**COG-ACNS1422: A Phase 2 Study of Reduced Therapy for Newly Diagnosed Average-Risk WNT-Driven Medulloblastoma Patients**

***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)**
**Patients must be consented and enrolled on APEC14B1 followed by enrollment on the ACNS1422 Pre-Enrollment Eligibility Screening (Step 0) the same day to complete the RAPID CENTRAL PATHOLOGY REVIEW. The APEC14B1 consent will cover the pre-enrollment eligibility screening (including pathology, molecular and imaging central reviews) for ACNS1422. See** Appendix IV, Sections 3.1.1, 14 and 15.

Pre-Enrollment Eligibility Screening Criteria

**The following criteria must be met prior to initiating the pre-enrollment eligibility screening criteria on ACNS1422 (Step 0).**

___2. Age - Patients must be greater than or equal to 3 years and less than 22 years at the time of planned enrollment on ACNS1422.

___3. Diagnosis - Patient is suspected to have newly diagnosed average-risk medulloblastoma by institutional diagnosis.
Please note: Patients with a pending result of the CSF cytology are eligible for **enrollment on APEC14B1 and enrollment on the ACNS1422 Pre-Enrollment Eligibility Screening**.

___4. Consent - Patient and/or their parents or legal guardians have signed informed consent for APEC14B1.

___5. Specimen Submission
The following specimens are projected to be submitted through APEC14B1 within 15 days of definitive surgery.

**Required Materials to be Submitted on APEC14B1**

| **Sample** | **When Obtained** | **Study** |
|---|---|---|
| Peripheral Blood (5 ml of blood in a purple top tube [EDTA]) should be kept at 4°C. During warm weather, blood should be shipped on a cold pack. | At time of diagnosis (within 15 days after surgery) | Sanger sequencing for mutations in *CTNNB1* (the gene encoding β-catenin) on germline DNA to determine if a sequence change is somatic or germline |
| Formalin Fixed Paraffin Embedded (FFPE) Sections: (cut sequentially from most representative block):<br>• 15 (5µm) minimum of unstained slides<br>• 20 (10µm) scrolls (2 tubes of 10 each)<br>• 1 H&E stained slide from all available paraffin blocks<br>• INI1 immunohistochemical stain performed at the submitting institution on a slide cut from a representative block | At time of diagnosis (within 15 days after surgery) | 1) IHC: β-catenin<br><br>2) Sanger sequencing for mutations in *CTNNB1* (the gene encoding β-catenin)<br><br>3) FISH studies:<br>*MYCN* and *MYC* amplification<br><br>4) DNA methylation array |
| Institutional Pathology Report (Once Available) | | |
| Optional but strongly recommended if available: (cut from same block as unstained slides):<br>• Submit 1 synaptophysin stain on a slide cut from a representative block.<br>• 1 GFAP immunohistochemical stain on a slide cut from a representative block. | At time of diagnosis (within 15 days after surgery) | IHC |

___6. Timing

**Patients must begin treatment within 36 days of definitive surgery (Day 0).**

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. Patients may begin therapy on the same day as enrollment.

___7. **All clinical and laboratory studies (but not including imaging studies) to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than fourteen (14) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within fourteen (14) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 14 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.**

___8. Age - Patients must be greater than or equal to 3 years and less than 22 years at the time of enrollment.

___9. Diagnosis - Patients must be newly diagnosed and have:

- **Eligibility confirmed by rapid central pathology and molecular screening review on APEC14B1** (See Section 3.1):
  - classical histologic type (non LC/A) WNT medulloblastoma
  - positive nuclear β-catenin by IHC
  - positive for *CTNNB1* mutation
  - negative for *MYC* and *MYCN* by FISH.

Please see exclusion criteria regarding metastatic disease in Section 3.3.9.1.

___10. CSF Cytology

Patient must have negative lumbar CSF cytology. CSF cytology for staging should be performed preferably 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.

Note: Patients with positive CSF cytology obtained prior to 14 days after surgery may have cytology repeated to determine eligibility and final CSF status.

