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Dear [redacted],

Enclosed please find Amendment #3A to protocol **ACNS1721**, *A Phase 2 Study of Veliparib (ABT-888, IND # 139199) and Local Irradiation, Followed by Maintenance Veliparib and Temozolomide, in Patients with Newly Diagnosed High-Grade Glioma (HGG) without H3 K27M or BRAF^{V600} Mutations*, for CTEP review.

Studies ACNS1721 and ACNS1723 include an eligibility pre-screening process (Step 0). This amendment is being submitted due to essential updates in the testing methods used during the mandatory rapid molecular central review performed during the eligibility pre-screening. The antibody used to test for Histone H3 K27M has been updated due to a discontinuation in the manufacturing of the previous antibody. The new antibody has been validated as detailed in the amended protocol. Additionally, Stratum 1 of ACNS1721, for patients with IDH wild-type HGG, closed to accrual as of January 24, 2020. The relevant sections of the protocol have been amended to indicate that Stratum 1 is now closed and that the Stratum 1 study objective is no longer under investigation.

Administrative changes have also been made; specific changes are detailed in the summary of changes tables below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

On behalf of the ACNS1721 Study Committee, we appreciate your review and support of this study. Please contact us if you have any additional questions.

Sincerely,

[redacted] Protocol Coordinator (for)
[redacted], MD, MS, ACNS1721 Study Chair,
[redacted], MD, Central Nervous System Committee Chair, and
[redacted], MD, COG Group Chair

SUMMARY OF CHANGES: PROTOCOL

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.	General	-	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Table of Contents	3-5	Revised for re-pagination.
4.	Study Committee	6-7	• Updated the contact information of study committee members. • Added two new committee members. • Updated the study Nurse and study Protocol Coordinator information.
5.	Abstract Experimental Design Schema 3.3.1 4.1	8 9 24 27	Added the following text to indicate closure of Stratum 1: **Please note Stratum 1 was closed to accrual on January 24, 2020.**
6.	2.1.1	12	A subheading was added to the background section to provide rationale of Stratum 1 closing in January 24, 2020.
7.	3.1	18	Revised the following text for clarification and consistency with the amended ACNS1723: • It is strongly suggested that sites submit required specimens no later than 13 days after diagnostic **biopsy or** surgery to meet the timing requirements outlined in Section 3.2.4. • Radiotherapy planning should begin as soon as possible at the local sites in order to permit commencement of radiotherapy within 31 calendar days of definitive surgery (see Section 17.0). **Please see Section 3.3.5 for definition of definitive surgery.**
8.	3.1.1.4	19	Revised the following text for clarification and consistency with the amended ACNS1723: The following specimens obtained at the time of diagnostic biopsy **or surgery** must be submitted through APEC14B1 ASAP, preferably within 13 calendar days of ~~definitive surgery~~ **the procedure**. See the APEC14B1 Manual of Procedures for further instructions and shipping details.
9.	3.2.4	23	Revised the following text for clarification and consistency with the amended ACNS1723: The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment and no later than 31 calendar days after definitive ~~diagnostic~~ surgery as per Section 3.3.5.
10.	3.3.4.3	25	Revised liver function criteria as follows for consistency with current COG CNS protocols: ~~SGPT (ALT) ≤ 3 x upper limit of normal (ULN) for age. For the purpose of this study, the ULN for SGPT is 45 U/L.~~

			SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
11.	3.3.5	25	Revised the following text to clarify the definition of definitive surgery and consistency with the amended ACNS1723: Patients must be enrolled and protocol therapy must be projected to begin no later than 31 days after definitive ~~diagnostic~~ surgery (Day 0). **If a biopsy only was performed, the biopsy date will be considered the date of definitive surgery. For patients who have a biopsy or incomplete resection at diagnosis followed by additional surgery, the date of the last resection will be considered the date of definitive surgery.**
12.	4.1.1 4.3.1	28 31	Revised the protocol language to provide a recommendation rather than a mandatory requirement. While preclinical and PK data suggest that veliparib may be most effective when administered 60–120 minutes prior to the daily dose RT, we recognize that this may not always be feasible, e.g. when RT is scheduled in the afternoon or evening.
13.	4.4.3 4.5.3	37 41	Revised Veliparib treatment details for Cycle 1 and Cycle 2 to allow evening administration of temozolomide, if necessary.
14.	6.2	54-57	Revised Temozolomide drug monograph to reflect current version.
15.	7.3	58	Revised table to include tumor and biology sample collection as an End of Therapy requirement for patients consenting to optional studies, consistent with Section 15.2.2.
16.	7.3	58	Revised language to maintain internal protocol consistency. The table above indicates required End of Therapy evaluations and ~~recommended~~ **required** Follow-Up imaging scans.
17.	9.1.1	59	A subheading was created to provide a section of rationale for statistical implications of Stratum 1 closure.
18.	9.2	62	Updated the plot displaying the historical control cohort of IDH mutated patients. The previous version of the plot did not include the 10 subjects from the Cell Metadata (n=6) and the HERBY cohorts (n=4). These patients were included in the design of the study and the quoted numbers in the text summarizing outcome but the combined data plot in the previous version of the protocol did not include them.
19.	15.2.1.3	83	• Updated labeling requirements as requested per BPC. • Updated the URL of Biopathology Center (BPC) Kit Management website.
20.	15.2.2.1	83	Removed references to other protocol sections (TDMs) that were considered unnecessary or confusing based on site feedback.
21.	15.2.2.3	84-85	Updated Jabado Lab contact information for specimen shipping.
22.	15.2.2.2.1	84	Revised instructions for peripheral blood preparation as follows to accommodate sites that may not have a refrigerated centrifuge that operates at 15,000 rpm. 5. For the second centrifugation step, centrifuge the supernatant (plasma) from Step 2 at 21000g (15,000 rpm **or the maximum speed available**) at +4°C for 10 minutes.
23.	16.2.1	85	To correct typographical error, “skip 0A” was replaced by “skip 0”.

24.	16.5 17.0 17.9.4	87 88 105	Scan submission language has been revised to reflect preferred submission through TRIAD. Alternative submission methods are still available to sites that do not have TRIAD enabled.
25.	17.6.4.2.1	95-96	Corrected a typographical error by revising “in an isotropic fashion” to “in an **an**isotropic fashion”. This change was made in several places.
26.	Appendix III	113-115 114	• Updated to reflect Dr. Chris Fuller’s transition from CCHMC to SUNY Upstate. • Updated to include details of EPR18340, the new validated antibody that will be used to test Histone H3 K27M. It replaces SAB5600095, for which manufacturing has been discontinued. It is not completely uncommon for IHC antibodies to be discontinued and replaced by an equivalent antibody. Going forward, this antibody (or its subsequent equivalent) will be utilized for the H3 K27M IHC assay.

Activated: 10/31/2018
Closed:

Version Date: 07/22/2021
Amendment: #3A

CHILDREN'S ONCOLOGY GROUP

ACNS1721

A Phase 2 Study of Veliparib (ABT-888, [redacted]) and Local Irradiation, Followed by Maintenance Veliparib and Temozolomide, in Patients with Newly Diagnosed High-Grade Glioma (HGG) without H3 K27M or *BRAF*^{V600} Mutations

A COG Groupwide Phase 2 Study

NCI Supplied Agent: Veliparib (ABT-888, NSC# 737664, [redacted])
IND Sponsor: DCTD, NCI

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To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#
Veliparib (ABT-888)	737664
Temozolomide	362856

IND#: [redacted]
IND Sponsor: DCTD, NCI

SEE SECTION 15.0 , SECTION 16.0, AND SECTION 17.0 FOR SHIPPING ADDRESSES

ABSTRACT

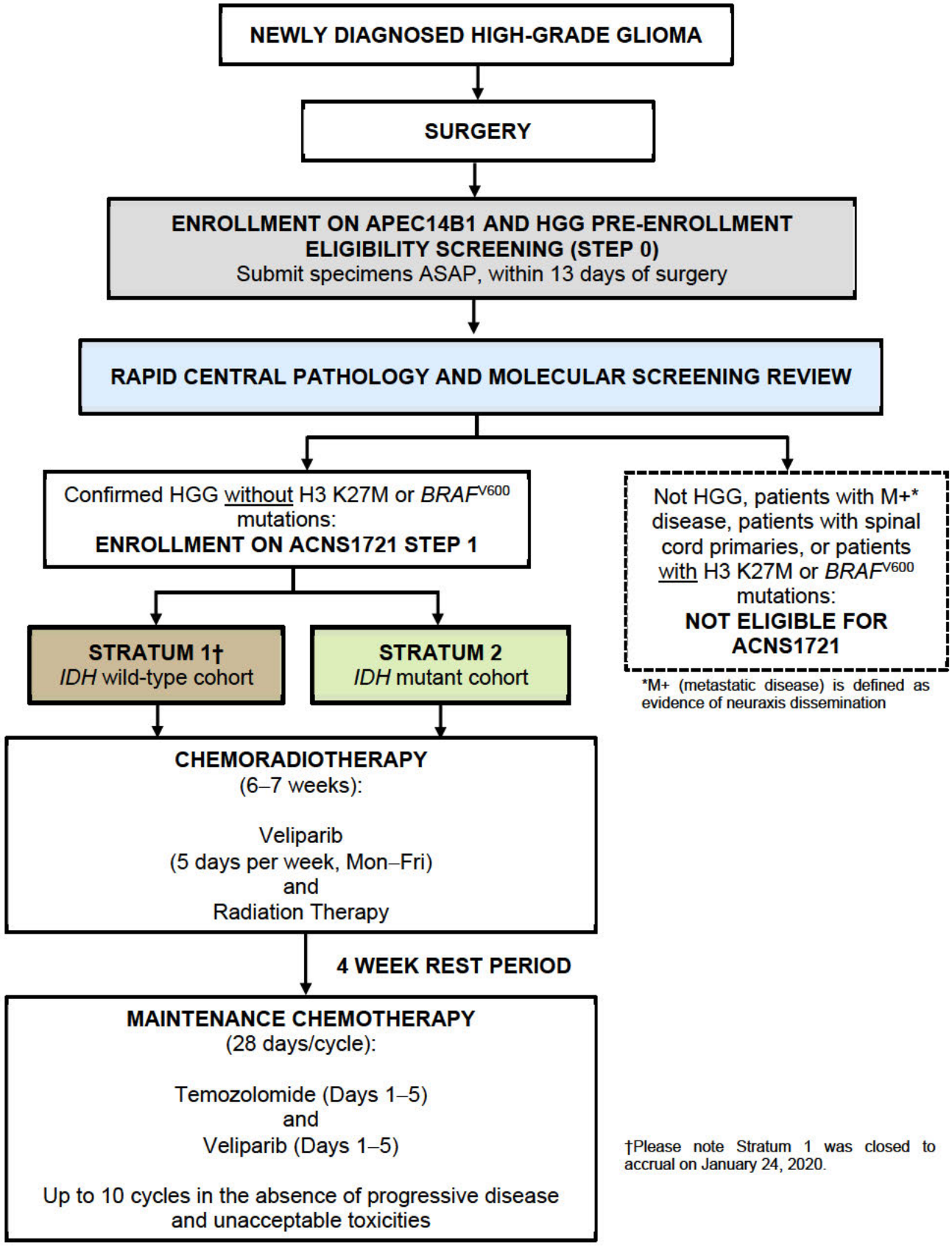
Recent landmark molecular genetic landscape studies of pediatric high-grade glioma (HGG) have established distinct, molecularly defined biological subgroups with striking differences in outcome. However, in the past accrual to Children's Oncology Group (COG) HGG studies was based purely on histopathological diagnosis, leading to considerable heterogeneity in regard to molecular features and tumor biology. As a result, these cohorts included very high-risk tumors with a dismal outcome, such as K27M mutant HGG, as well as favorable risk tumors, such as *IDH* mutant HGG.

In this study, we will select a subset of pediatric HGG based on molecular features at study entry that may be most likely to benefit from the experimental therapy. Outcome of this patient cohort will be compared to historical controls with closely matching molecular features.

Eligible patients will be treated with an experimental regimen that includes the Poly (ADP-ribose) polymerase (PARP) inhibitor, veliparib, during radiation therapy, followed by veliparib in combination with temozolomide. Veliparib has a biological rationale for use in pediatric HGG, and synergistic mechanisms of action in combination with either radiation therapy or temozolomide.

This study will test whether the proposed combination therapy will improve event-free survival in patients with newly-diagnosed HGG who are wild-type for H3 K27M, *IDH*, and *BRAF* (Stratum 1). The study will also include patients with *IDH* mutant glioma on a separate study arm (Stratum 2). Please note Stratum 1 was closed to accrual on January 24, 2020. Outcome for all patients will be compared to clinically and molecularly-matched historical control cohorts.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1 To determine whether veliparib (ABT-888), when added to radiotherapy (RT) and temozolomide, is efficacious for the treatment of patients with newly-diagnosed high-grade glioma (HGG) whose tumors' molecular profile are wild-type for H3 K27M, *BRAF*, and *IDH1/2*.

1.1.2 To determine whether veliparib (ABT-888), when added to RT and temozolomide, is efficacious for the treatment of patients with newly-diagnosed HGG whose tumors' molecular profile are wild-type for H3 K27M and *BRAF* and harbor an *IDH1/2* mutation.

1.2 Exploratory Objectives

1.2.1 To explore associations of genomic, transcriptomic, and/or epigenetic alterations of the tumors with treatment response and outcome.

1.2.2 To explore the extent to which patients with *BRCA1/2* gene alterations and other DNA damaged genes display tumor genomic features consistent with homologous repair deficiency (HRD), including large scale state transitions (LSTs), mutational signature 3, and an enrichment for deletions flanked by sequences of (micro) homology.

1.2.3 To explore the burden of high, moderate, and low penetrant germline alterations in HRD genes (such as *BRCA1*, *BRCA2*, *PALB2*, Fanconi complex genes, *ATM*, *CHEK2*, *RAD51B/C/D)*, mis-match repair genes (such as *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), and energy metabolism genes (such as *SDHA*, *SDHB*, *SDHC*, *SDHAF2*, *SDHD*, *IDH1*, *IDH2*, and *FH*).

1.2.4 To explore constitutional imprinting abnormalities associated with *EP300* and *IGF2* in peripheral blood from patients with HGGs.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

The outcome for pediatric patients with HGG remains poor. Single agent temozolomide (TEMO), when administered during and after RT, has been shown to significantly prolong progression-free survival (PFS) and overall survival (OS) in adults with glioblastoma (GBM); however, similar treatment strategies used in ACNS0126 (RT/TEMO→TEMO)[1] and ACNS0423 (RT/TEMO→TEMO+CCNU)[2] did not improve outcome in children with HGG when compared to a historical control study (CCG-945), which randomized patients to different adjuvant chemotherapy regimens. In the most recent COG HGG trial, ACNS0822, two different combined modality experimental arms containing vorinostat or bevacizumab were compared to a combined modality arm that included temozolomide.

Patients were randomized to receive either vorinostat, bevacizumab, or temozolomide during RT, and all patients received bevacizumab and temozolomide during maintenance. Based on the recommendation of the DSMC in 2014, ACNS0822 was closed to further patient entry and was permanently closed effective April 30, 2014. This recommendation was based on review of the available data in 95 patients on the phase 2 study. The data indicated that it was unlikely that either of the two experimental radiosensitization arms (vorinostat or bevacizumab) would demonstrate a greater one-year EFS when compared with the control arm (temozolomide) with the enrollment of the 13 additional randomized patients required for reaching the planned interim analysis.[3]

A number of recent landmark molecular genetic landscape studies of pediatric HGG have established distinct, molecularly defined biological subgroups with striking differences in outcome.[2, 4-8] However, in the past accrual to HGG studies was based purely on histopathological diagnosis, leading to considerable heterogeneity in regard to molecular features and tumor biology within each study. As a result, upon retrospective analysis it was apparent that these cohorts included very high risk tumors with a dismal outcome, such as K27M mutant HGG, as well as favorable risk tumors, such as *IDH* mutant HGG. Although EFS and OS were noted to be significantly improved in ACNS0423 compared to ACNS0126, with 3-year EFS of 0.22 (95% CI, 0.14-0.30) and 0.11 (95% CI, 0.05-0.18), respectively, molecular data from both studies is very limited, with *IDH1* mutational status available on a subset of patients on ACNS0423 only, but not on ACNS0126. Of note, *IDH1* mutations were observed in 16.3% (7/43) tumors analyzed on ACNS0423,[9] which represents a relatively high percentage compared to other pediatric HGG series, including 12.5% (8/64) *IDH1* mutant tumors in the subsequent ACNS0822 study. Given the lack of molecular data available on ACNS0126 and ANCS0423, it is impossible to discern with certainty whether the observed modest difference in outcome between the two sequential, nonrandomized studies is related to treatment versus a difference in patient cohorts, i.e., proportions of molecular high-risk versus favorable-risk tumors.

In this study, we will establish a new paradigm for "precision medicine" trials for pediatric HGG in COG, moving away from testing novel therapies in large, unselected, and molecularly heterogeneous pediatric HGG populations. Instead, we will enroll a subset of pediatric HGG patients based on molecular features at study entry that may be most likely to benefit from the experimental therapy. The outcome of this cohort will be compared to a historical control cohort with closely matching molecular features.

Eligibility will be limited to patients with tumors that, based on our current knowledge of HGG biology, may be the most likely to benefit from the experimental therapy combining a PARP1/2 inhibitor with chemoradiotherapy including temozolomide. We will exclude *BRAF* and H3 K27M mutant tumors from the study since current evidence indicates that *BRAF* mutant gliomas, which are rare in both adults and children, are enriched for pleomorphic xanthoastrocytomas (PXAs), secondary HGGs, and glioblastomas (GBMs) with a PXA-like molecular signature.[4] Molecular targeted agents specific for $BRAF^{V600E}$ (and also targeting similar BRAF activating mutations including $BRAF^{V600D/J/M/K/R}$) are FDA-approved, and are currently being explored in ongoing clinical trials in adult as well as pediatric gliomas. The PBTC-033 trial, which explored the use of veliparib in combination with RT and temozolomide in newly diagnosed DIPG, which are almost always K27M, was recently closed following a planned interim analysis due to futility with respect to the primary endpoint of improving overall survival. For the proposed study, initial central pathology review will include molecular testing to determine H3 K27M, *IDH*, and *BRAF* mutational status.

All eligible patients will be treated with veliparib during radiotherapy (RT) (54–59.4 Gy/30–33 fractions) followed by veliparib in combination with temozolomide post-RT. There is a strong biological rationale for the use of veliparib in combination with RT and temozolomide in the maintenance phase of pediatric HGG, as preclinical data would suggest synergistic mechanisms of actions in combination with RT and temozolomide (described in Section 2.2). In contrast to other available PARP inhibitors, veliparib crosses the blood-brain-barrier,[10] was shown to enhance the efficacy of temozolomide and XRT in orthotopic HGG models,[11] has available safety date in combination with XRT and temozolomide in pediatric patients,[12] and has successfully moved from phase 2 to phase 3 clinical development in adults with newly-diagnosed glioblastoma in the NCI-2015-00616 study. Patients will be enrolled in two strata: Stratum 1 will test whether the proposed therapy improves EFS in patients with newly-diagnosed HGGs that are wild-type for H3 K27M, *IDH*, and *BRAF* compared to a clinically and molecularly matched historical control cohort. Stratum 2 will be comprised of a cohort of patients with *IDH* mutations, a rare occurrence in pediatric HGGs; their outcome will be compared to a separate, clinically and molecularly matched historical control cohort. The presence of an *IDH* mutation is generally mutually exclusive with H3 K27M or *BRAF* mutations, and H3 K27M or *BRAF* mutant tumors are ineligible regardless of *IDH* status.

2.1.1 Closure of Stratum 1 (IDH Wild-Type Cohort) Effective January 24, 2020

Stratum 1 of ACNS1721, for patients with IDH wild-type HGG, was closed to accrual as of January 24, 2020. Closure of this stratum was based on the results of a planned interim analysis. The currently available data from the first 22 subjects suggested that the hypothesized superior outcome for the ACNS1721 treatment compared to the historical controls is unlikely. There were no concerns regarding excessive toxicities on this protocol.

2.2 Preclinical Studies

Veliparib, a potent oral PARP1/2 inhibitor, enhances the activity of DNA-damaging chemotherapeutic agents, including temozolomide. PARP has been identified as a therapeutic target in brain tumors, including pediatric HGGs,[13, 14] and veliparib in combination with temozolomide was studied in a phase 1/2 study of adults with recurrent GBM.[15] Preclinical data indicates that veliparib crosses the blood-brain-barrier[10] and enhances the efficacy of temozolomide in a subset of adult HGG, with *MGMT* promoter hypermethylation as a potential biomarker for sensitivity to veliparib.[11] In preclinical studies conducted by Su et al. at Baylor, veliparib treatment enhanced temozolomide cytotoxicity and prolonged animal survival in mouse orthotopic xenograft models of pediatric GBM, compared to temozolomide treatment alone. Veliparib preferentially accumulated in xenograft tumors versus neighboring normal brain, and the tumor to brain veliparib ratio was 8.25 ± 6 fold. At plasma concentrations that have been safely achieved in humans, veliparib treatment resulted in more than 90% PARP inhibition in mouse orthotopic xenograft tumors. Enhancement of temozolomide efficacy by veliparib was observed despite high MGMT activity in the xenograft models (Jack Su, unpublished data). Preclinical studies also indicate that veliparib may potentiate the effects of RT in HGG.[16]

IDH1 mutant gliomas have been noted to have increased radiosensitivity relative to *IDH1* wild-type gliomas by multiple groups. One group evaluated multiple *IDH1* mutant cell lines using *in vitro* (clonogenic survival assays, neutral comet assays, and γ-H2Ax assays) and *in vivo* (mutant, wild-type matched tumor xenograft) experiments and note

substantial differences in the colony surviving fraction, sensitivity to apoptosis, and capacity of homologous recombination in *IDH1* mutant and wild type tumors. Similar phenotypic effects could be perpetuated with the exogenous administration of 2-hydroxyglutarate (2HG) in *IDH* wild type cells thus confirming the key role that the oncometabolite plays in tumorigenesis and sensitivity to therapy.[17]

The mechanism of *IDH1* mutation driven susceptibility to genotoxic stress has been an active area of investigation. While early reports suggested that the impaired catalytic activity of *IDH1* and resultant alteration in the tolerance to oxidative stress was the primary mode of increased radiosensitivity in gliomas, recent findings now indicate that the oncometabolite is sufficient to cause altered radiosensitivity via epigenetic reprogramming.[17] Exogenous administration of 2HG or expression of the *IDH1* mutant led to the inhibition of specific alpha-ketoglutarate dependent dioxygenases (*KDM4A*, *KDM4B*) which result in epigenetic reprogramming and decreased homologous recombination dependent DNA repair in response to genotoxic stress.[18] Furthermore, increased radiosensitivity was noted to be dependent on *IDH1* activity, as inhibition with the inhibitor AGI-5198 led to improved homologous repair and reduced cell kill. Likewise, given the suggestion that altered oxidative stress may play a role in radiosensitivity in *IDH1* mutant tumors, the investigators measured NAD+ levels in mutant and wild type cells and noted that modulation of nicotinamide phosphoribosyltransferases did not substantially alter the homologous recombination repair capacity in *IDH1* mutant cells. Other groups have gone on to show that the impact of increased radiosensitivity is independent of oxygenation status.[19] Taken together, these data suggest that the oncometabolite 2HG produced by mutant *IDH1* leads to increased radiosensitivity via a novel potentially exploitable mechanism leaving cancer cells vulnerable to genotoxic stress due to impaired homologous recombination capacity.

The decreased activity of homologous recombination repair has been noted to be an alternative mechanism by which cells may acquire a *BRCA*-like phenotype. The acquisition of "*BRCA*-ness" is most commonly due to aberrations in genes participating in and regulating homologous recombination (*ATM*, *ATR*, *BAP1*, *BRCA1*, *BRCA2*, *FANCA*, *CDK12*, *CHEK2*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, etc.). PARP inhibition in the setting of *BRCA*-ness has resulted in substantial gains in primarily adult cancers including breast,[20] ovarian,[21, 22] gastric,[23] and patients known to be *BRCA* mutant carriers.[21, 24-30] The recent observation that the oncometabolite 2HG can facilitate this phenotype has inspired investigators to explore alternative therapeutic approaches which capitalize on this vulnerability.[31]

While pediatric tumors infrequently exhibit *BRCA* mutations, the findings by Sulkowski et al. have generated interest in employing synthetic lethality approaches in *IDH*-mutant tumors given that the 2HG oncometabolite can confer *BRCA*-ness.[17] PARP inhibition in *IDH1* mutant tumors has been shown to result in substantial activity both alone and in combination with other means of facilitating genotoxic stress (cisplatin, radiation)[32] across a range of cancer types. The decrease in double-stranded DNA repair in *IDH1* mutant gliomas with PARP inhibitor treatment was reversible with inhibitors of the mutant *IDH1* enzyme (AGI-5198) confirming the concerns of Molenaar et al. that the aberrant activity of the *IDH1* mutant enzyme is crucial to facilitating increased sensitivity to genotoxic stress.[33] PARP inhibition alone and in combination with other therapy led to increased killing in *IDH1* mutant cells. These in vitro findings have been extended to both patient derived primary glioma cells and a sarcoma flank subcutaneous xenograft model.

2.3 Clinical Studies in Patients with *IDH* wild-type HGG

Based on the preclinical data identifying *MGMT* promoter hypermethylation as a candidate biomarker for sensitivity to veliparib,[16] an ongoing phase 2/3 clinical trial is evaluating the combination of veliparib and temozolomide in adult patients with *MGMT* promoter methylated GBM (NCT02152982). The interim analysis of the phase 2 survival data met the criteria to allow the study to re-open to the phase 3 portion of the trial.

