

**COG-ACNS1833: A Phase 3 Randomized Non-Inferiority Study of Carboplatin and Vincristine versus Selumetinib (NSC# 748727, IND# 77782) in Newly Diagnosed or Previously Untreated Low-Grade Glioma (LGG) not associated with BRAF<sup>V600E</sup> Mutations or Systemic Neurofibromatosis Type 1 (NF1)**

**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. To expedite the central review process, it is strongly recommended that sites submit tissue on APEC14B1 and commence the enrollment process as soon as treatment for LGG is considered.
- \_\_\_ 2. Pathology slides from the time of diagnosis (see [Section 3.1.1.4](#)) must be submitted on APEC14B1 to the COG Biopathology Center (BPC) to allow for Pre-Enrollment Eligibility Screening on ACNS1833 (Step 0) prior to consent and enrollment on ACNS1833 Step 1. Central pathology and molecular reviews may take up to 21 days from receipt of required specimens, therefore, required specimens should be submitted as soon as possible in order to avoid treatment delays. **Patients must be enrolled on APEC14B1 before slides are shipped to the BPC.**
- \_\_\_ 3. Mandatory Specimen Submission  
The following specimens obtained at the time of diagnostic biopsy must be submitted through APEC14B1. To avoid treatment delays, specimens should be submitted as soon as treatment is considered. See the APEC14B1 Manual of Procedures for further instructions and shipping details.

**Required Materials to be Submitted on APEC14B1**

Sample	Study
<ul style="list-style-type: none"><li>- 1 H&amp;E stained slide from each representative block <b>AND</b></li><li>- 2 additional H&amp;E slides and 12 unstained slides, 5 µm sections, charged "plus" slides from one representative block, NO HEAT TREATMENT – AIR DRY ONLY.^</li></ul>	<ul style="list-style-type: none"><li>1) Central pathology review</li><li>2) BRAF FISH</li><li>3) ddPCR BRAF<sup>V600E</sup></li></ul>
<ul style="list-style-type: none"><li>- Institutional pathology report (include all current and prior pathology reports, along with any additional molecular or genetic testing results previously generated and any outside consultant's reports if available)</li><li>- APEC14B1 Specimen Transmittal Form*</li></ul>	

^ Do not submit blocks.

**\*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 ACNS1833.

- \_\_\_ 4. Age  
Patients must be ≥ 2 years and ≤ 21 years of age at the time of enrollment on ACNS1833 Step 0.
- \_\_\_ 5. Diagnosis
  - Patient is suspected of having previously-untreated low-grade glioma (LGG).
  - Patient does not have a known diagnosis of neurofibromatosis type 1 (NF1).
- \_\_\_ 6. Consent  
Patient and/or their parents or legal guardians have signed informed consent for eligibility screening on APEC14B1 Part A.
- \_\_\_ 7. Mandatory Rapid Central Pathology Screening Review
  - See [Appendix XIV](#) and [Section 13.0](#). All patients must have RAPID CENTRAL PATHOLOGY SCREENING REVIEW ON APEC14B1 PRIOR TO STUDY ENROLLMENT ON ACNS1833 STEP 1 in order to avoid discordant diagnosis criterion for treatment on ACNS1833. Required samples from the time of

diagnosis must be submitted on APEC14B1 to the BPC as soon as possible to allow for the pre-screening part of the protocol prior to enrolling on ACNS1833 Step 1.

- Rapid central review of the submitted specimens will occur via direct review of slides. Specimen distribution will be coordinated by the BPC. All samples will undergo central pathology review. Difficult cases will be discussed among the study neuropathologists so as to achieve a consensus review diagnosis.
- **If the diagnosis of low-grade glioma is confirmed by central review in a patient without NF1, it is recommended that discussions regarding the ACNS1833 consent be initiated with the patient/family.**

Note: The absence of NF1 is based on the institutional diagnosis.

— 8. 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.

