COG-ACNS2031: A Phase 3 Study of Sodium Thiosulfate for the Reduction of Cisplatin-Induced Ototoxicity in Children with Average-Risk Medulloblastoma and Reduced Therapy for Children with Medulloblastoma with Low-Risk Features

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. **Pre-Enrollment Eligibility Screening (Step 0)**
Prior to enrollment on a COG treatment study for medulloblastoma, 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 medulloblastoma treatment studies is provided in the APEC14B1 Manual of Procedures (MOP). Please refer to the APEC14B1 MOP for instructions on accessing the Medulloblastoma Pre-Enrollment Eligibility Screening (Step 0) forms.

___2. **Patients must follow the process detailed below:**

- **Consent to APEC14B1**
  - **Part A consent – Eligibility Screening**
  - **Part A consent – Molecular Characterization**
- **Enroll on APEC14B1 followed by same day enrollment on the Medulloblastoma Pre-Enrollment Eligibility Screening (Step 0)**
- **Complete the:**

RAPID CENTRAL PATHOLOGY REVIEW **Submitted_____Resulted_____**

RAPID CENTRAL MOLECULAR REVIEW **Submitted_____Resulted_____**

RAPID CENTRAL IMAGING REVIEW **Submitted_____Resulted_____**

RAPID CENTRAL AUDIOLOGY REVIEW **Submitted_____Resulted_____**

- **After receiving confirmation of eligibility for ACNS2031, enroll on ACNS2031 Step 1**
- **Patients must begin treatment within 31 days of definitive surgery (Day 0)** **Day 31_____**

NOTE: The APEC14B1 Part A consent (Eligibility Screening and Molecular Characterization) will cover the Pre-Enrollment Eligibility Screening (including pathology, molecular, imaging, and audiology central reviews) for the medulloblastoma treatment study.

See Appendix VI, Section 3.1.1, and Section 14.0.

___3. Pre-Enrollment Eligibility Screening Criteria

The following criteria must be met prior to initiating the Medulloblastoma Pre-Enrollment Eligibility Screening (Step 0) process.

- Age
  Patients must be greater than or equal to 3 years and less than 22 years of age at the time of enrollment on Step 0.
- Diagnosis
  Patient is suspected to have newly-diagnosed medulloblastoma by institutional diagnosis.

Please note: Patients with a pending result of CSF cytology tests are eligible for **enrollment on APEC14B1 and the Medulloblastoma Pre-Enrollment Eligibility Screening (Step 0)**.

Timing
Patients must begin treatment within 31 days of definitive surgery (Day 0).

Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

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

___4. Age
Patients must be ≥ 4 years and ≤ 21 years of age at the time of enrollment.

___5. Diagnosis
Patients must be newly diagnosed and have **eligibility confirmed by rapid central pathology and molecular screening reviews performed on APEC14B1 and via the Molecular Characterization Initiative** (see Section 3.1).

- **Average-Risk Cohort**
  Clinico-pathologic criteria:
  - M0 disease
  - No diffuse anaplastic histology

  AND
  Molecular criteria:
  - SHH, p53wt, *GLI2* normal, *MYCN* normal, no chromosome 14q loss
  - Group 3, *MYC* normal, no isochromosome 17q
  - Group 4, no chromosome 11 loss
- **Low-Risk Features Cohort**
  Clinico-pathologic criteria:
  - M0 disease
  - No diffuse anaplastic histology

  AND
  Molecular criteria:
  - Group 4, chromosome 11 loss

___6. CSF Cytology
Patients must have negative lumbar CSF cytology.

Note: CSF cytology for staging should be performed no sooner than 14 days post operatively to avoid false positive CSF. Ideally, CSF should be obtained between Day 14 and Day 21 to allow for final staging status before enrollment onto the study. Patients with positive CSF cytology obtained 0 to 14 days after surgery should have cytology repeated to determine eligibility and final CSF status. Patients with negative CSF cytology from lumbar puncture obtained 0 to 14 days after surgery do not need cytology repeated. Patients with negative CSF cytology from lumbar puncture obtained prior to surgery do not need cytology repeated post-operatively.

___7. Imaging
Patients must have eligibility confirmed by Rapid Central Imaging Review performed on APEC14B1. Patients must have ≤ 1.5 cm2 cross-sectional area of residual tumor (see Section 3.1.4). Whole brain MRI with and without gadolinium (see Section 16.2) and spine MRI with gadolinium (see Section 16.3) must be performed. **See Section 16.1 for required time points and Section 16.2, Section 16.3, Table 16.1, and Table 16.2 for additional details required for Rapid Central Imaging Review.**

___8. Weight
Patients must weigh > 10 kg.

___9. Timing
Patients must be enrolled, and protocol therapy must be projected to begin, no later than 31 days after definitive diagnostic surgery (Day 0). See Section 3.2.4.

