COG-ACNS1723: A Phase 2 Study of Dabrafenib (NSC# 763760) with Trametinib (NSC# 763093) after Local Irradiation in Newly-Diagnosed BRAFV600-Mutant High-Grade Glioma (HGG) (IND# 145355)

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

STUDY ENROLLMENT PROCEDURES:

___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 enrollment on the HGG Pre-Enrollment Eligibility Screening (Step 0) on the same day 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.

___2. 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 *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. 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.
- 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.

___4. 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 ACNS1723 STEP 1 in order to avoid discordant diagnosis criterion for treatment on ACNS1723. 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 ACNS1723 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.

___5. Mandatory Rapid Central Molecular Screening Review

See Appendix III, 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 ACNS1723 STEP 1 in order to avoid discordant diagnoses and to verify diagnosis criteria for treatment on ACNS1723. 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 ACNS1723 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.)

PATIENT ELIGIBILITY:

___1. 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**.

___2. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___3. **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 start of therapy. 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 laboratory evaluations must be re-checked within 48 hours prior to initiating therapy. 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 and a baseline spine MRI with 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.

___4. Age

Patients must be ≥ 3 years and ≤ 21 years of age at the time of enrollment.

___5. Diagnosis

Patients must have **eligibility confirmed by Rapid Central Pathology and Molecular Screening Reviews performed on APEC14B1 (see Section 3.1):**

- Newly diagnosed high-grade glioma with *BRAFV600*-mutation
- Negative results for H3 K27M by immunohistochemistry (IHC)
- Histologically confirmed high-grade glioma (WHO Grade III or IV) including but not limited to: anaplastic astrocytoma (AA), anaplastic pleomorphic xanthoastrocytoma (aPXA), anaplastic gangliogliomas (aGG), glioblastoma (GB), and high-grade astrocytoma, NOS

___6. Patients must have had histologic verification of a high-grade glioma diagnosis. CSF cytology by lumbar puncture must be done if clinically indicated and determined to be safe prior to study enrollment. If cytology proves positive, the patient would be considered to have metastatic disease and would, therefore, be ineligible.

___7. A pre- and post-operative brain MRI with and without contrast and a baseline spine MRI with contrast must be obtained prior to enrollment. The requirement for a post-operative MRI is waived for patients who undergo biopsy only. If the spine MRI is positive, the patient would be considered to have metastatic disease and would be ineligible.

___8. 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.

___9. Organ Function Requirements

- Adequate Bone Marrow Function defined as:
  - Peripheral absolute neutrophil count (ANC) ≥ 1000/µL
  - Platelet count ≥ 100,000/µL (transfusion independent)
  - Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

- 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 (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
  - 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.
- Central Nervous System Function defined as:
  - Patients with a seizure disorder may be enrolled if their seizures are well controlled while on non-enzyme inducing anticonvulsants permitted on this study (see Appendix VII).

___10. Timing

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

EXCLUSION CRITERIA:

___1. Patients with intrinsic brainstem or primary spinal cord tumors will be excluded.

___2. Patients with metastatic disease (defined as neuraxis dissemination either by imaging or by cytology) will be excluded.

___3. Prior Therapy

- Patients must not have received any prior tumor-directed therapy including chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant for the treatment of HGG other than surgical intervention and/or corticosteroids.
- Previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor.

___4. Patients with a history of a malignancy with confirmed activating RAS mutation.

___5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib, trametinib, and their excipients.

___6. Uncontrolled medical conditions (e.g., diabetes mellitus, hypertension, liver disease, or uncontrolled infection), psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol.

___7. Presence of active gastrointestinal (GI) disease or other condition (e.g., small bowel or large bowel resection) that will interfere significantly with the absorption of drugs.

___8. History of Hepatitis B Virus, or Hepatitis C Virus infection (patients with laboratory evidence of cleared Hepatitis B Virus and/or Hepatitis C Virus may be enrolled).

___9. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:

- Recent myocardial infarction (within the last 6 months);
- Uncontrolled congestive heart failure;
- Unstable angina (within last 6 months);

- Clinically significant (symptomatic) or known, uncontrolled cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker) except sinus arrhythmia within the past 24 weeks prior to the first dose of study treatment;
- Coronary angioplasty or stenting (within last 6 months);
- Intra-cardiac defibrillators;
- Abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram.

___10. Patients with a history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR), or predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension).

___11. Patients with presence of interstitial lung disease or pneumonitis.

___12. Female patients who are pregnant are ineligible since there is yet no available information regarding human fetal or teratogenic toxicities.

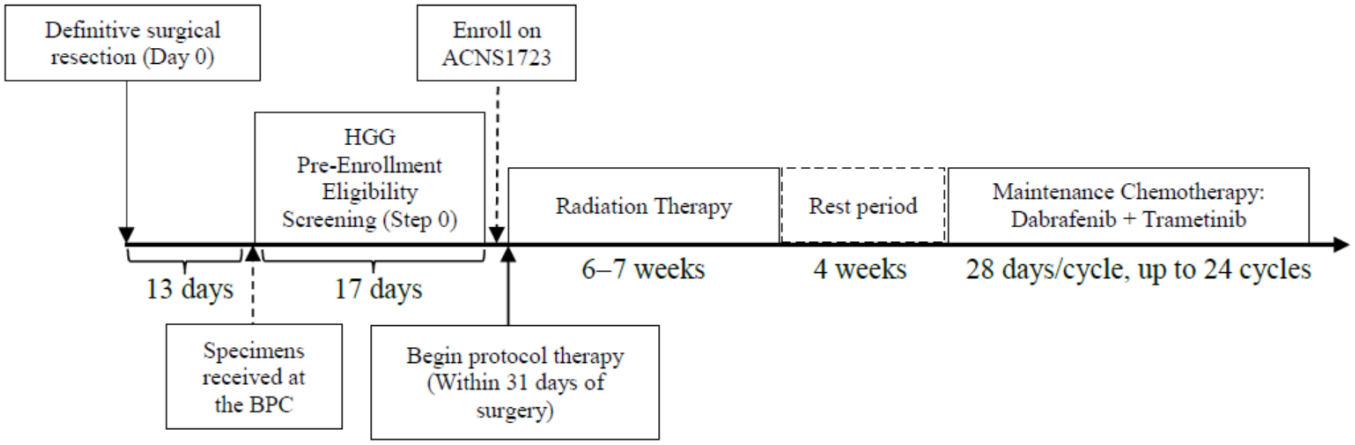
___13. Lactating females are not eligible unless they have agreed not to breastfeed their infants for the duration of the study and for 4 months following discontinuation of study therapy.

___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 (male or female) are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation and for 4 months following discontinuation of study therapy. Male patients (including those who have had a vasectomy) taking dabrafenib and trametinib combination therapy must use a condom during intercourse while on study and for 16 weeks after stopping treatment, and should not father a child during these periods. Women of childbearing potential should use effective non-hormonal contraception during therapy and for 4 weeks following discontinuation of dabrafenib and at least 4 months following the last dose of trametinib in patients taking combination therapy. Women should be advised that dabrafenib may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as barrier methods, should be used.

REQUIRED OBSERVATIONS:
As listed in eligibility criteria, also see 4.4.1 for pre-maintenance required observations.

TREATMENT PLAN:



TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0.

SPECIMEN REQUIREMENTS:
As listed in study enrollment procedures. Also see Section 15.2.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix XII.