COG-ACNS1723: A Phase 2 Study of Dabrafenib (NSC# 763760) with Trametinib (NSC# 763093) after Local Irradiation in Newly-Diagnosed BRAF^{V600}-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**
Prior to enrollment on this study, patients must be consented to and enrolled on APEC14B1, *the COG Project:EveryChild Registry, Eligibility Screening, Biology, and Outcome Study*, and *sites must complete the appropriate CNS/HGG screening forms*. RAPID CENTRAL PATHOLOGY and RAPID CENTRAL MOLECULAR reviews will be performed to confirm eligibility. Please refer to the APEC14B1 Manual of Procedures (MOP) for instructions on accessing the CNS/HGG screening forms.

Patients must be consented and enrolled on APEC14B1 Part A – Eligibility Screening and are highly recommended to consent to the NCI's CCDI Molecular Characterization Initiative (CCDI-MCI). The APEC14B1 Part A consent will cover the CNS/HGG 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 specimens obtained at the time of diagnostic biopsy or surgery must be submitted through APEC14B1 ASAP, preferably within 5 calendar days of the procedure.
Please note: See the APEC14B1 Manual of Procedures for a full list of detailed instructions for submitting required materials and for shipping details.

___3. **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.** Sites may use one of three options to obtain required targeted gene sequencing results for molecular review: 1) Participation in APEC14B1-MCI, with submission of whole exome test results; 2) Submission of clinical (CAP/CLIA certified or equivalent) local targeted sequencing results for all three required genes (*BRAF$_{v600}$, IDH1, IDH2*), or 3) Targeted central molecular testing through **Central molecular review results will be available within 24 calendar days of receipt of all required materials at the BPC (up to 30 calendar days total after surgical resection). For patients consenting to CCDI-MCI for molecular testing or relying on local targeted sequencing results, sites need to upload reports for central review as soon as they are available.** 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 initial CNS/HGG pre-enrollment eligibility screening registration. The information will also be available in RAVE. (Note: The BPC is not responsible for sending the results to sites).

Required Materials to be Submitted on APEC14B1

Material for HGG Pre-screening	**Study / Notes**
Central Pathology (Histology) Review: 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 5 (5 µm) unstained slides (charged / Plus slides)	1) Central pathology review 2) IHC: H3 K27M
Molecular Screening <u>If HGG prescreening and participating in MCI</u>: See next section of table for additional MCI requirements. **OR** If HGG prescreening by central testing only (not participating in MCI): 1 H&E stained slide and 10 (10 µm) scrolls (2 tubes with 5 scrolls each) cut sequentially. To achieve optimal nucleic acid yields, trim off excess paraffin from around tumor before cutting scrolls. **OR** <u>If HGG prescreening, relying on other clinical testing:</u> Clinical report(s) including TARGETED SEQUENCING results for BRAF and IDH1 and IDH2 genes. Note that immunohistochemistry will not be acceptable for BRAF/IDH1/IDH2 screening. Reports must include gene sequencing.	3) Targeted next generation sequencing for mutations in BRAF, IDH1, and IDH2 **Note: If specimens are not submitted for MCI within 5 days of surgery, scrolls are required to be submitted**.
For Patients enrolling on both MCI and HGG (ACNS1723/ACNS1821) pre-screening the following must be submitted in addition to the materials listed above:**	
Peripheral Blood (5 mL of blood in a purple top tube [EDTA]) should be **shipped on same day as collected** when possible and kept in a 4o C refrigerator until shipment. During warm weather, blood should be shipped on a cold pack.* ***Both blood and tumor tissue MUST BE received to start MCI testing***.	MCI: Germline DNA for Tumor/Normal DNA enhanced exome sequencing
If Snap Frozen Tumor Tissue cannot be obtained the following materials would be acceptable in place of frozen tissue: Formalin Fixed Paraffin Embedded (FFPE) block containing at least three 16-18 gauge tumor cores or tumor tissue (cumulatively amount of tissue in block should be approximately dime-sized). If block cannot be sent, then slides may be submitted (block used to section slides must meet the requirements specified above): • One H&E stained slide • 20-30 unstained, uncharged and air dried slides cut at 5 microns. Slides <u>must</u> be processed sequentially from **one block**. Slides from more than one block cannot be combined for testing. The H&E stained slide is created first and then unstained slides are cut sequentially after the section for H&E. All slides must be labeled with the section number (see labeling requirements below). Tissue should contain at least 60% tumor for all three tests to be performed, but please send even if less than 60% as enrichment may be possible or a subset of testing may still be possible.	MCI: 1) Archer FusionPlex Panel 2) Tumor/Normal DNA enhanced exome sequencing (would include BRAF, IDH1, and IDH2 sequencing for study screening) 3) DNA methylation array *(results for non□CNS metastatic tissue will be for research purposes only and will not be returned to sites)* *Tumor tissue from a primary site is preferred but tissue from a metastatic site is acceptable.* *For specimens requiring decalcification use EDTA. Acid decalcified specimens cannot be used for MCI.* **Tissue should not be previously embedded in OCT.**
Institutional Pathology Report in English A preliminary report may be submitted for initiation of screening, but submit the final report as soon as available. An operative or external consult report alone is not acceptable to meet this requirement. See the <u>Corresponding Pathology Report</u> section for more details.	***Required to initiate the MCI screening process.*** ***The name and date of birth must be included on the pathology report.***

