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August 6, 2014

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
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Dear Ms. Kruhm,

The study committee for **ACNS0927**, *A Phase 1/2 Study of Suberoylanilide Hydroxamic Acid (Saha, Vorinostat) and Local Irradiation, Followed by Maintenance Saha in Children with Newly Diagnosed Diffuse Intrinsic Pontine Gliomas (DIPG)* has provided Amendment #3A, dated 08/06/2014 for CTEP review. This amendment is being submitted in response to a Request for Amendment (RA) from Dr. Richard L. Piekarz (rpiekarz@nih.gov) received on April 3, 2014.

In this amendment, the vorinostat monograph has been modified to reflect the incorporation of the revised Comprehensive Adverse Events and Potential Risks (CAEPR) list for vorinostat provided by the NCI. The changes made due to this request are detailed below. Administrative updates have also been made throughout the protocol and are tracked.

The ACNS0927 study committee looks forward to approval of this amendment.

Sincerely,

Meg Stahlman, Protocol Coordinator (for)
Jack Su, MD, MS, Study Chair, ACNS0927

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.			Reference to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol.
2.	**Title Page**	1	The Version date and Amendment number have been updated with this amendment.
3.	**Table of Contents**	2-5	The table of contents has been updated.
4.	**Study Committee**	6-8	The contact information for multiple members has been updated Ashish Mark Ingle and Gencie Turner have been removed, Mehek Hasija has been replaced by Sung Tse as Research Coordinator, and Mark Krailo has replaced Baojiang Chen as Phase 2 Senior Statistician.
5.	**9.1**	37-42	• The SPEER grades have been updated. Added New Risk: • Also Reported on Vorinostat Trials But With the Relationship to Vorinostat Still Undetermined: Abducens nerve disorder; Cardiac disorders - Other (supraventricular arrhythmia); Euphoria; Eye disorders - Other (retinal tear); Gastroesophageal reflux disease; Gastrointestinal disorders - Other (duodenitis); Hyperuricemia; Irregular menstruation; Metabolism and nutrition disorders - Other (decreased total protein); Musculoskeletal and connective tissue disorders – Other (myositis); Oral pain; Skin and subcutaneous disorders – other (brittle nails); Somnolence; Stroke; Vaginal hemorrhage; Visceral arterial ischemia Decrease in Risk Attribution: • Changed to Reported But Undetermined from Less Likely: Alkaline phosphatase increased; Hypoalbuminemia; Hyponatremia; Musculoskeletal and connective tissue disorders - Other (muscle spasms) Provided Further Clarification: • General disorders and administration site conditions – Other (angioedema) is now reported as Immune system disorders – Other (angioedema). • Infections and infestations – Other (Herpes zoster) is now included in the previously reported risk "Infection".

#	Section	Page(s)	Change
			Deleted Risk: • Deleted from Reported But Undetermined: Arthralgia; Death NOS; Gingival pain; Hypernatremia; Hypoglycemia; Hypomagnesemia; Insomnia; Nasal congestion; Pharyngolaryngeal pain; Pruritus; Vascular disorders - Other (arterial thrombosis); Vasculitis The following COG template update has been made: Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees ~~can~~ **must** submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. ~~Alternatively, site personnel can fax completed Clinical Drug Requests (NIH 986) to the Pharmaceutical Management Branch at (301) 480-4612.~~ For questions about drug orders, transfers, returns, or accountability, call (~~301~~**240**) ~~496~~**276**-~~5725~~ **6575** Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime. The current version of the protocol contained Version 2.6 of the CAEPR. The following changes represent the changes from Version 2.6 to 2.7 of the CAEPR: • Vorinostat (SAHA, **Zolinza**, NSC 701852) • Below is the CAEPR for vorinostat (SAHA, **Zolinza**). • Version number and date updated • Relationship to Vorinostat (SAHA, **Zolinza**) • Specific Protocol Exceptions to Expedited Reporting (SPEER) **(formerly known as ASAEL)** • Also reported on vorinostat (SAHA, **Zolinza**) trials but with the relationship to vorinostat (SAHA, **Zolinza**) still undetermined: • Note: Vorinostat (SAHA, **Zolinza**) 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.
6.	**11.3.1**	46-47	The statistical section for Part B has been expanded to clarify the evaluable patients as follows: Efficacy Endpoints

#	Section	Page(s)	Change
			The primary endpoint for the evaluation of treatment efficacy will be event-free survival (EFS), defined as the time to disease progression, disease relapse, occurrence of a second neoplasm, or death from any cause, **or date of last follow-up** measured from the time of study enrollment. **Definitions of Evaluable** **Part B:** **Evaluable for Adverse Events and Efficacy** **Patients will be considered evaluable for adverse events and efficacy if they meet the following criteria: (1) the patient is eligible; (2) the patient receives one dose of vorinostat at the MTD determined in Phase 1 (230 mg/m^2/day) per protocol guidelines, and (3) if central review is required, the patient is confirmed to have eligible diagnosis.**

SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT A AND B

In accordance with the above discussion, the following specific revisions have been made to the Informed Consent Document(s). Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.			The version dates have been updated.
2.	**ICD A: During the study** **ICD B: Research study tests and procedures**	4	The following statement has been added to the ICD A section "During the Study" and ICD B section "Research Study Tests and Procedures": **The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. You may develop high or low levels of certain salts in the body which may require you to take another medicine to correct the salt level.**
3.	**What side effects or risks can I expect from being in the study?**	6-7	The risks table has been revised and now reflects the risk profile provided by CTEP in the "patient-friendly" condensed format. As noted by CTEP in the Request for Amendment the following Decrease in Risk Attribution: • Changed to Reported But Undetermined from Occasional: Muscle spasms The following statement has been added below the risk insert: **Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.**
4.	**What are the costs of taking part in this study?**	10	The following COG template update has been made: For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at **http://www.cancer.gov/clinicaltrials/learningabout**~~.http://cancer.gov/clinicaltrials/learning/insurance-coverage/. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.~~

#	Section	Page(s)	Change
5.	**What are my rights if I take part in this study?**	10	The following COG template update has been made: **During your follow-up visits, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/). To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all children on the study is completed, and not only when your child completes treatment.**
6.	**Where can I get more information?**	11	The following COG template updates have been made: 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.com~~**http:///www.childrensoncologygroup.org/familyhandbook**. **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**.

Activated: August 9, 2010 Version Date: 8/06/14
Closed: Amendment #: 3A

CHILDREN'S ONCOLOGY GROUP

ACNS0927

A PHASE 1/2 STUDY OF SUBEROYLANILIDE HYDROXAMIC ACID (SAHA, VORINOSTAT) AND LOCAL IRRADIATION, FOLLOWED BY MAINTENANCE SAHA IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPG)

Phase 1: Initial Participation Limited to the COG Phase 1 Consortium

Phase 2: Open to COG Institutions in the United States, Canada, Australia and New Zealand

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AGENT NSC# AND IND#'s
Vorinostat (SAHA) NSC# 701852 IND# 71976

SEE SECTION 8.3.6 AND 8.4.4 FOR SPECIMEN SHIPPING ADDRESSES

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 mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

This is a phase 1/2 study to determine the maximum tolerated dose (MTD) of suberoylanilide hydroxamic acid (SAHA; vorinostat) in combination with radiation therapy and the efficacy of administering vorinostat concurrently with radiation therapy, followed by maintenance therapy with vorinostat, in patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG).

This study consists of two parts: Part A, which is the phase 1 dose-finding study to define the MTD of vorinostat in combination with radiation therapy, and Part B, which is the phase 2 portion of the study to measure the efficacy of continuing vorinostat as maintenance therapy after radiation. Part A of the study will be completed within the COG Phase 1 Consortium. After completion of radiation and vorinostat, patients in Part A will continue to receive vorinostat as maintenance therapy at the MTD defined in ADVL0416. For Part B of the study, patients will receive vorinostat, at 230 mg/m^2/day (the MTD determined in Part A of the study), with concurrent radiation, and then continue maintenance therapy with vorinostat at the MTD defined in ADVL0416, for a maximum of 12 courses. Part B of the study will take place at member COG institutions, group wide.

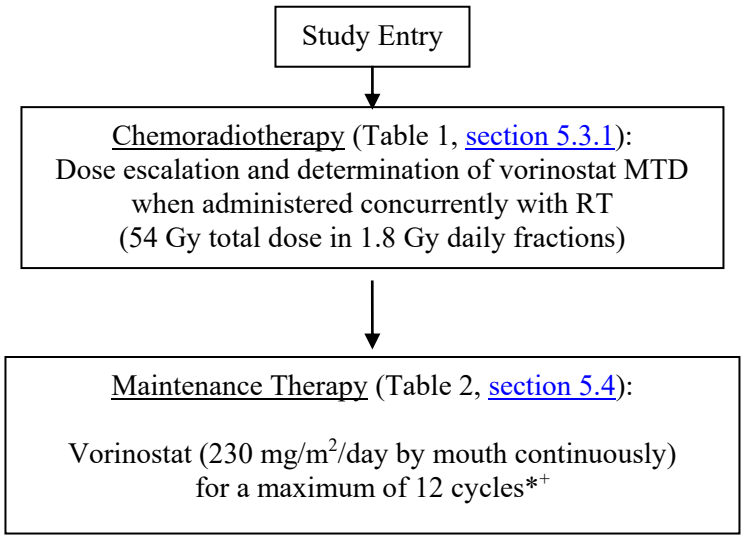
The primary endpoints for toxicity and safety monitoring of vorinostat in combination with radiation therapy include DLTs and toxic death. Toxicities for maintenance therapy will also be determined. The primary endpoint for the evaluation of treatment efficacy will be 1-year event-free survival (EFS), and a secondary endpoint will be overall survival (OS). EFS and OS outcomes will be compared to historical control data from ACNS0126 and CCG-9941.

Assessment of histone acetylation, HDAC2 level, and non-homologous end-joining (NHEJ) activity from peripheral blood mononuclear cells (PBMC) will be performed pre-treatment, at 2 weeks after starting vorinostat and radiation treatment, and at completion of vorinostat and radiation treatment. If paraffin-embedded tumor samples are available, then HDAC 2 level, NHEJ activity, and/or protein levels of key repair proteins in the NHEJ and homologous recombination repair (HRR) pathways will be determined. Any correlation between these biologic studies and clinical outcome will be explored.

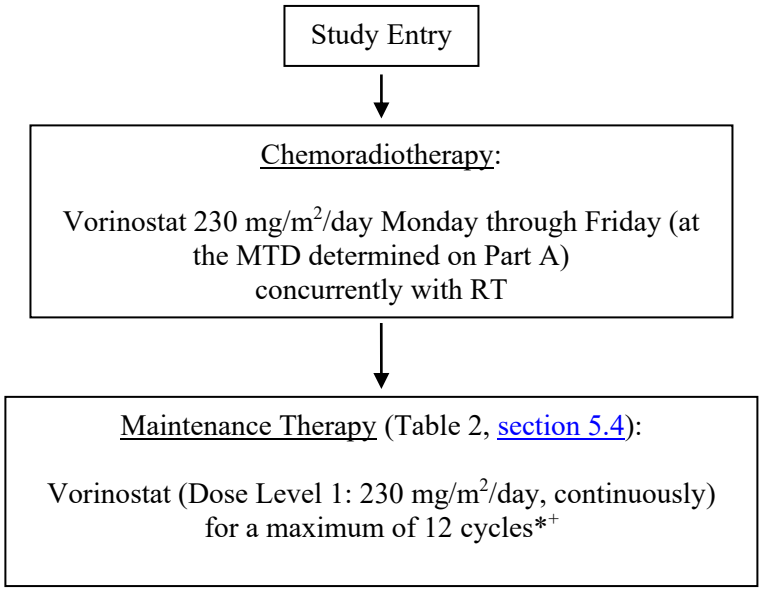
EXPERIMENTAL DESIGN SCHEMA

Part A (Phase 1 Consortium)

As of Amendment #2, Part A was completed.



Part B (Phase 2 Open to COG Institutions in the United States, Canada, Australia and New Zealand)



Each Maintenance therapy cycle is 28 days.

* Cycles will continue in the absence of disease progression or excessive toxicity.
+ Response evaluation per section 8.1 and section 12.4.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) or recommend a Phase 2 dose of vorinostat given concurrently with radiation in children with newly diagnosed diffuse intrinsic pontine glioma (DIPG).

1.1.2 To define and describe the toxicities of vorinostat given concurrently with radiation in children with newly diagnosed DIPG.

1.1.3 To determine, in the context of this phase I/II trial, the anti-tumor activity of combining vorinostat with radiation, followed by maintenance vorinostat for twelve courses, in children with newly diagnosed DIPG, as measured by 12-month event-free survival (EFS) and overall survival (OS).

1.1.4 To determine the toxicities of vorinostat for 12 additional courses after completion of vorinostat and radiation.

1.2 Secondary Aims

1.2.1 To measure NHEJ activity in PBMCs before treatment, at 2 weeks after starting vorinostat and radiation, and at end of radiation therapy.

1.2.2 To measure HDAC2 levels and assess histone acetylation in PBMCs before treatment, at 2 weeks after starting vorinostat and radiation, and at end of radiation therapy.

1.2.3 To quantify DNA repair proteins from the NHEJ and HHR pathways in tumors by either Western analysis or immunohistochemistry, if paraffin-embedded tumor is available.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Diffuse Intrinsic Pontine Gliomas in Children

Diffuse intrinsic pontine gliomas (DIPGs) in children remain essentially incurable. A recent review of 22 clinical trials of pediatric diffuse brainstem gliomas showed that only 92 out of 940 children survived, with identical progression free (PFS) or overall survival (OS) in recent trials compared to older series.[1] In children whose tumors were biopsied, the majority (153 out of 229 samples; 67%) were high-grade gliomas.[1] Clinical trials of hyperfractionated radiation, delivering up to 72 Gy radiation, showed no benefit over conventional (54-58 Gy) radiation.[2-8] Chemotherapy or biologic agents, whether given pre-irradiation,[2,8-10] with radiation, and/or after radiation,[3-7,9-18] including myeloablative regimen with stem cell rescue,[19,20] have also failed to improve PFS or OS. Collectively, these series showed dismal median PFS (5-8.8 months), median OS (8-12 months), and 2-year survival (5-15%).[1]

Because radiation often induces a temporary response and symptomatic improvement for children with DIPGs, concurrent administration of an agent with both an anti-glioma and a radiosensitizing effect may potentially improve outcome. Pre-clinical studies have shown that vorinostat (suberoylanilide hydroxamic acid, SAHA), an orally bioavailable histone deacetylase (HDAC) inhibitor, inhibits growth of malignant gliomas and enhances radiation sensitivity of these tumors. The maximum tolerated dose (MTD) of vorinostat as a single agent has been defined in a pediatric phase 1 study (ADVL0416). We therefore propose a phase I/II trial for children with newly diagnosed DIPG to study: 1) the MTD or recommended phase 2 dose of vorinostat given concurrently with radiation; and 2) the efficacy of vorinostat, given concurrently with radiation and then continued as maintenance therapy after radiation, as measured by 12-month and 18-month EFS and OS.