___11. Imaging

**Patients must have eligibility confirmed by rapid central imaging review on APEC14B1** of $\leq 1.5 cm^2$ maximal 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 at the following time points:

- Pre-operative to include an MRI of the brain with and without contrast (including post-contrast 3D T1WI and post-contrast FLAIR).
- Pre-operative spinal MRI with gadolinium. Post-operative staging spinal MRI with gadolinium may be obtained if pre-operative imaging is not possible or is suboptimal. Pre-operative spine imaging is strongly preferred, due to the potential of post-operative sequelae, which could affect metastasis detection.
- Post-operative brain MRI with and without gadolinium preferably within 72 hours of surgery

___12. Timing

Patients must be enrolled within 36 days of definitive diagnostic surgery (Day 0).

**Note: Patients must begin treatment within 36 days of definitive surgery** (See Section 3.2.4 and 8.2).

___13. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
  - Peripheral absolute neutrophil count (ANC) ≥ 1000/µL
  - Platelet count ≥ 100,000/µL (transfusion independent)
  - Hemoglobin ≥ 10.0 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.

- 3.3.6.3 Adequate Liver Function Defined As:
  - Total or direct bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 110 U/L (for the purpose of this study, the ULN for SGPT is 45 U/L)
- 3.3.6.4 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 on assisted ventilation at the time of study enrollment.

___14. Language

Patients must have receptive and expressive language skills in English, French, or Spanish to complete the QoL and Neurocognitive assessments (See Sections 3.2.5 and Appendix IX). If a patient meets these criteria but the parent/guardian speaks a language other than English, French, or Spanish, the patient may still be enrolled and tested, and the parent-report measures should be omitted.

**EXCLUSION CRITERIA:**

___1. Metastatic Disease

Patients with metastatic disease by either MRI evaluation (brain and spine) 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.

___3. Pregnancy and Breast Feeding

- Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.
- Lactating females are not eligible unless they have agreed not to breastfeed their infants.
- Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.
- Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

___4. Patients with a history of moderate to profound intellectual disability (i.e. IQ < 55) are not eligible for enrollment. PLEASE NOTE: Children with a prior history of attention deficit hyperactivity disorder (ADHD) or a specific learning disability (e.g., dyslexia) **are** eligible for this study.

**REQUIRED OBSERVATIONS:**

**Required Observations at Baseline and During Radiation Therapy**

See Section 17.0 for Radiation Therapy Guidelines. Note: If patient is removed off protocol therapy see Section 7.1.