While *MGMT* promoter methylation status has been identified as a strong prognostic factor regardless of therapy, as well as a predictive factor for significant survival benefit from temozolomide in adult glioblastoma,[34] the role of *MGMT* promoter methylation status as a biomarker in pediatric HGG is unclear. No randomized controlled HGG trials comparing RT + temozolomide to RT alone have been performed in children; hence, the value of *MGMT* promoter methylation as a predictive biomarker for benefit from temozolomide is unproven. While ACNS0126 showed shorter survival in patients with strong MGMT expression, no such difference was observed on ACNS0423. Of note, *MGMT* status on both trials was determined using immunohistochemistry, which is unreliable and no longer considered an acceptable test to determine *MGMT* status in glioma.[34] Remarkably, data from both retrospective[4] and prospective (ACNS0822) pediatric HGG studies that determined *MGMT* promoter methylation status using currently acceptable assays,[34] reveal that after removal of patients with *BRAF*, K27M, and *IDH1* mutant tumors, there is no association between *MGMT* promoter methylation status and progression-free or overall survival, as shown in Figures 1 and 2 below. This finding is in striking contrast to adult glioblastoma patients, where *MGMT* promoter methylation status has been validated as a highly reproducible prognostic and predictive biomarker across prospective, randomized clinical trials using RT and RT + temozolomide.[34] Therefore, the utility of *MGMT* promoter methylation status as an independent prognostic biomarker in pediatric HGG is not supported by the current data, and its role as a predictive biomarker for benefit from temozolomide in this population is unproven as well.

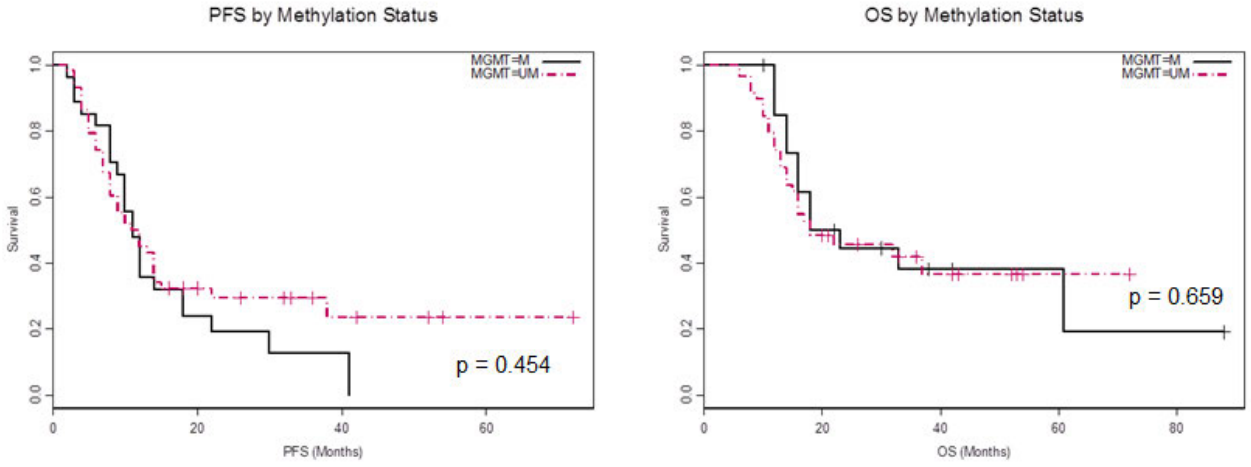


Figure 1. PFS (left panel) and OS (right panel) of 85 patients from the Heidelberg cohort[4] who were 3 and older, had no disease dissemination and their tumor did not harbor K27M, *IDH*, or *BRAF* mutation treated with RT + temozolomide according to the ACNS0126 protocol. Of these, 27 were *MGMT* promoter hypermethylated and 58 were not, as determined by genome-wide methylation profiling.

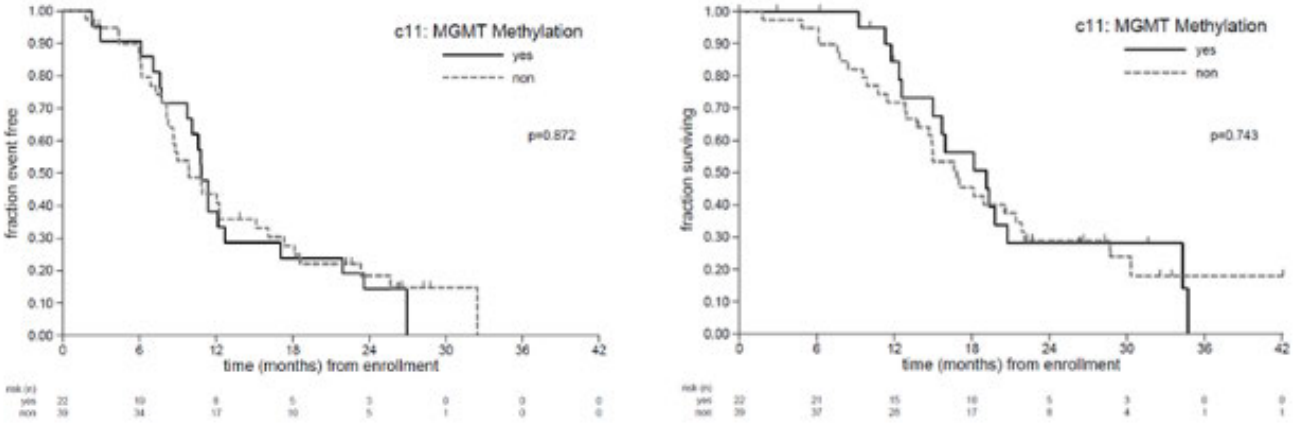


Figure 2. PFS (left panel) and OS (right panel) of 61 patients from the ACNS0822 cohort who were 3 and older, had no dissemination, their tumor did not harbor K27M, *IDH*, or *BRAF* mutation, and whose tumor was tested for MGMT promoter methylation by methylation-specific PCR. Of these, 22 were MGMT promoter hypermethylated and 39 were not.

The Adult Brain Tumor Consortium (ABTC) conducted a dose finding trial of veliparib during daily temozolomide with post-operative RT for glioblastoma. In the study, the hematologic toxicity of veliparib when administered with concurrent RT and temozolomide was severe enough that accrual was discontinued.[35] A subsequent NCI-sponsored phase 2/3 trial for adult patients with newly diagnosed glioblastoma and MGMT promoter hypermethylation (ClinicalTrials.gov Identifier: NCT02152982) has proceeded to the phase 3 portion and is currently enrolling patients. The Pediatric Brain Tumor Consortium (PBTC) completed two pediatric studies with veliparib: a phase 1 study (PBTC-027) for pediatric with recurrent/refractory CNS tumors, and a phase 1/2 study (PBTC-033) for newly-diagnosed pediatric patients with diffuse intrinsic pontine gliomas (DIPGs). Details regarding these studies are outlined below.

2.4 Clinical Studies in Patients with *IDH*-Mutant HGG

Malignant gliomas with mutations in *IDH1* or *IDH2* have been associated with better PFS and OS compared to wild-type in both pediatric and adult HGG.[36, 37] As a result, the WHO has gone on to define this group as a distinctive subgroup of glioblastoma and strongly recommends evaluating for the most common *IDH R132H* mutation using immunohistochemistry.[38] While *IDH* mutant gliomas can be found in as much as 36% of adult gliomas, 23% of HGG in children harbored the *IDH1* mutation in a retrospective series.[39] A secondary analysis of ACNS0423 revealed a total of 16.3% (7/43) of evaluable HGG samples to harbor an *IDH1* mutation.[40] This analysis confirmed that *IDH* mutations are rare (0/23 patients) in children below the age of 14 years, but noted that the incidence rises to as much as 36% (7/20 patients) throughout teenage and young adulthood.[40] Compared to *IDH* wild-type patients, the one year EFS and OS among *IDH* mutant versus wild-type patients on ACNS0423 were significantly more favorable at 86.5% vs. 64.8% and 100% vs. 81.6%, respectively.[40] Given the relative rarity of *IDH* mutant in pediatric patients, and paucity of data from randomized prospective studies, the optimal treatment for these patients remains unclear.

2.5 Pediatric Studies of Veliparib

The PBTC completed a phase 1 study (PBTC-027) for pediatric patients with recurrent/refractory CNS tumors.[41] When given concomitantly with veliparib at 25 mg/m^2 BID, the maximum tolerated dose (MTD) of temozolomide was established at 135 mg/m^2 (Days 1–5 per 28-day cycle), with myelosuppression as the dose-limiting toxicity (DLT) in this pre-treated patient population. The follow-up study (PBTC-033) explored upfront therapy in newly-diagnosed patients with DIPGs in a phase 1/2 design, with veliparib given concomitantly with RT, followed by veliparib in combination with temozolomide. The MTD of temozolomide when given with veliparib in this study was determined to be the same as in PBTC-027, and the study was closed because the primary endpoint of improved PFS was not met.

The use of veliparib in combination with radiation therapy, followed by combination therapy including temozolomide with veliparib, has not been explored prospectively in newly-diagnosed pediatric HGG patients (excluding DIPG).

2.6 Dosing Rationale

In the phase 1 PBTC-027 study for pediatric patients with recurrent/refractory CNS tumors,[41] the MTD of temozolomide was established at 135 mg/m^2 (Days 1–5 per 28-day cycle) when given concomitantly with veliparib at 25 mg/m^2 BID, with myelosuppression as the DLT in this pre-treated patient population. The subsequent follow-up study (PBTC-033) explored upfront therapy in newly-diagnosed patients with DIPGs in a phase 1/2 design, with veliparib given concomitantly with RT, followed by veliparib in combination with temozolomide. The study was closed because the primary endpoint of improved PFS was not met in the DIPG patient population. The MTD of temozolomide in combination with veliparib in this study was determined to be the same as in PBTC-027, despite an attempt to further escalate temozolomide dosing in this newly diagnosed population without prior therapy.[12] Based on these data, ACNS1721 will use the treatment regimen and MTD established in PBTC-033, i.e., oral veliparib 65 mg/m^2/dose BID 5 days per week (Mon–Fri) concurrent with RT (Chemoradiotherapy), followed by 4 week rest and subsequent Maintenance chemotherapy with oral temozolomide 135 mg/m^2/dose once daily (Days 1–5) and oral veliparib 25 mg/m^2/dose BID (Days 1–5, 28 days/cycle). Maintenance chemotherapy will continue for up to 10 cycles in the absence of progressive disease or unacceptable toxicities.

2.7 Genomic Analysis of Germline DNA

Recent studies have shown a significant number of childhood cancer patients harbor germline mutations.[42-45] Specifically, these studies have reported known pathogenic and likely pathogenic mutations. These analyses did not analyze germline mutational burden in biologic pathways or correlate somatic mutational signatures. Determining germline harbingers of alterations in mis-match repair pathways is important to identify candidates for immunotherapy and in DNA damage pathways to identify candidate patients for PARP inhibitor therapies.[46, 47]

Past and current initiatives have deployed various combinations of sequencing modalities for the detection of germline and somatic genetic alterations in cancer, including whole genome, whole exome, targeted capture, and RNA sequencing assays. In addition to the efforts characterizing the repertoire of genetic alterations in cancer, recent studies have demonstrated that certain patterns of somatic mutations and structural alterations may be

employed to define the mutational processes that shaped a given cancer genome. In fact, large-scale state transitions (LSTs), specific mutational signatures and patterns of structural rearrangements, have been shown to be present in cancers harboring *BRCA1/2* germline mutations. Thus, there is a need to elucidate more precisely the significance of mutations in other DNA damage repair genes, when detected in tumors and the germline, moreover, whether the impact differs from germ line to somatic, if mono- or bi- allelic alterations of these HR-related genes would be sufficient for a phenotype to be caused, and whether their biological impact would vary according to tumor type.[48]

Genomic studies of germline DNA are optional on this trial and will be performed in consenting patients only.

2.8 Genomic, Epigenomic, and/or Transcriptomic Analysis

Mutational screening for known recurrently mutated oncogenes and tumor suppressors in pediatric high-grade glioma, including but not limited to *PTEN*, *TP53*, *PDGFR*, *PI3K*, *BRAF*, *IDH1/2*, *H3F3A*, *HIST1H3B*, *SETD2* and *ATRX/DAXX*, as well as mutations conferring DNA repair defects sensitizing to PARP inhibition including but not limited to *BRCA1/2*, *RAD51*, *ATM*, and *FANCA1/2*, using either targeted sequencing or whole exome/genome sequencing or transcriptome analysis will be performed on DNA or RNA from tumor tissue. We hypothesize that patients with sensitizing mutations to PARP inhibition may have improved outcome compared to those with wild-type tumors.

Depending on tissue availability, we will perform additional genomic (targeted sequencing, whole genome sequencing, whole exome sequencing), epigenomic (ChIp-Seq, Whole Genome Bisulfide Sequencing, HiC-Technology), and transcriptomic (RNA sequencing) investigations to correlate the profile of potential alterations or epigenetic signature with therapeutic responses. This may help identify other relevant alterations that could be used in the future as molecular signature to evaluate potential responders at study enrollment. To this effect, we will use additional genomic, epigenomic, and/or transcriptomic analyses to identify methylation class, gene expression, mutations, and gene fusions. Whenever possible, germline DNA analysis will be performed in parallel to aid in somatic mutation calling and to identify underlying germline tumor predispositions (optional study). We will also assess whether mutational profiles/oncogenic drivers can be identified in the plasma. To this effect, we will use circulating tumor nucleic acids (ctDNA) extracted from the plasma to investigate if the presence of genetic alterations identified in the above described analysis can be used as biomarkers. The purpose of these correlative studies will be to assess whether plasma from these patients can be used as a surrogate marker of the tumor in order to monitor disease progression/regression and/or response to therapy.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Pre-Enrollment Eligibility Screening (Step 0)

Prior to enrollment on a COG treatment study for HGG, patients will be screened to determine which of the available treatment studies they may be eligible to enroll on. Screening will occur through APEC14B1, The Project:EveryChild Protocol: A Registry, Eligibility Screening, Biology, and Outcome Study. An overview of the currently available HGG treatment studies is provided in the APEC14B1 Manual of Procedures (MOP). Please refer to the APEC14B1 MOP for instructions on accessing the HGG Pre-Enrollment Eligibility Screening (Step 0) form.

Patients must be consented and enrolled on APEC14B1, followed by same day enrollment on the HGG Pre-Enrollment Eligibility Screening (Step 0) to complete the RAPID CENTRAL PATHOLOGY and RAPID CENTRAL MOLECULAR REVIEWS. The APEC14B1 consent will cover the Pre-Enrollment Eligibility Screening (including pathology and molecular central reviews) for the HGG treatment study. See Appendix IV, Section 3.1.1, Section 14.0, and Section 15.0.

Once the HGG Pre-Enrollment Eligibility Screening (Step 0) results are known, all eligibility criteria for the appropriate treatment study, including patient consent, must be met prior to enrollment on Step 1 of that treatment study.

- **To expedite the central review process, it is strongly recommended that sites submit tissue on APEC14B1 and commence the enrollment process as soon as diagnosis of HGG is suspected**.

- Pathology slides from the time of diagnosis (see Section 3.1.1.4) must be submitted on APEC14B1 to the COG Biopathology Center (BPC) ASAP, preferably within 13 calendar days of surgery to allow for the HGG Pre-Enrollment Eligibility Screening (Step 0) prior to consent and enrollment on Step 1 of the treatment trial. **Patients must be enrolled on APEC14B1 before slides are shipped to the BPC.**

  IMPORTANT NOTE: Delay of specimen submission (> 13 calendar days after surgery) will significantly delay the central review process and will not guarantee central review completion within the 31-day window from surgery to initiation of protocol therapy. It is **strongly** suggested that sites submit required specimens no later than 13 days after diagnostic biopsy or surgery to meet the timing requirements outlined in Section 3.2.4.

- **Sites will receive notification by e-mail regarding central histopathology review results within 7 calendar days of receipt of all required materials at the BPC. Results from the central molecular review will be available within 17 calendar days of receipt of all required materials at the BPC (up to 30 calendar days total after surgical resection).** The final screening eligibility determination will be made by one of the Study Pathologists once the histopathology and molecular results are available. Notification of patient eligibility/ineligibility for Step 1 enrollment on a treatment trial, based on histopathologic and molecular phenotyping results, will be sent to the e-mail addresses entered by the site during the initial CTSU OPEN HGG pre-enrollment screening. The information will also be available in RAVE. (Note: The BPC is not responsible for sending the final results to sites).

- Radiotherapy planning should begin as soon as possible at the local sites in order to permit commencement of radiotherapy within 31 calendar days of definitive surgery (see Section 17.0). Please see Section 3.3.5 for definition of definitive surgery.

3.1.1 Pre-Enrollment Eligibility Screening Criteria

The following criteria must be met prior to initiating the HGG Pre-Enrollment Eligibility Screening (Step 0).

3.1.1.1 Age

Patients must be ≥ 3 years and ≤ 25 years of age at the time of enrollment on Step 0.

Note: At the time of ACNS1721 Step 1 enrollment, patients will be stratified and age is a factor. See Section 3.3.1 for details.

3.1.1.2 Diagnosis

Patient is suspected of having localized newly-diagnosed HGG, excluding metastatic disease.

3.1.1.3 Consent

Patient and/or their parents or legal guardians have signed informed consent for eligibility screening on APEC14B1 Part A.

3.1.1.4 Mandatory Specimen Submission

The following specimens obtained at the time of diagnostic biopsy or surgery must be submitted through APEC14B1 ASAP, preferably within 13 calendar days of the procedure. See the APEC14B1 Manual of Procedures for further instructions and shipping details.

Required Materials to be Submitted on APEC14B1

Sample	Study
Formalin Fixed Paraffin Embedded (FFPE) tumor tissue: - 1 H&E stained slide from each block of tumor - 1 slide stained for GFAP - 1 slide stained for MIB1 (Ki67) - A minimum of 10 (5 µm) unstained slides (charged / Plus slides) - 4 (10 µm) scrolls (2 tubes with 2 scrolls each) cut sequentially; (Note: if tumor surface area < 1 cm^2, please submit 10 [10 µm] scrolls [2 tubes with 5 scrolls each]). **It is preferred that the unstained slides and scrolls come from the same block.**	1) Central pathology review 2) IHC: H3 K27M 3) Targeted next generation sequencing for mutations in *BRAF*, *IDH1*, and *IDH2*
- Institutional pathology report (also include any outside consultant's reports if available) - APEC14B1 Specimen Transmittal Form*	

***NOTE:** In order for the BPC to properly process specimens for testing, the APEC14B1 transmittal form must clearly indicate that the shipment includes specimens for Rapid Central Review and Central Testing for HGG Screening.

Optional but Strongly Recommended Materials to be Submitted on APEC14B1

Sample	Study
Formalin Fixed Paraffin Embedded (FFPE) tumor tissue: - 1 slide each with synaptophysin, EMA, and p53 immunohistochemical stains	1) Central pathology review 2) IHC: H3 K27M 3) Targeted next generation sequencing for mutations in *BRAF*, *IDH1*, and *IDH2*

3.1.2 Mandatory Rapid Central Pathology Screening Review

See Appendix IV and Section 14.0. All patients must have RAPID CENTRAL PATHOLOGY SCREENING REVIEW ON APEC14B1 PRIOR TO STUDY ENROLLMENT ON ACNS1721 STEP 1 in order to avoid discordant diagnosis criterion for treatment on ACNS1721. Required samples from the time of diagnosis must be submitted on APEC14B1 to the BPC ASAP, preferably within 13 calendar days of surgery to allow for the pre-screening part of the protocol prior to enrolling on ACNS1721 Step 1.

Sites will be notified by e-mail of the rapid central pathology review and H3 K27M IHC results within 7 calendar days of receipt of all required samples at the BPC. Notification of histopathologic eligibility/ineligibility will be sent to the e-mail addresses that were entered by the site during the initial CTSU OPEN HGG Pre-Enrollment Screening.

To expedite the central review process, it is strongly recommended that the site submit tissue through APEC14B1 and commence the process of enrollment as soon as a diagnosis of high-grade glioma is suspected. See Section 3.1.1 Pre-Enrollment Eligibility Screening Criteria.

Rapid central review of the submitted specimens will occur via direct review of slides. Slide / FFPE scroll distribution will be coordinated by the BPC. All samples will undergo central pathology review and H3 K27M IHC. Difficult cases will be discussed among the study neuropathologists so as to achieve a consensus review diagnosis.

Once the central pathology results are known and diagnosis is confirmed as HGG, it is recommended that discussions regarding the possible treatment studies be initiated with the patient/family.

3.1.3 Mandatory Rapid Central Molecular Screening Review

See Appendix IV and Section 15.0. All patients who have pathology confirmed must then have RAPID CENTRAL MOLECULAR SCREENING REVIEW ON APEC14B1 PRIOR TO STUDY ENROLLMENT ON ACNS1721 STEP 1 in order to avoid discordant diagnoses and to verify diagnosis criteria for treatment on ACNS1721. Required samples must be submitted on APEC14B1 to the BPC ASAP, preferably within 13 calendar days of surgery to allow for the pre-screening part of the protocol prior to enrolling on ACNS1721 Step 1.

For patients undergoing Rapid Central Molecular Review on APEC14B1, real time molecular characterization will occur at the Cincinnati Children's Hospital and Medical Center (CCHMC) in a CAP/CLIA certified laboratory. Specimens will have targeted Next-Generation Sequencing (NGS) analysis for determination of mutations involving *BRAF* and *IDH1/2*.

Results from the molecular screening will be available within 17 calendar days of receipt of all required samples at the BPC (up to 30 calendar days total after surgical resection). Patients will receive results from the treating physician. **Results from the molecular review for eligibility/ineligibility will be sent to the e-mail addresses that were entered by the site during the initial CTSU OPEN HGG Pre-Enrollment Screening.** (Note: The BPC is not responsible for sending final results to sites.)

3.2 Study Enrollment

3.2.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN 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. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

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.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.2.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.2.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a

transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- All patients have been consented and enrolled on APEC14B1 followed by enrollment on the HGG Pre-Enrollment Eligibility Screening (Step 0) on the same day to complete the Rapid Central Review.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.2.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment and no later than 31 calendar days after definitive surgery as per Section 3.3.5. **Patients who are started on protocol therapy on a phase 2 study prior to study enrollment will be considered ineligible**.

3.3 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 7 days at the time of enrollment. Laboratory tests need not be repeated if therapy starts within 7 days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. A pre- and post-operative brain MRI with and without contrast with sequences specified in Section 16.2 must be obtained prior to enrollment. The requirement for post-operative MRI is waived for patients who undergo biopsy only.

3.3.1 Age

Stratum 1 (*IDH* wild-type): Patients must be ≥ 3 years of age and ≤ 21 years of age at the time of enrollment. Please note Stratum 1 was closed to accrual on January 24, 2020.

Stratum 2 (*IDH* mutant): Patients must be ≥ 3 years of age and ≤ 25 years of age at the time of enrollment.

3.3.2 Diagnosis

Patients must have **eligibility confirmed by rapid central pathology and central molecular screening reviews performed on APEC14B1 (see Section 3.1):**

- Newly-diagnosed high-grade glioma such as anaplastic astrocytoma or glioblastoma.
- Negative results for H3 K27M by immunohistochemistry (IHC).
- Negative results for *BRAF*^{V600} mutation by Next-Generation Sequencing (NGS).

3.3.2.1 Patients must have histological verification of diagnosis. Patients with M+ disease (defined as evidence of neuraxis dissemination) are not eligible. CSF cytology is not required but may be obtained if clinically indicated prior to study enrollment. If cytology is positive, the patient would be considered to have metastatic disease and would, therefore, be ineligible.

3.3.2.2 Pre-operative and post-operative brain MRI with and without contrast must be obtained. The requirement for a post-operative MRI is waived for patients who undergo biopsy only. A spine MRI is not required, but may be obtained if clinically indicated. If the spine MRI is positive, the patient would be considered to have M+ disease (defined as neuraxis dissemination) and would be ineligible.

3.3.3 Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials under Standard Sections for Protocols.

3.3.4 Organ Function Requirements

3.3.4.1 Adequate Bone Marrow Function defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 1,000/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 gm/dL (can be transfused)

3.3.4.2 Adequate Renal Function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/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 utilizing child length and stature data published by the CDC.[49]

3.3.4.3 Adequate Liver Function defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

3.3.4.4 Central Nervous System Function defined as:

- Patients with seizure disorder may be enrolled if seizures are well-controlled (i.e., patients must not have required rescue medications for uncontrolled seizures within 14 days prior to enrollment).

3.3.5 Timing

Patients must be enrolled and protocol therapy must be projected to begin no later than 31 days after definitive surgery (Day 0). If a biopsy only was performed, the biopsy date will be considered the date of definitive surgery. For patients who have a biopsy or incomplete resection at diagnosis followed by additional surgery, the date of the last resection will be considered the date of definitive surgery.

3.3.6 Exclusion Criteria

3.3.6.1 Patients with the following histologies:

- Diffuse astrocytoma (Grade 2)
- Oligodendrogliomas (any grade)
- Pleomorphic xanthoastrocytoma (PXA, any grade)

3.3.6.2 Patients with primary tumor location of brainstem or spinal cord.

3.3.6.3 Patients with M+ disease (defined as neuraxis dissemination either by imaging or by cytology).

3.3.6.4 Patients with treatment-related AML (t-AML)/MDS or with features suggestive of AML/MDS.

3.3.6.5 Prior allogenic bone marrow transplant or double umbilical cord blood transplantation.

3.3.6.6 Prior Therapy

Patients must not have received any prior tumor-directed therapy including radiation therapy, chemotherapy (tumor-directed therapy), molecularly targeted agents, or immunotherapy for the treatment of HGG other than surgical intervention and/or corticosteroids.

3.3.6.7 Lumbar CSF cytology is not required, but may be performed if clinically indicated prior to study enrollment. If lumbar CSF cytology is positive, the patient is considered to have M+ disease and is ineligible.

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

3.3.6.8 Patients with gliomatosis cerebri type 1 or 2.

3.3.6.9 Patients who are not able to receive protocol specified radiation therapy.

3.3.6.10 Patients must not be currently receiving other anti-cancer agents.

3.3.6.11 Patients with known constitutional mismatch repair deficiency syndrome (CMMR-D)/biallelic mismatch repair deficiency (bMMRD).