2.1.2 Vorinostat and Other Histone Deacetylase Inhibitors

Nucleosomes, the basal unit of chromatin, are composed of DNA wrapped around histones with lysine-rich amino terminal tails. The positive charge of the amino tails attracts the negatively-charged DNA, and this interaction partly regulates the chromatin structure and gene expression.[21] Histone acetyltransferase (HAT) transfers an acetyl moiety to the lysines on the amino tails and neutralizes the positive charge of the histones, leading to decreased affinity for DNA, relaxation of chromatin, and transcriptional activation.[21,22] HDACs remove the acetyl groups and restore the negative charge, leading to chromatin compaction and transcriptional repression.[22,23] Dysregulation of histone acetylation has been implicated in the development of human cancers.[21,24] It is hypothesized that aberrant histone acetylation leads to inappropriate transcriptional repression and maintenance of the transformed state in human tumors. HDAC inhibitors are hypothesized to reactivate gene expression of critical pathways that are abnormally silenced in tumorigenesis, and indeed treatment of human tumor cells with HDAC inhibitors results in cell cycle arrest, apoptosis, and differentiation.[21,25] There are several classes of HDAC inhibitors, including butyric acid derivative (phenylbutyrate and AN-9), short-chain fatty acid (valproic acid), hydroxamic acids, benzamides (MS-275), and cyclic peptides (depsipeptide).[26,27] Vorinostat is one of the hydroxamic acid-based HDAC inhibitors. In contrast to depsipeptide and MS-275 which only inhibit selective members of class I HDAC (HDAC 1, 2, 3, and 8) or valproic acid which inhibits class I and class IIa HDACs (HDAC 4, 5, 7, and 9), vorinostat inhibits all classes of HDAC, including class IIb (HDAC 6 and 10) and IV (HDAC 11).[27,28] Whether a pan-HDAC inhibitor such as vorinostat has more potent or a broader range of anti-tumor efficacy versus a selective HDAC inhibitor such as MS-275 is unproven.

2.2 Preclinical Studies

2.2.1 Pre-Clinical Activity of Vorinostat in CNS Tumors

There have been several pre-clinical studies documenting vorinostat's *in vitro* and *in vivo* inhibition of malignant gliomas. Ugur et al.[29], Chinnaiyan et al.[30],Yin et al.[31], and Eyupoglu et al.[32] demonstrated that the concentration of vorinostat required for 50% growth inhibition (IC_{50}) of multiple malignant glioma cell lines and primary GBM explants were approximately 1-2 µM (264-528 ng/ml), and these concentrations were comparable to the safely achieved C_{max} in adult and pediatric clinical trials (see discussion below). Recently, it was also shown that *in vitro* vorinostat treatment inhibited growth of stem-like GBM cells in neurospheres equally effectively as it inhibited non-stem GBM tumor cells.[33] *In vivo* studies also confirmed that administration of vorinostat to mice with intracranial malignant glioma xenografts significantly prolonged their survival versus control animals.[29,31,32]

In addition to its documented activity in malignant gliomas, vorinostat also inhibits growth of other CNS tumors such as medulloblastoma[34,35] and supratentorial primitive neuroectodermal tumor.[36] Although there has not been any formal study of the CNS pharmacokinetics of vorinostat, two investigators demonstrated increased levels of acetylated histones in normal mouse brains and intracranial xenografts after vorinostat treatment.[35,37] In addition, it has recently been shown that in adults with GBM post-vorinostat treatment tumors had increased histone acetylation as well.[38] These studies provide indirect evidence that vorinostat crossed the blood-brain barrier and induced biological changes in normal brain and intracranial tumors.

2.2.2 HDAC Inhibitors Enhances Radiation Sensitivity of Malignant Gliomas

Several studies have shown that various HDAC inhibitors, including phenylbutyrate,[39] TSA,[40] AN-9,[41] MS-275,[42] and valproic acid[43,44] enhanced *in vitro* and *in vivo* radiosensitivity of malignant glioma cell lines. Chinnaiyan et al.[30] 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. Additional studies similarly demonstrated that vorinostat treatment enhanced radiation sensitivity of other solid tumors, [45-48] including intracranial breast cancer xenografts.[49] In most of the pre-clinical studies, optimal radiation enhancement was observed when HDAC inhibition preceded radiation by 24-72 hours and was continued concurrently with radiation.

Pre-clinical studies of vorinostat prior to radiation treatment demonstrate significantly reduced levels of DNA repair proteins in the non-homologous end-joining (NHEJ; Ku70, Ku80, DNA-PK) and homologous recombination repair (HRR; BRCA 1 and 2, ATM, and Rad51) pathways.[30,46] 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 in part mediated by decreased DNA repair proteins and impaired dsDNA break repair. Additional pre-clinical studies of the radiation potentiation by other HDAC inhibitors have also shown that expression of key DNA repair

proteins in the NHEJ and HRR pathways is significantly reduced[50-53] and dsDNA break repair is inhibited.[43,44]

2.2.3 NHEJ and HRR Possibly Mediating Radiation Resistance in Malignant Gliomas

Several pre-clinical studies have documented elevated expression of DNA repair proteins in the NHEJ and HRR pathway in radiation resistant glioma cell lines[54,55] or in response to irradiation,[54,56] and inhibition of these DNA repair proteins restored the radiation sensitivity of tumor cells.[57-60] Most recently, two functional studies demonstrated that expression of EGFRvIII, one of the most common mutations in adult GBM, enhanced glioma cell survival after radiation by accelerating repair of dsDNA breaks.[61,62] This enhanced survival after radiation was associated with elevated expression of DNA-PK, ATM, and Rad51 and abrogated by their respective inhibitors. Taken together, these pre-clinical data suggest that enhanced dsDNA break repair may mediate radiation resistance of malignant gliomas, and inhibition of NHEJ and HRR pathways may potentiate the sensitivity of these tumors to radiation. As vorinostat treatment has been associated with decreased expression of key DNA repair proteins in both the NHEJ and HRR pathways, it is a promising agent for radiation potentiation, and its clinical efficacy may correlate with inhibition of dsDNA break repair.

2.2.4 Clinical Significance of HDAC expression in Human Tumors

Although multiple studies have documented HDAC over-expression in various solid tumors[63-66] and correlated such over-expression with aggressive tumor biology and decreased survival,[67-69] HDAC expression in CNS tumors has been poorly and inconsistently documented.[70-73] Several pre-clinical studies, however, have shown that inhibition of HDAC2 appears to be critical for various aspects of HDAC inhibitors' anti-tumor effect, including chromatin decondensation and remodeling, transcriptional activation, and induced histone acetylation.[74-77] A clinical trial correlated HDAC2 expression in cutaneous T-cell lymphoma (CTCL) with biological aggressiveness and unfavorable clinical outcome.[69] Furthermore, several clinical trials have confirmed that baseline expression of HDAC2 in PBMCs (as surrogates for tumor specimens) correlated directly with increases in histone H3 and H4 acetylation after HDAC inhibitor treatment.[69,75,78,79] Therefore, baseline and post-treatment HDAC2 level in PBMCs may be an additional surrogate marker for measuring vorinostat's biologic effect in tumors.

2.3 Adult Studies of Vorinostat

2.3.1 Phase 1 and 2 Studies of Vorinostat

Early phase I trials of vorinostat in adults showed encouraging objective responses in various solid tumors[80,81] and hematologic malignancies,[80-82] with an impressive response rate up to 30% in patients with CTCL.[83,84] Subsequent phase 1 and 2 clinical trials of vorinostat as a single agent in adults with hematologic malignancies[85,86] and solid tumors,[87-91] however have yielded somewhat disappointing results, with few objective responses and stable disease being the most common outcome. Most recently, a phase 2 study of vorinostat in adults with recurrent glioblastoma multiforme demonstrated only 2 objective responses in 66 patients.[38]

The most common vorinostat regimen is 400 mg orally, once daily or 200 mg orally, bid continuously;[80,82-84,88,90,91] but alternative schedules (e.g. 200-400 mg bid x 14 days every 21 days) have also been evaluated.[38,85-87,89] The oral bioavailability is 43%, with an apparent half-life of 91-127 minutes.[80] Observed C_{max} in the 400 mg q day regimen averaged 658 +/- 439 ng/mL, exceeding the IC_{50} (264-528 ng/mL) required in pre-clinical studies to inhibit growth of malignant gliomas, either as a single agent[29-32] or to enhance the effect of radiation.[30]

Vorinostat was reasonably well tolerated in the adult trials. The most common grade 3 and 4 toxicities were fatigue, gastrointestinal (nausea/vomiting, anorexia, diarrhea, dehydration), hematologic (thrombocytopenia, lymphopenia, neutropenia, anemia), and metabolic (hypernatremia, hypokalemia). Grade 3 and 4 thrombocytopenia, the most common hematologic toxicity, occurred in 5-22% of patients.[38,80,82,83,85,87,89-91] However, the platelet count usually recovered to normal within 3-7 days after drug discontinuation.[28,80,82,85]

In earlier adult clinical trials, increased acetylation of H3 and H4 histones in PBMC was essentially observed in all patients across all dose levels.[80-82,85] Peak hyperacetylation of PBMC histones was observed 2-4 hours after a dose of vorinostat and generally returned to baseline level after 6-8 hours. Persistent hyperacetylation of PBMC histones was observed after 3 weeks on continuous dosing.[80] However, hyperacetylation of histones in tumors was less consistent, as Kelly et al.[80] and Galanis et al.[38] showed that only three out of five post-vorinostat tumor samples demonstrated increased histone H3 acetylation.

2.4 ADVL0416, A Pediatric Phase 1 Study of Vorinostat

2.4.1 Phase 1 Study of Vorinostat in Children (Fouladi et al., unpublished results)

In the recently completed COG phase 1 study of vorinostat (ADVL0416) in children with refractory solid tumors, vorinostat was administered orally once daily starting at 180 mg/m^2/day continuously, with dose escalations in 30% increments. The MTD for pediatric patients in ADVL0416 has been defined as 230 mg/m^2/day. At one dose level (300 mg/m^2/day) above the MTD, 4 out of 12 patients experienced DLTs (2 thrombocytopenia, 1 neutropenia, 1 hypokalemia). No dose-limiting thrombocytopenia or neutropenia were observed at the MTD (230 mg/m^2/day) or one dose level below (180 mg/m^2/day).

No objective response was observed with vorinostat as a single agent, although prolonged stable disease (median of 4 cycles, range 4-8 cycles) was observed in six patients, including a patient with a DIPG and another with a low-grade glioma. Two additional patients treated with vorinostat and 13-cis-retinoic acid (one medulloblastoma, one pineoblastoma) also had stable disease for 5 and 7 cycles.

There was wide interpatient variability in vorinostat pharmacokinetic, with no clear linear relationship between drug exposure (as measured by area-under concentration-time curve, AUC) and dose. Vorinostat exposure following a capsule formulation versus an oral suspension, at 230 mg/m^2/day, as measured by $AUC_{0->inf}$, was roughly similar (range 1415-9291 ng/ml*hr versus 1186-4780

ng/ml*hr, respectively). The observed C_{max} across all dose levels (range 269-780 ng/ml) was within or exceeded the IC_{50} range (264-528 ng/ml) required for inhibiting malignant gliomas in pre-clinical studies.[29-32]

A significant increase in PBMC histone H3 acetylation was not consistently observed in children who received vorinostat at 180 mg/m^2/day, whereas 15 out of 18 patients who received either 230 mg/m^2/day or 300 mg/m^2/day demonstrated more than a 2-fold increase in PBMC histone H3 acetylation.

2.5 Overview of Proposed Pediatric Study

This study is comprised of two parts. Part A is a phase 1 dose-finding study employing the rolling six phase 1 trial design, to define the MTD or recommended phase 2 dose of vorinostat in combination with radiation therapy, for children with newly diagnosed DIPG. Although the MTD of vorinostat as determined in ADVL0416 was 230 mg/m^2/day, given the expansive nature of DIPG and proximity to pons and medulla, it would be prudent to ensure that there is no synergistic toxicity when vorinostat is combined with radiation. Therefore, the starting dose of vorinostat for Part A of this trial will be 180 mg/m^2/day, Monday through Friday during radiation (Dose Level 1; Table 1, section 5.3.1). This starting dose is one dose level below the MTD (230 mg/m^2/day) determined in ADVL0416. One dose de-escalation (Dose Level 0, vorinostat 180 mg/m^2/day, 3 days a week during radiation therapy) will be studied if Dose Level 1 is not well tolerated. The phase 1 dose-finding study will conclude if Dose Level 2 (vorinostat 230 mg/m^2/day, Monday through Friday during radiation therapy) is well tolerated (Table 1, section 5.3.1). Part A of the study will only be open for enrollment to the institutions in the COG Phase 1 Consortium.

After completion of radiation and vorinostat, patients enrolled on Part A of the study will continue on maintenance therapy with vorinostat, provided that they meet all the on-study criteria and have no contraindication for continuing vorinostat. Patients will continue vorinostat at 230 mg/m^2/day continuously (Dose Level 1; Table 2, section 5.4), which was the MTD as determined in ADVL0416. Patients will continue vorinostat maintenance therapy for a maximum of 12 courses. Two dose de-escalations will be allowed in the event a patient experiences a DLT during maintenance (post RT) therapy.

Six patients were enrolled on Dose Level 1 (vorinostat 180 mg/m^2/day Monday through Friday during radiation treatment). None of these six patients had DLTs during course 1 of chemoradiotherapy. Six additional patients were then enrolled onto Dose Level 2 (vorinostat 230 mg/m^2/day Monday through Friday during radiation therapy), and none of these six patients experienced DLTs. According to the rolling-six study design, dose level 2 is determined to be the recommended Phase 2 dose during chemoradiation. Part B of the study will now be open to group-wide participation, and all future patients will receive vorinostat 230 mg/m^2/day, Monday through Friday, during the chemo-radiation phase.

Of the twelve patients who have received maintenance therapy (course 2 and beyond), two patients experienced grade 3 thrombocytopenia requiring dose de-escalation of vorinostat. No recurrent dose-limiting thrombocytopenia was observed after the dose reduction. One of these 2 patients who experienced grade 3 thrombocytopenia also experienced grade 4 neutropenia, and despite a dose reduction, this patient's grade 4 neutropenia recurred, necessitating discontinuation of maintenance protocol therapy. No

other dose limiting toxicities have been observed thus far in the 12 patients who have received maintenance therapy. Dose-limiting toxicities during the maintenance phase will continue to be monitored closely on a weekly basis, per toxicity monitoring rule specified in section 11.3.6, when PART B of the study opens for group-wide participation.