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

— 9. Patient Eligibility Criteria

• **Laboratory Studies**

- **All 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 seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > seven (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.**

• **Clinical Studies**

**For all patients, ECHO/EKG must be done within 4 weeks prior to enrollment with values that meet eligibility as per [Section 3.3.4.3](#). For all patients, ophthalmology toxicity assessments must be done within 4 weeks (28 days) prior to enrollment (see [Section 17.1](#)). For OPG patients, ophthalmology functional assessments must be done following biopsy and within 33 days prior to treatment (see [Section 17.2](#)).**

- **Disease/staging imaging studies, if applicable, must be obtained within 4 weeks (28 days) prior to enrollment (repeat if necessary).**

— 10. Age

Patients must be  $\geq 2$  years and  $\leq 21$  years at the time of enrollment.

— 11. Body Surface Area

Patients must have a body surface area (BSA) of  $\geq 0.5$  m<sup>2</sup> at enrollment.

— 12. Diagnosis

- Patients must have non-neurofibromatosis type 1 (non-NF1) low-grade glioma (LGG) without a *BRAFV600E* mutation **as confirmed by Rapid Central Pathology and Molecular Screening Reviews performed on APEC14B1 (see [Section 3.1](#))** and that has not been treated with any modality besides surgery. **Note:** Patients may be newly-diagnosed OR previously diagnosed, and there is no required timeframe between biopsy/surgery and treatment initiation.
  - Patients with residual tumor after resection or progressive tumor after initial diagnosis (with or without surgery) who have not received treatment (chemotherapy and/or radiation) are eligible.
  - Patients must have two-dimensional measurable tumor  $\geq 1$  cm<sup>2</sup> to be eligible.
- Eligible histologies will include all tumors considered low-grade glioma or low-grade astrocytoma (WHO Grade I and II) by 5th edition WHO classification of CNS tumors with the exception of subependymal giant cell astrocytoma.
- Patients with metastatic disease or multiple independent primary LGG are eligible.

13. Organ Function Requirements

- Adequate renal function defined as:
  - Creatinine clearance or radioisotope GFR  $\geq 70 \text{ mL/min}/1.73 \text{ m}^2$
  - OR
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 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
$\geq 16 \text{ years}$	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  $\leq 1.5 \times$  upper limit of normal (ULN) for age (children with a diagnosis of Gilbert's syndrome will be allowed on study regardless of their total and indirect [unconjugated] bilirubin levels as long as their direct [conjugated] bilirubin is  $< 3.1 \text{ mg/dL}$ ).
  - SGPT (ALT)  $\leq 135 \text{ U/L}$ . For the purpose of this study, the ULN for SGPT is 45 U/L.
  - Albumin  $\geq 2 \text{ g/dL}$
- Adequate cardiac function defined as:
  - LVEF  $\geq 53\%$  (or institutional normal; if the LVEF result is given as a range of values, then the upper value of the range will be used) by echocardiogram
  - QTc interval  $\leq 450 \text{ msec}$  by EKG
- Adequate bone marrow function defined as:
  - Absolute neutrophil count  $\geq 1,000/\mu\text{L}$  (unsupported)
  - Platelets  $\geq 100,000/\mu\text{L}$  (unsupported)
  - Hemoglobin  $\geq 8 \text{ g/dL}$  (may be supported)
- Adequate central nervous system function is defined as:
  - Patients with a known seizure disorder should be stable and should not have experienced a significant increase in seizure frequency within 2 weeks prior to enrollment.

14. Study Specific Requirements

- Hypertension
  - Patients 2–17 years of age must have a blood pressure that is  $\leq 95\text{th percentile}$  for age, height, and gender (see [Appendix XI](#)) at the time of enrollment (with or without the use of anti-hypertensive medications).
  - Patients  $\geq 18$  years of age must have a blood pressure  $\leq 130/80 \text{ mmHg}$  at the time of enrollment (with or without the use of anti-hypertensive medications).

Note for patients of all ages: Adequate blood pressure can be achieved using medication for the treatment of hypertension. See [Section 4.3.2](#).
- **Ophthalmology Toxicity Assessments**  
**All patients must have ophthalmology toxicity assessments performed within 4 weeks prior to enrollment.**  
See [Section 17.1](#) for details.
- Imaging  
For all patients, an MRI of the brain (with orbital cuts for optic pathway tumors) and/or spine (depending on the site(s) of primary disease) with and without contrast must be performed within 4 weeks prior to enrollment.
- 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  $\leq 16$  years of age. See [https://www.cogmembers.org/site/pages/default.aspx?page=Prot\\_reference\\_materials](https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials) under Standard Sections for Protocols.
- Patients must have the ability to swallow whole capsules.