3.3.6.12 Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.

3.3.6.13 Lactating females are not eligible unless they have agreed not to breastfeed their infants.

3.3.6.14 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.3.6.15 Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation and for 6 months after the last dose of protocol-specified chemotherapy.

3.3.7 Regulatory Requirements

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

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

4.0 TREATMENT PROGRAM

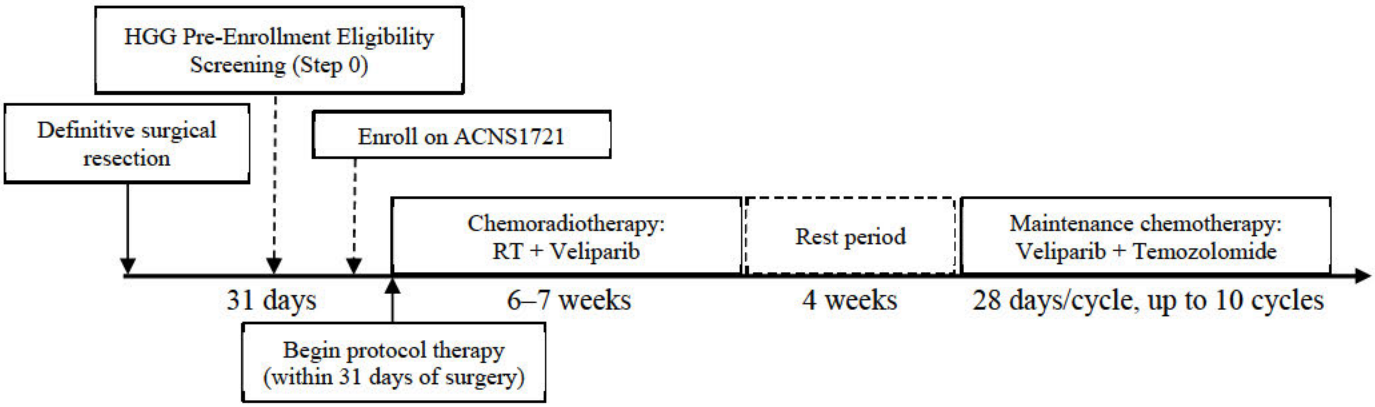
Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and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

4.1 Overview of Treatment Plan

This study will evaluate the efficacy of the proposed regimen in two molecularly defined pediatric newly-diagnosed HGG subgroups. Stratum 1 will enroll patients who are wild-type with respect to H3 K27M, *BRAF*, and *IDH1/2*. Stratum 2 will enroll patients who are positive for either *IDH1/2* mutation. Please note that patients with H3 K27M or *BRAF* mutations are ineligible for this study. Both strata will receive the same treatment regimen as described below. Please note Stratum 1 was closed to accrual on January 24, 2020.

Radiation therapy (RT) will be given in standard fractions (dose 54 to 59.4 Gy) over 6–7 weeks. During radiation, patients will receive veliparib concurrent with RT (Chemoradiotherapy), followed by a 4 week rest period. Four weeks after completion of RT, patients will start veliparib and oral temozolomide (Maintenance chemotherapy). Maintenance chemotherapy will continue for up to 10 cycles in the absence of progressive disease and unacceptable toxicities.

IMPORTANT NOTE: Patients must begin protocol therapy within 31 days of definitive surgery. If circumstances require, starting veliparib may be delayed up to 3 days if necessary, but veliparib must start no later than Day 34 after surgery and no later than the 4th day of RT (see Section 3.3.5, Section 4.1.1, and Section 8.2).



4.1.1 Chemoradiotherapy

Prior to beginning protocol therapy, obtain biology samples for patients who have provided consent. See Section 15.2 for details.

During radiation, patients will receive veliparib throughout RT as outlined below at 65 mg/m^2/dose PO BID x 5 days per week (typically Monday–Friday) concurrent with each day of RT. **If circumstances require, starting veliparib may be delayed up to 3 days if necessary, but veliparib must start no later than Day 34 after surgery and no later than the 4th day of RT (see Section 8.2).** If timing permits, the morning (AM) dose of veliparib should be given 60–120 minutes prior to daily RT. A missed dose of veliparib should not be made up, and veliparib will finish on the last day of RT.

RT will be given over 6–7 weeks during this course (see Section 17.0). The goal of treatment planning and dose prescription is that the dose to the International Commission on Radiation Units and Measurements (ICRU) reference point shall be 54 Gy given over 6 weeks. For patients whose tumors have not been completely resected and residual disease remains, the dose will be boosted to a total dose of 59.4 Gy (an additional 5.4 Gy boost). RT will be given in standard fractions. RT will be administered to a dose of 54 Gy in 30 daily fractions (or 59.4 Gy in 33 daily fractions if appropriate), treating 5 days per week (e.g., Monday–Friday) as outlined in Section 17.0. RT will not be interrupted for veliparib related toxicities (see Section 5.0), unless clinically indicated.

Chemoradiotherapy Phase								
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Week 7–10**
Veliparib, BID	Twice daily, Monday–Friday, for 6–7 weeks (AM dose should be given 60-120 minutes before RT)							Rest/Evaluation
Radiation Therapy	Daily, Monday–Friday for 6–7 weeks							

4.1.2 Maintenance Chemotherapy

All patients will receive Maintenance chemotherapy upon completion of Chemoradiotherapy and tumor evaluation, in the absence of disease progression and unacceptable toxicities (see Section 5.0). All patients will start Maintenance chemotherapy after a 4-week rest period at the end of Chemoradiotherapy

(approximately at Week 11) with 25 mg/m^2/dose PO BID of veliparib and 135 mg/m^2/dose PO daily of temozolomide for 5 days every 28 days, the recommended phase 2 doses (RP2Ds) from PBTC-027 and PBTC-033, respectively. Cycles will be repeated every 28 days. Dosing of veliparib and temozolomide will be based on the BSA determined prior to each cycle (see Appendix VII and Appendix VIII). Patients will continue on Maintenance chemotherapy for up to 10 cycles.

Disease evaluations should occur prior to every odd-numbered Maintenance cycle (see Section 4.5.2 for details).

Maintenance Chemotherapy						
Day	**1**	**2**	**3**	**4**	**5**	**6–28**
Veliparib (BID)	X	X	X	X	X	Rest/Evaluation
Temozolomide (once daily)	X	X	X	X	X	Rest/Evaluation

4.2 Concomitant Therapy Restrictions

4.2.1 General Restrictions for All Patients on Therapy

Since veliparib is a substrate of P-gp, OCT2, MATE1, and MATE2K, co-administration of veliparib with strong inhibitors of OCT2, MATE1, MATE2K, and/or P-glycoprotein (P-gp) may decrease veliparib renal clearance and increase its plasma exposure. Strong **inhibitors** of the kidney transporters OCT2, MATE1, MATE2K, and/or P-gp, such as trimethoprim (except when used for PCP prophylaxis as outlined in Section 4.2.1.1), cimetidine, clarithromycin, itraconazole, isavuconazole, verapamil, amiodarone, quinidine, carvedilol, dronedarone, lopinavir, saquinavir, telaprevir, tipranavir, dolutegravir, ritonavir, propafenone, quinidine, and ranolazine should be used with caution. Consider alternative agents, if reasonable alternative are available. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

Veliparib may inhibit OCT1 in the liver and MATE1 and MATE2K in the kidney at higher doses (e.g., 400 mg BID). Therefore, concomitant use of sensitive substrates of OCT1, MATE1, and MATE2K (such as dofetilide, metformin, and cimetidine) should be avoided if reasonable alternatives exist.

Valproic acid may decrease the oral clearance of temozolomide. Therefore, the use of valproic acid during Maintenance chemotherapy should be avoided if reasonable alternatives exist.

4.2.1.1

There have been multiple episodes of pneumocystis carinii pneumonia (PCP, also called *Pneumocystis jiroveci pneumonia*) reported in patients receiving temozolomide, particularly when taking corticosteroids. For this reason, patients should receive PCP prophylaxis during Maintenance chemotherapy, such as trimethoprim/sulfamethoxazole or an appropriate alternative. PCP prophylaxis may be discontinued 3 months after chemotherapy has discontinued.

4.2.1.2 Filgrastim (G-CSF) or biosimilar may be used at the treating physician's discretion to enhance neutrophil recovery when clinically indicated (e.g., for culture proven bacteremia or invasive fungal infection) or as outlined in Section 5.0. Routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

4.2.1.3 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Patients may receive daily prophylactic ondansetron or granisetron during the Chemoradiotherapy phase (receiving veliparib and radiation) per local practice. During Maintenance chemotherapy, patients should receive prophylactic ondansetron or granisetron during the 5-day course of veliparib and temozolomide, and such treatment may be continued beyond the 5-day period, if clinically indicated. Corticosteroids should not be used as anti-emetics. The use of additional anti-emetics will be at the treating physician's discretion.

4.2.1.4 Corticosteroid therapy is permissible consistent with good medical management. It is strongly recommended that corticosteroids should NOT be used as an antiemetic due to their effect on the blood brain barrier. Data on corticosteroid use will be collected at baseline and while patients are on therapy. Use of corticosteroids must be documented on the appropriate case report forms.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines

4.3 Chemoradiotherapy

4.3.1 Therapy Delivery Map (TDM) – Chemoradiotherapy

Chemoradiotherapy will last 6–7 weeks, followed by a 4-week rest period. This TDM is for all 6-7 weeks of Chemoradiotherapy. Please note that Day 1 of RT may not correspond to the first day of veliparib if veliparib administration is delayed.	_____ Patient COG ID number	_____ DOB

Criteria to start Chemoradiotherapy: ANC ≥ 1000/μL and platelets ≥ 100,000/μL (transfusion independent). RT should begin within 31 days of definitive surgical procedure. This TDM is 2 pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Veliparib (IND # 139199)	PO	65 mg/m^2/dose BID (see Appendix VII)	Daily with RT (5 days/week, Monday–Friday)	Veliparib should be given on the first day of RT but may be delayed up to 3 days if necessary. Veliparib must start **no later** than Day 34 after surgery and the 4th day of RT. If timing of RT permits, the AM dose of veliparib should be given 60–120 minutes prior to daily RT. **Veliparib is to be administered only on the days of scheduled RT. RT will be administered in 30 daily fractions (or 33 daily fractions if appropriate), treating 5 days per week (excluding weekends), over 6–7 weeks.** Total Daily Dose: 130 mg/m^2/day

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day of RT**	Veliparib (AM dose) mg	Veliparib (PM dose) mg	Studies
			Enter calculated dose above and actual dose administered below		
		1	mg	mg	a-h
		2	mg	mg	
		3	mg	mg	
		4	mg	mg	
		5	mg	mg	
		6	mg	mg	a-e
		7	mg	mg	
		8	mg	mg	
		9	mg	mg	
		10	mg	mg	
		11	mg	mg	a-e
		12	mg	mg	
		13	mg	mg	
		14	mg	mg	
		15	mg	mg	
		16	mg	mg	a-e
		17	mg	mg	
		18	mg	mg	
		19	mg	mg	
		20	mg	mg	
		21	mg	mg	a-e
		22	mg	mg	
		23	mg	mg	
		24	mg	mg	
		25	mg	mg	
		26	mg	mg	a-e
		27	mg	mg	
		28	mg	mg	
		29	mg	mg	
		30	mg	mg	
		31*	mg	mg	a-e
		32*	mg	mg	
		33*	mg	mg	
			*Days 31–33 are only for patients receiving the RT boost. See Section 4.1.1. ** Monday–Friday only. Do not administer on weekends. Following 6–7 weeks of ChemoRT and a 4-week rest period, patients will continue onto Maintenance chemotherapy when criteria to begin Maintenance chemotherapy are met (see Section 4.4.1), absent disease progression or unacceptable toxicity.		

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.3.2 Required Observations in Chemoradiotherapy

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

a. Physical exam
b. Height, weight
c. CBC/diff/platelets
d. Bilirubin, Creatinine
e. AST/ALT
f. Brain MRI (pre- and post-operative. Pre-operative MRI should be performed prior to enrollment onto the study.) The requirements for a post-operative MRI is waived for patients who undergo biopsy only.
g. Tumor tissue and blood for correlative biology studies: In consenting patients, samples will be collected at baseline for exploratory studies. See Section 15.2.2.
h. Pregnancy test: Female patients of childbearing potential require a negative serum or urine pregnancy test within 72 hours prior to starting treatment; sexually active patients must use an acceptable method of birth control.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications.)

4.3.3 Chemoradiotherapy Treatment Details

Criteria to start Chemoradiotherapy:

- Absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet Count ≥ 100,000/μL (transfusion independent)

Veliparib: PO
Days: Monday–Friday
Dose: 65 mg/m^2/dose BID (Total Daily Dose: 130 mg/m^2/day)

Veliparib will be given twice daily, Monday through Friday, throughout the duration of RT. Veliparib should be continued until the final day of radiation therapy with no breaks, except for Saturday/Sunday, or unless required due to toxicity.

Administer veliparib orally without regards to meals.

- Veliparib Capsules: Swallow capsules whole; do not chew or break.

- Veliparib Oral Solution: Do not mix veliparib oral solution directly in apple or grape juice; however, patients can drink apple juice or grape juice after the dose. Do NOT drink orange juice, other citrus based juices, or grapefruit juice while taking veliparib oral solution.

The first dose of veliparib should be given on the first day of RT, but may be delayed by up to 3 days if necessary. Veliparib must start no later than the 4th day of RT (Day 34 after surgery). A missed dose should not be made up. **Dosing will be based on the BSA determined at the beginning of radiation therapy.** The morning dose of veliparib should ideally be given 60–120 minutes prior to daily radiation treatment. For patients who require sedation for radiation treatment and are not able to take the oral medication due to local requirements for NPO prior to sedation, veliparib may be given nightly, and the daytime dose given shortly after the child awakens from sedation, adhering as closely to an every 12-hour schedule as possible. However, if local sedation guidelines permit, then the morning veliparib dose should be taken 60–120 minutes prior to radiation. Periodic adjustments in the timing of twice daily veliparib administration are allowed if needed to accommodate patient/family convenience, provided that the daytime dose is given as close to 60–120 minutes prior to daily RT whenever possible and adherence to an every 12-hour dosing schedule is attempted whenever possible.

For patients taking the oral solution, veliparib doses < 30 mg should be rounded to the nearest 1 mg [0.1 mL] (e.g., 11.4 mg to be rounded to 11 mg and 19.5 mg to be rounded to 20 mg). For doses between 30 to 100 mg, round oral solution doses to the nearest 2 mg [0.2 mL] (e.g., 45.4 mg should be rounded to 46 mg). Doses > 100 mg can be rounded to the nearest 10 mg [1 mL].

Doses of the capsule formulation should be rounded to the nearest 10 mg and can be divided unevenly if necessary to achieve to a total daily dose (e.g., 60 mg in AM and 50 mg in PM). See suggested capsule dosing tables in Appendix VII.

Patient veliparib wallet cards are provided in Appendix VI**.**

Note: Patients are not allowed to take a combination of capsules and the oral solution of veliparib for an individual dose.

If emesis occurs within 15 minutes of administration of veliparib, the dose should be repeated. A missed dose will not be made up, but the missed dose and reason for missing the dose should be recorded in the patient's record.

See Section 5.0 for Dose Modifications based on Toxicities.

Following 6-7 weeks of Chemoradiotherapy and a 4-week rest period, patients will continue onto Maintenance chemotherapy when criteria to begin Maintenance chemotherapy are met, absent disease progression or unacceptable toxicity.

4.4 Maintenance Chemotherapy – Cycle 1

4.4.1 Therapy Delivery Map (TDM) – Maintenance Chemotherapy – Cycle 1

Patients will receive up to 10 total cycles of Maintenance chemotherapy. Each cycle lasts 28 days. This TDM is for Cycle 1.	_____ Patient COG ID number _____ DOB

Criteria to start Cycle 1: ANC ≥ 1000/µL; platelets ≥ 100,000/µL (without transfusion within the last 7 days); creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2, **or** serum creatinine ≤ 1.5 x ULN; total bilirubin ≤ 1.5 x ULN; ALT < 2.5 x ULN; AST < 2.5 x ULN; and no evidence of progressive disease as assessed clinically and/or by imaging.
This TDM is two pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Veliparib (IND # 139199)	PO	25 mg/m^2/dose BID (see Appendix VII)	1–5	The morning dose of veliparib should be given 60–120 minutes prior to temozolomide. See Section 4.4.3 for dosing and administration instructions. Total Daily Dose: 50 mg/m^2/day
Temozolomide (TEMO)	PO	135 mg/m^2/dose once daily (see Appendix VIII)	1–5	

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Veliparib (AM dose) mg	Veliparib (PM dose) mg	TEMO mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	mg	mg	mg	a–h
		2	mg	mg	mg	
		3	mg	mg	mg	
		4	mg	mg	mg	
		5	mg	mg	mg	
		8				d
		15				d
		21				d
		28	Cycle 2 will start on Day 29 or when the criteria to begin the next cycle are met, whichever occurs later, absent disease progression or unacceptable toxicity.			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in Maintenance Chemotherapy – Cycle 1

a. Physical exam
b. Height, weight
c. Performance status
d. CBC/diff/platelets: Obtain weekly
e. Bilirubin, Creatinine.
f. AST/ALT
g. Brain MRI
h. Tumor tissue and blood for correlative biology studies: In consenting patients, samples will be collected for exploratory studies. See Section 15.2.2.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Maintenance Chemotherapy – Cycle 1

4.4.3 Maintenance Chemotherapy Treatment Details – Cycle 1

Each cycle of Maintenance chemotherapy lasts 28 days.

Prior to beginning Maintenance chemotherapy, obtain biology samples from patients who have provided consent. See Section 15.2 for details of optional biology specimen collection.

Criteria to start Cycle 1 of Maintenance chemotherapy:

- ANC ≥ 1000/μL
- Platelets ≥ 100,000/μL (without transfusion within the last 7 days)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2, **or** serum creatinine ≤ 1.5 x ULN
- Total bilirubin ≤ 1.5 x ULN, ALT < 2.5 x ULN, AST < 2.5 x ULN
- Patient has no evidence of progressive disease (see Section 10.4) as assessed clinically and/or by imaging studies

Veliparib: PO
Days: 1–5
Dose: 25 mg/m^2/dose BID (Total Daily Dose: 50 mg/m^2/day)

Veliparib will be given twice daily, and the morning (AM) dose should be given 60–120 minutes prior to the daily dose of temozolomide. Veliparib and temozolomide will be given on Days 1–5.

Alternatively, temozolomide may be given with the PM dose of veliparib, as long as:

1) temozolomide is given around the same time consistently every day
2) veliparib is administered 60-120 minutes prior to temozolomide to optimize the synergistic activity between the two agents.

Administer veliparib orally without regards to meals.

- Veliparib Oral Solution: Do not mix veliparib oral solution directly in apple/grape juice; however, patients can drink apple juice or grape juice after the dose. Do NOT drink orange juice, other citrus based juices, or grapefruit juice while taking veliparib oral solution (Days 1–5).

- Veliparib Capsules: Swallow capsules whole; do not chew or break.

For patients taking the oral solution, veliparib doses < 30 mg should be rounded to the nearest 1 mg [0.1 mL] (e.g., 11.4 mg to be rounded to 11 mg and 19.5 mg to be rounded to 20 mg). For doses between 30 to 100 mg, round oral solution doses to the nearest 2 mg [0.2 mL] (e.g., 45.4 mg should be rounded to 46 mg).

Doses of capsule formulation should be rounded to the nearest 10 mg and can be divided unevenly if necessary to achieve a total daily dose (e.g., 30 mg in AM and 20 mg in PM). See suggested capsule dosing tables in Appendix VII.

Patient veliparib wallet cards are provided in the Appendix VI.

Note: Patients are not allowed to take a combination of capsules and the oral solution of veliparib for an individual dose.

If emesis occurs within 15 minutes of administration of veliparib, the dose should be repeated once. A missed dose will not be made up, but the missed dose and reason for missing the dose should be recorded in the patient's record.

Temozolomide: PO
Days: 1–5
Dose: 135 mg/m^2/dose once daily

Temozolomide should be administered 60-120 minutes after the veliparib dose and should be given consistently around the same time every day.

Note: Temozolomide doses should be rounded to the nearest 5 mg capsule size (see Appendix VIII for suggested capsule formulation dosing tables). For patients unable to swallow capsules, the capsules can be opened and mixed with apple sauce or apple juice, which should be used immediately after mixing (preferred) or must be used in 2 hours after mixing (see Section 6.2 and Appendix V).

If emesis occurs within 15 minutes of taking a dose of temozolomide, then the dose may be repeated once. If emesis occurs after 15 minutes, the dose should not be repeated. Instructions for administration of oral temozolomide to young children are included in Appendix V.

Disease evaluations should occur prior to every odd number of Maintenance cycle (see Section 4.5.2) for details).

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Cycle 1 of Maintenance chemotherapy, subsequent cycles will start on Day 29 or when criteria to begin the next cycle are met, whichever occurs later, absent disease progression or unacceptable toxicity.

4.5 Maintenance Chemotherapy – Cycles 2–10

4.5.1 Therapy Delivery Map (TDM) – Maintenance Chemotherapy – Cycles 2–10

Patients will receive up to 10 total cycles of Maintenance chemotherapy. Each cycle lasts 28 days. This TDM is for one cycle of Cycles 2–10. Please indicate the cycle # below.	_____ Patient COG ID number _____ DOB

Criteria to start Cycle 2 and subsequent cycles: ANC ≥ 750/µL, platelets ≥ 75,000/µL (without transfusion within the last 7 days), serum creatinine ≤ 1.5 x ULN, total bilirubin ≤ 1.5 x ULN, ALT < 2.5 x ULN, AST < 2.5 x ULN, and no evidence of progressive disease as assessed clinically and/or by imaging. This TDM is two pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Veliparib (IND # 139199)	PO	25 mg/m^2/dose BID (see Appendix VII)	1–5	The morning dose of veliparib should be given 60–120 minutes prior to temozolomide. See Section 4.5.3 for dosing and administration instructions. Total Daily Dose: 50 mg/m^2/day
Temozolomide (TEMO)	PO	135 mg/m^2/dose once daily (see Appendix VIII)	1–5	

Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Veliparib (AM dose) mg	Veliparib (PM dose) mg	TEMO mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	mg	mg	mg	a–i
		2	mg	mg	mg	
		3	mg	mg	mg	
		4	mg	mg	mg	
		5	___mg	___mg	___mg	
		8				d
		15				d
		21				d
		28	Subsequent cycles will start on Day 29 or when the criteria to begin the next cycle are met, whichever occurs later, absent disease progression or unacceptable toxicity.			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.5.2 Required Observations in Maintenance Chemotherapy – Cycles 2–10

a. Physical exam
b. Height, weight
c. Performance status: Prior to each odd-numbered cycle of Maintenance chemotherapy (e.g., Cycle 1, Cycle 3, Cycle 5, etc.)
d. CBC/diff/platelets: Obtain weekly
e. Bilirubin, Creatinine
f. AST/ALT
g. Brain MRI: Prior to each odd-numbered cycle of Maintenance chemotherapy (e.g., Cycle 3, Cycle 5, etc.)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.5.3 Maintenance Chemotherapy Treatment Details – Cycles 2–10

Each cycle of Maintenance chemotherapy lasts 28 days.

Criteria to start Cycle 2 and subsequent cycles:

- Absolute neutrophil count (ANC) ≥ 750/µL
- Platelet Count ≥ 75,000/µL (without transfusion within the last 7 days)
- Serum creatinine ≤ 1.5 x ULN
- Total bilirubin ≤ 1.5 x ULN, ALT < 2.5 x ULN, AST < 2.5 x ULN
- The patient has no evidence of progressive disease (see Section 10.4) as assessed clinically and/or by imaging studies.

Disease evaluations should occur prior to every odd number of Maintenance cycle (see Section 4.5.2) for details).

Veliparib: PO
Days: 1–5
Dose: 25 mg/m^2/dose BID (Total Daily Dose: 50 mg/m^2/day)

Veliparib will be given twice daily, and the morning (AM) dose should be given 60–120 minutes prior to the daily dose of temozolomide. Veliparib and temozolomide will be given on Days 1–5.

Alternatively, temozolomide may be given with the PM dose of veliparib, as long as:

1) temozolomide is given around the same time consistently every day
2) veliparib is administered 60–120 minutes prior to temozolomide to optimize the synergistic activity between the two agents.

Administer veliparib orally without regards to meals.

- Veliparib Oral Solution: Do not mix veliparib oral solution directly in apple or grape juice; however, patients can drink apple juice or grape juice after the dose. Do NOT drink orange juice, other citrus based juices, or grapefruit juice while taking veliparib oral solution (Days 1-5 of each cycle).

- Veliparib Capsules: Swallow capsules whole; do not chew or break.

For patients taking the oral solution, veliparib doses < 30 mg should be rounded to the nearest 1 mg [0.1 mL] (e.g., 11.4 mg to be rounded to 11 mg and 19.5 mg to be rounded to 20 mg). For doses between 30 to 100 mg, round oral solution doses to the nearest 2 mg [0.2 mL] (e.g., 45.4 mg should be rounded to 46 mg).

Doses of capsule formulation should be rounded to the nearest 10 mg and can be divided unevenly if necessary to achieve a total daily dose (e.g., 30 mg in AM and 20 mg in PM). See suggested capsule dosing tables in Appendix VII.

Patient veliparib wallet cards are provided in the Appendix VI.

Note: Patients are not allowed to take a combination of capsules and the oral solution of veliparib for an individual dose.

If emesis occurs within 15 minutes of administration of veliparib, the dose should be repeated once. A missed dose will not be made up, but the missed dose and reason for missing the dose should be recorded in the patient's record.

Temozolomide: PO
Days: 1–5
Dose: 135 mg/m^2/dose once daily

Temozolomide should be administered 60-120 minutes after the veliparib dose and should be given consistently around the same time every day.