<u>NOTE</u>: 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.

* Blood submitted for MCI is a separate submission from the blood requested in Section VI for banking. The blood for MCI must be shipped with the MCI transmittal form.

** **Additional materials to be submitted for patients on MCI are provided in the table above to enable review of submission requirements for both screening and MCI in one place.**

Also see the APEC14B1 Manual of Procedures for additional ACNS1723 details.

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*

___4. Pre-Enrollment Eligibility Screening Criteria

The following criteria must be met prior to initiating CNS/HGG Pre-Enrollment Eligibility Screening.

- Age
  Patients must be ≤ 25 years of age at the time of enrollment on APEC14B1 Part A CNS/HGG pre-enrollment eligibility screening.
  Note: This required age range applies to the pre- enrollment eligibility screening for all HGG patients. Individual treatment protocols may have different age criteria.
- 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.

___5. Mandatory Rapid Central Molecular Screening Review

See Appendix III, Appendix IV and **Section 15.0. All patients who have pathology confirmed must 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.

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 ≤ 25 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 *BRAF*^{V600}-mutation
- Results for H3 K27M by immunohistochemistry (IHC) or sequencing
- 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) ≤ 135 U/L. 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 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.

EXCLUSION CRITERIA:

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

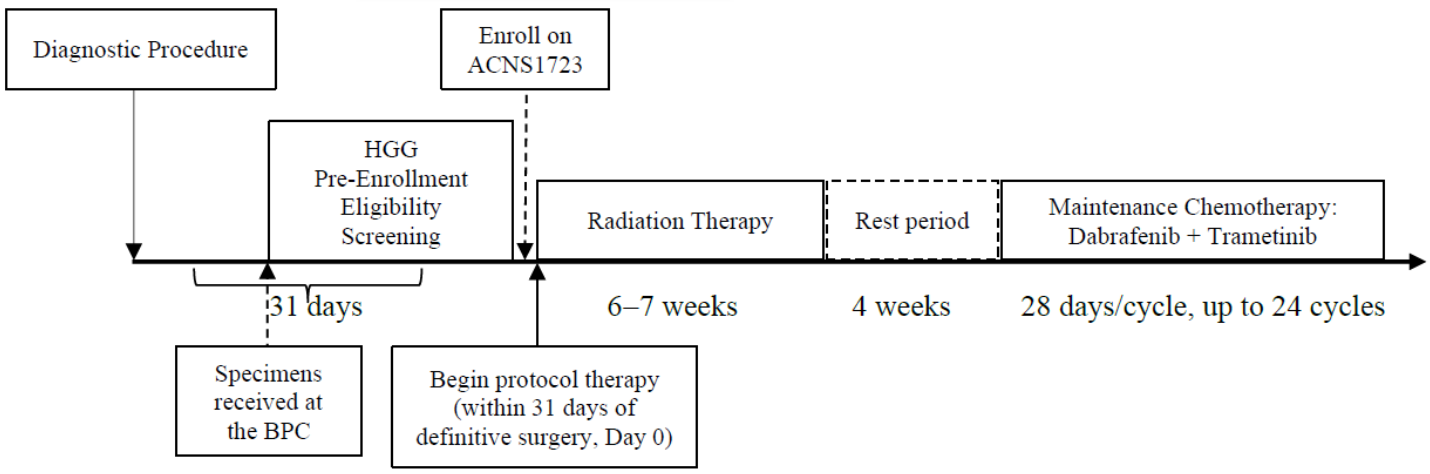
___2. Patients with metastatic disease (defined as neuraxis dissemination either by imaging or by cytology) will be excluded.
___3. Prior Therapy
- Patients must not have received any prior tumor-directed therapy including chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant for 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 4.4.2 for pre-maintenance required observations.

TREATMENT PLAN:



Note: Patients who do not start radiation therapy within 31 days of definitive surgery will be considered off study (see Section 8.2). Please see Section 3.3.5 for definition of definitive surgery (this may include biopsy only).

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 XIII.