It appears that thus far, at least with chronic dosing on this trial, hematologic DLT may be more prevalent than previously observed in the pediatric Phase I study (ADVL0416), in which patients most commonly received only 1 course of vorinostat. It is however worth noting that, due to the concern for intra-tumoral hemorrhage for our patient population, the definition for a dose-limiting thrombocytopenia (grade 3 < 50,000/μL), was intentionally defined more stringently than the typical definition of a dose-limiting thrombocytopenia (grade 4 < 25,000/μL) for a phase I study such as ADVL0416. We observed 2 out of 12 patients who experienced grade-3 thrombocytopenia with maintenance vorinostat, but it has been reassuring that recurrent grade-3 thrombocytopenia has not been observed after dose-reduction of vorinostat. Moving forward with conduct of PART B of the study, it is our expectation that repeated dosing of vorinostat during maintenance therapy may result in more patients experiencing dose-limiting thrombocytopenia than originally anticipated, but based on clinical observations from PART A of the study, we do not anticipate that discontinuation of maintenance vorinostat due to recurrent hematologic DLT will be a common occurrence. We have therefore modified the toxicity monitoring rule in Section 11.3.6 such that vorinostat dosing during maintenance will only be modified using the rule outlined in the Section 11.3.6.

Part B, the phase 2 portion of the trial, will be performed group-wide once the MTD of vorinostat during radiation is defined. Patients enrolling onto the phase 2 portion of the study will be enrolled at 230 mg/m^2/day, the MTD for vorinostat during radiation and continue on maintenance therapy as described above. The primary aim of Part B of the study is to determine the effect of administering vorinostat concurrently with radiation, followed by maintenance vorinostat for up to 12 courses, as measured by 1-year EFS and OS in children with newly diagnosed DIPG. Data collected from any patients enrolled at the MTD from Part A of the trial will be included in analyzing the outcome from Part B of the study.

Based on pre-clinical studies described in sections 2.2.2 through 2.2.4, we hypothesize that levels of HDAC2 and histone acetylation in PBMCs may be appropriate surrogate markers for vorinostat's biologic effect in tumor, and that vorinostat's inhibition of dsDNA break repair and NHEJ activity may correlate with its radiation potentiation. Therefore, we propose to study these biological parameters in PBMCs before and at 2 weeks after starting vorinostat and radiation therapy, and at completion of vorinostat and radiation. In addition, when DIPG tumor samples (paraffin embedded tissue blocks) are available, we also propose to determine levels of DNA repair proteins from the NHEJ (Ku70, Ku80, DNA-PK) and HRR (BRCA 1 and 2, Rad51) pathways by Western analysis or immunohistochemistry. Any correlation between these biological parameters and clinical outcome will be explored.

3.0 STUDY ENROLLMENT

3.1 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.

3.2 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.

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.

3.3 Reservation Requirements

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:
1. Log in to https://members.childrensoncologygroup.org.
2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.*
3. Click **Reservation**. *The Studies requiring Reservations page appears.*

Prior to obtaining informed consent and enrolling a patient, a reservation must be made

with the Statistical and Data Center through the eRDE system.

Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded from: https://members.childrensoncologygroup.org/_files/Help/eRDES_ReservationSystem_UserGuide.pdf

3.4 Institutional Pathology Report

Because DIPGs are often not biopsied, enrollment of patients with typical-appearing DIPG (see section 4.1.2) without an institutional pathology report is allowed. For patients with brainstem tumors not considered typical DIPG as defined in section 4.1.2, they will only be eligible if their tumors are biopsied and meet the eligibility criteria as defined in section 4.1.2. Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be faxed, with the corresponding shuttle sheet, to the Operations Center at (626) 447-2204. The fax should be sent to the attention of the study research coordinator and must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission to COG.

3.5 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.

3.6 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than seven (7) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. If more than 7 calendar days elapse between the date eligibility studies outlined in section 4.1.5 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies are required within 2 weeks prior to start of protocol therapy.

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 or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age: Patients must be > 36 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients with newly diagnosed diffuse intrinsic pontine gliomas (DIPGs), defined as tumors with a pontine epicenter and diffuse involvement of at least 2/3 of the pons, are eligible without histologic confirmation. Patients with brainstem tumors that do not meet these criteria or not considered to be typical intrinsic pontine gliomas will only be eligible if the tumors are biopsied and proven to be an anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma, or anaplastic mixed glioma. Patients with juvenile pilocytic astrocytoma, fibrillary astrocytoma, gangliogliomas, or other mixed gliomas without anaplasia are not eligible. Patients with disseminated disease are not eligible, and MRI of spine must be performed if disseminated disease is suspected by the treating physician.

4.1.3 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). 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.

4.1.4 Prior Therapy
Patients must not have received any prior treatment except dexamethasone and/or surgery.

4.1.5 Organ Function Requirements

4.1.5.1 Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

4.1.5.2 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
3 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.

4.1.5.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT (ALT) is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.5.4 Central Nervous System Function Defined as:

- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants (with the exception of valproic acid; see Section 4.2.2.5) and seizures are well controlled.

4.1.6 Patients must be able to swallow capsules or liquids. Patients dependent on NG tube feeding are not permitted to receive protocol therapy.

4.1.7 Timing

Enrollment must be no later than 28 days after the date of radiographic diagnosis or surgery, whichever is the later date.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

4.2.2 Concomitant Medications

4.2.2.1 Growth factor(s): Growth factors that support platelet or white cell number or function must not have been administered within the 7 days prior to enrollment.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.2.4 Anticonvulsants: Patients must not currently be receiving enzyme inducing anticonvulsants (see Appendix II for a list of enzyme inducing and non-enzyme inducing anticonvulsants).

4.2.2.5 Valproic Acid: Patients on valproic acid must discontinue valproic acid for at least 2 weeks before starting protocol therapy.

4.2.2.6 Anti-coagulant: Patients receiving coumadin, heparin, low-molecular weight heparin, or any other anti-coagulants are not eligible for study entry.

4.2.2.7 Anti-platelet agents: Patients receiving ASA (> 81 mg/day), non-steroidal anti-inflammatory drugs, clopidogrel (Plavix), dipyridamole (Persantine), or any other drug that inhibits platelet function are not eligible for study entry.

4.2.3 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.4 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

4.3 Regulatory

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

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

5.0 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).

5.1 Overview of Treatment Plan

All patients must begin therapy no later than 7 days after study enrollment. Enrollment must be no later than 28 days after the date of radiographic diagnosis or surgery, whichever is the later date. Radiation therapy (RT) will be administered in single daily fractions of 1.8 Gy for 30 treatments over 6-7 weeks. The total dose of radiation will be 54 Gy (see section 15.0). During radiation, patients on Part A of the study will receive vorinostat as per Table 1, section 5.3.1, for the duration of radiation treatment. Following completion of radiation therapy, patients will immediately begin maintenance therapy with vorinostat (see guidelines in section 5.4) for a maximum of 12 cycles.

Note: It is recommended but not required that Day 1 of the first cycle of protocol therapy begin on a Monday in order to extend the duration of radiation therapy in the first week.

Patients' doses are to be prescribed based on dosing nomogram in Appendix III.

Vorinostat is available as a 100-mg capsule or a 50 mg/mL pediatric suspension. The dosing for pediatric suspension should be rounded to the nearest 5 mg. **Dosing for vorinostat capsule should be determined according to the nomogram provided in Appendix III**, in which vorinostat doses have been rounded to the nearest 100 mg. **Please note that the absolute daily dose of vorinostat should not exceed 500 mg. Patients with a BSA < 1.25 m^2 should be given the pediatric suspension, since using capsules can lead to more than a 15% deviation in intended dosing.** Patients ≥ 1.25 m^2 should receive either capsules per the nomogram or suspension, but may not receive a combination of both. Vorinostat capsules should not be opened or crushed. Vorinostat should be taken with food whenever possible. If a patient vomits within 30 minutes after the dose of vorinostat is administered, that dose should be repeated. If a patient vomits after 30 minutes, the dose will not be repeated.

PART A: Phase 1 dose-finding study (Phase 1 Consortium institutions only)

As of Amendment #2, Part A was completed.

Part A of this study is the phase 1 dose-finding study to define the MTD or recommended phase 2 dose of vorinostat in combination with radiation therapy. Part A of the study will be completed within the COG Phase 1 Consortium institutions. Patients will start vorinostat on the first day of radiation therapy at the assigned dose level and schedule. Refer to Table 1, Section 5.3.1 for the dose escalation schema. Following completion of radiation therapy, patients enrolled in Part A of the study will continue maintenance vorinostat therapy per guidelines in Section 5.4.

Patients or their guardians will keep a diary to document the intake of each dose of vorinostat and potential side effects (see Appendices IV-A, IV-B, and IV-C). Please instruct patient/parents to record each dose on the diary immediately rather than waiting until a later time. Errors on the diary should be crossed out and initialed. The patient diary should be reviewed weekly with the patient and family during radiation treatment and at the completion of each treatment cycle during maintenance therapy, and drug should be accounted for at this time. These diaries should also be faxed to the COG Statistics and Data Center, with the corresponding shuttle sheet, at (626) 447-2204 after each treatment cycle.

PART B: Phase 2 component of the study (COG Groupwide)
Part B is the phase 2 portion of the study to determine the efficacy of combining vorinostat with radiation and then continuing vorinostat as maintenance therapy in children newly diagnosed with DIPG. Part B of the study will begin enrollment once the MTD for Part A has been determined. For Part B of the study, patients will receive vorinostat, at 230 mg/m^2/day Monday through Friday (the MTD determined in Part A of the study), with concurrent radiation, and then continue maintenance therapy with vorinostat (per guidelines in section 5.4) for a maximum of 12 courses. Part B of the study will take place at member COG institutions, group wide.

5.1.1 Vorinostat Administration During Radiation Therapy

As of Amendment #2, Part A was completed.

PART A: Patients on Part A of the study will start vorinostat on the first day of radiation therapy at the dose level assigned at enrollment. Refer to Table 1, section 5.3.1 for the Dose Escalation Schema.

PART B: Once the MTD of vorinostat for Part A of the study has been determined, patients on Part B of the study will start vorinostat on the first day of radiation therapy at 230 mg/m^2/day as determined on Part A of the study. See Appendix IX for Chemoradiotherapy Roadmap.

Vorinostat dosing during and throughout the radiation component of therapy should be based on BSA determined from height and weight at the start of radiation therapy. The absolute daily dose of should not exceed 500 mg.

Vorinostat should be given 60-120 minutes prior to radiation therapy, whenever feasible. For patients who must remain NPO for sedation prior to RT therapy, vorinostat should be given immediately prior to bedtime on the evening preceding the RT.

See Section 5.6 for definition of DLTs encountered during radiation therapy and Section 6.0 for vorinostat dose modifications.

If radiation is omitted because of holiday or other logistical reasons, patients should still continue their scheduled vorinostat without interruption.

5.1.2 Vorinostat Administration During Maintenance Therapy (Part A and B)

All patients (on Part A or Part B), upon completion of radiation therapy, will immediately continue vorinostat as maintenance therapy, provided that they continue to meet all on-study criteria and have not experienced toxicities necessitating interruption or discontinuation of vorinostat.

Dosing of vorinostat during maintenance therapy will be determined per guidelines in Section 5.4. See Appendix X for Maintenance Roadmap.

Vorinostat doses during the maintenance phase of therapy should be adjusted based on the BSA determined from height and weight obtained within one week prior to the beginning of each cycle. The absolute daily dose of vorinostat should not exceed 500 mg.

A cycle of maintenance therapy is defined as 28 days. Maintenance therapy may be continued for a maximum of 12 cycles in the absence of disease progression and/or excessive toxicities.

See section 5.6 for definition of DLTs encountered during maintenance therapy and section 6.0 for vorinostat dose modification.

5.2 Criteria for Starting Subsequent Cycles (Part A and B)

5.2.1 Chemoradiotherapy

Radiation therapy should not be interrupted for vorinostat-related DLTs unless clinically indicated.

5.2.2 Vorinostat Maintenance Therapy

A complete cycle of maintenance therapy is defined as 28 days. Cycles of maintenance therapy should not commence unless the ANC is ≥ 1,000/μL and platelet count is ≥ 100,000/μL. Missed doses of vorinostat during a cycle will not be made up. Maintenance therapy may be continued in the absence of disease progression (see section 5.4).

5.3 Dose Escalation Schema

5.3.1 Inter-Patient Escalation (Part A Chemoradiotherapy)

As of Amendment #2 Part A was completed.

Table 1: Oral Vorinostat Dosing During Radiation Therapy (Part A of Study)

Dose Level	Vorinostat Dose	Vorinostat Schedule
0	180 mg/m^2/dose	Monday, Wednesday, and Friday during radiation therapy
1*	**180 mg/m^2/dose**	**Monday through Friday during radiation therapy**
2	230 mg/m^2/dose	Monday through Friday during radiation therapy

***starting dose level**

The starting dose of vorinostat for Part A of the study will be Dose Level 1, 180 mg/m^2/day, Monday through Friday weekly during the duration of radiation therapy (on Days 1-5, 8-12, 15-19, 22-26, 29-33, and 36-40). If radiation continues into Days 43-48 then vorinostat should continue at the same dose and schedule until RT is completed.

The starting dose is one dose level below the MTD (230 mg/m^2/day) determined in ADVL0416. One dose de-escalation (Dose Level 0, 180 mg/m^2/day, Monday, Wednesday, and Friday weekly during radiation therapy) will be evaluated if Dose Level 1 is not well tolerated. The phase 1 dose-finding study will conclude if Dose Level 2 (230 mg/m^2/day, Monday-Friday weekly, during radiation therapy) is well tolerated.

Note: It is recommended but not required that Day 1 of the first cycle of protocol therapy begin on a Monday in order to extend the duration of radiation therapy in the first week.

If Dose Level 0 is not well tolerated, all subsequent patients will receive radiation without vorinostat.

Patients enrolled in Part A of the study, upon completion of vorinostat and radiation therapy, will continue vorinostat as maintenance therapy, per section 5.4, provided that they continue to meet the criteria to start subsequent cycles of therapy.

5.3.2 Part B Chemoradiotherapy

Once the MTD of vorinostat for Part A of the study has been determined, Part B of the study will begin enrollment, and subsequent patients will receive vorinostat at 230 mg/m^2/day as determined in Part A of the study. See Appendix IX for Chemoradiotherapy Roadmap.

5.3.3 Intra-Patient Escalation

Intra-patient dose escalation is not allowed in either Part A or Part B of the study.

5.4 Vorinostat Maintenance Therapy (Parts A and B)

At the conclusion of chemoradiotherapy, all patients will continue vorinostat maintenance therapy at Dose Level 1 (230 mg/m^2/day, continuously; Table 2) including those patients who had discontinued vorinostat during chemoradiotherapy because of DLTs.