Note: Temozolomide doses should be rounded to the nearest 5 mg capsule size (see Appendix VIII for suggested capsule formation dosing tables). For patients unable to swallow capsules, the capsules can be opened and mixed with apple sauce or juice, which should be used immediately after mixing (preferred) or must be used in 2 hours after mixing (see Section 6.2 and Appendix V).

If emesis occurs within 15 minutes of taking a dose of temozolomide, then the dose may be repeated once. If emesis occurs after 15 minutes, the dose should not be repeated. Instructions for administration of oral temozolomide to young children are included in Appendix V.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this cycle of Maintenance chemotherapy, subsequent cycles will start on Day 29 or when criteria to begin the next cycle are met, whichever occurs later, absent disease progression or unacceptable toxicity. Patients may continue for up to 10 cycles.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Levels Tables

The starting dose level of veliparib is 65 mg/m^2/dose BID during Chemoradiotherapy and 25 mg/m^2/dose BID during Maintenance therapy.

Table 1. Dose Levels for Veliparib during Chemoradiotherapy

Dose Level	Veliparib dose (mg/m^2/dose BID)
-2	35 mg/m^2/dose BID
-1	50 mg/m^2/dose BID
1*	**65 mg/m^2/dose BID**

*Starting dose level

Table 2. Dose Levels for Veliparib and Temozolomide during Maintenance Therapy

Dose Level	Veliparib Dose	Temozolomide Dose
-1	20 mg/m^2/dose BID	135 mg/m^2/day
1*	**25 mg/m^2/dose BID**	**135 mg/m^2/day**

*Starting dose level

5.2 Dose Modifications for Veliparib during Chemoradiotherapy

5.2.1 Hematological Toxicities

Note: Radiation therapy should not be interrupted unless clinically indicated.

5.2.1.1 Definition of Dose-Modifying Toxicity

Dose modifying toxicities will be defined as any of the following events that are at least possibly related to veliparib therapy.

- Platelets < 50,000/µL (thrombocytopenia ≥ Grade 3) requiring transfusions on ≥ 2 separate days within a 7-day period
- Platelets < 25,000/µL (thrombocytopenia Grade 4)
- ANC < 500/µL (neutropenia Grade 4)

5.2.1.2 Dose Modifications for Hematologic Toxicities

5.2.1.2.1 **If a patient experiences dose-modifying thrombocytopenia (platelets < 50,000/µL requiring transfusions on ≥ 2 separate days within a 7-day period *OR* platelets < 25,000/µL):**
Hold veliparib. Obtain twice weekly CBC until platelets ≥ 75,000/µL. Platelet transfusion is permissible and strongly encouraged for patients with platelets < 50,000/µL to minimize the risk of intra-tumoral hemorrhage.

- For patients on Dose Level 1 or Dose Level -1: Veliparib should be restarted at one dose lower (Table 1) once platelets recover to ≥ 75,000/µL (transfusion

independent). If platelet count is < 75,000/µL after withholding veliparib for > 14 days, veliparib during Chemoradiotherapy should be discontinued and restarted at the time of Maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).

- For patients on Dose Level -2: Veliparib during Chemoradiotherapy should be discontinued and restarted at the time of Maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).

5.2.1.2.2 **If a patient experiences dose-modifying neutropenia (ANC < 500/µL):**
Hold veliparib. Obtain twice weekly CBC until ANC > 750/µL. Patients may receive filgrastim (G-CSF) or biosimilar support at the discretion of the treating physician. If G-CSF is utilized, ANC determination for restart of veliparib must be after > 48 hours without G-CSF support.

- For patients on Dose Level 1 or Dose Level -1: Veliparib should be restarted at one dose level lower (Table 1) once ANC recovers to ≥ 750/µL. If ANC < 500/µL after withholding veliparib for > 14 days, veliparib during Chemoradiotherapy should be discontinued and restarted at the time of Maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).
- For patients on Dose Level -2: Veliparib during Chemoradiotherapy should be discontinued and restarted at the time of Maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).

5.2.2 Non-Hematological Toxicities

5.2.2.1 Definition of Dose-Modifying Toxicity (DMT)

- Any Grade 4 non-hematologic toxicity that is at least possibly related to veliparib.
- Any Grade 3 non-hematologic toxicity that is at least possibly related to veliparib, and is considered medically significant or sufficiently intolerable by patients requiring treatment interruption, with the exception of:
  - Grade 3 nausea and vomiting of < 7 days
  - Grade 3 elevation of transaminases that returns to levels meeting eligibility criteria within 7 days of study drug interruption and does not recur upon restarting drug
  - Grade 3 fever or infection of < 5 days in duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation

5.2.2.2 Dose Modifications for Non-Hematological Toxicities

Note: Radiation therapy should not be interrupted unless clinically indicated.

If any dose-modifying non-hematological toxicity as defined in Section 5.2.2.1 occurs that is at least possibly related to veliparib, hold veliparib. Restart veliparib at one dose level lower (Table 1) if the toxicity resolves to meet eligibility criteria (see Section 3.3.4) within 14 days. If the toxicity does resolve to meet eligibility criteria within 14 days, or if the patient is already on Dose Level -2, veliparib should be discontinued for the remainder of Chemoradiotherapy, but should be restarted at maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).

5.2.3 Veliparib-Related Toxicities Leading to Interruption of Radiation Therapy

5.2.3.1 Definition of Dose-Modifying Toxicity (DMT)

Any toxicity that is at least possibly related to veliparib that results in significant delay/interruption of > 2 weeks in the completion of RT.

5.2.3.2 Dose Modification for Veliparib-Related Toxicities that Lead to Interruption of Radiation Therapy

Veliparib should be discontinued for the remainder of Chemoradiotherapy, but should be restarted at Maintenance chemotherapy at the starting dose level for Maintenance chemotherapy (Table 2).

5.3 Dose Modifications for Veliparib and Temozolomide during Maintenance Chemotherapy

5.3.1 Hematological Toxicities

Dose modifying toxicities will be defined as any of the following events that are at least possibly attributable to veliparib or temozolomide.

5.3.1.1 Definition of Dose-Modifying Toxicity

- Platelets < 50,000/μL (thrombocytopenia ≥ Grade 3) requiring transfusions on ≥ 2 separate days in a 7-day period
- Platelets < 25,000/μL (thrombocytopenia Grade 4)
- ANC < 500/μL (neutropenia Grade 4) for > 7 days
- A delay of > 14 days in starting subsequent cycles of Maintenance due to ANC < 750/μL and/or platelet count < 75,000/μL

5.3.1.2 Dose Modifications for Hematologic Toxicities

5.3.1.2.1 **If a patient experiences dose-modifying thrombocytopenia (platelets < 50,000/μL requiring**

transfusions on ≥ 2 separate days in a 7-day period *OR* platelets < 25,000/µL *OR* delay of > 14 days in starting subsequent cycles of Maintenance chemotherapy due to platelet counts < 75,000/µL):
Hold veliparib and temozolomide. Obtain twice weekly CBC until platelets ≥ 75,000/µL. Platelet transfusion is permissible and strongly encouraged for patients with platelets < 50,000/µL to minimize the risk of intra-tumoral hemorrhage.

- Patients on Dose Level 1 should receive subsequent cycles at Dose Level -1 (Table 2).
- Patients on Dose Level -1 should be removed from protocol therapy.
- Refer to Section 5.4 (Management of Prolonged Hematological Toxicities while on Study Treatment) for additional guidelines.

5.3.1.2.2 **If patient experiences dose-modifying neutropenia (ANC < 500/µL for > 7 days *or* delay of > 14 days in starting subsequent cycles of Maintenance chemotherapy due to ANC < 750/µL):**
Hold veliparib and temozolomide. Obtain CBC twice weekly until ANC > 750/µL.

- Patients should have therapy restarted at the **same** dose level in the next cycle with myeloid growth factor support. If G-CSF is given, it can be started 24 hours after the lase dose of chemotherapy and continue until the post-nadir ANC is ≥ 2,000/µL. ANC determination for restart of veliparib must be after > 48 hours without G-CSF support.
- Patients on Dose Level 1 who experience recurrent dose-modifying neutropenia after myeloid growth factor is added should have subsequent cycles of treatment dose reduced to Dose Level -1 and receive myeloid growth factor.
- Patients on Dose Level -1 who experience dose-modifying neutropenia after addition of myeloid growth factor must be removed from protocol therapy.
- Refer to Section 5.4 (Management of Prolonged Hematological Toxicities while on Study Treatment) for additional guidelines.

5.3.1.2.3 Patients who experience a hematological toxicity that does not resolve to meet parameters to start subsequent cycles of therapy (ANC ≥ 750/µL and platelets ≥ 75,000/µL, transfusion independent) within 21 days after the planned start of the next treatment cycle (i.e., by Day 49) must be removed from protocol therapy. Refer to Section 5.4 (Management of Prolonged Hematological Toxicities while on Study Treatment) for additional guidelines.

5.3.2 Non-Hematological Toxicities

5.3.2.1 Definition of Dose-Modifying Toxicity

- Any Grade 4 non-hematologic toxicity that is at least possibly related to veliparib and/or temozolomide.
- Grade 3 non-hematologic toxicity that is at least possibly related to veliparib and/or temozolomide, and is considered medically significant or sufficiently intolerable by patients requiring treatment interruption, with the exception of:
  - Grade 3 nausea and vomiting of < 5 days
  - Grade 3 elevation of transaminases that returns to levels meeting eligibility criteria within 7 days of study drug interruption and does not recur upon restarting drug
  - Grade 3 fever or infection of < 5 days in duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
- Any non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

5.3.2.2 Dose Modifications for Non-Hematological Toxicities

For dose-modifying non-hematologic toxicities listed above that occur during Maintenance chemotherapy, veliparib and temozolomide will be withheld until the toxicity resolves to meet on eligibility criteria (see Section 3.3.4), and the patient will restart veliparib and temozolomide at Dose Level -1 (Table 2). Protocol therapy will be discontinued if a non-hematologic dose modifying toxicity occurs at Dose Level -1.

Patients who experience a dose-modifying non-hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle (i.e., by Day 49) must be removed from protocol therapy.

5.4 Management of Prolonged Hematological Toxicities while on Study Treatment

To date, four cases of Grade 4 myelodysplastic syndrome (MDS) and two cases of leukemia secondary to oncology therapy (one Grade 4 and one Grade 5) were observed on CTEP-sponsored studies utilizing veliparib. It is possible veliparib contributed to these adverse events; it is also possible that prior therapy with platinum or alkylating agents contributed to the development of MDS or leukemia. If a patient develops prolonged hematological toxicity that requires removal from protocol therapy and/or other signs or symptoms suggestive of MDS/leukemia, the patient should be further evaluated including a bone marrow aspirate with cytogenetics. Protocol therapy should be held and discontinued if AML/MDS is documented, and the patient should be managed appropriately.

6.0 DRUG INFORMATION

6.1 Veliparib

(ABT-888, A-861695.0) NSC# 737664, [redacted]) **(07/18/18)**

Source and Pharmacology:
Veliparib inhibits the formation of poly (ADP-ribose) (PAR) polymers *in vitro* and *in vivo*. PAR polymerase (PARP) is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair. PARP inhibition should enhance the effects of DNA-damaging agents on tumor cells defective in DNA damage repair. In a variety of nonclinical tumor models, including melanoma, breast, prostate, colon, and glioma, veliparib significantly enhanced the antitumor activity when dosed on a schedule that overlapped the administration of a DNA-damaging agent. Veliparib increases antitumor efficacy when added to DNA-damaging therapies such as temozolomide, cisplatin, carboplatin, cyclophosphamide, irinotecan, or radiation therapy.

Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress. Therefore, PARP inhibitors are proposed as sensitizing agents for a variety of DNA-damaging agents.

Pharmacokinetics (PK):
In adults, the exposure of veliparib is approximately dose-proportional over 10 through 500 mg twice daily (BID) dose range. The absorption of veliparib after oral dosing is relatively fast where veliparib plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life ($t_{1/2}$) of veliparib in adults is about 6 hours, with minimal accumulation following multiple BID dosing. Food does not have a significant effect on veliparib bioavailability. The administration of a high-fat meal had no significant effect on area under the plasma concentration-time curve (AUC) and only caused a slight decrease in veliparib maximum observed plasma concentration (C_{max}) (17%) and a delay of approximately 1 hour in time to maximum observed plasma concentration (T_{max}). The mean urinary recovery of unchanged veliparib was 73% and the total urinary recovery of veliparib (as parent compound and M8 metabolite) was 90%, which indicates that renal excretion is a major pathway in veliparib elimination. Mild to moderately severe hepatic dysfunction had no significant effect on veliparib PK. However, there was a trend of increase in veliparib AUC in subjects with moderate and severe renal dysfunction.

In children with recurrent CNS tumors receiving veliparib in combination with temozolomide,[41] 1st PK analysis showed that drug exposure was suboptimal at veliparib 15 mg/m^2/dose BID compared with adults receiving veliparib at 40 mg BID. The second PK analysis included 7 patients who received veliparib at 20 mg/m^2/dose BID and 3 patients who received veliparib at 25 mg/m^2/dose BID. While veliparib exposure at 20 mg/m^2/dose BID was still suboptimal, the 3 patients who received 25 mg/m^2/dose BID showed a mean $AUC_{0-12\,h}$ of 2 ± 0.64 µg•h/mL and day 4 Cmax of 372 ± 148 ng/mL, which achieves similar exposure observed in adults and predicted to maximize chemopotentiation.

Potential Drug Interactions:
Nonclinical studies suggest veliparib is a substrate of P-glycoprotein (P-gp), OCT2, and MATE1/MATE2K transporters. Co-administration of veliparib with strong inhibitors of

P-gp, OCT2, and MATE1/MATE2K drugs may result in a decrease of veliparib renal clearance and an increase in veliparib plasma concentration. Therefore, use caution when administering veliparib with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs. At high dose (e.g., 400 mg BID), veliparib may inhibit OCT1 in the liver and MATE1/MATE2K in the kidney.

Veliparib is NOT a potent inhibitor of the major human CYPs and does not significantly induce activities of major human CYP isoforms, suggesting a negligible potential for CYP-mediated drug-drug interactions as a perpetrator at the anticipated therapeutic concentrations.

In humans, veliparib clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites. Drug-associated with kidney toxicities or kidney diseases could change veliparib pharmacokinetics. Use caution when concomitantly administering veliparib with other nephrotoxic agents (e.g., platinum agents, aminoglycosides, etc.) or in patients with pre-existing renal impairment.

Potential drug-drug interactions (DDI) with veliparib are being evaluated in combination studies. There was no significant PK interaction between veliparib and temozolomide, carboplatin/paclitaxel, folinic acid/fluorouracil/irinotecan (FOLFIRI), and capecitabine/5-fluorouracil. Preliminary results also indicate the absence of a DDI between veliparib and carboplatin/gemcitabine or carboplatin/etoposide.

Patient Care Implications:
Patients may feel fatigue or tiredness. Loss of appetite and losing weight are common. Provide appropriate supportive care for diarrhea.

Based on veliparib mechanism of action and preclinical studies, teratogenicity is a potential risk for this agent. Patients (male and female) of childbearing potential must agree to use adequate birth control during study participation and 4 months after completion of veliparib administration. It is not known whether veliparib is excreted in human milk. Veliparib should not be administered to lactating patients.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Veliparib (ABT-888, NSC 737664)

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

f for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for veliparib (ABT-888).

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 2.4, May 13, 2018[13]

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			**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)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	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 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
VASCULAR DISORDERS			
		Thromboembolic event[35]	

[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]Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on veliparib (ABT-888) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that veliparib (ABT-888) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)
INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Shingles; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Radiation recall reaction (dermatologic)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) -Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Extrapyramidal disorder; Intracranial hemorrhage; Lethargy; Memory impairment; Movements involuntary; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (emotional instability); Psychosis; Restlessness
RENAL AND URINARY DISORDERS - Dysuria; Hematuria; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail changes; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: Veliparib (ABT-888) 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.

Formulation and Stability:
Capsules: Veliparib capsules are available in 10 mg, 20 mg, 40 mg, 50 mg, and 100 mg immediate release capsules. The inactive ingredients are microcrystaline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. It may contain FD&C blue#1, FD&C yellow #6, or FD&C yellow #5. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 16 capsules or 64 capsules.

Veliparib capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).

Oral solution: Veliparib oral solution is supplied as a **10 mg/mL** colorless solution in 100 mL amber glass bottle. The inactive ingredients of the Oral Solution are: Sodium citrate tribasic, Citric Acid, Sodium Benzoate, Xylitol, Sodium Hydroxide. Oral solution must be dispensed in the original bottle. Veliparib oral solution bottles must be stored upright.

Storage:
Capsules: Store the original bottle at 15° to 25° C (59° to 77° F).

Oral Solution: Store intact bottles at controlled room temperature between 15°– 25°C (59°F to 77°F); protect from freezing.

Stability:
Capsules: Shelf-life stability studies for veliparib capsules are on-going.

Oral Solution: Shelf-life stability studies for veliparib Oral Solution (**intact bottles**) will have a firm expiration date. Once the intact bottle is opened, the solution is stable up to **30 days at 25°C**. Stability of the solution administered in Baxa, Union Plastic or Neo-med oral syringes is up to **4 hours at 25°C**.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Administer veliparib orally without regard to meals. Do not make up for missed doses. Veliparib can be re-dosed if vomited within 15 minutes of administration.

Capsules: Swallow whole; do not chew or break.

Oral Solution: Do not mix veliparib solution directly in juice. Patients can drink apple juice or grape juice after the dose. Do NOT drink orange juice, other citrus-based juices, or grapefruit juice on the days that veliparib oral solution is administered.

Supplier:
Veliparib is supplied by AbbVie and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Obtaining the Agent

Agent Ordering:
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. 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), NIH Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Accountability

Agent Inventory Records:
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI

Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability:
The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and an active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.2 TEMOZOLOMIDE

(Temodar®, Temodal®) NSC #362856 **(05/28/20)**

Source and Pharmacology:
An orally or intravenously administered alkylating agent, a second generation imidazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. The cytotoxic effects of MTIC are manifested through alkylation (methylation) of DNA at the O^6, N^7 guanine positions which lead to DNA double strand breaks and apoptosis. Temozolomide is noncell cycle specific.

Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median T_{max} increased by 2-fold (from 1-2.25 hours) when temozolomide was administered after a modified high-fat breakfast. A pharmacokinetic study comparing oral and intravenous temozolomide in patients with primary CNS malignancies showed that at 150 mg/m^2 dose temozolomide IV and oral capsules are bioequivalent with respect to both C_{max} and AUC of temozolomide and MTIC. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%. Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. About 38% of the administered temozolomide total radioactive dose is recovered in the urine. Overall

clearance of temozolomide is about 5.5 L/hr/m^2. Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m^2/day. A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

The table below lists the anticipated toxicity profile of temozolomide (oral):

Incidence	Toxicities
Common (>20% of patients)	Constipation, nausea, vomiting, anorexia, alopecia, headache, seizure, fatigue
Occasional (4-20% of patients)	Peripheral edema, skin rash, pruritus, xeroderma, erythema of skin, diarrhea, dysphagia, dizziness, ataxia, hemiparesis, asthenia, fever, stomatitis, abdominal pain, dysgeusia, weight gain, platelet count decreased, white blood cell count decreased, lymphocyte count decreased, urinary incontinence or frequency, cough, dyspnea, infection, anxiety, depression, insomnia, gait disturbance, amnesia, paresthesia, drowsiness, visual disturbances, back pain, arthralgia/myalgia
Rare (≤ 3% of patients)	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hyperbilirubinemia, transaminitis, injection site reaction (IV formulation), interstitial pneumonitis, pancytopenia (may be prolonged), myelodysplastic syndrome, leukemia secondary to oncology chemotherapy, infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatotoxicity, cholestasis, anemia, aplastic anemia
Pregnancy & Lactation	**Pregnancy Category D** Adequate, well-controlled studies have not been conducted in humans. Women of childbearing potential should be advised against becoming pregnant while taking temozolomide and for at least 6 months following the end of therapy. Temozolomide administration to rats and rabbits at 3/8 and 3/4 the human dose resulted in the development of malformations of the external organs, soft tissues, and skeleton. These animal studies also demonstrated embryolethality (increased resorptions) at similar doses. There is no information available regarding the transmission of temozolomide during lactation; women should avoid breastfeeding while receiving temozolomide.

Formulation and Stability:
Temozolomide capsules are available in six different strengths (5, 20, 100, 140, 180, 250 mg). The capsules vary in size, color, and imprint according to strength. In the US, capsules are packaged in 5-count and 14-count bottles. In other countries temozolomide may be packaged in 5-count, 14-count or 20-count bottles. Temozolomide capsules are stored at 25 °C (77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F).

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

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

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day.

Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

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

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10 mg/mL suspension triturate the contents of ten 100 mg capsules (1000 mg), 500 mg povidone K-30 and 25 mg anhydrous citric acid dissolved in 1.5 mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100 mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension should be stored in the refrigerator at 2–8°C (36–46°F) for no more than 2 weeks after preparation. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension.[50]

Extemporaneous temozolomide 10 mg/mL suspension can also be prepared using 100 mg temozolomide capsules mixed in Ora-Mix SF®. Open contents of the required number of 100 mg temozolomide capsules into a mortar and add Ora-Mix SF® until a paste forms. Add more vehicle until a liquid is formed (for each 100 mg capsule add 10 mL of Ora-Mix SF®). Transfer desired volume to a glass or polyethylene terephthalate bottle. Label the container, assigning a beyond-use-date of 30 days, for storage under refrigeration only.[51]

Alternatively, the capsules can be opened and mixed with apple sauce or juice, which should be used immediately after mixing or must be used in 2 hours after mixing (refer to Appendix V in the protocol).

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

7.0 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 (except where explicitly prohibited within the protocol).

7.1 Research Studies for which Patient Participation is Required

7.1.1 Rapid Central Pathology and Molecular Review

Patients should be consented and enrolled on APEC14B1 followed by enrollment on the HGG Pre-Enrollment Eligibility Screening (Step 0) on the same day. See Section 3.1 for complete details regarding Pre-Enrollment Eligibility Screening and Section 3.1.1.4 for a list of required materials to be submitted on APEC14B1.

7.2 Research Studies for which Patient Participation is Optional

In consenting patients, correlative biology studies will be performed. See Section 15.2 for complete details.

7.3 End of Therapy & Follow-up

STUDIES TO BE OBTAINED	End of Therapy	Every 3 months for Year 1 (i.e., 3, 6, 9, 12 months)	Every 4 months for Year 2 (i.e., 16, 20, 24 months)	Every 6 months for Year 3 (i.e., 30, 36 months)	Once yearly for Years 4–10
Physical Exam with VS	X				
Ht, Wt, BSA	X				
CBC, differential, platelets	X				
Creatinine, bilirubin	X				
AST/ALT	X				
Brain MRI	X	X	X	X	X
Tumor and biology samples (in consenting patients, see Section 15.2.2)	X	X (at 6 and 12 months)	X (at 20 months)	X (at 30 months)	

The table above indicates required End of Therapy evaluations and required Follow-Up imaging scans. In addition, see COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: End of Therapy data should be submitted per the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Relapse or progressive disease (see Section 10.4).
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Completion of planned therapy.
d) Physician determines it is in patient's best interest.
e) Unacceptable toxicity due to protocol therapy (see Section 5.0).
f) Development of a second malignancy, including bone marrow findings consistent with acute myeloid leukemia (AML)/MDS. Note: Patients who develop MDS/AML on treatment should discontinue protocol therapy and be managed appropriately.
g) Patient becomes pregnant.
h) Patient starts breastfeeding.
i) Repeat eligibility studies (if required) are outside the parameters required for eligibility (see Section 3.3).

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

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient did not start radiation treatment within 31 days of definitive surgery (see Section 3.3.5).
d) Patient did not start veliparib treatment within 34 days of definitive surgery (see Section 4.1.1).
e) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
f) Withdrawal of consent for any further data submission.
g) The tenth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

For both strata, we will use an information-based design and the final analysis will be conducted when the specified number of events are attained. For Stratum 1, we expect to enroll 65 eligible and evaluable patients in approximately 3 years and we expect follow each patient for at least 1 year before the expected number of events (i.e., 35) is observed. For Stratum 2, we plan to enroll 30 eligible patients during the same period. The number of events needed to achieve the specified power under the design assumptions for this stratum is 13. We expect that we will need to follow the last patient for 3 years before 13 events are observed. Only patients who pass the screening process and start protocol defined treatment within 31 days (34 days for veliparib) of surgery will be eligible and evaluable for assessing efficacy. Patients who pass the screening process but are not able to start treatment within 31 days (34 days for

veliparib) of surgery will not be eligible and will be replaced. The maximum projected sample size for this study is 115 to account for ineligible/inevaluable patients. We expect we will need to molecularly screen up to 220 subjects to achieve the targeted sample size of eligible and evaluable patients.

Stratum 1 is the primary stratum that will control accrual for this trial. If accrual to Stratum 1 is completed and 30 patients have not yet been enrolled on Stratum 2, we will consult the COG Leadership and COG DSMC regarding whether accrual to Stratum 2 should continue.

9.1.1 Closure of Stratum 1 IDH (Wild-Type Cohort) Effective January 24, 2020

Stratum 1 of ACNS1721, for patients with IDH wild-type HGG, was closed to accrual as of January 24, 2020. Closure of this stratum was based on the results of a planned interim analysis. The available data from the first 22 subjects at the time of interim analysis suggested that the hypothesized superior outcome for the ACNS1721 treatment compared to the historical controls was unlikely. There were no concerns regarding excessive toxicities on this protocol.

