COG-ACNS1831: A Phase 3 Randomized Study of Selumetinib (IND # 77782) versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) Associated Low-Grade Glioma (LGG)

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. Prior to obtaining informed consent and enrolling a patient, a reservation must be made. See Section 3.1.3

___2. 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.

___3. Randomization
Randomization will take place at the time a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

___4. **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 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 >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. Imaging studies, if applicable, must be obtained within 4 weeks (28 days) prior to enrollment (repeat the tumor imaging if necessary). For all patients, ophthalmology toxicity assessments must be done within 4 weeks (28 days) prior to enrollment. For OPG patients, ophthalmology functional assessments must be done within 33 days prior to treatment. For all patients, ECHO/EKG must be done within 4 weeks prior to enrollment with values that meet eligibility as per Section 3.2.4.3.**

___5. Age
Patients must be ≥ 2 years and ≤ 21 years at the time of enrollment.

___6. Patients must have a body surface area (BSA) of ≥ 0.5 m^2 at enrollment.

___7. Diagnosis
Patients must have Neurofibromatosis Type 1 (NF1) based on clinical criteria (see Appendix XIII) and/or germline genetic testing.

___8. Patients must be newly diagnosed or have previously diagnosed NF-1 associated LGG that has not been treated with any modality other than surgery.

___9. For patients with optic pathway gliomas (OPGs):
- Newly-diagnosed patients with OPG are eligible if there are neurologic symptoms (including visual dysfunction, as defined below) or other exam findings associated with the tumor.
- Previously-diagnosed patients with OPG are eligible if they have new or worsening neurologic symptoms (including visual dysfunction, as defined below) or have tumor growth.
- For both newly-diagnosed and previously-diagnosed OPG, the patient may be eligible, irrespective of whether there has been tumor growth or other neurological symptoms or worsening, if they meet at least one of the following visual criteria:
  - Visual worsening, defined as worsening of visual acuity (VA) or visual fields (VF) documented within the past year (by examination or history); **OR**
  - Significant visual dysfunction (defined as VA worse than normal for age by 0.6 logMAR [20/80, 6/24, or 2.5/10] or more in one or both eyes).

___10. For patients with LGG in other locations (i.e., not OPGs):
- Newly-diagnosed patients with LGG are eligible if there are neurologic symptoms or other exam findings associated with the tumor.
  NOTE: Newly-diagnosed patients with LGG without associated neurologic symptoms or exam findings are not eligible.
- Previously-diagnosed patients with LGG are eligible if they have new or worsening neurologic symptoms or have tumor growth.

___11. Although not required, if a biopsy/tumor resection is performed, eligible histologies will include all tumors considered LGG 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.

___12. Patients must have two-dimensional measurable tumor ≥ 1 cm^2.

___13. Patients with metastatic disease or multiple independent primary LGGs are allowed on study.

___14. Organ Function Requirements
- 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
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

    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) ≤ 3 x upper limit of normal (ULN) = 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 ≥ 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 ≥ 1,000/µL (unsupported)
  - Platelets ≥ 100,000/µL (unsupported)
  - Hemoglobin ≥ 8 g/dL (may be supported)
- Adequate central nervous system function is defined as:
  - Patients with a known seizure disorder should be stable and should have not experienced a significant increase in seizure frequency within 2 weeks prior to enrollment.

___15. Study Specific Requirements

Hypertension

- Patients 2−17 years of age must have a blood pressure that is ≤ 95th percentile for age, height, and gender at the time of enrollment (see Appendix XI).
- Patients ≥ 18 years of age must have a blood pressure ≤ 130/80 mmHg at the time of enrollment (with or without the use of antihypertensive medications).
  Note: Adequate blood pressure can be achieved using medication for the treatment of hypertension. See Section 4.3.2.

___16. Ophthalmology Toxicity Assessments

All patients must have ophthalmology toxicity assessments performed within 4 weeks prior to enrollment. See Section 17.2 for details.

