with getting *[insert if vorinostat used in phase 3:* vorinostat and/or] bevacizumab occurs, your study doctor will talk to you about these options.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

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During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years from now since all of the people on the study need to have completed treatment.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at XXXXX

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at XXXX

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX

WHERE CAN I GET MORE INFORMATION?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available at: http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Optional Research Questions

Please note: This section of the informed consent form is about the optional research tests of this study. You may take part in this additional research if you want to. You can still be a part of the treatment study even if you say 'no' to taking part in these additional research tests.

Please read the sentences below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

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1. You may have tumor samples from any biopsies or surgeries I may have had. I understand that this tissue will be used to study certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

2. You may take samples of my blood during treatment for research about certain proteins and gene changes in high-grade glioma tumors. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

3. I agree to have special MRI scans taken for research studies at the time standard MRI scans are taken for my treatment if I have residual tumor on the MRI before starting therapy. I understand the results will not be reported to me or to my doctor and will not become part of my health record.

   Yes_____ No_____ _____ / _____
   Initials Date

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SIGNATURE

I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# IRB Approved:

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Attachment #1
Treatment and Procedures Common to all Patients with High-Grade Gliomas

Central Line
For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Methods for Giving Drugs
Drugs will be given by tablet or liquid swallowed through the mouth **(PO)**.

Temozolomide Chemoradiotherapy for Subjects on Treatment Arm B
Subjects on Arm B will receive a commonly used chemotherapy for newly diagnosed high-grade glioma during chemoradiotherapy treatment. The table below shows the chemotherapy that subjects on Arm B will receive.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	Every Day, for 42 days

Maintenance Therapy with Temozolomide
Temozolomide is commonly used during maintenance therapy for newly diagnosed high-grade glioma. Each cycle of maintenance therapy lasts about 28 days. The table below shows this maintenance chemotherapy treatment.

Drug	How the drug will be given	Days
Temozolomide	PO (preferably at bedtime)	1 – 5 of each cycle

The risks of temozolomide are shown in **Attachment #2**.

Standard Radiation Therapy for Subjects on All Treatment Arms
All subjects will receive standard radiation therapy while on this study. Standard radiation therapy for high-grade glioma is radiation therapy to the brain 5 days a week for 6 weeks. The amount of radiation you receive on this study will be the standard amount used to treat newly diagnosed high-grade glioma. The risks of standard radiation therapy are shown in **Attachment #2**.

Standard Tests and Procedures
The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.
- Frequent labs to monitor blood counts and blood chemistries.
- Urine tests to measure how your kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.
- MRI scans to monitor your response to treatment.
- Tests to monitor liver functioning.

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Attachment #2
Risks of Chemotherapy Drugs and Radiation Used to Treat High-Grade Gliomas

Risks and side effects related to temozolomide include those which are:

Likely	Less Likely	Rare But Serious

• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Nausea
• Vomiting
• Constipation
• Loss of appetite
	• Diarrhea
	• Headache
	• Tiredness
	• Difficulty swallowing
	• Dizziness
	• Anxiety or depression
	• Difficulty sleeping
	• Rash
	• Itching
	• Increased need to urinate
	• Urinary tract infections
	• Mouth sores
	• Fluid build-up in legs and arms
	• Hair loss
	• Elevation in the blood of certain enzymes found in the liver
	• Visual disturbances that may cause double vision
	• Forgetfulness or confusion
	• Aches and pains in muscles and joints
	• Pain in the abdomen
		• Convulsions
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening
		• Partial paralysis or weakness of one side of the body
		• Blood clots which may be life-threatening
		• A new cancer or leukemia resulting from this treatment

Radiation Risks

All types of radiation therapy have side effects. Some side effects depend on the location of the tumor. Some go away during or soon after treatment (short-term effects), and others may appear later (long-term effects). In addition, the side effects of radiation can be made worse by other treatments that are given (surgery, chemotherapy, or other medicine). There may be side effects that we do not know about yet. The list below gives possible short-term and long-term side effects.

Short-term: **Possible short–term side effects of radiation therapy include nausea and vomiting; fatigue (tiredness) and loss of appetite; irritation or redness of the skin and hair loss corresponding to the entrance and exit points of the radiation beams; rarely there is peeling of the skin at the site of irradiation; if the ear canal or middle ear receives a significant doses there may be an increase in the amount of ear wax (cerumen), there may also be a feeling of fullness that may last for weeks or months although this should be uncommon; in general, blood counts are not reduced by treatment of small volumes of the brain, for those children who have received chemotherapy and G-CSF prior to radiation therapy there may be a transient lowering of counts during treatment although this would most likely be due to the prior chemotherapy. Hospitalization should not be required during radiation therapy. In the event that you require general anesthesia or sedation during**

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radiation therapy, the short term side effects of treatment listed above may be slightly worse, including fatigue and loss of appetite.

Long-term: **The occurrence and severity of long-term side effects of radiation therapy to the brain depend on the age of the patient at the time of treatment, the area of the brain that requires treatment, complications that arise from the tumor or treatments prior to radiation therapy such as surgery and chemotherapy. Growth hormone deficiency after radiation therapy is common. Less common are deficiencies in thyroid hormone, stress (adrenal) hormone, and the hormones required for puberty. Any type of hearing loss after radiation therapy alone occurs only in the minority of cases and many years after treatment. Combined with chemotherapy, such as that used in this study, hearing loss maybe seen within one to two years after radiation therapy. Radiation therapy may affect the ability to learn and, generally speaking, overall performance in school. Radiation therapy may also affect growth and development by decreasing the growth of bone and soft tissues that are in the field of treatment. Permanent hair loss occurs rarely. The doses of radiation used in this study are generally accepted as safe, meaning that the chance of breakdown of normal tissue (necrosis) or significant blood vessel damage that would result in stroke or permanent neurologic damage is very rare. With any type of radiation therapy there is always the chance that another tumor may appear years later in tissues that are in the field of radiation.**

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Attachment #3
Certificate of Confidentiality

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.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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