9.2 Study Design

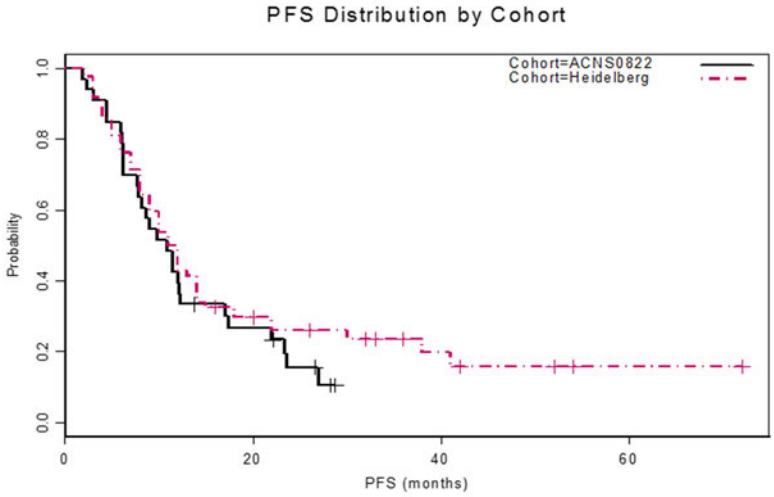
This study will evaluate the efficacy of the planned regimen in two molecularly defined pediatric newly-diagnosed HGG subgroups. Stratum 1 will enroll patients who are wild-type with respect to H3 K27M, *BRAF*, and *IDH1/2*. Stratum 2 will enroll patients whose tumors are positive for *IDH1/2* mutation and wild-type for *BRAF* and H3 K27M. The primary efficacy endpoint is EFS in both strata and the efficacy of the regimen used in this study will be assessed by comparing the stratum-specific EFS outcome to clinically and molecularly matched historical controls. These historical controls have been derived from Korshunov et al., and from ACNS0822 for Stratum 1 and from Korshunov et al., ACNS0822, ACNS0423, the recent *Cell* meta-analysis paper, and the HERBY trial for Stratum 2.[4] These historical data sets that will be used for these comparisons have already been extracted and will be stored in the COG file share for this study for ease of access at future analysis points. These data will not be updated as these cohorts are quite mature at the time of the design of this study.

Stratum 1:
The following is a description of the historical control cohort used in this stratum.

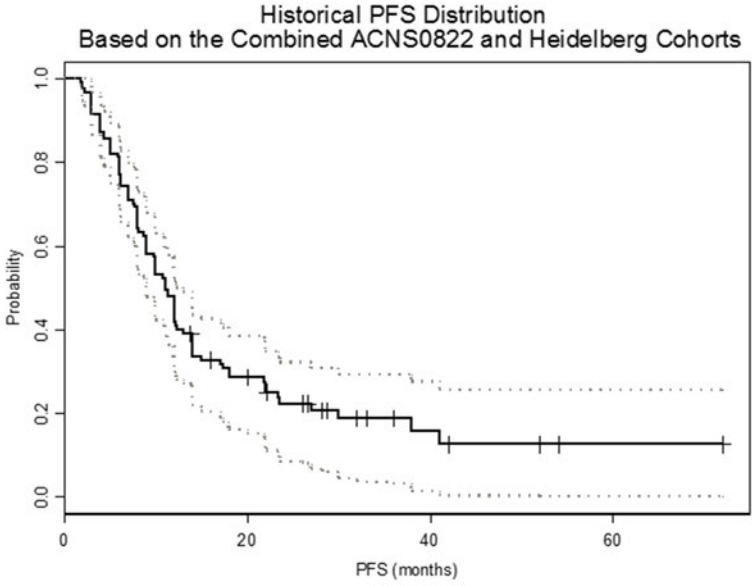
ACNS0822: ACNS0822 is the most recently completed COG phase 2 frontline HGG trial. The phase 2 trial enrolled 90 eligible patients and while patients were randomized among 3 regimens, the results did not indicate any difference among these arms. Thus, for the purposes of this study, the data from these 3 regimens will be combined. Of the 90 eligible patients, 62 had adequate biology information to be included in our analyses and 34 met the molecular eligibility criteria defined as no H3 K27M mutant, *IDH1/2* mutant, or $BRAF^{V600}$ mutant tumors.

Korshunov et al. Cohort (aka Heidelberg Cohort): The second cohort which will be used to construct our historical control group for Stratum 1 is derived from the cohort analyzed by Korshunov et al.[4] This cohort included 140 patients who were aged 3 years and older, had tumors outside the brainstem and had non-disseminated disease. Of these, 84 (60%) were also negative for H3 K27M, *IDH*, and *BRAF* mutations. This group of 84 subjects will be included in the historical control cohort.

To determine if there are systematic differences between these two cohorts that may preclude us from combining them for the purpose of constructing a larger historical control cohort for the proposed trial, we analyzed both of these cohorts simultaneously. The plot below displays the PFS distribution by cohort and suggests no notable differences between these two data sets. The logrank p-value associated with the PFS comparisons is 0.296. There were no secondary malignancies reported as the first event in these cohorts so EFS and PFS are the same.



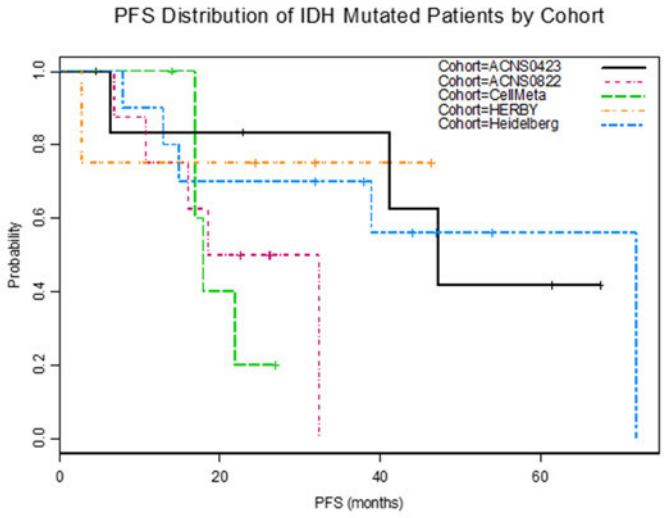
Combining these data into one dataset (n=118), we obtain the following PFS curve which we propose to use as our historical control cohort against which the outcome of the current trial will be compared. This cohort contains 91 progression events with 1-, 2- and 5- year PFS estimates (±se) given as 42.6% (±4.6%), 22.2% (±4.2%), and 12.5% (±4.6%), respectively.



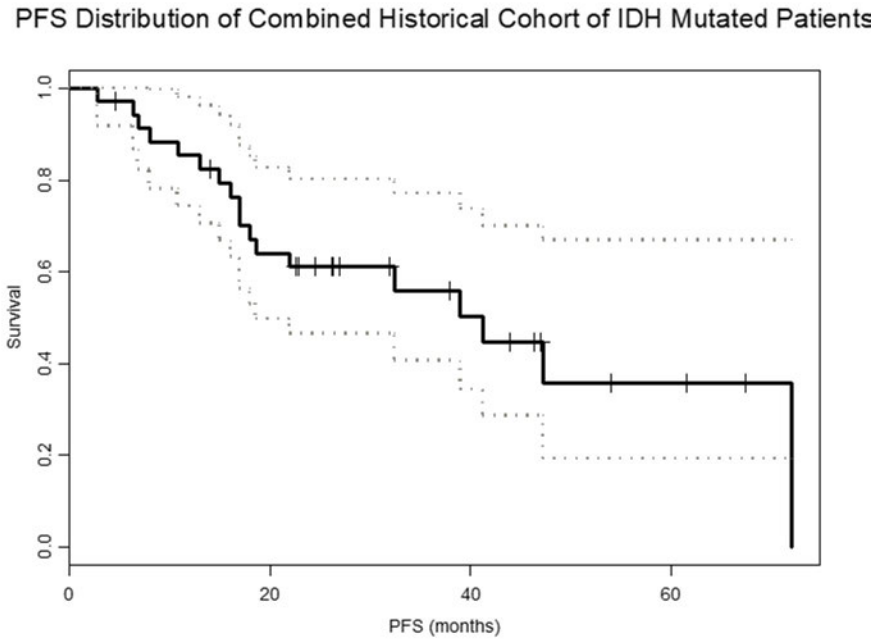
Using the approach proposed by Korn and Freidlin which was further refined by Wu and Xiong, we will employ a group sequential approach based on a 1-sided log rank test to

estimate the sample size and monitor for futility in this stratum.[52, 53] Using the methodology described in Wu and Xiong and the empirical Kaplan-Meier estimate to model the EFS distribution, the design proposed here requires 65 patients to detect a HR=0.55 with 5% type I error and 90% power. HR=0.55 translates to approximately 20% improvement in PFS at 1 and 2 years. The design also stipulates that all patients will be followed for at least 1 year post-accrual completion with an estimated accrual duration of approximately 3 years. Interim monitoring for futility only will be done using an alpha-spending approach based on the gamma family with γ=-4. The expected number of PFS events (total information) during the entire duration of the trial is 35 and we will conduct the first interim analysis starting with the 10th failure, which is expected to occur approximately 2 years after accrual initiation. Subsequently, interim analyses will be conducted approximately annually corresponding with the DSMC reports. We expect to conduct no more than 3 interim analyses.

Stratum 2:
Stratum 2 will enroll patients with *IDH* mutant tumors. Of note, *IDH* mutations are generally mutually exclusive with H3 K27M and *BRAF* mutations. Given the fact that *IDH* mutations generally occur in patients who are in their teenage or early 20s, eligibility is extended to 25 years in this stratum. Due to the rarity of these tumors, historical data are somewhat sparse. In the Heidelberg cohort, only 10 (7.1%) patients had IDH mutations among the 140 patients who were aged 3 years and older, had tumors outside the brainstem and had non-disseminated disease. In the ACNS0822 cohort, 8/62 (12.9%) had *IDH* mutations. *IDH* information was also available from a subset of patients treated on the ACNS0423 study. ACNS0423 was a phase 2 study which preceded ACNS0822. This study enrolled 108 eligible patients with similar eligibility criteria and treated them with temozolomide + RT followed by 6 cycles of temozolomide + lomustine. Among these, *IDH* mutations were assessed in 43 patients and 7 (16.3%) were identified as *IDH* positive. We were also able to obtain data from 6 additional *IDH* patients included in the recent *Cell* meta-analysis paper and 4 patients from the HERBY study (personal communication, Chris Jones). The PFS distributions of *IDH* mutated patients from these 5 studies are given in the Kaplan-Meier (KM) plot below. While there is some variability, these PFS distributions are not statistically different from each other (logrank p-value=0.325). Similarly here as well, PFS and EFS distributions are the same.



We will use the combined group from these 5 cohorts as our historical control. This cohort includes 35 patients and 18 PFS events for patients whose median age is 16.9 years (range 11.7–28). The KM plot of the combined cohort is given below. The estimated 1, 2, and 5 year PFS estimates (±se) are 85.4% (±6.05%), 61.1% (±8.5%), and 35.8% (±11.4%), respectively.



Using the same methodology as in Stratum 1, we will employ a group sequential approach based on a 1-sided logrank test to estimate the sample size and monitor for futility in this stratum. Using the methodology described in Wu and Xiong and the KM estimate to model the PFS distribution, the design proposed here requires 30 patients to detect a HR=0.45 with 10% type I error and 80% power. HR=0.45 translates to approximately 8% improvement in PFS at 1 year and 19% at 2 years. The design also stipulates that all patients will be followed for at least 3 years post-accrual completion with an estimated accrual duration of 2–3 years. Interim monitoring for futility only will be done using an alpha-spending approach based on the gamma family with $\gamma = -4$. The expected number of PFS events (total information) during the entire duration of the trial is 13 and we will conduct the first interim analysis starting with the 5th failure which is expected to occur at the end of accrual if the treatment is effective. Otherwise if the treatment has the same efficacy as historical controls, we expect to observe 6 events 2–2.5 years after actual initiation. Subsequently, interim analyses will be conducted approximately annually corresponding with the DSMC reports. We expect to conduct approximately 3 interim analyses.

9.3 Methods of Analysis

For both strata, the primary analysis for EFS will be based on a 2-sample, 1 sided logrank test. For each stratum we will also consider Cox models that incorporate known prognostic factors as feasible including resection status (GTR vs. < GTR) and tumor grade (Grade 3 vs. 4), etc. to ensure that these variables do not have undue influence on the overall outcome. For patients with measurable disease at baseline, we will also report the objective response rate.

9.4 Evaluability for Toxicity and Efficacy Assessments

All patients who start radiation therapy and receive at least 1 dose of veliparib will be evaluable for toxicity and efficacy assessments. The latter refers to the primary endpoint of EFS and secondary endpoints of objective response and OS.

9.5 Analysis Plan for Exploratory Objectives

For the biology/molecular data, we will provide a frequency table summarizing the number of patients with each aberration/alteration detected in germline and/or tumor samples. For longitudinal plasma samples used to assess circulating tumor DNA, we will summarize the percentage of patients with samples as well as display/summarize any changes in molecular markers. When feasible we will explore the association of these aberrations with EFS/OS and objective response rates via Cox models and fisher exact tests, respectively. We will also explore associations between genetic variants and clinical/demographic variables including age, resection status, histology, etc. For analyses exploring associations of a large number of potential markers with clinical outcome, we will utilize false discovery rate approaches in order to control family-wise error rate.

9.6 Gender and Minority Accrual Estimates

The total estimated sample size of eligible and evaluable patients for this study is 95 patients (65 in Stratum 1 and 30 in Stratum 2). In order to accommodate for possible ineligible and inevaluable patients, we expect that the maximum number of enrolled patients will be 115. The gender and minority distribution of the study population is expected to be:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	4	0	0	6
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	5	5	0	1	11
White	36	40	5	10	91
More Than One Race	0	0	0	0	0
Total	44	49	5	11	109

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0

Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	5	1	0	0	6
More Than One Race	0	0	0	0	0
Total	5	1	0	0	6

This distribution was derived from ACNS0822 and ACNS0423, the two previous COG studies conducted in this patient population.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

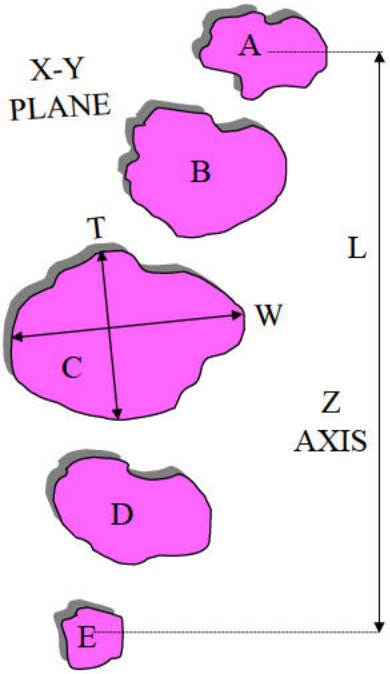
10.2 Methodology to Determine Tumor Measurement

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

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. Either T1, T2 weighted/FLAIR images are used – whichever gives the best estimate of tumor size. The following section describes the methodology.

1. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups. This longest measurement of the tumor is referred to as the width (W).

2. The perpendicular measurements should be determined – transverse (T) measurement, perpendicular to the width in the selected plane.



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

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

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

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

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

4. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted and change in extent/thickness assessed on follow up studies. **Note that patients with leptomeningeal disease are not eligible for enrollment on this study.**

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

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

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

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

10.3 Selection of Target and Non-Target Lesions

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

10.4 Response Criteria for Target Lesions

1. Response criteria are assessed in 2 dimensions – the product of W x T.

2. To assess response/progression, the ratio is calculated:

$$\frac{\text{W x T (current scan)}}{\text{W x T (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence.

4. Response Criteria for target lesions:

   Complete Response (CR): Disappearance of all target lesions.

   Partial response (PR): ≥ 50% decrease in the sum of the products of the two perpendicular diameters of target lesions, compared to baseline measurement.

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

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

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

   Therefore, patients will not be considered to have progressive disease and will not be removed from protocol therapy for radiographic worsening secondary to local tumor enlargement (LTE), defined as increase in maximal bi-dimensional tumor area of 25% or more but less than 50%, and with no new lesions on any MRI performed within 3 months from completion of RT (i.e., on the required MRI 4 weeks after completing RT, or the scan performed prior to Cycle 3 of the Maintenance). Thus, during and for 3 months after completion of RT, patients should only be removed from protocol therapy for progressive disease if there is 50% or more

increase in tumor area (with or without neurological worsening), OR if there is the appearance of one or more new lesions on the MRI outside the radiation port.

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

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

10.5 Response Criteria for Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

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

11.2 Determination of Reporting Requirements

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

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

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

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

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

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease Progression*" in the system organ class (SOC) "*General disorders and administration site conditions.*" Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions"*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero*." Any Pregnancy loss should be reported expeditiously, as **Grade 4** "***Pregnancy loss***" under the "***Pregnancy, puerperium and perinatal conditions***" SOC. Do NOT report a Pregnancy loss as a Grade 5 event since CTEP-AERs recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4 "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List [ASAEL].)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using

multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements – Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at:
https://eapps-ctep.nci.nih.gov/ctepaers.

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.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days –** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days –** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is

an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 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; 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.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG 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.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">7 Calendar Days</td><td>7 Calendar Days</td><td rowspan="2">24-Hour Notification
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1–4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**

11.11 Reporting of Adverse Events for Commercial Agents – CTEP-AERS Abbreviated Pathway

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

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

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

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

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

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

11.12 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.

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 toxicities reported via CTEP-AERS and all Grade 3 and higher Adverse Events. In addition, we will capture all instances of CNS necrosis that are Grade 2 or greater.

12.0 STUDY REPORTING AND MONITORING

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

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

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

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

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

12.3 CRADA/CTA

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.

13.0 SURGICAL GUIDELINES

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

13.1 Neurosurgical Procedures

There are no standard neurosurgical procedures for high-grade astrocytomas. An attempt should be made to perform maximal safe surgical resection. The extent of surgical resection will depend upon the location and growth features of the tumor. It is suggested that navigational guidance (stereotaxy, intra-operative MRI, ultrasound) be used in an effort to guide surgical resection. Patients potentially eligible for this study must undergo at least tissue sampling that results in a pathologic interpretation. **No patient will be eligible for this study without a pathological diagnosis.**

13.2 Definitions of Extent of Resection

Note: An attempt should be made to estimate the volume of the residual tumor in cm^3.

13.2.1 Biopsy Only

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

13.2.2 Partial Resection

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

13.2.3 Subtotal Resection

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

13.2.4 Near Total Resection (Extensive Subtotal Resection)

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

13.2.5 Gross Total Resection

Resection of all visible tumor.

13.3 Imaging Confirmation of Extent of Resection

See Section 16.0 for Neuroimaging Guidelines. All patients must have confirmation of the neurosurgical staging of the extent of resection with a post-operative MRI with and without contrast. It is strongly encouraged that the post-operative imaging of the brain be done within 48 hours of surgery if possible, but if unable to be done at that time (or post-operative changes obscure potential residual tumor) must be done prior to enrollment. The requirement for a post-operative MRI is waived for patients who undergo biopsy only.

13.4 Peri-operative Corticosteroids

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

Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of dexamethasone in divided doses every 6–12 hours. Corticosteroids may be discontinued during the peri-operative period; however, every attempt should be made to taper and discontinue corticosteroid therapy as soon as clinically feasible (7 days).

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Before entering patients on this trial, clinicians should discuss this protocol with their pathologist and provide them with the APEC14B1 protocol and list of the required materials that will need to be submitted for the rapid central pathology screening review.

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed and to request that all HGG patient specimens be forwarded to the COG Biopathology Center (BPC), as required. The BPC will NOT request materials.

14.1 Required Rapid Central Pathology Review

See APEC14B1 and Section 3.1 for required materials for the Rapid Central Screening Review.

The pathologic classification of tumors is becoming increasingly complex since there is considerable variation in the histological features of patients. Central review is therefore critical to ensuring that the diagnosis is accurate and that patients are treated appropriately. Central pathologic review will be performed on all diagnostic specimens (whether resected or biopsied). The classification and grading of the tumors will be performed according to the 2016 WHO Central Nervous System (CNS) criteria. The submission of pathology material shall be made directly from the participating institutions. Results of the review will be given to the treating institution.

If there is a discrepancy between the institutional diagnosis and the diagnosis on the rapid screening central review of a patient, then a discussion between the local and study pathologists will take place to attempt to reach a consensus, however, the decision of the study pathologists will be used to confirm eligibility. At least ONE of the central review pathologists will need to confirm eligibility prior to enrollment. Slides will be stored at the COG BPC for quality control purposes.

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Required Studies

15.1.1 Rapid Central Molecular Screening Review

In patients who have pathology confirmed by central pathology review, Rapid Central Molecular Screening Review will be performed on genomic DNA extracted from FFPE tissue. See Section 3.1.1.4 for details. These specimens are submitted via APEC14B1.

15.2 Optional Studies

15.2.1 Genomic Analysis of Germline DNA

Genomic analysis of germline DNA will be performed in consenting patients. If a patient has consented to optional banking on APEC14B1, we will request use of some of the banked blood sample to study germline DNA on ACNS1721. **If a patient has not submitted a banked blood sample on APEC14B1 but consents to correlative biology studies on ACNS1721, please collect a peripheral blood sample before treatment begins.** Leftover samples will be banked at the COG Biopathology Center.

15.2.1.1 Specimen Requirements

At pre-treatment, please collect 4–10 mL of peripheral blood, **preferably** in a 10 mL *Streck* Cell Free DNA tube. Purple top EDTA tubes may be used if *Streck* tubes are not available at the institution. Please note that *Streck* tubes will not be provided for ACNS1721 correlative studies. Samples should be collected prior to beginning protocol therapy, but can be collected within the first 5 days of treatment if needed.

Note: A minimum of 5 mL of blood is required if using *Streck* tubes to maintain sample integrity.

15.2.1.2 Specimen Processing

The blood should be shipped whole and unprocessed to the BPC on the day of collection. If a specimen cannot be shipped the day of collection, then blood in EDTA tubes should be kept at 4°C while blood in *Streck* tubes must be kept at room temperature. Ship blood on the next working day.

15.2.1.3 Specimen Labeling and Shipping

Use a waterproof marker to label the tube with the COG patient ID number, BPC number, specimen type (blood), and the collection data.

The BPC provides a shipping label to sites in North America. Please access the BPC Kit Management system at https://kits.bpc-apps.nchri.org to print a shipping label. Blood may be shipped Monday through Friday for receipt on Tuesday through Saturday. If blood is shipped on a Friday, please check "Yes" for Saturday delivery.

Include a Specimen Transmittal Form with each shipment.

Please ship blood in EDTA tubes on a cold pack during warm months. Blood collected in *Streck* tubes should not be shipped with a cold pack. Samples should be shipped by FedEx Priority Overnight to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205

Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

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

15.2.2 Genomic, Transcriptomic, and Epigenetic Analysis

In consenting patients, please submit peripheral blood and frozen tumor for the biology studies as outlined in the table below.

15.2.2.1 Specimen Schedule and Requirements

Samples should be collected as outlined below and shipped to the Jabado Lab (see Section 15.2.2.3):

Sample	Amount	Container	Taken at the following time points:
Peripheral blood	5–10 mL per timepoint	*Streck* Cell-Free DNA tubes **preferred**. Purple top EDTA tubes may be used if *Streck* tubes are not available.	• Pre-treatment/diagnosis • At the first MRI post-Chemoradiotherapy • At the end of treatment MRI • During follow-up with the 6, 12, 20, and 30 month MRI (see Section 7.3)
Frozen tumor	Any amount available	Cryovial or Eppendorf tube, without media	Tumor resection (at time of diagnosis)

Note: A minimum of 5 mL of blood is required if using 10 mL *Streck* tubes to maintain sample integrity.

15.2.2.2 Specimen Preparation

Note: Frozen samples (tissue, plasma, buffy coat) may be stored for up to 6 months at -80°C. Samples should not be batched.

15.2.2.2.1 **Peripheral Blood**

Whole blood should be collected **preferably** in 10 mL *Streck* tubes (Cell-Free DNA BCT®). If *Streck* tubes are not available at the institution, K2 EDTA (BD Vacutainer®) tubes can be used and the same centrifugation steps followed. Please note that *Streck* tubes will not be provided for ACNS1721.

Whole blood should be separated into plasma and blood cells by two consecutive centrifugations:

1. Centrifuge at 800g (2900 rpm) at +4°C for 10 minutes to separate blood, buffy coat, and plasma.

2. Remove the top layer of plasma and place in an Eppendorf tube in 1.5 mL aliquots for subsequent centrifugation (Step 5).

3. Remove "buffy coat" (concentrated leukocyte band) and store in plastic screw-cap (cryo)vial or Eppendorf tube at -80°C.

4. Store the lower layer of blood in a separate plastic screw-cap (cryo)vial or Eppendorf tube at -80°C.

5. For the second centrifugation step, centrifuge the supernatant (plasma) from Step 2 at 21000g (15,000 rpm or the maximum speed available) at +4°C for 10 minutes.

6. Remove the resulting supernatant (plasma) and store in a cryovial in 2 mL aliquots at -80°C.

   Optional: The pellet from the centrifugation at Step 5 can be combined with the buffy coat from Step 3.

15.2.2.2.2 **Frozen Tumor Sample**

Frozen tumor samples should be stored in a cryovial or Eppendorf tube, without media.

15.2.2.3 Specimen Labeling and Shipping

Please contact the Jabado Lab at [redacted] before specimens are shipped to obtain a FedEx account number. Specimens should be labeled with the patient ID, tumor location (if applicable), and date and time of collection. For plasma, please note the

time from collection to sample processing if possible. Specimens should be shipped frozen on dry ice to the receiving institution. Ship specimens for overnight, Tuesday through Friday delivery only, with the institutional pathology report, diagnosis, age, and gender of the patient to:

Nada Jabado Laboratory
Attn: [redacted]
Research Institute of the McGill University Health Center
Glen Site
1001 Decarie Blvd.
Rm E01.4380
Montreal, QC H4A 3J1
Canada

15.2.2.4 Site Contact

For questions, please email the following site personnel:

[redacted]
Phone: [redacted]
Email: [redacted]

15.2.2.5 Methodology at the Jabado Lab

Note: If the patient consented to banking, then any leftover specimens will be sent from the Jabado Lab to the COG Biopathology Center for banking.

