

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^{V600E} 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.

Pre-Enrollment Eligibility Screening Prior to enrollment on this study, patients must be consented to and enrolled on APEC14B1 - A, and sites must complete the appropriate CNS/LGG 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 APEC14B1-CNS screening forms.

The APEC14B1 Part A consent will cover the CNS/LGG PreEnrollment Eligibility Screening (including pathology and molecular central reviews) for ACNS1833. See Appendix XIV, Section 3.1.1, Section 13.0, and Section 14.0.

Once the CNS/LGG Pre-Enrollment Eligibility Screening results are known, all eligibility criteria, including patient consent, must be met prior to enrollment on Step 1 of ACNS1833.

• **To expedite the central review process, it is strongly recommended that sites submit tissue on APEC14B1-CNS as soon as treatment for LGG is considered. Patients must be enrolled on APEC14B1 and initialized to APEC14B1-CNS before slides are shipped to the BPC.**

• Pathology slides from the time of diagnosis or other surgery (see Section 3.1.1.4) must be submitted on APEC14B1-CNS to the COG Biopathology Center (BPC) to allow for the CNS/LGG Pre-Enrollment Eligibility Screening 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.

• **Sites will receive notification by e-mail regarding central histopathology review results within 10 calendar days of receipt of all required samples at the BPC. Results from the central molecular review will be available within 21 calendar days of receipt of all required samples at the BPC. For patients participating in the MCI, sites must upload MCI reports for central review as soon as they are available.** The final screening eligibility determination prior to ACNS1833 Step 1 enrollment will be made by the Study Pathologist or designee once the histopathology and molecular results are available. Notification of patient eligibility/ineligibility for ACNS1833 Step 1 enrollment, based on histopathologic and molecular results, will be sent to the e-mail addresses entered by the site during the initial CNS/LGG pre-enrollment eligibility screening registration. The information will also be available in RAVE. (Note: The BPC is not responsible for sending results to sites).

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

- ___ 1. Age : patients must be ≥ 2 years and ≤ 21 years of age at the time of enrollment on CNS/LGG Pre-Enrollment Eligibility Screening.
- ___ 2. Diagnosis
 - Patient is suspected of having previously-untreated low-grade glioma (LGG).
 - Patient does not have a known diagnosis of neurofibromatosis type 1 (NF1).
- ___ 3. Consent

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

- 4. **Mandatory Specimen Submission** The required specimens obtained at the time of diagnostic biopsy or other surgery 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**
- 5. See section 3.1.2 for Mandatory Rapid Central Pathology Screening Review
- 6. **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.
- 7. **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 8 weeks (56 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 8 weeks (56 days) prior to enrollment (repeat if necessary).**
- 8. **Body Surface Area**
Patients must have a body surface area (BSA) of ≥ 0.5 m² at enrollment.
- 9. **Diagnosis**
 - Patients must have non-neurofibromatosis type 1 (non-NF1) low-grade glioma (LGG) without a *BRAF^{V600E}* 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 ≥ 1 cm² 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.
- 10. Patients with metastatic disease or multiple independent primary LGG are eligible.
- 11. **Organ Function Requirements**
 - Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m²
 - OR
 - A serum creatinine based on age/sex 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

≥ 16 years	1.7	1.4
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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 (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 mg/dL).
 - SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
 - Albumin ≥ 2 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 ≤ 450 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 ≥ 8 g/dL (may be supported)
- Adequate central nervous system function is defined as:
 - Patients with a known seizure disorder must be stable and must not have experienced a significant increase in seizure frequency within 2 weeks prior to enrollment.

12. Study Specific Requirements

- Hypertension
 - Patients 2–17 years of age must have a blood pressure that is ≤ 95 th percentile for age, height, and sex (see [Appendix XI](#)) at the time of enrollment (with or without the use of anti-hypertensive medications).
 - Patients ≥ 18 years of age must have a blood pressure $\leq 130/80$ 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 8 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 8 weeks prior to enrollment.
- 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.
- 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 (with the exclusion of laser interstitial thermal therapy (LITT)) 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. 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 1 week after stopping study therapy are not eligible.
Note: Women study participants of child-bearing potential must use acceptable contraception during the study and for 1 week (7 days) after the last dose of selumetinib. Men study participants with sexual partners who are pregnant or who are of child-bearing potential must use acceptable contraception during the study and for 1 week (7 days) after the last dose of study agent. Acceptable contraception includes implants, injectables, or oral contraceptives (all combined with barrier methods), some IUDs, vasectomy or abstinence.
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
- ___7. 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.
- ___8. 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 Perform at baseline and at end of induction
- 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/-PA/-A and PedsQL Generic Module: Perform at baseline (± 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^{V600E}* 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: Also See Section 14.

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.