Assent of children age 14 and older is a necessary condition for proceeding with research.

## **EXCLUSION CRITERIA**

- \_\_\_ 1. Prior Therapy
  - Patients must not have received any prior tumor-directed therapy including chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant. Prior surgical intervention is permitted.  
See [Section 4.3](#) for concomitant therapy restrictions for patients during treatment.
  - Patients with a concurrent malignancy or history of treatment (other than surgery) for another tumor within the last year are ineligible.
- \_\_\_ 2. Patients with diffuse intrinsic pontine tumors as seen on MRI (> 2/3 of pons involvement on imaging) are not eligible even if biopsy reveals Grade I/II histology.
- \_\_\_ 3. Patients may not be receiving any other investigational agents.
- \_\_\_ 4. Patients with any serious medical or psychiatric illness/condition, including substance use disorders or ophthalmological conditions, likely in the judgment of the investigator to interfere or limit compliance with study requirements/treatment.
- \_\_\_ 5. Patients who, in the opinion of the investigator, are not able to comply with the study procedures are not eligible.
- \_\_\_ 6. Pregnancy and Breastfeeding
  - Female patients who are pregnant are not eligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
  - Lactating females who plan to breastfeed their infants are not eligible.
  - Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 12 weeks after stopping study therapy are not eligible.  
Note: Women of child-bearing potential and males with sexual partners who are pregnant or who could become pregnant (i.e., women of child-bearing potential) should use effective methods of contraception for the duration of the study and for 12 weeks after stopping study therapy to avoid pregnancy and/or potential adverse effects on the developing embryo.
- \_\_\_ 7. Pre-existing conditions, if applicable.
  - Cardiac Conditions
    - Known genetic disorder that increases risk for coronary artery disease. Note: The presence of dyslipidemia in a family with a history of myocardial infarction is not in itself an exclusion unless there is a known genetic disorder documented.
    - Symptomatic heart failure
    - NYHA Class II-IV prior or current cardiomyopathy
    - Severe valvular heart disease
    - History of atrial fibrillation
  - Ophthalmologic Conditions
    - Current or past history of central serous retinopathy
    - Current or past history of retinal vein occlusion or retinal detachment
    - Patients with uncontrolled glaucoma  
If checking pressure is clinically indicated, patients with IOP > 22 mmHg or ULN adjusted by age are not eligible
- \_\_\_ 8. Treatments and/or medications patient is receiving that would make her/him ineligible, such as:
  - Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to study enrollment even if less than 100% of the daily recommended dosing for vitamin E.
  - Recent surgery within a minimum of 2 weeks prior to starting study enrollment, with the exception of surgical biopsy, placement of a vascular access device or CSF diverting procedure such as ETV and VP shunt.  
Note: Patients must have healed from any prior surgery.
- \_\_\_ 9. Patients who have an uncontrolled infection are not eligible.

## **REQUIRED OBSERVATIONS:**

### Required Observations on CV Arm (Arm 1) – Induction

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

- a. Medical history and physical exam
- b. Neurologic exam
- c. Height, weight
- d. CBC with diff/platelets
- e. Creatinine, bilirubin
- f. Electrolytes, BUN, Ca++, PO4, Mg++
- g. AST, ALT, urinalysis, albumin
- h. Performance status
- i. Pulse oximetry; before Cycle 1
- j. Brain and/or spine MRI (as clinically indicated to monitor disease)
- k. Pregnancy test (*urine or serum*)
- l. Ophthalmology functional assessment (*in all patients with OPG*): Evaluation includes TAC in all patients, and HOTV in patients developmentally able to perform. Perform at baseline (following biopsy and within 33 days prior to treatment) and the end of Induction. See [Section 17.0](#).
- m. Vineland Motor Scale (*in patients with motor deficits*): Perform at baseline. See [Section 18.0](#).
- n. BRIEF-2 and PedsQL Generic Module: Perform at baseline ( $\pm$  2 weeks). See [Section 19.0](#)
- o. Ophthalmology toxicity assessment; all patients must have ophthalmology toxicity assessments performed within 4 weeks prior to enrollment. See [Section 17.1](#).