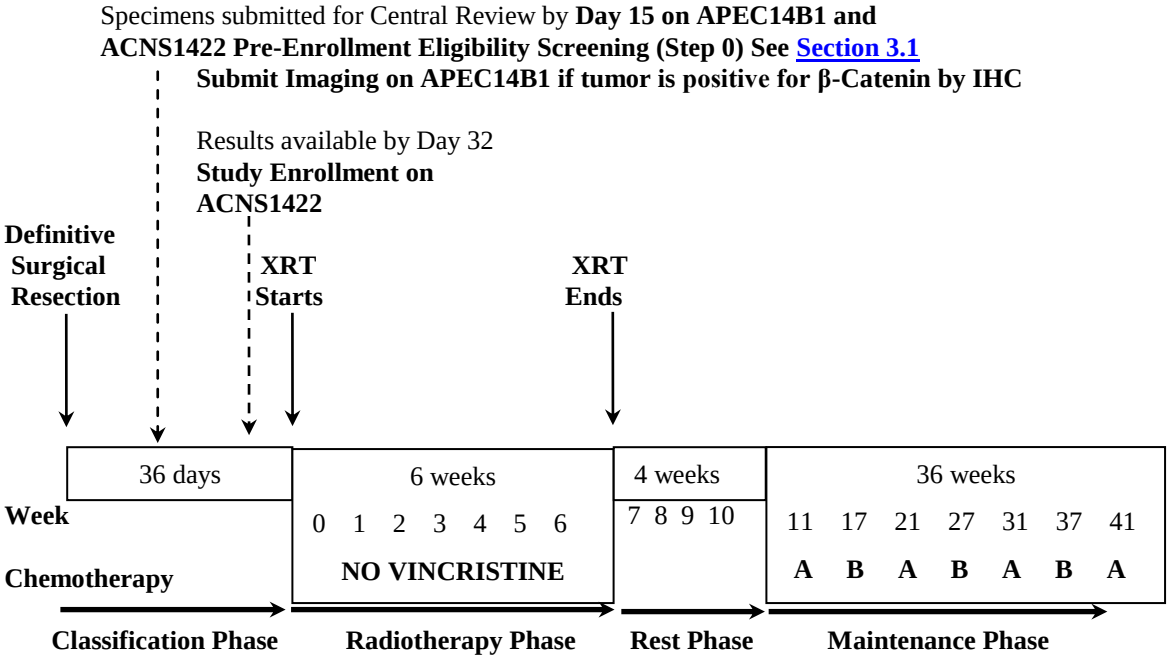
**Observation**

- History
- Physical exam, including height and weight
- Neurologic exam
- MRI of brain with and without gadolinium and MRI of spine with gadolinium
- CSF Cytology
- Audiogram or BAER[1] (See Appendix X)
- Endocrine evaluation[2]
- CBC, diff, platelets
- Serum creatinine or GFR or creatinine clearance based on age/gender (See Section 3.3.6.2)
- Electrolytes (including BUN, calcium, magnesium, sodium, potassium, phosphate)
- Tissue submission for biology studies (See Sections 7.2 and 15.1)
- Pregnancy test [3]

1. All audiologic reports must be scanned and submitted electronically using the COG RAVE system within one week after the tests have been completed for retrospective central review.
2. 2-Endocrine evaluation includes: thyroid function evaluation (free T4 and TSH), GH, IGF-1, IGFBP3 (if available), prolactin, LH, FSH, estradiol or testosterone (depending on pubertal status and sex).
3. 3 -Obtain in females of childbearing potential.

**TREATMENT PLAN:**

**Overview of Treatment Plan**




**Radiotherapy (6 Weeks) (See Section 4.3 for required observations during RT and Section 17.0 for RT guidelines)**

XRT – 18 Gy CSI

36 Gy Boost to tumor bed (for a sum of 54 Gy)

**Maintenance –7 Cycles of Chemotherapy - Alternating Cycles A and B**

Cycle A (42 Days) Cycles 1, 3, 5, 7 (Section 4.4)

- CISplatin (75 mg/m$^2$) IV over 6 hours on Day 1
- Lomustine (CCNU) (75 mg/m$^2$) orally on Day 1
- VinCRIStine (1.5 mg/m$^2$, maximum dose 2 mg) IV push or infusion via minibag as per institutional policy on Days 1, 8, and 15

Cycle B (28 Days) Cycles 2, 4, 6 (Section 4.5)

- Cyclophosphamide (1000 mg/m$^2$) IV over 30-60 minutes on Days 1 and 2
- VinCRIStine (1.5 mg/m$^2$, maximum dose 2 mg) IV push or infusion via minibag as per institutional policy on Days 1 and 8
- 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 on Days 1 and 2.

**Enrollment on ACNS1422 must be preceded by central rapid pathology, molecular and imaging confirmation of average-risk WNT-driven medulloblastoma on APEC14B1.**

**Radiotherapy planning should begin as soon as possible to permit commencement of radiotherapy within 36 days of definitive surgery**. Patients will receive 18 Gy craniospinal radiation, with a conformal boost to the tumor bed of 36 Gy for a sum of 54 Gy. See Sections 4.3 and 17.0.

**Maintenance Chemotherapy** (Sections 4.4 and 4.5) begins 4 weeks after completion of radiotherapy (Week 11) and when ANC ≥ 750/µl and platelets ≥ 75,000/µl. If a subject cannot begin maintenance therapy within 6 weeks of radiotherapy completion, then he/she will be taken off protocol therapy (See Section 8.1). Seven (7) cycles of chemotherapy will be delivered in an ABABABA pattern. A central venous access device is recommended prior to the start of Maintenance.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines under Standard Sections for Protocols.

**TOXICITIES AND DOSAGE MODIFICATIONS:**
See Section 5.

**SPECIMEN REQUIREMENTS:**
Required Rapid Central Pathology Screening Review
Also see Section 15.

**RAPID CENTRAL IMAGING REVIEW:**
See above.