15.2.2.5.1 **Plasma**

Cell-free circulating DNA (cfDNA) will be isolated from approximately 2.5 mL of plasma obtained from centrifugation of ~5 mL of blood. RNase H-dependent PCR (rhPCR), which is an amplification step specific for mutant copies of genes of interest, will be performed on the isolated DNA. Digital droplet PCR (ddPCR) will be performed on a portion of the resulting products to analyze the presence of mutant and wild-type copies of the genes of interest. Alternatively, direct NGS can be performed on the cfDNA, depending on the quantity and quality of material.

15.2.2.5.2 **Tumor**

DNA and RNA will be extracted from frozen tumor tissue for genomic, transcriptomic, and epigenetic analysis such as Whole Blood Exome Sequencing, Whole Genome Sequencing, Whole Genome Bisulfide Sequencing, transcriptome, and methylation, among other techniques.

16.0 NEUROIMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

16.1 Timing of MRIs and Retrospective Central Imaging Review

Sites are required to submit imaging scans for retrospective central imaging review. To document the initial extent and degree of residual tumor, standard whole brain MRI with and without contrast (gadolinium) must be performed at the following time points:

1. Brain MRI: Pre- and post-operative* MRIs should be performed prior to enrollment onto the study
2. Brain MRI: Prior to each odd-numbered cycle of Maintenance chemotherapy
3. Brain MRI: At the end of therapy
4. Brain MRI: Every 3 months for Year 1 in follow-up (3, 6, 9, 12 months)
5. Brain MRI: Every 4 months for Year 2 in follow-up (16, 20, 24 months)
6. Brain MRI: Every 6 months for Year 3 in follow-up (30, 36 months)
7. Brain MRI: Once yearly for Years 4–10 in follow-up
8. Brain MRI: At progression/relapse (if outside the timepoints noted above)

*It is strongly encouraged that the post-operative brain MRI be done within 48 hours of surgery if possible, but if unable to be done at that time (or post-operative changes obscure potential residual tumor) must be done prior to enrollment. The requirement for a post-operative MRI is waived for patients who undergo biopsy only.

Tumor response assessment will be performed at each site. For all patients, submit all MRI studies with their corresponding reports to the address in Section 16.5. Please note that results from the retrospective central imaging review will not be returned to the site.

16.2 Whole Brain MRI With and Without Contrast

Pre- and post-operative brain MRIs with and without contrast (gadolinium) are required to document the degree of residual tumor. It is strongly encouraged that the post-operative brain MRI be done within 48 hours of surgery if possible, but if unable to be done at that time must be done prior to enrollment. The requirement for a post-operative MRI is waived for patients who undergo biopsy only.

16.2.1 Required Sequences on 1.5T or 3T machine

Pre-contrast:

1. Loc
2. Sagittal T1; 5 mm skip 0
3. Axial T2 FLAIR; 5 mm skip 0
4. Axial DWI; 5 mm skip 0
5. Axial GRE; 2.5 mm skip 0
6. Axial T1; 5 mm skip 0

7. Axial FSE T2; 5 mm skip 0
8. *Strongly recommended if available*: 3D isovolumetric Axial T2 Flair

Post-contrast:

9. Coronal T1 post contrast; 5 mm skip 0
10. Sagittal T1 post contrast; 5 mm skip 0
11. Axial T1 post contrast; 5 mm skip 0
12. *Strongly recommended if available*: 3D isovolumetric T1 post-contrast

16.2.2 Optional Sequences (depending on tumor)

Pre-contrast:

1. Sagittal or coronal FSE T2; 5 mm skip 0
2. Axial DTI
3. Susceptibility weighted imaging (SWI, mIP SWI, filtered phase, magnitude)

Post-contrast:

4. Axial T1 (DSC) or T2* (DCE) perfusion

Notes:

- No fat saturation
- Flow compensation not used on coronal and sagittal T1 post contrast

16.3 Tumor Response Assessment

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

16.4 Extracranial Disease Progression

If imaging obtained for a clinical indication reveals extracranial disease progression (e.g., spinal cord or other organs), submission of diagnostic scans is required.

16.5 Submitting Scans

Submission of Diagnostic Imaging data in digital format is required. Submission of the digital files and reports via TRIAD is preferred; however, if TRIAD has not been enabled at your site, to avoid delays in imaging submission, alternative submission methods are available. Instructions for TRIAD setup can be found in Section 17.0. The files can be submitted via sFTP. Information to obtain an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Sites using Dicommunicator@QARC.org may submit imaging via that application.

Questions regarding the submission of imaging studies and reports should be sent to: DataSubmission@qarc.org.

17.0 RADIATION THERAPY GUIDELINES

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

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities.

To view the ACNS1721 HGG Contouring Atlas, please visit www.qarc.org and under NCI Groups, select COG and follow the link titled "COG Contouring Atlases."

Submission of the radiation therapy treatment plan in digital format as DICOM RT is required. Submission of the digital files and reports via TRIAD is preferred. Instructions for TRIAD setup are provided below. See the IROC Rhode Island website (https://irocri.qarc.org/) for digital data submission information.

Digital RT Data Submission Using TRIAD (if TRIAD is available at your site):
TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM, DICOM RT and other non-DICOM digital files. TRIAD anonymizes and validates the DICOM and DICOM RT images as they are transferred.

TRIAD Access Requirements:

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site user must be on the site's membership roster in RSS/CTSU and be assigned the 'TRIAD site user' role. Users should contact their site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. CRAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

IROC Rhode Island will facilitate the central reviews.

Submission of imaging and RT data via TRIAD is preferred; however, if TRIAD has not been enabled at your site, to avoid delays in imaging submission, alternative submission methods are available. The files can be submitted via sFTP. Information to obtain an sFTP account and submission instructions can be found at www.qarc.org. Follow the link labeled digital data. Sites using Dicommunicator@QARC.org may submit imaging via that application. Submit the Diagnostic imaging scans, along with their corresponding reports, to the address listed in Section 17.9.5.3.

Contact IROC Rhode Island with questions or for additional information.

17.1 Radiation Therapy Timing

Radiation therapy (RT) is to start within 31 days of the definitive surgical procedure (Day 0). To ensure compliance with this requirement, practitioners should not await central pathology review or confirmation of eligibility to initiate RT planning.

Diagnostic MRIs may be used for RT treatment planning if additional MRIs in the treatment position cannot be obtained or if repeating an MRI is likely to result in excessive cost to the patient's family without insurance reimbursement. A separate CT scan is required for all RT planning.

17.2 Radiation Therapy Credentialing

17.2.1 All therapy units used on this protocol must have their calibrations verified by IROC Houston (Radiologic Physics Center). The table in Section 17.3 indicates allowable modes of treatment delivery.

17.2.2 IMRT/VMAT

Institutions treating with intensity-modulated or volumetric-modulated arc therapy (IMRT/VMAT) and not previously credentialed for use of IMRT in COG trials must irradiate IROC Houston's head and neck phantom. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.

17.2.3 Proton Therapy

Each beam line used to treat patients on this study must be approved for clinical use by the IROC Houston QA Center. The proton therapy method may be scattering, uniform scanning, or pencil beam scanning depending on institutional availability and approval status for that mode of operation. Investigators using proton beam radiation must comply with current NCI proton therapy guidelines as outlined in the Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, available at http://rpc.mdanderson.org/RPC/home_page/Proton_guidelines.htm. **Irradiation of the proton head and neck phantom is required as well as baseline proton credentialing.**

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org			
	Treatment Modality			
	3D	IMRT	Proton	Key Information
Facility Questionnaire	X	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	X	To determine if your institution has completed the requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation		X	X	The IMRT head and neck phantom study or proton head and neck phantom provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site (http://irochouston.mdanderson.org).
Baseline Approval			X	Proton centers must complete baseline approval for participation in the protocol. Details about the proton approval process can be found at http://irochouston mdanderson.org.
Credentialing Notification Issued to:				
Institution				Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and COG that all desired credentialing requirements have been met.

17.3 Radiation Therapy Equipment

17.3.1 Equipment Modality

X-rays with nominal energy of 4 MV or greater (3D CRT, IMRT/VMAT), or proton beam (single/double scatter), uniform scanning, and/or pencil beam scanning using single-field uniform dose (SFUD) or intensity-modulated proton therapy (IMPT). Co-60 is not allowed for patients treated on this study.

Table 3.

Equipment	Photons (> 4 MV)	IMRT (4–10 MV)	Protons
Linear Accelerator	X	X	
Proton Beam			X

17.4 Radiotherapy Planning and Treatment Verification Imaging

17.4.1 Pre-Operative Imaging

A contrast-enhanced pre-operative MRI scan is required. A slice thickness less than or equal to 3 mm in the cranial caudal dimension is recommended (see Section

16.2.1). Isovolumetric sequences should be used whenever possible (see Section 16.2.1, #11 and #12). The following sequences are needed to evaluate the full-extent of tumor: T1-weighted (T1W) without contrast, T1-weighted (T1W) with contrast, T2-weighted (T2W) without contrast, and T2W FLAIR.

17.4.2 Post-Operative Imaging (if resection was performed)

17.4.2.1 A post-operative MRI scan (unless only a biopsy was performed) with and without contrast is required for trial entry. A slice thickness less than or equal to 3 mm in the cranial caudal dimension is recommended. The following sequences are needed to evaluate the full-extent of tumor: T1W without contrast, T1W with contrast, T2W without contrast, and T2W FLAIR.

17.4.2.2 Additional sequences which improve the delineation of the operative bed include susceptibility weighted-imaging, T2*, and/or GRE sequences. Diffusion weighted (DWI) and perfusion imaging (Perf) may be useful for delineating residual tumor and these sequences are encouraged. Diffusion tensor imaging (DTI) may be useful for illustrating proximal white matter tracts at risk for tumor spread.

17.4.3 Planning CT Scan

All patients will undergo CT treatment planning for this protocol. Slices of ≤ 0.3 cm thick shall be taken throughout the extent of the irradiated volume. CT (volumetric)-based planning is required to optimize dose to the target volume while protecting normal tissues. In the event that a patient must start emergently with a non-volumetric treatment plan, a volumetric plan must be started within three fractions of the treatment start and the previously utilized beams must be incorporated into the composite plan.

17.4.4 Imaging Registration

Use of fusion image registration software is required.

17.5 Treatment Delivery Verification Imaging

17.5.1 Photons

Weekly orthogonal planar imaging **or** volumetric cone-beam CT (CBCT) imaging is required for verification of correct patient positioning. Daily CBCT or orthogonal planar images are required if a PTV margin of 3 mm is used (see Section 17.9.5.2). If daily CBCT is not possible, then documentation of the use of a head fixation system or verification system is required. Orthogonal AP and lateral images should be used to verify isocenter relative to simulation scans.

17.5.2 Protons

When proton radiation is employed, daily image guidance with either 2-D or volumetric imaging is required. Volumetric imaging for position verification may be in-room kV or MV cone beam or conventional CT imaging. When volumetric

imaging is available for daily treatment verification, a tolerance of no more than 5 mm tissue discrepancy along the beam path within the 20% isodose line is suggested prior to re-planning although this threshold may be relaxed if the patient has been planned with conservative robustness planning parameters. Evaluation of a QA plan based on repeat CT sim is strongly suggested when there is any concern for suspected or visualized changes in anatomy (ventricular shift, changes in body circumference, changes in size or position of the resection cavity, etc.).

17.6 Radiotherapy Target Volumes

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study. Treatment planning will be based on the following definitions. Radiotherapy (RT) volumes for this study will be determined by the collective information (operative note, MRI, CT) that delineates the extent of disease both prior to and following surgical resection or biopsy. Representative cases with pictures and further detail can be found at https://www.qarc.org/cog_protocol_resources.htm.

17.6.1 Photons

17.6.1.1 Gross tumor volume (GTV) is the volume occupied at diagnosis by disease.

17.6.1.2 Clinical target volume (CTV) includes the GTV and sites with potential occult tumor involvement adjacent to the GTV that may be clinically involved.

17.6.1.3 Planning target volume (PTV) is the CTV surrounded by a geometric margin to account for variability in setup, or motion during treatment.

17.6.2 Protons

17.6.2.1 GTV is the same for protons and photons.

17.6.2.2 CTV is the same for protons and photons.

17.6.2.1 PTV is the same for protons and photons.

The planning target volume (PTV) for proton therapy will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center. When proton therapy is used, the PTV will be used for dose reporting and not specifically for treatment planning. **The goal of treatment planning will be CTV coverage at 100% directly with specific measures taken for each specific uncertainty.**

When passive scattering techniques are used, additional beam specific PTVs may be required for planning as the PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator for scattered beams, (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 2–7 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator for scattered beams, setup margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 17.7.6.

When pencil beam scanning techniques are used with scenario-based optimization (also known as robust optimization), the plan may be optimized to CTV as described in Section 17.7.6.2.2. The above defined PTV should be reviewed in either case to confirm sufficient coverage.

17.6.3 Recommended Target Volumes

17.6.3.1 GTV_PreOp: This is the full extent of initially involved tissue apparent on review of the CT, and MR imaging prior to resection. This volume is only defined for resected cases.

17.6.3.2 GTV_Cavity: This is the CSF space that fills the area where parenchymal normal brain resided prior to resection. The resection cavity is best delineated using T2, T2*, and Susceptibility Weighted Imaging (SWI). GTV_Cavity will only be delineated as a target volume in cases where a subtotal resection has been performed.

17.6.4 Required Target Volumes

17.6.4.1 Gross Target Volumes (GTV)

17.6.4.1.1 GTV1

- **Definition:** GTV1 will include all the tissues initially involved with disease and the entire residual tumor defined by the post-operative MRI scans.
- **Imaging used for target volume delineation:** The GTV1 will include both enhancing and non-enhancing areas of the tumor. The GTV1 will take into account any changes in brain anatomy that have occurred as a result of tumor resection and/or CSF shunt placement. T1W, T2W, and FLAIR sequences of the MRI scans should all be reviewed and the sequence that best defines the extent of initial disease should be used to determine the GTV1.

Note – Large Resection Cavities: Portions of the surgical cavity may represent areas cut due to surgical approach and not in contact with tumor. Coverage of the entire surgical cavity may result in excessively large treatment volumes which do not reflect an at risk region for tumor spread. The inclusion of GTV cavity in GTV1 is at the discretion of the treating radiation oncologist.

Note – Surgical Tract: In deep seated brain tumors where a substantial amount of normal brain parenchyma is traversed in the surgical approach, the treating radiation oncologist may consider the exclusion of the surgical tract if the surgical tract extends beyond the pre-operative tumor volume defined by GTV PreOp delineated on the pre-operative brain MRI.

17.6.4.1.2 GTV2

- **Definition:** GTV2 will include only the area of residual disease based on the post-operative MRI scans. The GTV2 should exclude regions of residual tumor which are within 5 mm proximal to either the brainstem or optic chiasm. This volume is not defined for cases that are completely resected as GTV1 would be equivalent to GTV2.
- **Imaging used for target volume delineation:** The GTV2 will include both enhancing and non-enhancing areas of the tumor. The GTV2 will take into account any changes in brain anatomy that have occurred as a result of tumor resection and/or CSF shunt placement. T1W, T2W, T2W FLAIR, DWI and Perf sequences of the MRI scans should all be reviewed and the sequence that best defines the extent of residual disease should be used to determine the GTV2.

Note: A 3 mm isotropic expansion of the brainstem is useful for exclusion of the GTV2 volume. Areas of restricted diffusion or increased perfusion should be considered highly likely to harbor residual tumor and should be included in the GTV2 volume.

17.6.4.2 Clinical Target Volume (CTV)

- **Definition:** The CTV includes the GTV with an added margin that is intended to treat subclinical microscopic disease and is anatomically confined. Anatomically confined that the CTV may exclude the inner table of the bony calvarium,or the operative cavity (GTV_Cavity).

17.6.4.2.1 CTV1

- **Primary supratentorial tumors:** CTV1 will be expanded in an anisotropic fashion by 1–1.5 cm. A 1 cm expansion is recommended. A 1.5 cm expansion is appropriate when GTV1 is in close proximity to a major white matter tract and this area is at increased risk. When white matter tracts are deemed at risk, the CTV1 may be anisotropic to illustrate the directionality of that tract. For example, if a deep seated temporal lobe tumor is in close proximity to the medial longitudinal fasciculus, the CTV1 would extend 1.5 cm in the anterior posterior direction and would be more conservative in areas of grey matter greater than 1 cm distal to GTV1.
- **Primary infratentorial tumors (cerebellar, non-brainstem):** CTV1 will be expanded in an anatomically constrained anisotropic fashion by 1–1.5 cm. Care should be taken to include the middle cerebellar peduncles when the primary tumor is in close proximity.

Note – Large Resection Cavities: CTV1 may exclude the volume created by a 3 mm contraction of the GTV Cavity volume when the conditions specified above in Section 17.6.4.1.1 are met. The exclusion of the operative cavity in cases with extensive surgical resections is at the discretion of the treating radiation oncologist. In cases where the at-risk region is unclear, please contact the radiation oncology PIs.

Note – Surgical Tract: The CTV should be allowed to extend into the proximal aspect of the surgical tract to allow for potential inaccuracies in registration, brain shift, or distortions in brain anatomy following resection. The CTV should not extend beyond the bony margins of the calvarium.

17.6.4.2.2 CTV2

- **Definition:** CTV2 will include the GTV2 plus a 0.5 cm margin in all dimensions. The CVT2 should exclude regions of residual tumor which are within 5 mm proximal to either the brainstem or optic chiasm.
- This volume is not defined for cases that are completely resected.
- **Primary supratentorial tumors:** CTV2 will be expanded in the cranial and caudal directions by 0.5–1 cm. For residual disease abutting major white matter tracts, a 1 cm expansion may be appropriate. When GTV2 is not adjacent major white matter tracts, a 0.5 cm is recommended. For example, if an

incompletely resected occipital lobe tumor is in close proximity to the corpus callosum, the residual disease should be expanded 1 cm along the callosum but only 0.5 cm into adjacent grey matter >0.5 cm distal from residual disease.

- **Primary infratentorial tumors (cerebellar, non-brainstem):** CTV2 will be expanded in an anatomically constrained anisotropic fashion by 0.5–1 cm. CTV2 should not extend within 5 mm of the brainstem even when residual disease is noted.

Note – Defining Anisotropic CTV Margins: DTI may aid the definition of CTV1 and CTV2 as it will nicely delineate the major white matter tracts. Major white matter tracts include but are not limited to arcuate fasciculus (superior longitudinal fasciculus), superior and inferior occipito-frontal fasciculi, cingulum, uncinate and inferior longitudinal bundle, callosal tracts and corona radiata.

17.6.4.3 Planning Target Volume (PTV)

- **Definition:** The PTV includes the CTV with an added margin that is intended to account for patient movement and setup variability. While beam specific PTVs may be required for passive scatter technique plans, the PTV used for dose reporting (PTV1 and PTV2) should be created based on isotropic expansions as defined below.

17.6.4.3.1 PTV1

- PTV1 will include the CTV1 plus a 3–5 mm margin in all dimensions. The PTV will extend beyond bone margins, but shall not extend 3 mm beyond the proximal skin surface. A 3 mm expansion from CTV1 is recommended for all intracranial targets (supra- and infratentorial).

17.6.4.3.2 PTV2

- PTV2 will include the CTV2 plus a 3–5 mm margin in all dimensions. The PTV may extend beyond bone margins, but shall not extend beyond the skin surface. A PTV2 is not defined for gross totally resected intracranial tumors (i.e., if there is not a CTV2, there will not be a PTV2).

17.7 Radiation Therapy Dose

17.7.1 Prescription

All radiotherapy plans should be prescribed to a prescription isodose line encompassing the relevant target volume. Integrated boost radiotherapy plans are not permitted.

17.7.2 Dose Definition

Photon dose is specified in Gray (Gy)-to-muscle. For proton beams, the absorbed dose, ICRU 78's DRBE, is specified in Gy (RBE), using a standard RBE of 1.1 with respect to Cobalt-60. Cobalt-Gray-Equivalents are equal to Gy RBE when an RBE factor of 1.1 is used.

17.7.3 Fractionation

The protocol-specified dose per fraction is 1.8 Gy. The treatment should be limited to one fraction per day. Five fractions should be given per week. There may be an exception if a department is closed on a major holiday but an effort should be made to minimize days missed. Efforts should be made to minimize the occurrence of orphan fractions (one fraction at treatment start at the end of a week or a solitary fraction the last week of therapy).

17.7.4 Tissue Heterogeneity

Calculations that take into account tissue heterogeneity are required for CT-based planning techniques to generate dose distributions and treatment calculations from CT densities. When protons are used, tissue heterogeneity calculations should be performed with the CT-based treatment planning system to generate dose distributions from the proton relative stopping power. Proton therapy should be used with extreme caution when any of the treatment beams traverse critical structures such as the brainstem or optic apparatus.

17.7.5 Target Prescription Dose Guidelines

Supratentorial and infratentorial primary brain malignant gliomas will receive a total dose of between 54.0 and 59.4 Gy in 30–33 fractions over 6–7 weeks.

17.7.5.1 **Gross Total Resection:** The total dose will be 54.0 Gy if a gross total resection has been performed.

17.7.5.2 **Incomplete Resection:** If the tumor has not been completely resected, the residual disease will be boosted to a total dose of 59.4 Gy.

17.7.5.3 **Dose to PTV1 and PTV2:** All patients receive a total dose of 54.0 Gy to PTV1. Patients with an incomplete resection receive an additional dose of 5.4 Gy to PTV2.

17.7.6 Coverage Goals

17.7.6.1 **Photon Planning:** At least 95% of the protocol-specified dose should encompass 100% of the PTV1, and the maximum dose to PTV1 in the absence of PTV2 should be no greater than 110% of the protocol dose for PTV1 as evaluated by DVH. When optic nerve and chiasm constraints are at risk of being exceeded secondary to attempts to cover PTV2 with 5940 cGy, relaxed coverage of PTV2 is permitted such that

at least 95% of the protocol specified dose should encompass 95% of PTV2.

17.7.6.2 **Proton Planning:** At least 95% of the protocol-specified dose should encompass 100% of the CTV1, and the maximum dose to PTV1 in the absence of PTV2 should be no greater than 110% of the protocol dose for PTV1 as evaluated by DVH. When optic nerve and chiasm constraints are at risk of being exceeded secondary to attempts to cover CTV2 and PTV2 with 5940 cGy, relaxed coverage of CTV2 and PTV2 is permitted. For protons, the PTV should be used to confirm appropriate coverage regardless of planning technique utilized. Two methods are acceptable for evaluating sufficient coverage according to various treatment delivery uncertainties. The same criteria for coverage will be used for proton and photon plans.

17.7.6.2.1 **Geometric margins with static dose cloud approximations:** For scattered and uniform scanning beams, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and setup and internal margins (SM and IM). These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the setup and internal margins (SM and IM). The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. Most proton centers use 3.5% of the maximum water-equivalent depth of the CTV to account for CT HU uncertainty and then add another 3 mm to account for uncertainties in beam range calibration and compensator fabrication. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should ensure proximal coverage of the target volume. A PTV should be created by a uniform expansion from CTV for reporting purposes. The expansion margin should be consistent with SM and IM and is typically 3 mm for a static target volume when daily imaging is performed.

17.7.6.2.2 **Scenario-based robust planning:** Scenario-based margins are a method for robust planning under setup uncertainty where the plan is optimized using a sum of a plan evaluation criterion over a set of scenarios simulating various geometric perturbations and changes in tissue density within a predefined range. Penalties in the voxel-wise summands are weighted by a distribution of coefficients defined such that the method is mathematically equivalent

to the use of conventional geometric margins if the scenario doses are calculated using the static dose cloud approximation. Scenarios are typically discretized into variations in setup and range uncertainty. Setup uncertainty scenarios should mirror the expected variations in setup (3–5 mm for this study) that would be accounted for using the PTV concept. Specifically, if the expected setup uncertainty is 3 mm, then 3 mm variations in the anterior/posterior, left/right and cranial/caudal dimension should be evaluated across all combinations. Likewise, variations in proton range are accounted for across a range of values for tissue density expected within normal clinical practice to account for organ motion, particle range uncertainty and tissue density heterogeneity variations. Range error variations have been suggested to vary by 3–5% and should be considered for the nominal case and undershoot/overshoot scenarios.

17.7.6.3 When targets are superficial the PTV is often modified to not come within 3 mm of the skin. As a result, shallow planning target volumes may come within close proximity to clinical or gross tumor volumes. A potential exception is when the range margin is smaller than the PTV expansion (e.g., 3 mm). As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

17.7.7 Treatment Delays and/or Interruptions

No treatment breaks in the radiation therapy component of this combined modality treatment are recommended or anticipated. Skin reactions should be treated supportively. Low blood counts are generally related to systemic therapy and are not caused or worsened by local field brain RT. In the case of severe or unusual toxicities, the radiation oncology co-PI or study chair should be notified. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation (RT-2 form – see Section 17.9.4).

17.7.8 Treatment Technique

17.7.8.1 Two-dimensional planning is not allowed in this study and, as such, a volumetric 3DCRT, IMRT, or proton plan should be used at therapy initiation.

17.7.8.2 Patient Position and Immobilization

Reproducible setups are critical and the use of immobilization devices such as a short mask are recommended for all pediatric patients and required for patients being treated with IMRT or proton therapy.

