

**COG-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 BRAFV600 Mutations**

FAST FACTS

Eligibility Reviewed and Verified By

MD/DO/RN/LPN/CRA Date _____

MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

PATIENT ELIGIBILITY:

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

- ___1. 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.
- ___2. **Pre-Enrollment Eligibility Screening (Step 0)**
Patients must be consented and enrolled on APEC14B1, the COG Project:EveryChild Registry, Eligibility Screening, Biology, and Outcome Study, followed by same day enrollment on the ACNS1721 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 ACNS1721. See Appendix IV, Section 3.1.1, Section 14.0, and Section 15.0.
Please refer to the APEC14B1 MOP for institutions on accessing the HGG Pre-Enrollment Eligibility Screening (Step 0) Forms.
- ___3. **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.**
- ___4. 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 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.**
- ___5. **Pre-Enrollment Eligibility Screening Criteria**
The following criteria must be met prior to initiating the HGG Pre-Enrollment Eligibility Screening (Step 0).
 - 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.
 - Diagnosis
Patient is suspected of having localized newly-diagnosed HGG, excluding metastatic disease.
 - Consent
Patient and/or their parents or legal guardians have signed informed consent for eligibility screening on APEC14B1 Part A.
 - Mandatory Specimen Submission
The following specimens obtained at the time of diagnostic biopsy must be submitted through APEC14B1 ASAP, preferably within 13 calendar days of definitive surgery. 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 cm², 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 <i>BRAF</i> , <i>IDH1</i> , and <i>IDH2</i>
- 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) 3) Targeted next generation sequencing for mutations in <i>BRAF</i> , <i>IDH1</i> , and <i>IDH2</i>

___ 6. 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.

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.

___ 7. 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 diagnostic 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.**

___ 8. Age

Stratum 1 (IDH wild-type): Patients must be ≥ 3 years of age and ≤ 21 years of age at the time of enrollment.

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

___ 9. 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 *BRAFV600* mutation by Next-Generation Sequencing (NGS).

___ 10. 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.

___11. 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.

___12. 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.

___13. Organ Function Requirements

- 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)
- Adequate Renal Function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² OR
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
3 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

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

- Adequate Liver Function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
 - SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- 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).

___14. Timing

Patients must be enrolled and protocol therapy must be projected to begin no later than 31 days after definitive diagnostic surgery (Day 0).

The CIRB has determined that assent of children age 14 and older is necessary.

EXCLUSION CRITERIA:

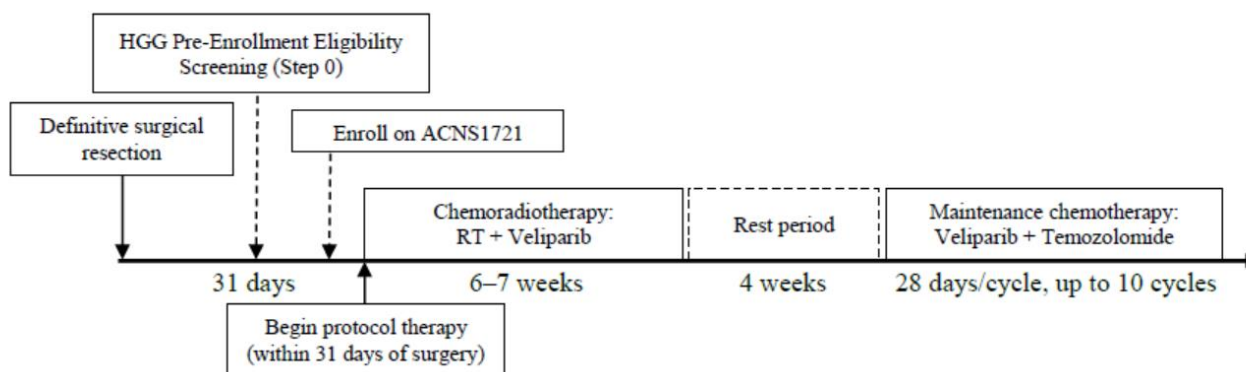
- ___1. Patients with the following histologies:
 - Diffuse astrocytoma (Grade 2)
 - Oligodendrogliomas (any grade)
 - Pleomorphic xanthoastrocytoma (PXA, any grade)
- ___2. Patients with primary tumor location of brainstem or spinal cord.
- ___3. Patients with M+ disease (defined as neuraxis dissemination either by imaging or by cytology).
- ___4. Patients with treatment-related AML (t-AML)/MDS or with features suggestive of AML/MDS.
- ___5. Prior allogenic bone marrow transplant or double umbilical cord blood transplantation.
- ___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.
- ___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.
- ___8. Patients with gliomatosis cerebri type 1 or 2.
- ___9. Patients who are not able to receive protocol specified radiation therapy.
- ___10. Patients must not be currently receiving other anti-cancer agents.
- ___11. Patients with known constitutional mismatch repair deficiency syndrome (CMMR-D)/biallelic mismatch repair deficiency (bMMRD).
- ___12. Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.
- ___13. Lactating females are not eligible unless they have agreed not to breastfeed their infants.
- ___14. Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.
- ___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.

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.

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).

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.

SPECIMEN REQUIREMENTS:

As listed above. Also see Section 15.