Table 2: Oral Vorinostat Dosing During Maintenance Therapy

Dose Level	Vorinostat Dose	Vorinostat Schedule
-1	230 mg/m^2/dose	Monday, Wednesday, and Friday, every week
0	230 mg/m^2/dose	Monday through Friday, every week
1*	**230 mg/m^2/dose**	**Daily without interruption**

* Initial dose level for all patients post-XRT. This dose was the single agent MTD of vorinostat defined in ADVL0416.

See Section 5.6 for definition of DLTs encountered during maintenance therapy and Section 6.0 for vorinostat dose modification. See Appendix X for Maintenance Roadmap.

5.5 Grading of Adverse Events

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).Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.6 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are at least possibly, probably or definitely attributable to vorinostat. For Part A of the study, the observation period for the purpose of dose-escalation will be the entire duration of radiation therapy (approximately 6 to 7 weeks). For Part B of the study, DLTs observed at any time during protocol therapy will be documented.

Dose limiting hematological and non-hematological toxicities are defined separately, as detailed below.

5.6.1 Interruption of Radiation Therapy

The interruption of planned radiation for 5 consecutive days or 10 days total.

5.6.2 Non-hematological dose-limiting toxicity

- Any Grade 4 non-hematological toxicity

- Any Grade 3 non-hematological toxicity with the specific exclusion of:
  - Grade 3 nausea and vomiting of < 5 days duration
  - Grade 3 elevation of ALT/AST that returns to levels meeting initial eligibility criteria within 7 days of study drug interruption and does not recur upon study drug re-challenge. Note: For the purposes of this study the ULN for ALT/AST is defined as 45 U/L.
  - Grade 3 fever or infection < 5 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
  - Grade 3 diarrhea that improves to grade 1 or better within 48 hours of starting anti-diarrhea treatment
- Any Grade 2 non-hematological toxicity that persists for > 7 days and is considered medically significant or sufficiently intolerable by patients that it requires treatment interruption

5.6.3 Hematological dose limiting toxicity

- Grade 3 thrombocytopenia (platelet count < 50,000/µL)
- Grade 4 neutropenia
- A delay of > 14 days in starting the subsequent cycle of vorinostat due to ANC < 1,000/µL and/or platelet < 100,000/µL (definition of this DLT applicable only during maintenance therapy)

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dose modification or use of Filgrastim.

6.1 Dose Modification for DLT During Vorinostat and Concurrent Radiation (Parts A and B)

For vorinostat-related non-hematologic DLTs during radiation therapy, vorinostat will be withheld until the toxicity resolves to meet on study parameters, and the patient will restart vorinostat at one dose level lower (see Table 1 below), if not already at Dose Level 0.

Table 1: Oral Vorinostat Dosing During Radiation Therapy

Dose Level	Vorinostat Dose	Vorinostat Schedule
0	180 mg/m^2/dose	Monday, Wednesday, and Friday during radiation therapy
1	180 mg/m^2/dose	Monday through Friday during radiation therapy
2 (Starting Dose)	**230 mg/m^2/dose**	**Monday through Friday during radiation therapy**

For vorinostat-related hematologic DLTs, vorinostat will be withheld until criteria in 6.1.1 and 6.1.2 are met, and vorinostat will be restarted at one dose level lower, if not already at Dose Level 0. If the same DLT is experienced at the lower dose level then vorinostat should be discontinued. If a different DLT is encountered, then the patient may restart vorinostat at the next lower dose level, if not already at Dose Level 0.

In the event of hematological DLT, a CBC should be checked twice weekly until recovery of ANC ≥ 1,000/µL and platelet ≥ 100,000/µL. A patient who experiences any DLT despite being treated on Dose Level 0 will then complete radiation therapy without vorinostat. **Radiation should be continued despite vorinostat-related DLT, unless there is a strong clinical contraindication.**

6.1.1 Platelet transfusion is permissible and strongly encouraged for patients with dose-limiting thrombocytopenia (platelet count < 50,000/µL) to minimize risk of intra-tumoral hemorrhage. Vorinostat should not be restarted until platelet count has recovered to ≥ 100,000/µL (transfusion independent). **Radiation should not be interrupted unless clinically indicated.**

6.1.2 Patients with grade 4 neutropenia may receive filgrastim (G-CSF) support but should re-start vorinostat at the next lower dose level (See Table in Section 6.1). Vorinostat should not be restarted until the ANC is ≥ 1,000/µL and for at least 48 hours without G-CSF support. **Radiation should not be interrupted unless clinically indicated.**

Patients who experience vorinostat-related DLTs during radiation will continue vorinostat dosing during maintenance therapy (per guidelines in section 5.4), provided that they meet the criteria to start subsequent cycles of therapy and all vorinostat-related toxicities have resolved to baseline.

6.2 Dose Modification During Maintenance Phase (Parts A and B)

For non-hematologic DLTs during maintenance therapy, vorinostat will be withheld until the toxicity resolves to meet on study parameters, and then vorinostat may be restarted per section 6.2.3.

For hematologic DLTs during maintenance therapy, vorinostat will be withheld until criteria in 6.2.1 and 6.2.2 are met, and then vorinostat will be restarted per 6.2.3. Counts should be checked twice weekly until recovery of ANC ≥ 1,000/µL and platelet ≥ 100,000/µL.

6.2.1 Platelet transfusion is permissible and strongly encouraged for patients with dose-limiting thrombocytopenia (platelet count < 50,000/µL). Vorinostat should not be restarted until platelet count has recovered to ≥ 100,000/µL. (transfusion independent). These patients should receive vorinostat at the next lower dose level for subsequent cycles; however, if the patient is already at Dose Level –1, then vorinostat will be discontinued. See Section 5.4

6.2.2 For dose-limiting neutropenia, filgrastim (G-CSF) is permitted as clinically indicated. Vorinostat should not be started until ANC recovers to ≥ 1,000/µL for at least 48 hours without G-CSF support. Patients should start the subsequent cycle at the next lower dose level, without G-CSF support; however, if a patient experiences dose-limiting neutropenia at Dose Level –1, then vorinostat will be discontinued. See Section 5.4

6.2.3 Once study parameters are met as described above for vorinostat-related DLTs, vorinostat will be restarted at one dose level lower, if not already at Dose Level -

1. If the same DLT is experienced at the lower dose level, then vorinostat should be discontinued. If a different DLT is encountered, then the patient may restart vorinostat at the next lower dose level, if not already at Dose Level -1. Patients experiencing a DLT at Dose Level -1 will discontinue vorinostat. See Section 5.4

6.3 DSMB Monitoring of Toxicities During Maintenance

Toxicities during the maintenance component of this study will be monitored at regular intervals by the DSMB, and the maintenance dose of vorinostat will be reduced if the monitoring rule is met. (See section 11.3.6 for toxicity monitoring rules).

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

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

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered in accordance with sections 6.1 and 6.2 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified when growth factors are initiated.

7.5 Concomitant Medications

Anticonvulsants: Patients must not receive enzyme inducing anticonvulsants while on protocol therapy. (Please see Appendix II for a list of enzyme inducing and non-enzyme inducing anticonvulsants.)

Anti-coagulant: Patients must not receive coumadin, heparin, low-molecular weight heparin, or any other anti-coagulant while on protocol therapy.

Anti-platelet agent: Patients must not receive ASA (> 81 mg/day), non-steroidal anti-inflammatory drugs, clopidogrel (Plavix), dipyridamole (Persantine), or any other drug that inhibits platelet functions while on protocol therapy.

7.6 Management of Diarrhea

Previous trials have shown that the frequency and severity of diarrhea rarely hindered administration of vorinostat and could be managed with loperamide. Patients with diarrhea must be monitored and treated for signs and symptoms of dehydration promptly. Should diarrhea develop, patients should be treated with loperamide every 2-3 hours while awake and every 4 hours while asleep, until the patient has a 12-hour diarrhea-free interval. The table below gives the recommend weight-based doses:

Weight-Specific Guidelines for Therapeutic Use of Loperamide*

Weight	Initial (loading) loperamide dose	Subsequent daytime loperamide dose	Subsequent nighttime loperamide dose
8-10 kg	1 mg	0.5 mg every 3 hours	0.75 mg every 4 hours
10-20 kg	1 mg	1 mg every 3 hours	1 mg every 4 hours
20-30 kg	2 mg	1 mg every 3 hours	2 mg every 4 hours
30-43 kg	2 mg	1 mg every 2 hours	2 mg every 4 hours
> 43 kg	4 mg	2 mg every 2 hours	4 mg every 4 hours

* The total daily dose should not exceed 16 mg.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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).

8.1 Required Clinical, Laboratory and Disease Evaluations

All enrollment/eligibility studies must be performed within 1 week prior to study enrollment (unless otherwise specified). If more than 7 calendar days elapse between the date eligibility studies outlined in section 4.1.5 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies are required within 2 weeks prior to start of protocol therapy.

STUDIES TO BE OBTAINED	Pre-Study	During Radiotherapy	Start of Each Cycle of Vorinostat Maintenance
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Height, weight, BSA	X		X
Performance Status	X		
CBC, differential, platelets	X	Weekly[4]	Weekly[4]
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, SGPT, bilirubin	X	Weekly	X
Total protein/albumin	X	-	X
Tumor Disease Evaluation: - MRI of brain with gadolinium	X		Before Maintenance Therapy Cycle 2, then every 2 cycles x 2, then every 3 cycles[5]
- MRI of spine with gadolinium	X[6]		
Pregnancy Test[1]	X		
Patient Diary[2] – Part A Only		End of vorinostat and XRT	End of each cycle
Correlative Studies[3]	X[3]	X[3]	

1 Patients of childbearing potential require a negative pregnancy test prior to starting treatment and must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

2 Review patient diary weekly with the patient and family during radiation treatment and at the completion of each treatment cycle during maintenance therapy. Fax a copy with the corresponding shuttle sheet at the end of radiotherapy and at the end of each cycle of maintenance therapy to the COG Statistics and Data Center (626) 447-2204.

3 If patient consents; see section 8.3.2 for timing of correlative studies. The correlative biology samples should be obtained the day of weekly CBC collection, if possible.

4 Patients with hematologic DLT should have CBC repeated twice weekly until recovery as specified in Sections 6.1 and 6.2.

[5] Scans should be obtained prior to cycles 2, 4, 6, 9, and 12 of Maintenance Therapy. See Section 12.0 for Evaluation Criteria. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

[6] Patients with suspected disseminated disease must have MRI of spine performed. Patients with disseminated disease are not eligible.

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

8.2 **Required Observations Following Completion of Protocol Therapy**

The following studies are required until the patient is off study as defined in section 10.2. These observations are not applicable to patients enrolled on Part A who are NOT treated at the MTD.

STUDIES TO BE OBTAINED	3 Months	6 Months	9 Months	Every 6 Months up to 24 Months (Months 12, 18, 24)	Annually up to 60 Months (Months 36, 48, 60)
History	x	x	x	x	x
Physical Exam with vital signs	x	x	x	x	x
Height, weight, BSA	x	x	x	x	x
CBC, differential, platelets[1]	x	x			
Creatinine, SGPT, bilirubin[1]	x	x			
Electrolytes including Ca^{++}, PO_4, Mg^{++2}	x	x			
Disease evaluation[2]	x	x	x	x	x

[1] Repeated as clinically indicated

[2] Repeat sooner if suspected disease recurrence/progression

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

8.3 **Correlative Studies**

These optional studies are to be obtained for all patients on Part A or Part B of the study who have provided consent for correlative studies.

8.3.1 NHEJ activity, HDAC2 level, and histone acetylation in PBMCs

PBMCs will be isolated using Lymphoprep solution (Axis-Shield, Oslo, Norway), and protein lysates will be prepared by standard techniques. NHEJ activity will be analyzed via a published assay.[92] HDAC2 level will be quantified using Western analysis. Histone acetylation will be quantified using either Western analysis or a PathScan® Acetylated Histone H3 and H4 Sandwich ELISA Kit (Cell Signaling, Danvers, MA).

8.3.2 Sampling Schedule (See Appendix V)

Blood samples should be collected prior to the first dose of vorinostat and radiation, two weeks after starting vorinostat and radiation (any weekday, except Friday, during 3rd week of radiation), and at the end of radiation and vorinostat (any weekday, except Friday, during the last week of radiation). Blood samples should be collected **2-4 hours after the morning dose of vorinostat**. Blood samples should be obtained the day of weekly CBC collection, if possible. For patients required to be NPO at night for sedation obtain blood samples in the

morning.

8.3.3 Sample Collection and Handling Instructions

Whole blood samples (a minimum of 5-10 ml for children < 12 kg, and 10-20 ml for children ≥ 12 kg) should be collected in either **heparinized (green tops, either sodium or lithium heparin is acceptable) or ACDA (yellow top) tubes.** ACDA tubes are preferred if available. **DO NOT collect blood samples on a Friday.** Record the exact time that the sample is drawn along with the exact time that the drug is administered (see Appendix VI).

8.3.4 Sample Processing

No processing is required. Keep the whole blood at room temperature until the time of shipping.

8.3.5 Sample Labeling

Each tube must be labeled with the patient's COG identification number, the study number (ACNS0927), and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form (Appendix VI), which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

Each sample should be shipped immediately on the day of collection. Please follow packaging instructions on the Correlative Study Form (Appendix VI) Samples should be shipped at room temperature and by priority overnight via express carrier (**Monday through Thursday only**).

Jack Su, MD; Attention: Elizabeth Hinojosa
1102 Bates St., Room 1030
Baylor College of Medicine
Houston, TX 77030
(832) 824-4688 or (832) 822-4306

Prior to shipping, please contact Dr. Jack Su (832-822-4306, jmsu@txch.org), or Dr. Li (832-824-4580, xxli@txch.org) for notification of sample shipment.

8.4 Tumor Specimens

8.4.1 Description of Studies

If formalin-fixed, paraffin-embedded (FFPE) tumors are available, immunohistochemical staining of HDAC2, Ku70, Ku80, DNA-PK, BRCA1 and 2, Rad51, and ATM will be performed by standard techniques.

8.4.2 Sample Collection and Processing

If FFPE tumors are available, fifteen to twenty unstained PLUS glass slides, containing 5-micron thick tumor sections, should be prepared.

8.4.3 Sample Labeling

Each tube and slide must be labeled with the patient's COG identification number, the study number (ACNS0927), and the date when tumor was biopsied.

8.4.4 Sample Shipping Instructions

Slides from FFPE tumors should be shipped at room temperature, with appropriate packing to prevent breakage of slides. Detailed instructions regarding sample labeling and shipping can be found in **Appendix VIII.**

Shipments should be sent to the following address:

Jack Su, MD; Attention: Elizabeth Hinojosa
1102 Bates St., Room 1030
Baylor College of Medicine
Houston, TX 77030
(832) 824-4688 or (832) 822-4306

Prior to shipping, please contact Dr. Jack Su (832-822-4306, jmsu@txch.org) or Dr. Adekunle Adesina (832-824-5859, aadesina@bcm.edu or amadesin@texaschildrenshospital.org) for notification of sample shipment.