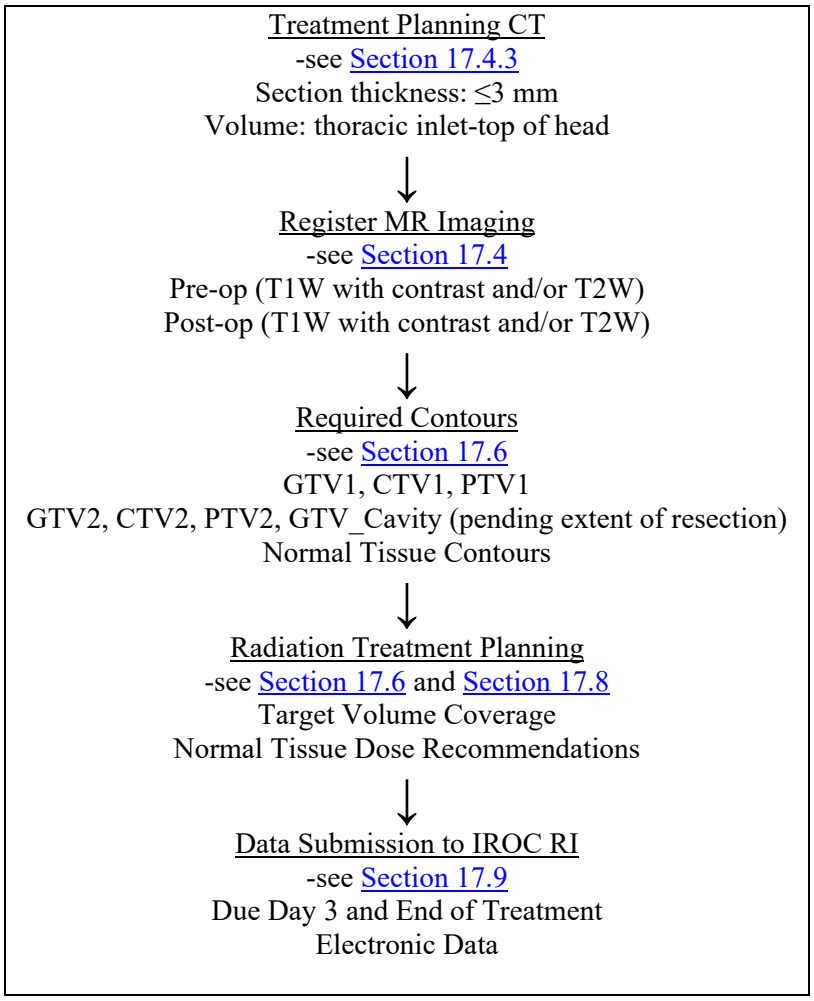
17.7.8.3 Beam Configuration

- 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 often required to minimize dose to normal tissue.
- When protons are used, efforts should be made to limit the distal edge of multiple beams from ranging out within the same geometric region adjacent a critical structure (brainstem, optic apparatus). Multi-field arrangements which have hinge angles > 60 degrees between each beam may limit the potential for distal edge convergence on critical structures such as the brainstem.[54]
- Scenario based plan optimization strategies (see Section 17.7.6.2.2) may be useful in evaluating beam position for the most robust beam arrangement to expected setup variations.
- When post-operative epidural fluid collections or large air cavities are present, photon treatment is recommended as large variations in range uncertainty may preclude target coverage or result in excess radiation dose to at risk critical structures.

17.7.8.4 Beam Modifiers

- **Field Shaping:** Multi-leaf collimators are to be used for beam shaping. Apertures for protons will be done with either brass or cerrobend apertures or proton-specific multi-leaf collimation for scattered and uniform scanning beams. Pencil beam scanning does not require additional accessories for field shaping although apertures to further refine beam penumbra are allowed when critical structures are at risk.
- Means of obtaining a more uniform photon dose distribution are encouraged (i.e., wedges used with 3D conformal radiotherapy, compensators with non-MLC based IMRT, etc.).
- Special considerations: Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

17.7.9 Treatment Planning Procedures



17.8 Organs at Risk

The organs 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 (see Section 17.9.4). In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines.

17.8.1 Cochleae

- D50% < 3500 cGy – Goal (single cochlea)
- D50% < 2000 cGy – Preferred (single cochlea)
  - Comment – There is no dose limit for the cochleae.
  - Structure definition - Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

17.8.2 Optic Globes

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

17.8.3 Spinal Cord

- D0.1cc < 5400 cGy – Maximum
  - Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage during treatment of PTV1.
  - 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; 2 mm, n=30; 2.5 mm, n=24; 3 mm, n=20). Using these guidelines, only the superior-most 6 cm of anatomic spinal cord is contoured.

17.8.4 Optic Nerves and Chiasm

- D50% < 5400 cGy and D0.1cc < 5600 cGy – Maximum
  - Comment – Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the coverage may be relaxed. Recall that tumor components within 5 mm of the optic apparatus should be excluded from GTV2 (see Section 17.7.6.1).
  - 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. A T1

MRI with < 5 mm slices or 3D volumetric T1 is recommended for appropriate target definition.

17.8.5 Optic Nerves and Chiasm PRV

- D50% < 5600 cGy and D10% < 5800 cGy – PRV
  - Comment – Effort should be made to avoid direct treatment of the optic PRV without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the coverage may be relaxed for PTV2 such that 95% of PTV2 receives > 95% of the prescribed boost dose. Recall that tumor components within 5mm of the optic apparatus should be excluded from GTV2 (see Section 17.7.6.1).
  - Structure definition – The optic nerve and chiasm should be combined and expanded uniformly 3 mm.

17.8.6 Brainstem

- D50% < 5240 cGy, D10% < 5600 cGy and D0.1cc < 5880 cGy – Goal
  - Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the coverage may be relaxed for PTV2 such that 95% of PTV2 receives > 95% of the prescribed boost dose (see Section 17.7.6.1).
  - Structure Definition - The brainstem may be contoured on the treatment planning CT or MR and will include the midbrain, pons, and medulla. The cranial extent will be inferior to the third ventricle and optic tracts. The caudal extent will end at the foramen magnum.

17.9 Dose Calculations and Reporting

Table 4.

Required DVH Reporting Data	
Description	**Standard Name**
Right Optic Nerve	OpticNrv_R
Left Optic Nerve	OpticNrv_L
Optic Chiasm	OpticChiasm
Brainstem	Brainstem
Spinal Cord	SpinalCord
Right Cochlea	Cochlea_R
Left Cochlea	Cochlea_L
Body	External
Unspecified Tissue	
GTV_Pre-Op (if required)	GTV_Pre-Op
GTV_Cavity (if required)	GTV_Cavity
GTV1	GTV1
CTV1	CTV1
PTV1	PTV1

GTV2 (if defined)	GTV2
CTV2 (if defined)	CTV2
PTV2 (if defined)	PTV2

17.9.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy 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. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record Form.

17.9.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The 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. A DVH for "Body" shall also be submitted to enable calculation of the required volumes. "Body" is defined as the outer contour of the patient on the treatment planning CT data set.

17.9.3 Treated Volume (mL), Irradiated Volume (mL) and Conformity Index (CI)

The treated volume (TV) is the tissue volume that receives therapeutic dose. For the purpose of this protocol this would include the prescribed total dose of either 54 Gy or 59.4 Gy and 95% of the prescribed dose would be either 56.4 Gy or 51.3 Gy. This information may be used by the investigators, along with the absolute volume of the PTV, to calculate the conformity indexes (CI) CI100% and CI95%, respectively. The irradiated volume (IV) is the tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance. The descriptive statistics for these and other tissue volumes maybe used for correlation with unusual side effects or to develop practical guidelines for future high-grade brain tumor protocols.

Table 5.

Required Volumes to Report (mL)
TV95%=V56.4Gy
TV100%=V59.4Gy
IV35=V35Gy
IV45=V45Gy
IV54=V54Gy
PTV1/2
CTV1/2
GTV1/2
Entire Brain
Unspecified Tissue

17.9.4 Quality Assurance Documentation

Institutions are required to submit the treatment plan as DICOM RT. Radiation therapy planning digital data submissions must include the treatment planning CT and MRI, structures, plan, and dose files. MRI time points and sequences required for digital data submission include the pre-operative T1W, T1W with contrast, T2W and T2 FLAIR sequences while the post-operative sequences should include T1W, T1W with contrast, T2W, and T2 FLAIR.

Submission by TRIAD is preferred (see Section 17.0). Alternatively, sites may submit data sFTP. Instructions for data submission by sFTP are on the IROC Rhode Island web site at http://irocri.qarc.org/ under "Digital Data." All items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data or submitted separately.

Please submit the following data within 3 days of the start of radiation therapy, detailed treatment data shall be submitted for on treatment review.

17.9.5 Submissions

17.9.5.1 External beam Treatment Planning System

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- MRI studies that have been fused with the planning CT are required to be submitted along with the digital RT data. The corresponding spatial registration files should also be submitted, if available.

17.9.5.2 Supportive Data

- All diagnostic imaging and reports used to plan the target volume. This includes CT or MRI PRIOR to attempted surgical resection of the primary tumor.
- For protons, a description of the rationale for the PTV margins.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC RI 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.
- RT-1/IMRT Dosimetry Summary Form; or Proton Reporting Form (whichever is applicable).

17.9.5.3 Within 1 week of the completion of radiotherapy, the following data shall be submitted for all patients:

- The RT-2 Radiotherapy Total Dose Record form.

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas and reference points.
- Documentation listed above showing any modifications from original submission. Data not included with the digital submission should be forwarded to:

IROC Rhode Island
Building B, Suite 201
640 George Washington Highway
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Email: DataSubmission@qarc.org

Questions regarding the dose calculations or documentation should be directed to:
COG Protocol Dosimetrist
IROC Rhode Island
Phone: (401) 753-7600
Email: physics@qarc.org

17.10 Definitions of Deviations in Protocol Performance

Deviation Type	Variation Acceptable	Deviation Unacceptable
Prescription Dose	Prescribed or computed dose for PTV1 or PTV2 differs from protocol specified dose by 6–10%	Prescribed or computed dose for PTV1 or PTV2 differs from protocol specified dose by > 10%
Dose Volume Compliance	- 95% isodose covers < 100% but > 95% of CTV1 (0–54 Gy) **or** - 0–10% PTV1 or PTV2 receives > 110% of the prescription dose	- 90% isodose surface covers < 100% of CTV1 (0–54 Gy) **or** - > 10% of PTV1 or PTV2 receives > 110% of the prescription dose
Volume	CTV1 margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion, without written or scenarios outlined that permit reduced CTV1 margins	CTV1 does not encompass MR-visible residual tumor (0–54 Gy)
Organs at Risk	Dose to any OAR exceeds the goal dose stated in Section 17.8.	Dose to any OAR exceeds the maximum dose stated in Section 17.8.

17.11 Patterns of Failure Evaluation

The patterns of failure for patients with localized high grade glioma may be described as local, distant, or a combination of local and distant and are based primarily on imaging

evaluation of the neuraxis, radiotherapy isodose lines, timing, and imaging appearance at failure relative to the first post-RT baseline MRI. The monitoring of EFS will assess the rate of failure. Local failure is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Determining the patterns of failure will require an assessment of tumor recurrence with respect to targeting and dosimetry. Failure may be described as in-field, marginal or out-of-field when focal irradiation techniques are used. Out-of-field failure is recurrence that occurs entirely outside of the CTV and is synonymous with distant failure. In-field failure is recurrence that originated entirely within the volume that was targeted to receive the prescription dose (CTV). Marginal failure is recurrence originating on the margin of the volume targeted to receive the prescription dose (CTV) and may be described in terms of location or the dose received. There is no universally accepted analytical method to assess pattern of failure and to determine whether failure is in-field, marginal or out-of-field. The pattern of failure will be assessed qualitatively and quantitatively by registering MR data obtained at the time of failure to the dosimetry from the original treatment plan. Failures will be determined qualitatively to be "in-field" when the recurrence appears to have originated from within and remains confined to the CTV, "marginal" when a portion of the recurrence is within the CTV but the majority of the recurrence is outside of the CTV, "distant" when the recurrence does not involve the CTV. Recurrences will be quantitatively categorized as in-field, marginal, or out-of-field based on the proportion of the recurrence that received at least 95% of the prescription dose. This requires contouring of the recurrence and computation of the dose-volume histogram. Marginal failure occurs when between 20 and 80% of the recurrence volume receives more than 95% of the prescription dose, thus, in-field failure occurs when more than 80% of the recurrence volume receives more than 95% of the prescription dose and out-of-field failure occurs when less than 20% of the volume received more than 95% of the prescription dose. Any method has significant limitations, however, since the point of origin for tumor recurrence cannot be ascertained with absolute certainty and does not explicitly determine marginal failure.

Imaging appearance at local failure will be classified as to whether the failure was called due to a new area of enhancement on T1W post contrast MRI outside of the treatment field, enlargement of a previously contrast enhancing mass lesion greater than 25% of the product of the perpendicular diameters (or sum of the product of the perpendicular diameters if multiple contrast enhancing areas are present on the post-RT baseline scan), increasing steroid requirements with stable/smaller tumor size, clinical deterioration not due to treatment, pathologically proven treatment failure with residual viable tumor (greater than 70% of biopsied specimen), or other undefined reason for calling treatment failure. The timing of treatment failure should be classified as either less than 12 weeks or greater than 12 weeks following radiotherapy completion.

Distant failure is defined as the appearance of tumor at sites other than known prior sites of disease. Distant failure most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Distant failures may be further classified according to the type (leptomeningeal, nodular, and/or infiltrative flair abnormalities in areas beyond the 20% isodose line) not attributable to treatment effect. Combined local and distant failure is defined when evaluation of the entire neuraxis reveals local and distant failure.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for ACNS1721 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
  Note: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab
→Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX II: YOUTH INFORMATION SHEETS

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

ACNS1721

A Study of the Drug Veliparib with Radiation Therapy in Patients with Newly-Diagnosed High-Grade Glioma

1. We have been talking with you about your cancer. The type of cancer you have is called high-grade glioma. High-grade glioma (HGG) is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have HGG. 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 certain type of treatment will help to keep your cancer away for a longer length of time than the normal treatment for this disease.

3. Patients who are part of this study will be treated with radiation (X-rays) followed by anti-cancer medicines.

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 you get a treatment that works better to get rid of the cancer than the normal treatment. But we don’t 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.” A risk to you in this study is bad health problems from the anti-cancer medicines. If this happens you may need treatment for the problems. There is the risk that the cancer may grow back while you are taking the anti-cancer medicines. There is also a risk that the cancer may spread into other areas of your brain or spine. Other things may happen to you that we don’t yet know about.

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

7. We are asking your permission to collect extra blood and tumor tissue. We want to see if there are ways to tell how the cancer will react to treatment. These samples would be taken when other standard blood tests are being done, so there would be no extra blood draws. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

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

ACNS1721

A Study of the Drug Veliparib with Radiation Therapy in Patients with Newly-Diagnosed High-Grade Glioma

1. We have been talking with you about your cancer. The type of cancer you have is called high-grade glioma. High-grade glioma (HGG) is a type of cancer that grows in the brain. The words "high-grade" mean that the tumor is growing and spreading quickly. 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 HGG. 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 certain type of treatment will help to keep your cancer away for a longer length of time than the normal treatment for this disease.

3. Patients who are part of this study will be treated with radiation (X-rays) followed by anti-cancer medicines.

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 you get a treatment that works better to get rid of the tumor than the normal treatment. But we don't 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." A risk to you in this study is bad health problems from the anti-cancer medicines. If this happens you may need treatment for the problems. There is the risk that the tumor may grow back while you are taking the anti-cancer medicines. There is also a risk that the tumor may spread into other areas of your brain or spine. Other things may happen to you that we don't yet know about.

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

7. We are asking your permission to collect extra blood and tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

APPENDIX III: DETAILS OF RAPID CENTRAL PATHOLOGY AND MOLECULAR CENTRAL PATHOLOGY REVIEW

Central Pathology Review

Consistent with all prior COG HGG studies, patient eligibility for this trial will be limited to tumor histology consistent with anaplastic astrocytoma or glioblastoma according to the current 2016 World Health Organization (WHO) classification.[38]

The coordination of the central pathology review will be performed by the Children's Oncology (COG) Biopathology Center (BPC), at the Research Institute of Nationwide Children's Hospital, in Columbus, Ohio. The BPC is a CAP certified biorepository and has affiliated CAP/CLIA-certified Histology, Anatomic Pathology, and Cytogenetic/Molecular Genetics laboratories within the Department of Pathology and Laboratory Medicine at Nationwide Children's Hospital. The BPC already performs centralized testing for COG Acute Lymphoblastic Leukemia, Neuroblastoma, and Central Nervous System (CNS) committees. The Biopathology Center serves as the COG effector arm of the COG Pathology Discipline Committee and the biorepository for COG solid and liquid tumors. The BPC is directed by Dr. Nilsa Ramirez, while centralized laboratory testing for the BPC is directed by Dr. Julie Gastier-Foster.

Patients diagnosed with HGG locally will be required to consent to the COG Every Child protocol (APEC14B1) to allow for the pre-screening part of the protocol prior to enrolling on the treatment protocol. After consent is obtained, formalin-fixed paraffin embedded (FFPE) material and, if available, fresh tumor tissue will be submitted directly to the COG Biopathology Center. Patients will also have the option of submitting additional material for biology studies via ACNS1721 or consenting to the banking of any leftover material from the specimens collected for the required studies for tumor banking and research studies through the Every Child Protocol.

Details of required specimens for submission can be found in Section 3.1.1.4. Required samples should be shipped with the corresponding pathology report for central neuropathology review by the treating institution. Central Neuropathology review will be performed by Dr. Chris Fuller, State University of New York Upstate Medical University (SUNY Upstate), with Dr. Chris Pierson, Neuropathologist at Nationwide Children's Hospital in Columbus, Dr. Bonnie Cole at Seattle Children's Hospital in Seattle, or their designees acting as backup reviewers.

Slides will be reviewed to confirm the presence of histological features consistent with anaplastic astrocytoma or glioblastoma according to the current 2016 World Health Organization (WHO) classification. Consistent with all prior COG HGG trials, only patients with a histological diagnosis compatible with anaplastic astrocytoma or glioblastoma are eligible for this trial. Difficult cases will be discussed among the study neuropathologists so as to achieve a consensus review diagnosis.

Histone H3 K27M immunohistochemistry

The testing for Histone H3 K27M IHC will be performed by the Department of Pathology and Laboratory Medicine at the Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, OH. Under the direction of Dr. Sarangarajan Ranganathan, the Pathology Department houses Histology/Anatomic Pathology and Clinical Pathology laboratories, which are CAP/CLIA certified (CLIA ID number: 36D0656333; CAP Laboratory number: 1667801; Cincinnati BioBank CAP Biorepository number: 8678477; Date of validation: 01/27/2016). Dr. Christine Fuller at SUNY Upstate will review the H3 K27M immunohistochemistry results in conjunction with H&E images (to confirm tumor content for all testing). The CCHMC Pathology Department routinely performs H3 K27M immunohistochemistry for clinical

diagnostic purposes, as well as for molecular classification of samples for the Diffuse Intrinsic Pontine Glioma (DIPG) Registry.

IHC using a Histone H3 K27M mutant-specific antibody will be undertaken on 5 µm sections of formalin-fixed paraffin-embedded (FFPE) tumor tissue as previously described.[1] With Amendment 3A, a commercially available primary monoclonal antibody to Histone H3 K27M (EPR18340, Abcam, Cambridge, MA, USA; catalog # ab190631, or subsequent equivalent) will be applied at a concentration of 1:1000 with diaminobenzidine (Ultraview DAB) as the chromogen to reveal antigen-antibody complexes. The assay is performed on the Ventana Benchmark Ultra (Tucson, AZ). Appropriate positive and negative controls will be used.

H3 K27M IHC sections will be scored for tumor cell nuclear positivity, as this represents the presence of H3 K27M mutation within the respective tumor sample. Cytoplasmic and membranous staining of tumor cells is not specific and will not constitute an H3 K27M-mutated tumor. In H3 K27M mutant gliomas, the mutation is generally present in all tumor cells; therefore tumors with scattered nuclei comprising 5% or fewer of tumor nuclei are not regarded as positive.

Results will be presented to treating institutions as positive (H3 K27M mutant) or negative (H3 K27M wildtype) by Medidata RAVE notification. In addition, the report will include the histopathological diagnosis (glioblastoma, anaplastic astrocytoma) according to the World Health Organization (WHO) 2016 CNS Tumor Classification. The treating physician will communicate results to patients.

The H3 K27M immunohistochemistry assay was previously optimized and validated in the Histology/Anatomic Pathology laboratory in the Department of Pathology and Laboratory Medicine at Cincinnati Children's Hospital Medical Center for physician ordering and testing following College of American Pathologists (CAP)/CLIA standards. The laboratory follows all criteria required for the set-up and validation of antibodies as established by the CAP and CLIA. The anti-H3 K27M antibody was validated according to CAP/CLIA guidelines using a range of dilutions and pretreatment conditions on a Ventana Benchmark Ultra immunostainer. DIPG and other HGG tissue samples with previously documented H3 K27M mutant positive status (inclusive of cases with documented mutations of H3.3, H3.1, and H3.2) served as positive controls while the secondary antibody was omitted for negative controls. Upon completion of the optimization runs EDTA pretreatment and an antibody dilution of 1:1000 were considered optimal. Individual FFPE slides from 20 HGG samples (with known H3 K27M status) were stained under the optimized conditions. All known H3 K27M mutant positive cases showed diffuse strong nuclear positivity with H3 K27M IHC (11 out of 11 cases with majority of tumor cell nuclei staining positive), while all known H3 K27M wildtype cases show absent nuclear positivity for this same IHC (9 out of 9 with 5% or fewer tumor cell nuclei staining positive). Note that the validation of this H3 K27M mutant-specific monoclonal antibody (EPR18340, Abcam, Cambridge, MA, USA) was essentially identical to that performed for the previously-used H3 K27M monoclonal antibody (SAB5600095, Sigma-Aldrich, St Louis, MO, USA); with Amendment 3A, the former antibody is replacing the latter, as SAB5600096 manufacturing has been discontinued. It is not completely uncommon for IHC antibodies to be discontinued and replaced by an equivalent antibody. Therefore, with Amendment 3A, a commercially available primary monoclonal antibody to Histone H3 K27M, EPR18340, Abcam, Cambridge, MA, USA; catalog # ab190631, or subsequent equivalent, will be utilized for the H3 K27M IHC assay.

Central pathology review on all samples will initially only include histopathological review and H3 K27M IHC. The results will be reported to the clinical PI within 7 days of receipt of all required tissue. Patients will receive results from the treating physician. Histopathologically confirmed HGG samples that are negative for nuclear H3 K27M staining will proceed to further molecular characterization (Mutational Analysis of *BRAF* and *IDH1/2* by Next-Generation DNA Sequencing) as described below.

Mutational Analysis of *BRAF* and *IDH1/2* by Targeted Next-Generation DNA Sequencing

Mutational testing of *BRAF* codon 600 and *IDH1* codon 132/*IDH2* codon 172 will be performed by the Precision Medicine Laboratory at Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, OH. This is a CAP/CLIA-certified Genetics laboratory within the Department of Human Genetics at CCHMC, under the direction of Dr. D. Brian Dawson. The Department of Pathology and Laboratory Medicine at CCHMC houses the affiliated CAP/CLIA-certified Histology/Anatomic Pathology and Clinical Pathology laboratories. Dr. Christine Fuller, Neuropathologist at SUNY Upstate, will examine H&E slides/images (to confirm tumor content for all testing) and coordinate specimen submission to this laboratory.

With Amendment 2, testing for both *IDH1* codon 132/*IDH2* codon 172 and *BRAF* will be performed on the AmpliSeq 50 gene Focus Center Hotspot Panel V2 assay (Illumina, San Diego, CA). The Focus Cancer Panel (FCP) is a curated targeted resequencing assay for identifying somatic mutations in 50 clinically relevant cancer genes. Genomic DNA is isolated from FFPE tissue and is PCR amplified using oligonucleotide primers predesigned for ~2800 COSMIC mutations. Prepared libraries are sequenced on the Illumina MiSeqDx. The raw sequence data is aligned to the reference genome (HG19) and variants are annotated and reported using GenomOncology (Cleveland, OH). The minimum required sequencing depth is 500x. The analytical sensitivity is 5% variant allele frequency (VAF) for detection of SNVs and indels. SNV and indel variants in *IDH1* codon 132, *IDH2* codon 172, and *BRAF* will be reported. Miscellaneous findings (mutations) detected in the other 47 genes covered by this panel will be recorded under the heading "Miscellaneous molecular findings," though will not factor in directly relative to patient stratification for this COG study.

The FCP at CCHMC has been previously optimized and validated in accordance with current CAP and CLIA standards for molecular testing, and it is routinely utilized as a reportable clinical test at CCHMC. The assay has been validated for FFPE samples. For the purposes of the study, genomic DNA extracted from FFPE tissue will be run on the Illumina Ampliseq NGS platform as of Amendment 2. Note that the validation of the Focus Cancer Panel (AmpliSeq Cancer Hotspot Panel v2, Illumina, San Diego, CA, USA) corresponds to that performed for the previously-used dual NGS platforms using both the Ion Ampliseq Cancer Hotspot Panel (Life Technologies, Carlsbad, CA, USA) and the Illumina TruSeq Cancer Hotspot Panel (Illumina, San Diego, CA, USA); with Amendment 2, the former Focus Cancer Panel is replacing the latter due to obsolescence of the TruSeq Custom Amplicon platform.

Upon completion of sequencing, the data undergoes three tiers of data analysis:

Primary analysis: Independent to the biological meaning of the sequence

a. Converting raw cycle data to raw intensities which are then normalized resulting in per base sequence and quality information which is then output as a FASTQ file.
b. Alignment to the reference (HG19, GRCh37) resulting in a BAM File.
c. Removal of sequencing duplicates.
d. Variant calling resulting in a Variant Call File (VCF).

Secondary analysis:

a. Variant annotation using several curated databases (dbSNP, COSMIC, 1000 Genome). Secondary analysis is performed by GenomOncology (GO) Workbench – a sequencing data analysis and reporting software suite customized by the vendor to i) pull together sequencing data from the MiSeqDx, ii) assess run/sample/variant quality based on thresholds determined during validation, and iii) following tertiary analysis, output results into a physician-ready final report.

Tertiary analysis:

a. Independent and combined review by a Genomic Analyst and either an Oncologist and/or Molecular Geneticist and/or Molecular Pathologist. Combining sequencing metric data with biological relevance (actionability) to determine variant status.
b. Final report generation.