___10. 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:
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
4 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 utilizing child length and stature data published by the CDC.

OR - a 24 hour urine Creatinine clearance ≥ 70 mL/min/1.73 m^2
OR - a GFR ≥ 70 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

Note: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

- Adequate liver function defined as:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 135 U/L*
    **Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*
- Central nervous system function defined as:
  - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled (see Section 4.2.2 for a list of anticonvulsants that should be avoided while receiving vincristine).
  - Patients must not be in status epilepticus, a coma or assisted ventilation at the time of study enrollment.
- Auditory function defined as:
  Patients must have normal hearing (defined as SIOP Grade 0) in at least one ear confirmed by **rapid central audiology review** performed on APEC14B1 prior to enrollment (see Section 3.1.5 and Appendix VIII).

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

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

EXCLUSION CRITERIA:

___1. Metastatic Disease
Patients with metastatic disease by either MRI evaluation or lumbar CSF cytology are not eligible. **Patients who are unable to undergo a lumbar puncture for assessment of CSF cytology are ineligible.**

___2. Prior Therapy
Patients must not have received any prior radiation therapy or chemotherapy (tumor-directed therapy) other than surgical intervention and/or corticosteroids.
Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.

___3. Patients must not have any known hypersensitivity to STS, sulfates/sulfites, or other thiol agents (eg, amifostine, Nacetylcysteine, MESNA, and captopril).

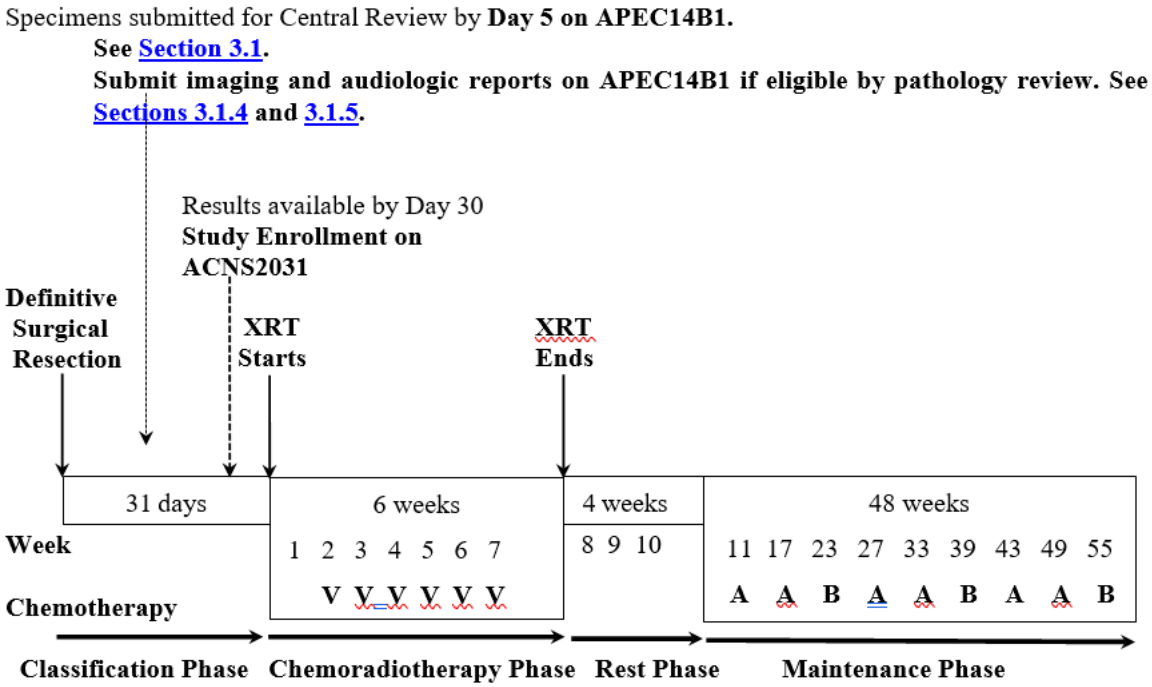
___4. Pregnancy and Breastfeeding
- Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

REQUIRED OBSERVATIONS:

Required Observations – Chemoradiotherapy

a. Medical history and physical exam (including neurologic exam): Perform at baseline and weekly during RT.
b. Height, weight: Perform at baseline.
c. CBC with differential and platelets: Perform at baseline and weekly during RT.
d. Serum creatinine or GFR or creatinine clearance based on age/gender: Perform at baseline.
e. Electrolytes (including BUN, calcium, magnesium, sodium, potassium, phosphate), liver function (including bilirubin and ALT): Perform at baseline.
f. Endocrine evaluation: Perform at baseline. Includes: thyroid function evaluation (free T4 and TSH), IGF-1, IGFBP3, prolactin, LH, FSH, estradiol or testosterone (depending on pubertal status and sex).
g. Pregnancy test: Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.
h. Specimens for biobanking (in consenting patients): See Section 15.2 for details.
i. Household Survey and Parent-Report Measures of COG Standardized Neuropsychological and Behavioral Battery: Perform at study entry (± 4 weeks). See Section 18.0 for details._15.2_Optional_Studies

TREATMENT PLAN:
Enrollment on ACNS2031 must be preceded by rapid central pathology, molecular, and imaging confirmation of average-risk or low-risk medulloblastoma, as well as rapid central audiology reviews performed on APEC14B1. See Section 3.0 for details.



***V:** VinCRIStine will be given once weekly Weeks 2-7 during radiation for a total of 6 doses. VinCRIStineshould be started one week after initiation of radiation therapy and given weekly thereafter.

All patients will receive Chemoradiotherapy followed by Maintenance therapy as outlined below. Patients enrolled in the average-risk cohort will receive a standard CSI dose of 23.4 Gy (with a 30.6 Gy boost to the tumor bed) while patients enrolled in the low-risk features cohort will receive a reduced CSI dose of 18 Gy (with a 36 Gy boost to the tumorbed).

A central venous access device is recommended prior to the start of Chemoradiotherapy.

Chemoradiotherapy

Average-Risk Cohort:

- XRT – 23.4 Gy CSI + IFRT boost 30.6 Gy
- VinCRIStine (1.5 mg/m^2, maximum dose 2 mg) IV infusion weekly x6 duringradiation

(See Section 4.3 and Section 17.0)

Low-Risk Features Cohort:

- XRT – 18 Gy CSI + IFRT boost 36 Gy
- VinCRIStine (1.5 mg/m^2, maximum dose 2 mg) IV infusion weekly x6 duringradiation

(See Section 4.3 and Section 17.0)

Maintenance Chemotherapy

All Patients:

- 9 cycles (AAB AAB AAB)
- Cycle A (42 days) – Cycles 1, 2, 4, 5, 7, 8 (See Section 4.4)
    - Lomustine (CCNU) (75 mg/m^2) orally on Day 1
    - VinCRIStine (1.5 mg/m^2, maximum dose 2 mg) IV infusion via minibagper institutional policy on Days 1, 8, and 15
    - CISplatin (75 mg/m^2) IV over 6 hours on Day 1
    - Sodium thiosulfate (STS) anhydrous (12.8 grams/m^2) IV over 15 minutesbeginning 6 hours after the completion of CISplatin infusion on Day 1
- Cycle B (28 days) – Cycles 3, 6, 9 (See Section 4.5)
    - Cyclophosphamide (1000 mg/m^2) IV over 30-60 minutes on Days 1 and 2
    - MESNA (200 mg/m^2/dose) IV infusion over 15-30 minutes starting 15- 30 minutes prior to or at the same time as cyclophosphamide and repeated at 4 and 8 hours after the start of cyclophosphamide infusion on Days 1 and 2
    - VinCRIStine (1.5 mg/m^2, maximum dose 2 mg) IV infusion via minibag per institutional policy on Days 1 and 8

Chemoradiotherapy planning should begin as soon as possible to permit commencement of chemoradiotherapy within 31 days of definitive surgery.

Maintenance Chemotherapy begins 4 weeks after completion of chemoradiotherapy (Week 11) and when ANC ≥ 750/µL and platelets ≥ 75,000/µL.

There will be both **rapid** and **retrospective central reviews** of audiology, depending on the time point of the evaluation. See Appendix VIII for details on what needs to be includedin the reports and when they must be submitted in Rave.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

BIOLOGY REQUIREMENTS:
Optional Studies: 10 mL in a PAXgne (Streck tube).
Also see Section 15.2.

APPENDIX VI: ACNS2031 RAPID CENTRAL PATHOLOGY, MOLECULAR, IMAGING, ANDAUDIOLOGY SCREENING REVIEW SCHEMA (PRIOR TO STUDY ENROLLMENT)