9.0 AGENT INFORMATION

9.1 VORINOSTAT

(Zolinza®, suberoylanilide hydroxamic acid, SAHA) **(06/06/14)**
NSC# 701852, IND#71976

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.
DDI

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.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Vorinostat (SAHA, Zolinza, 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 evehts that are protocol specific exceptions to expedited reporting to NCI (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 1076 patients.* Below is the CAEPR for Vorinostat (SAHA, Zolinza).

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 2.8, December 18, 2013[1]

Adverse Events with Possible Relationship to Vorinostat (SAHA, Zolinza) (CTCAE 4.0 Term) [n= 1076]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***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)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		

	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 3)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	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, Zolinza) trials but with the relationship to vorinostat (SAHA, Zolinza) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (supraventricular arrhythmia); 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; Eye disorders - Other (retinal tear)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (duodenitis); Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Oral pain; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (angioedema)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Vascular access complication; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged[4]; Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased[4]; Investigations - Other (increased lactate dehydrogenase); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (decreased total protein); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Chest wall pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (myositis); 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 - Abducens nerve disorder; 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; Somnolence; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Euphoria; 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 - Irregular menstruation; Pelvic pain; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (brittle nails)

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Visceral arterial ischemia

Note: Vorinostat (SAHA, Zolinza) 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.

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 4 weeks when stored at room temperature, away from excessive heat and humidity.

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.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 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/protocolDevelopment/default.htm#agents_drugs 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/docs/return_form.pdf.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Radiographic evidence of progressive disease (see section 12.0).
b) Clinical evidence of disease progression that can not be clearly attributed to weaning of dexamethasone, side effects from anti-epileptics, electrolyte disturbance, infection/sepsis, or other clinical events not related to protocol therapy.
c) Adverse Events requiring removal from protocol therapy (see section 6.0).
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Non-compliance that, in the opinion of the investigator, does not allow for ongoing participation.
f) Completion of 12 cycles of maintenance therapy.
g) Physician determines it is not in the patient's best interest.
h) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) and serum creatinine) are outside the parameters required for eligibility prior to the start of vorinostat and radiation (see section 8.1).
i) A patient becomes pregnant while receiving protocol therapy.
j) Development of a second malignancy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RDE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent (patients on Part A NOT enrolled at the MTD)
b) The fifth anniversary of the date the patient was enrolled on this study (patients on Part A enrolled at the MTD and all patients enrolled on Part B)
c) Death.
d) Lost to follow-up.
e) Withdrawal of consent for any further data submission.
f) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

There will be two parts in this study, for patients with newly diagnosed diffuse intrinsic pontine gliomas:

PART A: Phase I dose-finding component
PART B: Phase II component

A minimum of 2 evaluable patients will be entered at each dose level for determination of MTD in Part A. Accrual to Part B of the study will only open once the MTD or recommended phase 2 dose has been determined in Part A. Review of patient accrual onto a recent COG study of DIPG, ACNS0126, enrolled 63 patients in 15 months; hence the expected annual accrual for this study is 50 patients (2-3 patients per month in phase 1, and 4-5 patients per month in phase 2), which will permit completion of this study within 1.6 years. A maximum of 80 patients is anticipated. Twelve patients were enrolled on Part A and Phase II will enroll up to 68 patients to obtain 65 eligible patients for a maximum of 870 patients.

11.2 Part A of the Study

11.2.1 Definitions

Evaluable For Adverse Effects

Any patient who receives the study drug will be evaluable for Adverse Effects. However, for the consideration of dose escalation, patients must be fully evaluable for toxicity. Any patient who experiences DLT at any time during protocol therapy is considered fully evaluable for Adverse Effects. Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines are also considered fully evaluable for Adverse Effects. Patients who are not fully evaluable for Adverse Effects at a given dose level will be replaced.

Maximum Tolerated Dose

The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See section 5.6) during the chemoradiotherapy component in part A of the study. In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

- One of the DLTs does not appear to be related to dose
- The Adverse Effects are readily reversible
- The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, then dose escalation can proceed.

11.2.2 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study[92] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see section 11.2.1 for exception to rule).

Patients enrolled on Part A will continue on maintenance therapy as described in section 5.4.

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.3 Part B of the Study

The second portion of the study will begin after selecting the treatment dose for vorinostat in the phase I portion (Part A) of the study. The primary aim of this part of the study is to determine the effect on event-free survival and overall-survival, of administering vorinostat concurrently with radiation therapy, followed by maintenance vorinostat for twelve courses, in patients with diffuse intrinsic pontine gliomas. This portion of the trial will be performed group wide once the recommended dose of vorinostat during radiation is defined. Data collected from any patients enrolled at the MTD from the phase 1 component of the trial will be utilized in the Phase 2 study.

11.3.1 Efficacy Endpoints

The primary endpoint for the evaluation of treatment efficacy will be event-free survival (EFS), defined as the time to disease progression, disease relapse, occurrence of a second neoplasm, or death from any cause, or date of last follow-

up measured from the time of study enrollment.

Definitions of Evaluable

Part B:
Evaluable for Adverse Events and Efficacy
Patients will be considered evaluable for adverse events and efficacy if they meet the following criteria: (1) the patient is eligible; (2) the patient receives one dose of vorinostat at the MTD determined in Phase 1 (230 mg/m^2/day) per protocol guidelines, and (3) if central review is required, the patient is confirmed to have eligible diagnosis.

The secondary efficacy endpoint is overall survival (OS), which is defined as the time to death from any cause.

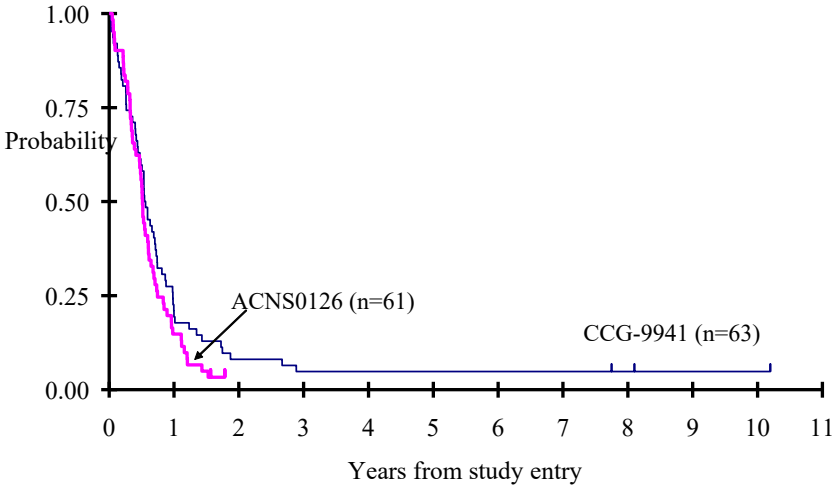
Primary Toxicity Endpoints:
For purposes of analysis, toxicities are classified by whether they are attributed to initial therapy (XRT/vorinostat) or to maintenance therapy (vorinostat). XRT/vorinostat-specific toxicities are listed in sections 5.6.1 to 5.6.3. Maintenance vorinostat toxicities are the same as DLTs defined in XRT/vorinostat section above, excluding 5.6.1. Toxic death is death predominantly attributable to treatment-treated causes. Toxic deaths occurring following the start of maintenance will be attributed to maintenance therapy, except when the death is clearly related to radiation necrosis or other XRT-specific toxicities.

11.3.2 Comparison with Baseline Established from Historical Control

The most recent relevant historical data on the outcome for patients with DIPGs is derived from CCG-9941 and ACNS0126. Figure 1 presents an event-free survival plot for the 61 eligible DIPG patients on ACNS0126 and compares them to a similar cohort of 63 patients from CCG-9941. The one-year EFS was 15 ± 5% for ACNS0126 and 21 ± 5% for CCG-9941. For the planning of the current trial, the combined data of ACNS0126 and CCG-9941 will be used as the historical control data. Figure 2 presents an approximation of the failure time distribution up to one year by an exponential failure time model. Fitting an exponential model to the combined data yields λ=1.54/year, and that one-year EFS estimated from this model is 21%.

The goal of this study is to compare outcome using historical control data described above as a baseline for comparison. We wish to detect a one-third reduction in the risk of failure as a result of this therapy. This corresponds to a 1-year EFS of 36%. Using the Woolson[93,94] one-sample log-rank test, with a one-sided 5% test of significance and 80% power, a total of 50 failures is obtained under the null hypothesis, which requires an enrollment of 65 patients in 15-18 months.

Figure 1: Event-Free Survival for DIPG



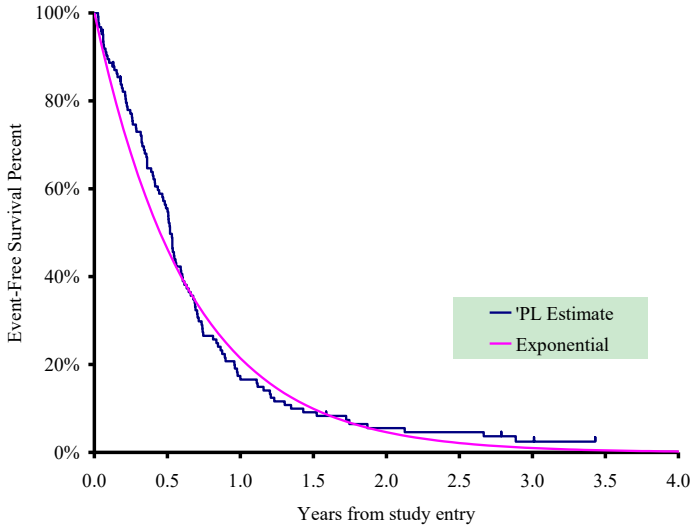


Figure 2: Event Free Survival from Combined Data ACNS0126 and CCG 9941 Product Limit Estimate and Exponential Model

11.3.3 Analysis of Toxicity

The analysis of toxicity will focus on estimates of the rates of chemoradiotherapy-phase DLT and rates of maintenance phase toxicities. Estimates will be obtained using life-table methods, with an event defined as the first occurrence of a primary toxicity. Patients who have progression or recurrence of disease will be censored in these analyses. Appropriate adjustment will be made to the rates estimates to account for potential effects of the initial vorinostat dose selection.

11.3.4 Interim Monitoring of event-free survival

Interim monitoring will be based on the Lan-Demets criterion, with spending function αt^2. The time point for 100% information is defined as 1.5 years after the last patient has enrolled. Analysis year, percent information, and critical

values for interim monitoring are listed in the table below. Let Z_t be the Z-value of the one-sample one-sided log rank statistic computed at some interim look with corresponding percent information or information fraction t. Let $B_t = Z_t\sqrt{t}$. For example, the first interim analysis will begin in analysis year 1, which is at time that 37% information will be available. According to the table, if $B_{0.37}$ exceeds the critical Z-value, 2.47, then the study will be flagged for review.

Analysis Year	Number of Events under null hypothesis	% Information	One-Sided Z-Value	Nominal one-sided p-value
1	21	37%	2.47	0.0068
1.5	39	69%	2.05	0.02
2	51	90%	1.87	0.024
2.5	55	98%	1.85	0.03
3.0	56	100%	1.88	0.03

At each time of interim monitoring, we will also calculate the conditional probability that the test statistics will be less than the final monitoring boundary at the final projected analysis time, under the alternative hypothesis viz., 1-year EFS of 36% for patients. If the conditional probability is less than 0.1, the study will be considered for termination because there will be little chance of concluding protocol therapy to be superior to historical outcome.

11.3.5 Monitoring for Toxic Death

No serious problems are expected with toxic death (TDR). We will nevertheless monitor rates of toxic death. The maximum tolerable TDR is 5%. If TDR is truly 5%, there is a 40% chance that there will be at least 1 toxic death among the first enrolled 10 patients, and a 72% chance that there will be at least 1 toxic death among the first 25 enrolled patients. Statistical monitoring rules will not be used. Rather, a careful review of treatment and patient safety will be undertaken when the first toxic death occurs. The 2nd toxic death on study will lead to accrual suspension.

11.3.6 Monitoring for Toxicity

Toxicities will be monitored separately in chemoradiotherapy and maintenance phase. The number of patients who discontinue vorinostat due to recurrent dose-limiting toxicities as specified in the Study Endpoints section will be monitored using the following rule:

If 3 or more of the first 16 patients or 7 or more of the first 48 patients discontinue vorinostat due to recurrent dose-limiting toxicities, then a careful review of treatment and patient safety will be undertaken. The operating characteristics of this stopping rule are summarized in the table.

True proportion of Toxicity	Probability of Stopping
0.05	0.05
0.07	***0.12***
0.1	0.31
0.15	0.67
0.2	***0.90***
0.25	0.98
0.3	0.99

Toxicities for the maintenance phase component of the trial will be monitored closely at regular intervals by the DSMB, and the vorinostat dose during maintenance therapy will be reduced if the monitoring rule is met.

11.4 Gender and Minority Accrual Estimates

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

Ethnic Category	Females	Males	Total
Hispanic or Latino	8	1	9
Not Hispanic or Latino	34	37	71
Ethnic Category: Total of All Participants*	42	38	80
Racial Categories			
American Indian/Alaska Native	1	0	1
Asian	1	0	1
Black or African American	6	10	16
Native Hawaiian or Other Pacific Islander	0	0	0
White	34	28	62
Racial Categories: Total of All Subjects*	42	38	80

The distribution was derived from ACNS0222.

11.5 Correlative Studies

The following measurements will be obtained for analysis of the secondary aims:

(1) H3 and H4 acetylation in PBMC: Pre- and post-treatment levels of H3 and H4 acetylation in PBMCs will be measured. Degree of acetylation in peripheral blood monocytes will be divided into quartiles and coded as none, mild, moderation or marked.
(2) NHEJ activity in PBMC: NEHJ activity is another possible inhibitory target for vorinostat. Whether there is a decreased NHEJ activity will be determined.
(3) Quantifying DNA repair proteins from paraffin-embedded blocks: for immunohistochemistry from tumor blocks, the intensity will be graded from 1 to 3; for Western analysis, a percentage of the intensity relative to the tumor with the highest level will be measured.

With a total of 65 patients in Part B and unknown compliance rate in submitting samples, the analysis of above correlative studies will be exploratory in nature. Descriptive statistics will be used to summarize the biological/laboratory measures and the changes in these measures across time-points. Mean and standard deviation will be used to summarize continuous measures; log transformation may be considered when appropriate. Categorical measures will be described by percentages with binary confidence intervals and frequency tables. Exploratory analyses to correlate the biological/laboratory measures with disease outcome will be performed. Log rank tests will be used to explore the prognostic significance of a categorical factor on EFS or OS. Cox proportional hazards models will be used to explore the effect of a continuous marker on EFS/OS, and will be used for exploratory multivariate analysis examining the effect of the predictor of interest with adjustments for other patient characteristics or risk factors.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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).