During test validation, patient samples, cell lines and commercial samples were sequenced, including inter- and intra-platform repeats. Only samples with one or more gold standard (GS) or concordant variants in genomic regions covered by our test were included in the validation (GS included Foundation Medicine (for patient samples) and Acrometrix Hotspot Frequency Ladder, HD200 and HD730 (commercial samples)).

Reportable Range: For NGS applications, the reportable range can be defined as the portion of the genome for which sequence information can be reliably derived for a defined test system. This is defined by the combined BED files for the two platform specific panels, plus flanking regions meeting or exceeding variant level quality metrics as defined above.

Reference Range: For NGS applications, the reference range can be defined as the range of normal sequence variations that the assay is designed to detect within a defined population. Our test looks at over 20,000 bases and, as such, it is not possible to identify every possible variant that might appear in the normal population within that range. However, we classify variants as normal variation or clinically significant as they are identified using focused Oncologist/Molecular Director review as well as dbSNP, COSMIC, CIViC database, St. Jude PeCan Data Portal and 1000 Genome data through the GO Workbench in order to determine variant significance within the defined population, i.e., based on the patient's diagnosis. Furthermore, the GO Workbench tracks the final decision for each specific variant, showing whether or not it has been identified before and how it was previously classified.

Precision – Repeatability: > 98% concordance and Reproducibility: > 97% concordance

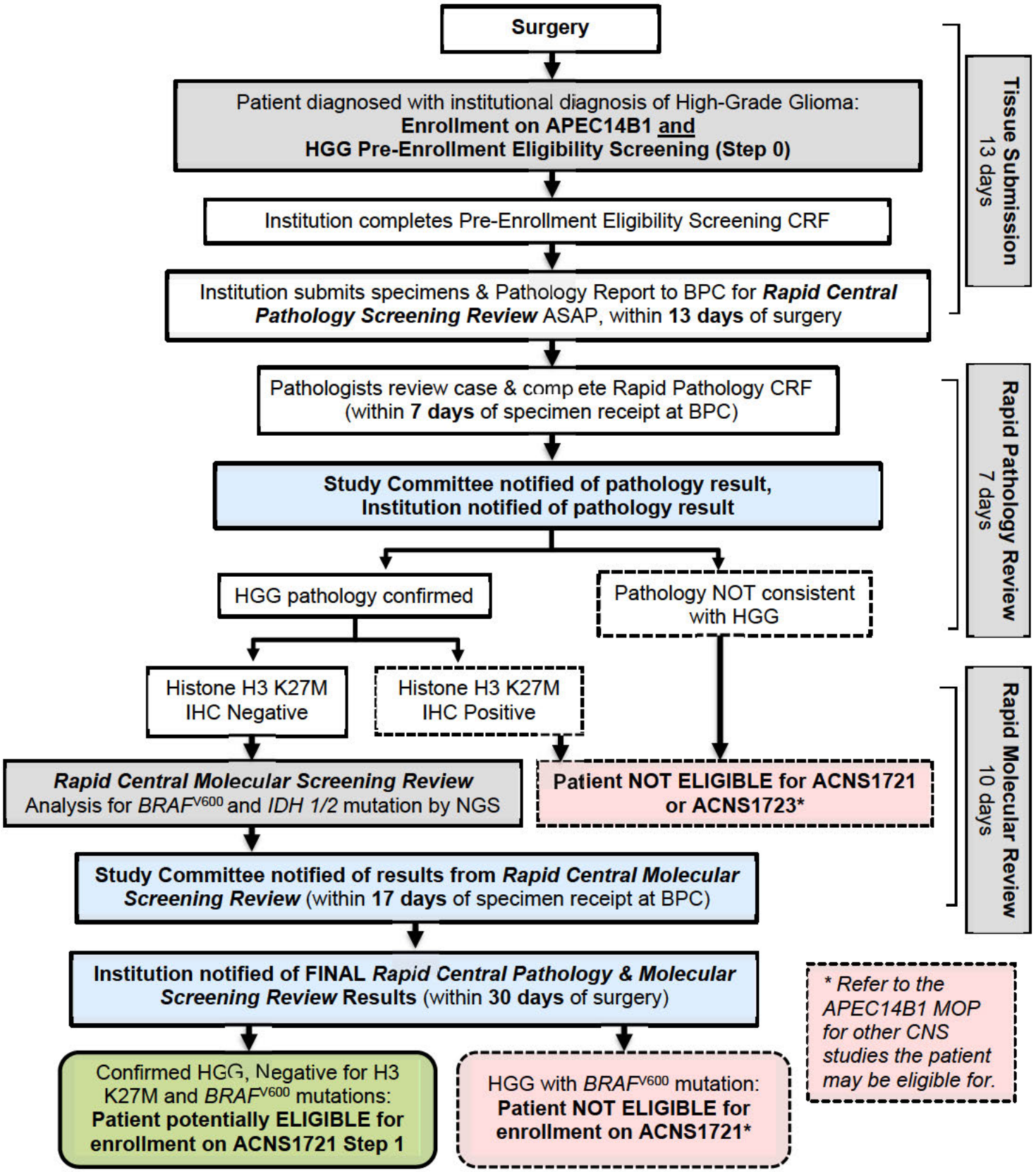
Interfering Substances: Prior comparison of variant cells between DNA extracted from matched fresh/frozen samples and FFPE samples indicated excellent concordance.

Inherent Error Rate of Platform: The platform error rate was reported in 'A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeqDX sequencers' by Quail, MA *et al.* in BMC Genomics.

MiSeq- 0.8%

Repetitive regions overlapping target regions in both assays were identified using the UCSC Table Browser found at http://genome.ucsc.edu/cgi-bin/hgTables. The panel target definition files (BED files) for each panel were uploaded to the table browser. The target definitions were used to intersect to RepeatMasker, Interrupted Repeats, and Simple Repeats tables to identify repeat elements overlapping the target regions. The table browser was also used to determine regions of homology and G/C content.

APPENDIX IV: ACNS1721 RAPID CENTRAL PATHOLOGY AND MOLECULAR SCREENING REVIEW SCHEMA (PRIOR TO STUDY ENROLLMENT)



APPENDIX V: INSTRUCTIONS FOR TEMOZOLOMIDE PREPARATION, ADMINISTRATION AND SAFE HANDLING

Patient Name: _____ **Cycle#:** _____ **Date Range:** _____

Temozolomide *is an oral medicine for the treatment of cancer. This information sheet will help you prepare, administer, store, and dispose of the medicine. Please read the information before preparing and giving the medicine. If you have any questions, please contact:*_____

WHAT DO I NEED?

Your Temozolomide dose is: _____mg

- You should use the following number of capsules for each dose):

Number of temozolomide capsules per dose					
5 mg	20 mg	100 mg	140 mg	180 mg	250 mg

- Give each dose by mouth one time each day for 5 days in a row.
- You should take the temozolomide on the following days: _____

Supplies:

- Temozolomide capsules (see the table above)
- Disposable pad or paper towels
- Disposable gloves and mask and a pair of goggles (eye protection)
- Disposable cup and disposable spoon
- A container to collect waste (zip top plastic bag or medical waste bag or container)
- A small amount of applesauce or apple juice
  - Two teaspoons (10 mL) should be enough. A single-serving container of applesauce may be used, but the patient must be able to eat the entire contents of the container to ensure the full dose is taken.
  - Food should be cool or close to room temperature when administered; do not use hot or boiling food

HOW DO I STORE THE MEDICINE AND WASTE?

Store the medication in the original bottle away from food and out of the reach of children or pets. Store the waste container out of the reach of children or pets. Return the container to the clinic during your next visit.

WHAT SAFETY MEASURES SHOULD I TAKE?

*If the medicine gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. If you spilled the medicine on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention if the skin becomes red, irritated, or if you are concerned. Call your doctor or nurse immediately at:*_____

and/or contact the Poison Center at 1-800-222-1222.

HOW DO I PREPARE THE MEDICINE?

CAUTION: If you are pregnant, could become pregnant, or are breast-feeding, DO NOT prepare or administer this medicine.

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Wash your hands with soap and water; dry them well.
4. Put on disposable gloves, disposable mask, and a pair of goggles or eye protection.
5. Place a disposable pad or paper towel on the clean working space and place all supplies on the pad or paper towel.
6. Fill a cup with a small amount of apple juice or applesauce (or use pre-filled applesauce cup).
7. Open each capsule required for the daily dose over the cup with the apple juice or applesauce.
   - Hold one capsule over the center of the cup.
   - To open, pinch both ends of one capsule with gentle pressure. Slowly rotate one end in small, back and forth movements while holding the other end steady until the capsule sections begin to separate.
   - Gently separate the ends so the powder falls into the center of the food. Look inside each end of the capsule. Tap and shake each end of the capsule until all medicine powder is out of the capsule.
   - Repeat the steps above for each capsule needed.
8. The medicine will not dissolve completely if mixing in apple juice. Keep extra apple juice on hand to add to any remaining powder left at the bottom of the cup. If you need more apple juice or applesauce, remove your gloves before touching the main container. Wear new gloves before adding the additional apple juice or applesauce to the medicine to prevent contaminating the main container with any powder that may be on your gloves.
9. Give the medicine mixture to the patient immediately.

HOW DO I TAKE/GIVE THE MEDICINE?

- Take/give an anti-nausea medicine 30-60 minutes before the temozolomide only if instructed to do so by your doctor.
- Take/give temozolomide 60-120 minutes after the morning veliparib dose
- Take/give temozolomide at around the same time each day with or without food.
- When you are finished, place all used supplies in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- If the dose is vomited within 15 minutes, the dose should be repeated. If the dose is vomited more than 15 minutes after the dose, do not repeat the dose. If the patient is unable to take a dose, or a dose is accidentally missed, place the remaining medicine from this dose in the waste container, seal, and contact your doctor or nurse for instructions.

APPENDIX VI: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug **veliparib (ABT-888)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Veliparib may interact with certain transporter proteins that help move drugs in and out of cells.

- The proteins in question are ***OCT1/2, OATPs, MATE1, MATE2K, and P-gp.*** Veliparib is a substrate of P-gp, OCT2, and MATE1/2K and may be affected by other drugs that inhibit these protein transporters. Veliparib is an inhibitor of OATPs, OCT1/2, and MATE1/2K, and may affect transport of other drugs in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Veliparib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Use caution when administering veliparib with other medicines that need certain **transport protein to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call

your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____. June 2017

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **veliparib (ABT-888).** This clinical trial is sponsored by the NCI**. Veliparib (ABT-888)** may interact with drugs that need certain transport proteins in your body. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Use caution as veliparib (ABT-888) may interact** with medicines that stop transport proteins **MATE1/2K, OCT2, and P-gp** to process further in the body**.** ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements. ➢ Do NOT drink orange juice, other citrus based juice, or grapefruit juice on the days you take veliparib oral solution. ➢ Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____**.**

APPENDIX VII: SUGGESTED VELIPARIB CAPSULE DOSING TABLES

Veliparib Dose Calculation (Capsules) During Chemoradiotherapy

Dose Level 1: 65 mg/m^2/dose PO BID			
BSA range (m^2)	**Total Daily Dose (mg)**	**A.M. Dose (mg)**	**P.M. Dose (mg)**
0.50–0.57	70	40	30
0.58–0.65	80	40	40
0.66–0.73	90	50	40
0.74–0.80	100	50	50
0.81–0.88	110	60	50
0.89–0.96	120	60	60
0.97–1.03	130	70	60
1.04–1.11	140	70	70
1.12–1.19	150	80	70
1.2–1.26	160	80	80
1.27–1.34	170	90	80
1.35–1.42	180	90	90
1.43–1.49	190	100	90
1.5–1.57	200	100	100
1.58–1.65	210	110	100
1.66–1.73	220	110	110
1.74–1.8	230	120	110
1.81–1.88	240	120	120
1.89–1.96	250	130	120
1.97–2.03	260	130	130
2.04–2.11	270	140	130
2.12–2.19	280	140	140
2.2–2.26	290	150	140
2.27–2.34	300	150	150
2.35–2.42	310	160	150
≥ 2.43	320	160	160

Dose Level -1: 50 mg/m²/dose PO BID			
BSA range (m^2)	**Total Daily Dose (mg)**	**A.M. Dose (mg)**	**P.M. Dose (mg)**
0.50–0.54	50	30	20
0.55–0.65	60	30	30
0.66–0.74	70	40	30
0.75–0.84	80	40	40
0.85–0.94	90	50	40
0.95–1.05	100	50	50
1.06–1.15	110	60	50
1.16–1.25	120	60	60
1.26–1.34	130	70	60
1.35–1.45	140	70	70
1.46–1.54	150	80	70
1.55–1.65	160	80	80
1.66–1.74	170	90	80
1.75–1.85	180	90	90
1.86–1.94	190	100	90
1.95–2.05	200	100	100
2.06–2.14	210	110	100
2.15–2.25	220	110	110
2.26–2.34	230	120	110
2.35–2.44	240	120	120
2.45–2.5	250	130	120

Dose Level -2: 35 mg/m²/dose PO BID			
BSA range (m^2)	**Total Daily Dose (mg)**	**A.M. Dose (mg)**	**P.M. Dose (mg)**
0.50–0.64	40	20	20
0.65–0.78	50	30	20
0.79–0.92	60	30	30
0.93–1.07	70	40	30
1.08–1.21	80	40	40
1.22–1.35	90	50	40
1.36–1.5	100	50	50
1.51–1.64	110	60	50
1.65–1.78	120	60	60
1.79–1.92	130	70	60
1.93–2.07	140	70	70
2.08–2.21	150	80	70
2.22–2.35	160	80	80
2.36–2.50	170	90	80

Veliparib Dose Calculation (Capsules) During Maintenance Chemotherapy

Dose Level 1: 25 mg/m²/dose PO BID			
BSA range (m^2)	**Total Daily Dose (mg)**	**A.M. Dose (mg)**	**P.M. Dose (mg)**
0.50–0.69	30	20	10
0.70–0.90	40	20	20
0.91–1.09	50	30	20
1.10–1.29	60	30	30
1.30–1.49	70	40	30
1.50–1.69	80	40	40
1.70–1.89	90	50	40
1.90–2.10	100	50	50
2.11–2.30	110	60	50
2.31–2.50	120	60	60

Dose Level -1: 20 mg/m²/dose PO BID			
BSA range (m^2)	**Total Daily Dose (mg)**	**A.M. Dose (mg)**	**P.M. Dose (mg)**
0.50–0.69	20	10	10
0.70–0.90	30	20	10
0.91–1.12	40	20	20
1.13–1.37	50	30	20
1.38–1.62	60	30	30
1.63–1.87	70	40	30
1.88–2.12	80	40	40
2.13–2.37	90	50	40
2.38–2.5	100	50	50

APPENDIX VIII: SUGGESTED TEMOZOLOMIDE CAPSULE DOSING TABLES

Temozolomide Dosing Tables

135 mg/m²/day					
Min BSA (m²)	Max BSA (m²)	Daily TMZ Dose (mg)	Min BSA (m²)	Max BSA (m²)	Daily TMZ Dose (mg)
0.2	0.2	25	1.36	1.38	185
0.21	0.24	30	1.39	1.42	190
0.25	0.27	35	1.43	1.46	195
0.28	0.31	40	1.47	1.49	200
0.32	0.35	45	1.5	1.53	205
0.36	0.38	50	1.54	1.57	210
0.39	0.42	55	1.58	1.61	215
0.43	0.46	60	1.62	1.64	220
0.47	0.49	65	1.65	1.68	225
0.5	0.53	70	1.69	1.72	230
0.54	0.57	75	1.73	1.75	235
0.58	0.61	80	1.76	1.79	240
0.62	0.64	85	1.8	1.83	245
0.65	0.68	90	1.84	1.87	250
0.69	0.72	95	1.88	1.9	255
0.73	0.75	100	1.91	1.94	260
0.76	0.79	105	1.95	1.98	265
0.8	0.83	110	1.99	2.01	270
0.84	0.87	115	2.02	2.05	275
0.88	0.9	120	2.06	2.09	280
0.91	0.94	125	2.1	2.12	285
0.95	0.98	130	2.13	2.16	290
0.99	1.01	135	2.17	2.2	295
1.02	1.05	140	2.21	2.24	300
1.06	1.09	145	2.25	2.27	305
1.1	1.12	150	2.28	2.31	310
1.13	1.16	155	2.32	2.35	315
1.17	1.2	160	2.36	2.38	320
1.21	1.24	165	2.39	2.42	325
1.25	1.27	170	2.43	2.46	330
1.28	1.31	175	2.47	2.49	335
1.32	1.35	180	2.50	2.50	340

APPENDIX IX: POSSIBLE DRUG INTERACTIONS

Temozolomide

Some drugs, food, and supplements may interact with temozolomide. Examples include:

Drugs that may interact with temozolomide*
• Clozapine, leflunomide, natalizumab, tofacitinib, valproate products

Food and supplements that may interact with temozolomide**
• Echinacea

**Sometimes these drugs are used with temozolomide on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

REFERENCES

1. Bechet D, Gielen GG, Korshunov A, et al.: Specific detection of methionine 27 mutation in histone 3 variants (H3K27M) in fixed tissue from high-grade astrocytomas. Acta Neuropathol 128:733-41, 2014
2. Jakacki RI, Cohen KJ, Buxton A, et al.: Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. Neuro Oncol, 2016
3. Sturm D, Witt H, Hovestadt V, et al.: Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell 22:425-37, 2012
4. Korshunov A, Ryzhova M, Hovestadt V, et al.: Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. Acta Neuropathol, 2015
5. Dominik Sturm, Brent A. Orr, Umut H. Toprak, et al.: New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs. Cell 164:1060-1072, 2016
6. Bady P, Sciuscio D, Diserens AC, et al.: MGMT methylation analysis of glioblastoma on the Infinium methylation BeadChip identifies two distinct CpG regions associated with gene silencing and outcome, yielding a prediction model for comparisons across datasets, tumor grades, and CIMP-status. Acta Neuropathol 124:547-60, 2012
7. Cohen KJ, Pollack IF, Zhou T, et al.: Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol 13:317-23, 2011
8. Schwartzentruber J, Korshunov A, Liu XY, et al.: Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 482:226-31, 2012
9. Fontebasso AM, Papillon-Cavanagh S, Schwartzentruber J, et al.: Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma. Nat Genet 46:462-6, 2014
10. Muscal JA, Thompson PA, Giranda VL, et al.: Plasma and cerebrospinal fluid pharmacokinetics of ABT-888 after oral administration in non-human primates. Cancer Chemother Pharmacol 65:419-25, 2010
11. Lemasson B, Wang H, Galban S, et al.: Evaluation of Concurrent Radiation, Temozolomide and ABT-888 Treatment Followed by Maintenance Therapy with Temozolomide and ABT-888 in a Genetically Engineered Glioblastoma Mouse Model. Neoplasia 18:82-9, 2016
12. Baxter P, Su J, Li X-n, et al.: EPT-15A Phase 1/2 Clinical Trial of Veliparib (ABT-888) and Radiation Followed by Maintenance Therapy with Veliparib and Temozolomide (TMZ) in Patients with Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG): A Pediatric Brain Tumor Consortium Interim Report of Phase II Study. Neuro-Oncology 18:iii27-iii27, 2016
13. Leonetti C, Biroccio A, Graziani G, et al.: Targeted therapy for brain tumours: role of PARP inhibitors. Curr Cancer Drug Targets 12:218-36, 2012
14. Smith SJ, Long A, Barrow JH, et al.: Pediatric high-grade glioma: identification of poly(ADP-ribose) polymerase as a potential therapeutic target. Neuro Oncol 13:1171-7, 2011
15. Robins HI, Zhang P, Gilbert MR, et al.: A randomized phase I/II study of ABT-888 in combination with temozolomide in recurrent temozolomide resistant glioblastoma: an NRG oncology RTOG group study. J Neurooncol 126:309-16, 2016
16. Barazzuol L, Jena R, Burnet NG, et al.: Evaluation of poly (ADP-ribose) polymerase inhibitor ABT-888 combined with radiotherapy and temozolomide in glioblastoma. Radiation oncology 8:65, 2013
17. Sulkowski PL, Corso CD, Robinson ND, et al.: 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. Sci Transl Med 9, 2017
18. Lu Y, Kwintkiewicz J, Liu Y, et al.: Chemosensitivity of IDH1-Mutated Gliomas Due to an Impairment in PARP1-Mediated DNA Repair. Cancer Res 77:1709-1718, 2017

19. Kessler J, Guttler A, Wichmann H, et al.: IDH1(R132H) mutation causes a less aggressive phenotype and radiosensitizes human malignant glioma cells independent of the oxygenation status. Radiother Oncol 116:381-7, 2015
20. Isakoff S: ABT-888 and Temozolomide for Metastatic Breast Cancer and BRCA1/2 Breast Cancer. , 2009
21. Lederman JA: Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer., 2008
22. Oza A: Study to Compare the Efficacy and Safety of Olaparib When Given in Combination With Carboplatin and Paclitaxel, Compared With Carboplatin and Paclitaxel in Patients With Advanced Ovarian Cancer., 2010
23. Bang Y-J: Efficacy Study of Olaparib With Paclitaxel Versus Paclitaxel in Gastric Cancer Patients., 2010
24. de Bono J: A Study to Assess the Safety and Pharmacokinetics of an Inhibitor of Poly ADP-Ribose Polymerase-1 (PARP). , 2007
25. Tutt A: Study to Assess the Efficacy and Safety of a PARP Inhibitor for the Treatment of BRCA-positive Advanced Ovarian Cancer (ICEBERG 2). 2007
26. Tutt A: Study to Assess the Efficacy and Safety of a PARP Inhibitor for the Treatment of BRCA-positive Advanced Breast Cancer (ICEBERG 1). , 2007
27. Inc. T: A Study of MK4827 in Participants With Advanced Solid Tumors or Hematologic Malignancies (MK-4827-001 AM8). 2008
28. Kaufman B: Open Label Study to Assess Efficacy and Safety of Olaparib in Confirmed Genetic BRCA1 or BRCA2 Mutation Pats. , 2010
29. Lee J-M: AZD2281 Plus Carboplatin to Treat Breast and Ovarian Cancer. , 2011
30. Pfizer: Study of Talazoparib, a PARP Inhibitor, in Patients With Advanced or Recurrent Solid Tumors., 2011
31. Lord CJ,Ashworth A: BRCAness revisited. Nat Rev Cancer 16:110-20, 2016
32. Bair MJ: Learning from our learners: implications for pain management education in medical schools. Pain Med 12:1139-41, 2011
33. Molenaar RJ, Botman D, Smits MA, et al.: Radioprotection of IDH1-Mutated Cancer Cells by the IDH1-Mutant Inhibitor AGI-5198. Cancer Res 75:4790-802, 2015
34. Wick W, Weller M, van den Bent M, et al.: MGMT testing--the challenges for biomarker-based glioma treatment. Nature reviews. Neurology 10:372-85, 2014
35. Kleinberg L, Supko JG, Mikkelsen T, et al.: Phase I adult brain tumor consortium (ABTC) trial of ABT-888 (veliparib), temozolomide (TMZ), and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM) including pharmacokinetic (PK) data. Presented at the 2013 ASCO Annual Meeting, June 1, 2013, 2013
36. Paugh BS, Qu C, Jones C, et al.: Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol 28:3061-8, 2010
37. Yan H, Parsons DW, Jin G, et al.: IDH1 and IDH2 mutations in gliomas. N Engl J Med 360:765-73, 2009
38. Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131:803-20, 2016
39. Setty P, Hammes J, Rothamel T, et al.: A pyrosequencing-based assay for the rapid detection of IDH1 mutations in clinical samples. J Mol Diagn 12:750-6, 2010
40. Pollack IF, Hamilton RL, Sobol RW, et al.: IDH1 mutations are common in malignant gliomas arising in adolescents: a report from the Children's Oncology Group. Childs Nerv Syst 27:87-94, 2011
41. Su JM, Thompson P, Adesina A, et al.: A phase I trial of veliparib (ABT-888) and temozolomide in children with recurrent CNS tumors: a pediatric brain tumor consortium report. Neuro Oncol 16:1661-8, 2014

42. Walsh M, Wu G, Edmonson M, et al.: Incidence of Germline Mutations in Cancer-Predisposition Genes in Children with Hematologic Malignancies: a Report from the Pediatric Cancer Genome Project. Blood 124:127, 2014
43. Zhang J, Walsh MF, Wu G, et al.: Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med 373:2336-2346, 2015
44. Parsons DW, Roy A, Yang Y, et al.: Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. JAMA Oncol, 2016
45. Mody RJ, Wu YM, Lonigro RJ, et al.: Integrative Clinical Sequencing in the Management of Refractory or Relapsed Cancer in Youth. Jama 314:913-25, 2015
46. Robson M, Im SA, Senkus E, et al.: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 377:523-533, 2017
47. Mateo J, Carreira S, Sandhu S, et al.: DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 373:1697-708, 2015
48. Popova T, Manie E, Rieunier G, et al.: Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. Cancer Res 72:5454-62, 2012
49. Schwartz GJ,Gauthier B: A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr 106:522-6, 1985
50. Trissel LABRF, Zhang YB,Koontz SEPB: Temozolomide stability in extemporaneously compounded oral suspensions. Int J Pharm Compd 10:396-9, 2006
51. Lingertat-Walsh K, Weilnau J, Cober MP, et al.: Stability of extemporaneously compounded temozolomide 10 mg/mL suspensions in Oral Mix SF® in glass and plastic bottles and plastic syringes. J Oncol Pharm Pract 27:78-87, 2021
52. Korn EL,Freidlin B: Conditional power calculations for clinical trials with historical controls. Stat Med 25:2922-31, 2006
53. Wu J,Xiong X: Survival trial design and monitoring using historical controls. Pharm Stat 15:405-11, 2016
54. Grassberger C, Trofimov A, Lomax A, et al.: Variations in linear energy transfer within clinical proton therapy fields and the potential for biological treatment planning. Int J Radiat Oncol Biol Phys 80:1559-66, 2011