### Additional Required Observations for Arm 1

- p. Audiogram or BAERs: Perform at baseline and, if abnormal at baseline, as clinically indicated or per institutional guidelines.

### Additional Required Observations on Selumetinib Arm (Arm 2)

- q. Vital signs
- r. ECG: May be omitted if treatment starts within 4 weeks of the ECG used to determine eligibility.
- s. ECHO: Perform at baseline.
- t. CPK: Perform at baseline.
- u. Ophthalmology functional assessment (*in all patients with OPG*): Evaluation includes TAC in all patients, and HOTV in patients developmentally able to perform. Perform at baseline (following biopsy and within 33 days prior to treatment), every 12 weeks (after Cycles 3, 6, 9, 12, 15, 18, 21, and 24), and as clinically indicated for any new visual complaints while on therapy. See [Section 17.0](#).
- v. Medication Diary (see [Appendix IX](#)): Medication diaries should be reviewed after Week 2 of Cycle 1 and after completion of each treatment cycle, and uploaded into RAVE.

## TREATMENT PLAN:

### 1. Overview of Treatment Plan

This study is a randomized, two-arm phase 3 study comparing carboplatin and vincristine (CV) versus selumetinib in the treatment of non-NF1 low-grade glioma without *BRAF<sup>V600E</sup>* mutations. Patients will be randomized 2:1 to selumetinib or CV following enrollment. Patients will receive either the CV arm (Arm 1) or selumetinib arm (Arm 2).

- Carboplatin/Vincristine (Arm 1)

- Patients assigned to CV will receive 1 cycle of Induction (12 weeks) followed by 8 cycles of Maintenance (6 weeks/cycle). Patients will receive treatment for 60 weeks total (approximately 15 months), unless progressive disease or unacceptable toxicity occurs. Patients will undergo imaging evaluations at baseline and then every 12 weeks until the completion of therapy (see [Section 15.0](#)).
  - Patients with optic pathway glioma (OPG) must have ophthalmology evaluations using Teller Acuity Cards (TAC) testing while receiving protocol therapy. In addition, in patients who are developmentally able, HOTV testing must be performed at the same time points as TAC testing (see [Section 17.0](#)).
  - Patients with motor deficits at enrollment must have motor function assessments using the Vineland Motor Scale (see [Section 18.0](#)).
  - Mandatory neurocognitive and QOL assessments are outlined in [Section 19.0](#). See additional eligibility criteria for these assessments detailed in [Section 19.1.2](#).

- Selumetinib (Arm 2)

- Patients assigned to selumetinib will receive up to 27 cycles of treatment (28 days/cycle) for approximately 2 years, unless progressive disease or unacceptable toxicity occurs. Patients will undergo imaging evaluations every 12 weeks until the completion of therapy (see [Section 15.0](#)).
  - Patients with OPG must have ophthalmology evaluations using TAC testing while receiving protocol therapy. In addition, in patients who are developmentally able, HOTV testing must be performed at the same time points as TAC testing (see [Section 17.0](#)).
  - Patients with motor deficits at enrollment must have motor function assessments using the Vineland Motor Scale (see [Section 18.0](#)).
  - Mandatory neurocognitive and QOL assessments are outlined in [Section 19.0](#). See additional eligibility criteria for these assessments detailed in [Section 19.1.2](#).

## TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

## SPECIMEN REQUIREMENTS:

In addition to the pathology review materials listed above, the following materials are requested for patients who agree to the optional biobanking.

- \_\_\_\_ 1. **Blood in EDTA tube:** Prior to the start of protocol therapy, please collect 5–10 mL of peripheral blood in a purple top EDTA tube.
- \_\_\_\_ 2. **Tumor tissue:** Please submit snap-frozen tumor tissue from pretreatment. One 100 mg piece of tumor tissue is requested.
- \_\_\_\_ 3. **FFPE slides:** 10 to 20 unstained 5-μm sections mounted on charged “plus” slides from pretreatment tumor tissue are requested, if available.

If any of these samples have been submitted under APEC14B1 these samples do not need to be duplicated for ACNS1833.

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