12.2 Methodology to Determine Tumor Measurement

In order to completely document the assessment of response, the two-dimensional tumor measurements for all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Newly occurring lesions should also be enumerated in these reports, and changes in lesions should be described.

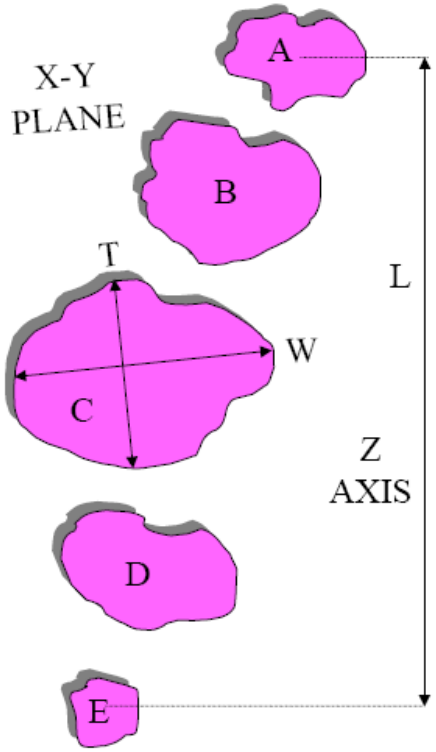
Tumor response criteria for this study are to be determined by changes in size using the maximal 2-dimensional cross-sectional tumor measurements, T x W (product of the longest diameter of the tumor [width (W)] and its longest perpendicular diameter [transverse (T)], using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). This will allow comparison with historical studies as outlined in the statistical design section, such as CCG-9941 and ACNS0126, which used cross-sectional measurements in their determination of response status.

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

The following section describes the methodology.

(See drawing below for illustration)

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) tumor extent in the plane perpendicular to the selected plane).
4. Leptomeningeal tumor spread is not a target lesion, as its presence at diagnosis would make the patient ineligible for this brainstem glioma study. The presence and location of leptomeningeal tumor spread at relapse should be noted.



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

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

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

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

12.4 **Response Criteria for Target Lesions**

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

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

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

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

Progressive Disease (PD): Progressive disease is defined as 25% or more increase in the sum of the product of the perpendicular diameters of the target lesions, taking as reference the smallest sum of products observed since the start of treatment, or the appearance of one or more new lesions.

12.5 **Overall Response Assessment**

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

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

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

12.6 **Best Response**

Two objective status determinations of disease status, by MRI, obtained on two consecutive determinations, separated by at least a 4 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

1st Status	2nd Status	3rd Status	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 **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.

13.2 **Determination of reporting requirements**

Reporting requirements may include the following considerations: 1) whether the patient has received at least one dose of an investigational agent on this study; 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; and 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.

13.3 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria*
The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

Step 2: Grade the adverse 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 or an investigator held 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 Table A or Table 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.*

13.4 Reporting methods

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

  An CTEP-AERS report must be submitted by the following method:

  Electronically submit the report via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/CTEP-AERS.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; email:

COGQA@childrensoncologygroup.org attention: COG CTEP-AERS 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.**

13.5 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.

  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 CTEP-AERS system by the original submitter of the report at the site.

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

13.6 Other recipients of adverse event reports

COG will forward reports and supporting documentation to the Study Chair.

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.

13.7 Reporting of Adverse Events for investigational agents

Reporting requirements are provided in Table A and Table B. The investigational agent used in this study is vorinostat.

Table A: For Part A of the Study Only

Phase 1 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2[3]	Grade 2	Grade 3[3]		Grade 3[3]		Grades 4 & 5[2, 3]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	5 Calendar Days	Not Required	24-Hour; 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:**
CTEP-AERS 24-hour notification (via CTEP-AERS 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 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although an CTEP-AERS 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."**

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete CTEP-AERS 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 CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 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 CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, including Grade 4, does not require expedited reporting unless unexpected.

- Lymphopenia, including Grade 4, does not require expedited reporting unless unexpected.

- Grade 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Abdominal pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
INFECTIONS AND INFESTATIONS	Infection
INVESTIGATIONS	Activated partial thromboplastin time prolonged
INVESTIGATIONS	Alkaline phosphatase increased
INVESTIGATIONS	Blood bilirubin increased
METABOLISM AND NUTRITION DISORDERS	Hypoalbuminemia
METABOLISM AND NUTRITION DISORDERS	Hypocalcemia
METABOLISM AND NUTRITION DISORDERS	Hypokalemia
METABOLISM AND NUTRITION DISORDERS	Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Musculoskeletal and connective tissue disorder - Other (muscle spasms)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia

As referenced in the CTEP Adverse Event Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

Table B: For Part B of the Study Only
Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: CTEP-AERS 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		Grades 4 & 5[2]	Grades 4[3] & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	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:**
CTEP-AERS 24-hour notification (via CTEP-AERS 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

CTEP-AERS 5 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

[2] Although an CTEP-AERS 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 CTEP-AERS for CTEP IND agents within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete CTEP-AERS 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 CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- 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 CTEP-AERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS.

13.8 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 CTEP-AERS 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 CTEP-AERS reportable events, Grade 3 and higher Adverse Events and any events which constitute a dose limiting toxicity (DLT) per the protocol.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

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

1. Non-computerized Information: Roadmaps (Part A only), Pathology Reports, Surgical Reports. These forms are faxed, with the corresponding shuttle sheet, to the Statistics & Data Center at (626) 447-2204.

2. Reference Labs, Biopathology Reviews, and QARC data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. 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.

14.3 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) 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/industryCollaborations2/intellectual_property.htm) 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 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 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 NCI, 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 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 Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).. 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 by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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:

Email: ncicteppubs@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.

14.4 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility into the study database.

In addition, during Part A study data and the study chair's evaluations of patients' eligibility, evaluability and dose limiting toxicities will be reviewed by the Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

15.0 RADIATION THERAPY GUIDELINES

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities.

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).

15.0.1 General Guidelines

This is a phase 1/2 study to determine the maximum tolerated dose (MTD) of suberoylanilide hydroxamic acid (SAHA; vorinostat) in combination with radiation therapy, followed by maintenance therapy with vorinostat, in patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG). All patients will receive radiation therapy on this protocol with the targeted volume based on the extent of disease defined by neuroimaging prior to radiation therapy. This study specifies a 1 cm clinical target volume margin and mandates the use of CT-MR registration to define the target volume. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons and electronic data submission is required. Proton therapy is not allowed.

15.0.2 Treatment Planning Specifics

The guidelines for this study were developed based on the performance of COG investigators when executing the guidelines in prior COG trials. The goal of the treatment planning process is to develop a plan to deliver a uniform dose to the planning target volume which includes all known tumor plus the specified clinical target volume margin. The protocol specified total dose is 54 Gy using conventional fractionation. Because the total dose does not exceed the recommended dose limits for the spinal cord and optic chiasm, volume reductions are not required nor recommended.

15.0.3 Required Benchmark and Questionnaires

Radiation therapy will be administered using photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). 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 irradiate the RPC head and neck phantom. 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. For information regarding the IMRT phantoms, please contact the RPC (http://rpc.mdanderson.org/rpc).

15.0.4 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.

15.1 Indications for Radiation Therapy

All patients enrolled on this protocol will receive concurrent chemotherapy and radiation therapy.

15.2 Timing

15.2.1 All patients should be seen in consultation by a radiation oncologist at the time of study enrollment. The purpose of the consultation is to participate in the initial evaluation and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning. If additional imaging studies are pursued, thin section MR (T2-weighted and FLAIR) sequences should be obtained for registration to the CT data set to assist in treatment planning.

15.2.2 There are no contraindications to radiation therapy. There are, however, some restrictions with regard to concomitant medications and eligibility as detailed in section 4.2.2. Patients receiving corticosteroids must be on a stable or decreasing dose for the prior 7 days to be eligible. Patients taking valproic acid must discontinue this 2 weeks prior to protocol therapy. In addition, patients must not be receiving enzyme-inducing anticonvulsants (see appendix II for a list of enzyme inducing and non-inducing anticonvulsants). Within these constraints, corticosteroids and anticonvulsants should be used as clinically indicated and tapered as soon as possible. Prophylactic anticonvulsants are strongly discouraged.

15.2.3 Please see section 5.1.1 for details of timing of vorinostat administration. Vorinostat should be administered between 1-2 hours prior to each radiation therapy fraction when feasible, beginning with the first fraction. Younger patients with NPO requirements due to sedation during RT will be allowed to take vorinostat 6 hours prior to each fraction, or the night before each fraction.

15.3 Emergency Irradiation

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol and urgent irradiation is not envisioned under any circumstance.

15.4 Equipment and Methods of Delivery and Verification

Equipment	Photons (any energy)	IMRT (4-10MV)
Linear Accelerator	X	X

15.4.1 Treatment planning

CT (volumetric) based planning is required to optimize dose to the PTV while protecting normal tissues. Organs at risk within the irradiated volume should be contoured. A DVH is necessary to determine target coverage and evaluate dose to normal tissues. CT section thickness should be $\leq$ 5mm although 2-3mm is preferred.

15.4.2 In-room verification of spatial positioning

15.4.2.1 Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

15.4.2.2 Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging. Please submit representative axial images showing the isocenter and the correct alignment in relationship to the patients' position. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

15.5 Target Volumes

15.5.1 General comments

International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study where applicable. 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 CSF shunting procedure. The investigators recognize that resection and shunting are unlikely for these patients. The sequence that best defines the extent of disease and post-operative tumor bed (when applicable), should be used to determine the GTV and registered to the treatment planning CT. Most patients with DIPG require a combination of MR sequences to delineate the extent of disease. MR T2 and FLAIR sequences are most likely to be those chosen for registration to the treatment planning CT data set. The GTV, CTV and PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

15.5.2 Definitions for GTV, CTV and PTV

- Gross tumor volume (GTV) is based on the most recent MRI and/or post-operative MRI examination (if resection was done) and includes gross residual tumor and the tumor bed at the primary site. In defining the GTV, the investigator should consider all imaging studies that have defined the extent of tumor and the tissues involved anatomically. The GTV in most cases will be the T2 or FLAIR abnormality on the appropriate MR sequence. Tissue defects resulting from surgical approaches, when undertaken, will not be included as part of the GTV when not previously involved by tumor. Investigators should register the immediate pre-irradiation MR imaging sequences that demonstrated tumor and contour the GTV.

- Clinical target volume (CTV) includes the GTV with an added margin of 1 cm. This is meant to treat subclinical microscopic disease and is anatomically confined (i.e., the CTV is limited to the confines of the bony

calvarium, falx and tentorium where applicable or extends up to but not beyond neuroanatomic structures through which tumor extension or invasion is certain not to have occurred). The CTV may be manually moved inward to the inner table of the bony calvarium. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires treatment planning MR and/or diagnostic MR imaging data with image section thickness ≤ 5mm.

- Planning target volume (PTV) includes a margin which is added to the CTV in 3-dimensions. It is geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 3 or 5mm. The use of a PTV margin of 3mm requires written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging. For this study, IGRT is defined as 2- or 3-dimensional digital imaging positioning. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient. The PTV margin chosen by the treating investigator requires treatment planning MR and/or diagnostic MR imaging data with imaging section thickness ≤ the chosen PTV margin.

15.6 Target Dose

15.6.1 Dose Definition

Photon dose is to be specified in centigray (cGy)-to-muscle.

15.6.2 Prescribed dose and fractionation

The total dose to the isodose surface encompasses the PTV will be 5400cGy administered in 30 fractions of 180cGy. The patient should be treated with one fraction per day. All fields should be treated each day.

Table 15.6.2 Prescribed Doses and Fractionation

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

15.6.3 Dose uniformity

At least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of the PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

15.6.4 Tissue heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. For questions about heterogeneity corrections or approved algorithms, please contact QARC (www.QARC.org).

15.6.5 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 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 treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

15.7 Treatment Technique

15.7.1 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 are required to minimize dose to normal tissues.

15.7.2 Field Shaping

Field shaping will be done with either customized cerrobend blocking or multileaf collimation.

15.7.3 Simulation including patient positioning and immobilization

15.7.3.1 Patient positioning

Reproducible setups are critical. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

15.7.3.2 Immobilization devices

Standard immobilization devices for the brain or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

15.7.4 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

15.7.5 Motion Management and Margins to Account for Target Volume Changes During Treatment

Considering motion of target volumes is important. Brain tumors susceptible to

cyst expansion should be monitored closely. Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele, or steroid use should be monitored carefully with repeat imaging when indicated.

A description of the method used and evidence of the remaining tumor motion (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT) should be submitted **on the Motion Management Reporting Form** with the Quality Assurance Documentation materials as noted in Section 15.10.

15.8 Organs at Risk

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

Dose Constraints

15.8.1 Cochleae

- D50% ≤ 3500cGy – Goal (each cochlea)
- D50% ≤ 2000cGy – Preferred (each 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.

15.8.2 Optic Globes

- D90% ≤ 500cGy, D50% ≤ 1000cGy and D10% ≤ 3500cGy – Goal
- D90% ≤ 1000cGy, 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. In the event that the recommended maximum dose constraints provided in this section would be exceeded, 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.

15.8.3 Right and Left Optic Nerves and Chiasm

- D90% ≤ 1000cGy, D50% ≤ 5400cGy and D10% ≤ 5600cGy – Goal
- D90% ≤ 5400cGy, 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. In the event that the recommended maximum dose constraints provided in this section would be exceeded, 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.

15.8.4 Spinal Cord

- D90% ≤ 300cGy, D50% ≤ 2600cGy and D10% ≤ 5700cGy - Goal
- D90% ≤ 900cGy, D50% ≤ 5000cGy and D10% ≤ 5900cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage.
- 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). Using these guidelines, only the superior-most 6cm of anatomic spinal cord is contoured.

15.9 Dose Calculations and Reporting

15.9.1 Prescribed Dose

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

15.9.2 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 for the primary tumor, 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.

Table 15.9a Required DVH data:

Required DVH
Total Brain
Optic Nerves (L+R)
Optic Chiasm
Brainstem
Spinal Cord
Cochleae (L+R)
Unspecified Tissue

15.10 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.

External beam Treatment Planning System

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. When using IMRT, orthogonal isocenter images are sufficient.
- Isodose distributions for the treatment plan in the axial, sagittal and coronal planes at the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method must be clearly indicated.
- Dose volume histograms (DVH) for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in Section 15.8. 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.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Beams-eye-view (BEV) of portals showing collimator, beam aperture, target volume and critical structures are required when not using IMRT.