Contact Brooke Geddie – she is the credentialed ophthalmologist for these assessments.

___17. 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.

For patients who undergo a surgery on the target tumor (not required), a pre- **and** post-operative* MRI of the brain (with orbital cuts for optic pathway tumors) or spine (depending on the site(s) of primary disease) with and without contrast must also be performed within 4 weeks prior to enrollment. See Section 15.1 for details.

*The post-operative MRIs should be performed ideally within 48 hours after surgery if possible.

___18. 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.

___19. Patients must have the ability to swallow whole capsules.

___20. Language

Patients must have receptive and expressive language skills in English or Spanish to complete the QOL and neurocognitive assessments (see Section 19.0).

The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the 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 precautions 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 may not be receiving any other investigational agents.

___3. Patients with any serious medical or psychiatric illness/ condition, including substance use disorders likely in the judgement of the investigator to interfere or limit compliance with study requirements/treatment are not eligible.

___4. Patients who, in the opinion of the investigator, are not able to comply with the study procedures are not eligible.

___5. 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.

___6. Lactating females who plan to breastfeed their infants are not eligible.

___7. 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.

___8. 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 o If checking pressure is clinically indicated, patients with IOP > 22 mmHg or ULN adjusted by age are not eligible
  - Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor, or strabismus) or longstanding orbito-temporal plexiform neurofibroma (PN, such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study.

___9. 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 placement for vascular access or CSF diverting procedures such as ETV and VP shunt.
  Note: Patients must have healed from any prior surgery prior to enrollment.

___10. 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: Perform at baseline, weekly, and at the end of Induction.
b. Neurologic exam: Perform at baseline, weekly, and at the end of Induction.
c. Height, weight: Perform at baseline, weekly, and at the end of Induction.
d. CBC with diff/platelets: Perform at baseline, weekly, and at the end of Induction.
e. Creatinine, bilirubin: Perform at baseline, on Day 43, and at the end of Induction.
f. Electrolytes, BUN, Ca++, PO4, Mg++: Perform at baseline, on Day 43, and at the end of Induction.
g. AST, ALT, urinalysis, albumin: Perform at baseline, on Day 43, and at the end of Induction.
h. Performance status
i. Pulse oximetry: Perform at baseline before Cycle 1
j. MRI of the brain (with orbital cuts for optic pathway tumors) and/or spine (depending on the site(s) of primary disease): Perform at baseline and at the end of Induction.
k. Pregnancy test *(urine or serum)*: Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
l. Ophthalmology functional assessment *(in all patients with OPG)*: Evaluation includes Teller Acuity Cards in all patients, and HOTV in patients developmentally able to perform. Perform at baseline (within 33 days prior to treatment) and at 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. Cogstate, BRIEF, and PedsQL Brain Tumor Module: Perform at baseline (within 4 weeks prior to starting therapy). See Section 19.0.
o. OCT (*in consenting patients with OPG*): Perform at baseline (see Section 20.0).
p. Audiogram or BAERs: Perform at baseline and, if abnormal at baseline, as clinically indicated or per institutional guidelines.

ADDITIONAL CONSIDERATIONS AND REQUIRED OBSERVATIONS ON SELUMETINIB ARM (ARM 2)

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

a. ECG: May be omitted if treatment starts within 4 weeks of the ECG used to determine eligibility.
b. ECHO: Perform at baseline and every 12 weeks (after Cycles 3, 6, 9, 12, 15, 18, 21, and 24).
c. CPK: Perform at baseline, after Cycles 1−9, and every 3 cycles thereafter (after Cycles 12, 15, 18, 21, and 24).
d. OCT (*in consenting patients with OPG*): Perform at baseline and after Cycles 6 and 12. See Section 20.0.
e. 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.
f. COG Standardized Battery: In consenting patients, perform 9−12 months post-treatment initiation. See Section 19.0.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Optional tissue and blood. See Section 14.0.

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