Digital Data

- Submission of the treatment plan in digital format is required. Please refer to www.QARC.org and click on "Digital Data" for guidelines regarding digital submission. All submissions, including those that are digital, require hard copy submission of the other items included in this list. If there are any problems with digital data submission, please contact QARC.

Supportive Data

- All diagnostic imaging used to plan the target volume. This includes CT or MRI 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 a PTV margin of 3 mm is used, written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging. See section 15.5.2
- Motion Management Reporting Form (if applicable, see Section 15.10).

Forms

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

These data should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway Suite 201
Lincoln, Rhode Island 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, Rhode Island 02865-4207

15.11 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 and Coverage		
	>10% PTV received > 110% of the protocol dose *or* 95% isodose covers < 100% of CTV	> 20% of PTV received >110% of the protocol dose or 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		
	Dose to any OAR exceeds the goal dose stated in 15.8	Dose to any OAR exceeds the maximum dose stated in 15.8

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: 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
Valproic Acid	Depakote, Depakene
Zonisamide	Zonegran
Enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxycarbazepine	Trileptal

APPENDIX III: VORINOSTAT DOSING NOMOGRAM FOR CAPSULE FORMULATION

Vorinostat (SAHA) Dose Based on BSA (m^2) and Assigned Dose Level*				
Dose Level	**200 mg**	**300 mg**	**400 mg**	**500 mg**
180 mg/m^2	1.25-1.42	1.43– 1.95	1.96 – 2.49	≥ 2.5
230 mg/m^2		1.25 – 1.42	1.43 – 1.95	≥ 1.96

*Patients with BSA < 1.25 m^2 or unable to swallow capsules will receive the vorinostat suspension rounded to the nearest 5 mg (See section 9.1.5 for preparation guidelines.)

APPENDIX IV-A: PATIENT DIARY FOR VORINOSTAT CAPSULE ADMINISTRATION DURING CHEMORADIOTHERAPY (Part A only)

COG Patient ID:_____ ACC # : _____ Institution :_____
Please do not write patient name on this form.

Please write the date, time and dose of vorinostat given. **NOTE: Vorinostat capsules should be swallowed whole.** If you vomit within 30 minutes after taking the medication, that dose should be repeated. If you vomit after 30 minutes, the dose will not be repeated. Make note of other drugs and supplements taken. Return the completed diary to your institution after each treatment cycle. Your institution will fax this document with the corresponding shuttle sheet, to the COG Statistics & Data Center at (626) 447-2204 after each treatment cycle.

EXAMPLE					
WEEK 1	***Date***	***Time*** **(Circle AM or PM)**		***Dose Given***	***Comments***
Day 1	*1/15/09*	*8:30*	*(am)/pm*	*Vorinostat XX mg*	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Dose Level: ____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Number of Days per Week to be Taken: 3 or 5 (circle one). If 3, then for days vorinostat is not to be taken, put an "X" in the Date Column.

WEEK 1	**Date**	**Time** **(Circle AM or PM)**		***Dose Given***	**Comments**
Day 1			**am/pm**	Vorinostat: _____ mg	
Day 2			**am/pm**	Vorinostat: _____ mg	
Day 3			**am/pm**	Vorinostat: _____ mg	
Day 4			**am/pm**	Vorinostat: _____ mg	
Day 5			**am/pm**	Vorinostat: _____ mg	
WEEK 2	**Date**	**Time** **(Circle AM or PM)**			**Comments**
Day 8			**am/pm**	Vorinostat: _____ mg	
Day 9			**am/pm**	Vorinostat: _____ mg	
Day 10			**am/pm**	Vorinostat: _____ mg	
Day 11			**am/pm**	Vorinostat: _____ mg	
Day 12			**am/pm**	Vorinostat: _____ mg	
WEEK 3	**Date**	**Time** **(Circle AM or PM)**		***Dose Given***	**Comments**

Day 15			**am/pm**	Vorinostat: _____ mg	
Day 16			**am/pm**	Vorinostat: _____ mg	
Day 17			**am/pm**	Vorinostat: _____ mg	
Day 18			**am/pm**	Vorinostat: _____ mg	
Day 19			**am/pm**	Vorinostat: _____ mg	
WEEK 4	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 22			**am/pm**	Vorinostat: _____ mg	
Day 23			**am/pm**	Vorinostat: _____ mg	
Day 24			**am/pm**	Vorinostat: _____ mg	
Day 25			**am/pm**	Vorinostat: _____ mg	
Day 26			**am/pm**	Vorinostat: _____ mg	
WEEK 5	**Date**	**Time (Circle AM or PM)**		***Dose Given***	**Comments**
Day 29			**am/pm**	Vorinostat: _____ mg	
Day 30			**am/pm**	Vorinostat: _____ mg	
Day 31			**am/pm**	Vorinostat: _____ mg	
Day 32			**am/pm**	Vorinostat: _____ mg	
Day 33			**am/pm**	Vorinostat: _____ mg	
WEEK 6	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 36			**am/pm**	Vorinostat: _____ mg	
Day 37			**am/pm**	Vorinostat: _____ mg	
Day 38			**am/pm**	Vorinostat: _____ mg	
Day 39			**am/pm**	Vorinostat: _____ mg	
Day 40			**am/pm**	Vorinostat: _____ mg	
WEEK 7 (if applicable)	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 43			**am/pm**	Vorinostat: _____ mg	

Day 44			**am/pm**	Vorinostat: _____ mg	
Day 45			**am/pm**	Vorinostat: _____ mg	
Day 46			**am/pm**	Vorinostat: _____ mg	
Day 47			**am/pm**	Vorinostat: _____ mg	

ADDITIONAL COMMENTS:

Signature: _____ Date::_____

APPENDIX IV-B: PATIENT DIARY FOR VORINOSTAT PEDIATRIC SUSPENSION DURING CHEMORADIOTHERAPY (Part A only)

COG Patient ID:_____ **ACC # :** _____ **Institution :**_____
Please do not write patient name on this form.

Please write the date, time and dose of vorinostat given. If you vomit within 30 minutes after taking the medication, that dose should be repeated. If you vomit after 30 minutes, the dose will not be repeated. Make note of other drugs and supplements taken. Return the completed diary to your institution after each treatment cycle. Your institution will fax this document with the corresponding shuttle sheet, to the COG Statistics & Data Center at (626) 447-2204 after each treatment cycle.

EXAMPLE					
WEEK 1	***Date***	***Time*** **(Circle AM or PM)**		***Suspension Taken Amount (mL)***	***Comments***
Day 1	*1/15/09*	*8:30*	*(am)/pm*	*Vorinostat XX mL*	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ **Dose Level:** ____ **Start Date**: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Number of Days per Week to be Taken: 3 or 5 (circle one). If 3, then for days vorinostat is not to be taken, put an "X" in the Date Column.

WEEK 1	**Date**	**Time** **(Circle AM or PM)**		***Suspension Taken Amount (mL)***	**Comments**
Day 1			**am/pm**	Vorinostat: _____ mL	
Day 2			**am/pm**	Vorinostat: _____ mL	
Day 3			**am/pm**	Vorinostat: _____ mL	
Day 4			**am/pm**	Vorinostat: _____ mL	
Day 5			**am/pm**	Vorinostat: _____ mL	
WEEK 2	**Date**	**Time** **(Circle AM or PM)**			**Comments**
Day 8			**am/pm**	Vorinostat: _____ mL	
Day 9			**am/pm**	Vorinostat: _____ mL	
Day 10			**am/pm**	Vorinostat: _____ mL	
Day 11			**am/pm**	Vorinostat: _____ mL	
Day 12			**am/pm**	Vorinostat: _____ mL	

WEEK 3	**Date**	**Time** **(Circle AM or PM)**		***Suspension Taken Amount (mL)***	**Comments**
Day 15			**am/pm**	Vorinostat: _____ mL	

Day 16			**am/pm**	Vorinostat: _____ mL	
Day 17			**am/pm**	Vorinostat: _____ mL	
Day 18			**am/pm**	Vorinostat: _____ mL	
Day 19			**am/pm**	Vorinostat: _____ mL	
WEEK 4	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 22			**am/pm**	Vorinostat: _____ mL	
Day 23			**am/pm**	Vorinostat: _____ mL	
Day 24			**am/pm**	Vorinostat: _____ mL	
Day 25			**am/pm**	Vorinostat: _____ mL	
Day 26			**am/pm**	Vorinostat: _____ mL	
WEEK 5	**Date**	**Time (Circle AM or PM)**		***Suspension Taken Amount (mL)***	**Comments**
Day 29			**am/pm**	Vorinostat: _____ mL	
Day 30			**am/pm**	Vorinostat: _____ mL	
Day 31			**am/pm**	Vorinostat: _____ mL	
Day 32			**am/pm**	Vorinostat: _____ mL	
Day 33			**am/pm**	Vorinostat: _____ mL	
WEEK 6	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 36			**am/pm**	Vorinostat: _____ mL	
Day 37			**am/pm**	Vorinostat: _____ mL	
Day 38			**am/pm**	Vorinostat: _____ mL	
Day 39			**am/pm**	Vorinostat: _____ mL	
Day 40			**am/pm**	Vorinostat: _____ mL	
WEEK 7 (if applicable)	**Date**	**Time (Circle AM or PM)**			**Comments**
Day 43			**am/pm**	Vorinostat: _____ mL	
Day 44			**am/pm**	Vorinostat: _____ mL	

Day 45			**am/pm**	Vorinostat: _____ mL	
Day 46			**am/pm**	Vorinostat: _____ mL	
Day 47			**am/pm**	Vorinostat: _____ mL	

ADDITIONAL COMMENTS:

Signature: _____ Date::_____

APPENDIX IV-C: PATIENT DIARY FOR VORINOSTAT (CAPSULE OR PEDIATRIC SUSPENSION) DURING MAINTENANCE THERAPY (PART A ONLY)

COG Patient ID:_____ **ACC # :** _____ **Institution :**_____
Please do not write patient name on this form.

Please write the date, time and dose of vorinostat given. **NOTE: Vorinostat capsules should be swallowed whole**. If you vomit within 30 minutes after taking the medication, that dose should be repeated. If you vomit after 30 minutes, the dose will not be repeated. Make note of other drugs and supplements taken. Return the completed diary to your institution after each treatment cycle. Your institution will fax this document with the corresponding shuttle sheet, to the COG Statistics & Data Center at (626) 447-2204 after each treatment cycle. **Use a new form for each cycle of maintenance therapy.**

EXAMPLE					
WEEK 1	***Date***	***Time*** **(Circle AM or PM)**		***Capsule (mg) or Suspension (mL) Amount Taken***	***Comments***
Day 1	*1/15/09*	*8:30*	*(am)/pm*	_____mg or ____ mL	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ **Dose Level:** ____ **Start Date**: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Number of Days per Week to be Taken: 3 or 5 or 7 (circle one). If 3 or 5, then for days vorinostat is not to be taken, put an "X" in the Date Column.

DAY	**Date**	**Time** **(Circle AM or PM)**		***Capsule (mg) or Suspension (mL) Amount Taken***	**Comments**
Day 1			**am/pm**	_____mg or ____ mL	
Day 2			**am/pm**	_____mg or ____ mL	
Day 3			**am/pm**	_____mg or ____ mL	
Day 4			**am/pm**	_____mg or ____ mL	
Day 5			**am/pm**	_____mg or ____ mL	
Day 6			**am/pm**	_____mg or ____ mL	
Day 7			**am/pm**	_____mg or ____ mL	
Day 8			**am/pm**	_____mg or ____ mL	
Day 9			**am/pm**	_____mg or ____ mL	
Day 10			**am/pm**	_____mg or ____ mL	
Day 11			**am/pm**	_____mg or ____ mL	

Day 12			**am/pm**	_____mg or ____ mL	
Day 13			**am/pm**	_____mg or ____ mL	
Day 14			**am/pm**	_____mg or ____ mL	
Day 15			**am/pm**	_____mg or ____ mL	
Day 16			**am/pm**	_____mg or ____ mL	
Day 17			**am/pm**	_____mg or ____ mL	
Day 18			**am/pm**	_____mg or ____ mL	
Day 19			**am/pm**	_____mg or ____ mL	
Day 20			**am/pm**	_____mg or ____ mL	
Day 21			**am/pm**	_____mg or ____ mL	
Day 22			**am/pm**	_____mg or ____ mL	
Day 23			**am/pm**	_____mg or ____ mL	
Day 24			**am/pm**	_____mg or ____ mL	
Day 25			**am/pm**	_____mg or ____ mL	
Day 26			**am/pm**	_____mg or ____ mL	
Day 27			**am/pm**	_____mg or ____ mL	
Day 28			**am/pm**	_____mg or ____ mL	

APPENDIX V: BLOOD SAMPLE COLLECTION GUIDE FOR CORRELATIVE BIOLOGY STUDIES (PART A AND PART B OF STUDY)

Peripheral blood samples to be collected during vorinostat and radiation treatment:
Blood samples should be collected:

- prior to the first day of vorinostat and radiation
- two weeks after starting vorinostat and radiation (any weekday, except Friday, during 3rd week of radiation)
- at the end of radiation and vorinostat (any weekday, except Friday, during the last week of radiation)

The correlative biology samples should be obtained the day of weekly CBC collection, if possible.

For the second and third samples, blood should be collected **2-4 hours after the morning dose of vorinostat**. For patients required to be NPO overnight for sedation and must take vorinostat the night before, obtain blood samples in the morning. Blood samples can be obtained either by venipunctures or through central lines.

Whole blood samples (a minimum of 5 ml for children < 12 kg, and 10 ml for children ≥ 12 kg) should be collected in either **heparinized (green tops, either sodium or lithium heparin is acceptable) or ACDA (yellow top) tubes. DO NOT collect blood samples on a Friday.**

APPENDIX VI: CORRELATIVE STUDY FORM (PART A AND PART B OF STUDY, DURING RADIATION THERAPY)

This completed form should be sent with each shipment of samples for correlative studies. Prior to shipping, please contact Dr. Jack Su (832-822-4306, jmsu@txch.org) or Dr. Xiao-Nan Li (832-822-4277, xxli@txch.org) for notification of sample shipment. **Samples should be shipped immediately on the same day of collection**. **DO NOT SHIP SAMPLES ON A FRIDAY OR WEEKEND**.

- Seal the original tube(s) with paraffin and place the tube(s) inside an insulated container
- Place the container in a Styrofoam box.
- Between April-October: please ship with a single ice pack placed in the Styrofoam box (ice pack should not be placed directly next to the samples). An ice pack is not necessary when shipping between November-March.
- Package sample as appropriate for biologic material

COG No._____ Acc. No:_____ Institution:_____

Vorinostat Dose Level _____, _____mg/m^2/day, a) M through F **OR** b) M, W, F (circle one)

List the scheduled time and actual times that blood was obtained.

PBMC Collection	**Administration of Vorinostat**		**Date Sample Collected**	**Time Sample Collected**		**WBC Count***	
	Date	**Time**		**Scheduled**	**Actual**		
Prior to Day 1 radiation therapy and first dose of vorinostat.	Date:_____	Time:_____	Date:_____	Time:_____	Time:_____	WBC Count:_____	Date Drawn:_____
2-4 hours after am vorinostat, on a weekday except Friday, during the **3rd week of vorinostat and radiation**	Date:_____	Time:_____	Date:_____	Time:_____	Time:_____	WBC Count:_____	Date Drawn:_____
2-4 hours after am vorinostat, on a weekday except Friday, during **the last week of vorinostat and radiation**	Date:_____	Time:_____	Date:_____	Time:_____	Time:_____	WBC Count:_____	Date Drawn:_____

* Provide the most recently taken white blood cell count. The correlative biology samples should be obtained the day of weekly CBC collection, if possible.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature:_____ Date:_____
(site personnel who collected sample)

APPENDIX VII: YOUTH INFORMATION SHEETS (PART B ONLY)

INFORMATION SHEET REGARDING RESEARCH STUDY ACNS0927 (Part B only) (for children from 7 through 12 years of age)

A Study of Adding Vorinostat to Treatment for Newly Diagnosed DIPG Brain Tumors

1. We have been talking with you about your brain tumor, called a DIPG. Your brain tumor is a type of cancer that grows in the area of the brain that controls things like your breathing and your heart beat. 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 hard to treat. 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 get rid of DIPG than the normal treatment.

   The normal treatment is the use of high-energy x-rays to get rid of the cancer cells. But this x-ray treatment may only work for a short time. Sometimes it does not work at all. Study doctors want to see if giving a drug during the x-ray treatment will help get rid of more cancer cells. Study doctors also want to see if giving the drug after x-ray treatments will help get rid of any cancer cells that may still be in the brain. Study doctors hope this new treatment will work better than the normal treatment to get rid of cancer cells.

3. Children who are part of this study will be treated with an anti-cancer medicine called vorinostat. Vorinostat is a medicine that you will swallow. You will take it during the time you are having the x-ray treatments. At the end of the x-ray treatment you will take more vorinostat as long as you do not have bad effects from it and your cancer does not get any worse. Treatment with the vorinostat may last up to about a year. Doctors will check you often to see how the treatment is working.

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 treatment will work better than the normal treatment to get rid of the tumor. 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 have bad health problems from the vorinostat. If this happens you may need treatment for the health problems. 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.

7. We are asking your “okay” to collect some extra blood three times during your treatment. One of the blood samples would be taken when other standard blood tests are being performed. The second sample would be taken during the third week of vorinostat and radiation. The third sample would be taken during the last week of vorinostat and radiation. So, there would be two extra blood draws. Sometimes doctors do an operation to find out if you have cancer. If you had an operation, we are also asking your “okay” to study any tissue the doctors took out during this operation. We want to see if there are ways to tell how the cancer will react to treatment. You can still take part in this study even if you do not allow us to collect the extra blood samples or the tissue for research.

INFORMATION SHEET REGARDING RESEARCH STUDY ACNS0927 (Part B only)
(for teens from 13 through 17 years of age)

A Study of Adding Vorinostat to Treatment for Newly Diagnosed DIPG Brain Tumors

1. We have been talking with you about your brain tumor, called a diffuse intrinsic pontine glioma or DIPG, for short. DIPG brain tumors are a type of cancer that grows in the lowest part of your brain called the brain stem. The brain stem is the area of the brain that controls your breathing, blood pressure, and heart rate. DIPG tumors are hard to treat. 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 been newly diagnosed with DIPG and it is hard to treat. 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 get rid of DIPG than the standard treatment for this disease.

   The standard treatment for this kind of tumor is radiation therapy (the use of high-energy x-rays) to get rid of the cancer cells. But radiation therapy may only work for a short time. Sometimes it does not work at all. Study doctors want to see if giving a drug during the radiation therapy will help get rid of more cancer cells. Study doctors also want to see if giving the drug after radiation therapy will help get rid of any cancer cells that may still be in the brain. Study doctors hope this new treatment will work better than the standard treatment to get rid of cancer cells.

3. Children and teens who are part of this study will be treated with radiation therapy once a day for 30 days. During this time you will also take a drug called vorinostat. Vorinostat is a medicine that you will swallow. At the end of radiation therapy, you will then take more vorinostat as long as you do not have side effects from it and your cancer does not get any worse. Treatment with the vorinostat may continue for up to a year. You will have tests and scans done regularly to check how you are doing and how the treatment is working.

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 treatment will work better to get rid of the tumor than the standard 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.” The risks to you from this study are that you may have side effects from the combination of radiation therapy with vorinostat, or the vorinostat alone. Some possible side effects include things like being very tired, an upset stomach, and not being able to keep food down. 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.

7. We are asking your permission to collect additional blood three times during your treatment. One of these blood samples would be taken when other standard blood tests are being performed, on the first day you have radiation therapy. The second blood sample would be taken during the third week of radiation therapy. The last blood sample would be taken during the last week of radiation therapy. So, there would be two extra blood draws. We are also asking your permission to study tumor tissue that may have been removed during surgery to diagnose your cancer. We want to see if there are ways to tell how the cancer will respond to treatment. You can still be treated on this study even if you do not allow us to collect the extra blood samples and/or tumor tissue for research.

APPENDIX VIII: TUMOR SPECIMEN (PART A AND PART B OF STUDY)

Patient ID #: _____ Study ID: **ACNS0927**

Accession #: _____ Date: _____

Please do not write patient names on this form or on samples.

Sample Labeling:

Samples should be labeled with the following information:

Protocol number:	**ACNS0927**
Institution:	_____
Patient ID #:	_____
Accession #:	_____
Sample Date:	_____

Shipment of Tumor Tissue:

Slides from FFPE tumors should be shipped at room temperature, with appropriate packing to prevent breakage of slides.

Jack Su, MD; Attention: Elizabeth Hinojosa
1102 Bates St., Room 1030
Baylor College of Medicine
Houston, TX 77030
(832) 824-4688 or (832) 822-4306

Prior to shipping, please contact Dr. Jack Su (832-822-4306 or jmsu@txch.org), Dr. Li (832-822-4277 or xxli@txch.org), or Dr. Adekunle Adesina (832-824-5859, aadesina@bcm.edu or amadesin@texaschildrenshospital.org) for notification of sample shipment.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____
(site personnel who collected samples)

Date:_____

APPENDIX IX: ACNS0927 CHEMORADIOTHERAPY ROADMAP (PART B)

Acc # _____ COG Pt # _____ Ht _____ cm Wt _____ kg BSA _____ m^2
Dose of Vorinostat _____ mg/m^2/day Record Nomogram Dose _____g (see Appendix III of the protocol)

Radiation therapy (RT) will be administered in single daily fractions of 1.8 Gy for 30 treatments over 6-7 weeks. The total dose of radiation will be 54 Gy (see section 15.0). During radiation, patients will receive vorinostat 230 mg/m^2/day Monday through Friday weekly during the duration of radiation therapy (on Days 1-5, 8-12, 15-19, 22-26, 29-33, and 36-40). **If radiation continues into Days 43-47 then vorinostat should continue at the same dose and schedule until RT is completed**. Vorinostat dosing during and throughout the radiation component of therapy should be based on BSA determined from height and weight at the start of radiation therapy. The absolute daily dose of vorinostat should not exceed 500 mg. Vorinostat should be given 60-120 minutes prior to radiation therapy, whenever feasible. If a patient vomits within 30 minutes after the dose of vorinostat is administered, that dose should be repeated. If a patient vomits after 30 minutes, the dose will not be repeated.

Week	Day	Date Due	Date Given	Therapy vorinostat _____mg (Record calculated dose)	RT	Required Observations for Radiation Therapy (see Section 8.0 for details)	Comments
	Pre	_____	_____	(Record Actual Dose)		1, 2, 3, 4, 5, 6[&], 7, 8, 9, 10	
1	1	_____	_____	**vorinostat** _____mg	**RT**		
	2	_____	_____	**vorinostat** _____mg			
	3	_____	_____	**vorinostat** _____mg			
	4	_____	_____	**vorinostat** _____mg			
	5	_____	_____	**vorinostat** _____mg			
2	8	_____	_____	**vorinostat** _____mg	**RT**	1, 2, 5[+]	
	9	_____	_____	**vorinostat** _____mg			
	10	_____	_____	**vorinostat** _____mg			
	11	_____	_____	**vorinostat** _____mg			
	12	_____	_____	**vorinostat** _____mg			
3	15	_____	_____	**vorinostat** _____mg	**RT**	1, 2, 5[+], 10	
	16	_____	_____	**vorinostat** _____mg			
	17	_____	_____	**vorinostat** _____mg			
	18	_____	_____	**vorinostat** _____mg			
	19	_____	_____	**vorinostat** _____mg			
4	22	_____	_____	**vorinostat** _____mg	**RT**	1, 2, 5[+]	
	23	_____	_____	**vorinostat** _____mg			
	24	_____	_____	**vorinostat** _____mg			
	25	_____	_____	**vorinostat** _____mg			
	26	_____	_____	**vorinostat** _____mg			
5	29	_____	_____	**vorinostat** _____mg	**RT**	1, 2, 5[+]	
	30	_____	_____	**vorinostat** _____mg			
	31	_____	_____	**vorinostat** _____mg			
	32	_____	_____	**vorinostat** _____mg			
	33	_____	_____	**vorinostat** _____mg			
6	36	_____	_____	**vorinostat** _____mg	**RT**	10	
	37	_____	_____	**vorinostat** _____mg			
	38	_____	_____	**vorinostat** _____mg			
	39	_____	_____	**vorinostat** _____mg			
	40	_____	_____	**vorinostat** _____mg		1[$], 2[$], 3[$], 5[$], 7[$@]	
The section below is to be completed only if radiation continues into Days 43-47. Then vorinostat should continue at the same dose and schedule until RT is completed.							
7	*43*	_____	_____	***vorinostat*** _____*mg*	***RT***		
	44	_____	_____	***vorinostat*** _____*mg*			
	45	_____	_____	***vorinostat*** _____*mg*			
	46	_____	_____	***vorinostat*** _____*mg*			
	47	_____	_____	***vorinostat*** _____*mg*		*1[$], 2[$], 5[$], 7[$]*	

+Patients with hematologic DLT should have CBC repeated twice weekly until recovery as specified in Sections 6.1 and 6.2.
&Patients of childbearing potential require a negative pregnancy test prior to starting treatment and must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
$ These studies to be performed prior to Maintenance Therapy @ Not required if continuing radiation therapy into days 43-47

1. History, Creatinine, Bilirubin, SGPT, Electrolytes including Ca^{++}, PO_4, Mg^{++}
2. Physical exam with vital signs
3. Height, weight, BSA
4. Performance Status
5. CBC, differential, platelets.
6. Pregnancy test
7. Total protein/albumin
8. Tumor Disease Evaluation (MRI of brain with gadolinium)
9. Tumor Disease Evaluation (MRI of spine with gadolinium). Patients with suspected disseminated disease must have MRI of spine performed. Patients with disseminated disease are not eligible.
10. Correlative Studies (If patient consents; see Section 8.3.2 for timing of correlative biology studies. Blood samples should be collected 2-4 hours after the morning dose of vorinostat. The blood samples should be obtained the day of weekly CBC collection, if possible.)

APPENDIX X: ACNS0927 MAINTENANCE ROADMAP (PART A AND B)

Acc # _____ COG Pt # _____ Ht _____ cm Wt _____ kg BSA _____ m^2 _____Cycle # _____

Dose of Vorinostat _____ mg/m^2/day Record Nomogram Dose _____g (see Appendix III of the protocol)

At the conclusion of chemoradiotherapy, all patients will continue vorinostat maintenance therapy daily without interruption at Dose Level 1 (230 mg/m^2/day, continuously; Section 5.4, Table 2), including those patients who had discontinued vorinostat during chemoradiotherapy because of DLTs. Vorinostat doses during the maintenance phase of therapy should be adjusted based on the BSA determined from **height and weight obtained within one week prior to the beginning of each cycle**. **The absolute daily dose of vorinostat should not exceed 500 mg.** If a patient vomits within 30 minutes after the dose of vorinostat is administered, that dose should be repeated. If a patient vomits after 30 minutes, the dose will not be repeated. A cycle of maintenance therapy is defined as 28 days. Maintenance therapy may be continued for a maximum of 12 cycles in the absence of disease progression and/or excessive toxicities.

Day	Date Due	Date Given	Therapy vorinostat _____mg (Record calculated dose)	Required Observations for Maintenance Therapy (see Section 8.0 for details)	Comments
1	_____	_____	**vorinostat** _____mg	1, 2, 3, 4+, 5, 6*	
2	_____	_____	**vorinostat** _____mg		
3	_____	_____	**vorinostat** _____mg		
4	_____	_____	**vorinostat** _____mg		
5	_____	_____	**vorinostat** _____mg		
6	_____	_____	**vorinostat** _____mg		
7	_____	_____	**vorinostat** _____mg		
8	_____	_____	**vorinostat** _____mg	4+	
9	_____	_____	**vorinostat** _____mg		
10	_____	_____	**vorinostat** _____mg		
11	_____	_____	**vorinostat** _____mg		
12	_____	_____	**vorinostat** _____mg		
13	_____	_____	**vorinostat** _____mg		
14	_____	_____	**vorinostat** _____mg		
15	_____	_____	**vorinostat** _____mg	4+	
16	_____	_____	**vorinostat** _____mg		
17	_____	_____	**vorinostat** _____mg		
18	_____	_____	**vorinostat** _____mg		
19	_____	_____	**vorinostat** _____mg		
20	_____	_____	**vorinostat** _____mg		
21	_____	_____	**vorinostat** _____mg		
22	_____	_____	**vorinostat** _____mg	4+	
23	_____	_____	**vorinostat** _____mg		
24	_____	_____	**vorinostat** _____mg		
25	_____	_____	**vorinostat** _____mg		
26	_____	_____	**vorinostat** _____mg		
27	_____	_____	**vorinostat** _____mg		
28/1	_____	_____	**vorinostat** _____mg	4+, 6*	

*Before Cycle 2, then every 2 cycles x 2, then q 3 cycles
+Patients with hematologic DLT should have CBC repeated twice weekly until recovery as specified in Sections 6.1 and 6.2.

1. History, Creatinine, Bilirubin, SGPT, Electrolytes including Ca^{++}, PO_4, Mg^{++}
2. Physical exam with vital signs
3. Height, weight, BSA
4. CBC, differential, platelets.
5. Total protein/albumin
6. Tumor Disease Evaluation (MRI of brain with gadolinium).Scans should be obtained prior to cycles 2, 4, 6, 9, and 12. See Section 12.0 for Evaluation Criteria. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

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