

**COG-ACNS0332: Efficacy of Carboplatin Administered Concomitantly With Radiation and Isotretinoin as a Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients**

**FAST FACTS**

**Eligibility Reviewed and Verified By**

\_\_\_\_\_ MD/DO Date \_\_\_\_\_

\_\_\_\_\_ RN 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. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 10 calendar days after the date of study enrollment.
- \_\_\_ 2. All patients must begin therapy within 31 days of diagnostic surgery.
- \_\_\_ 3. Randomization will take place at the time a patient is entered On Study via RDE. Patients will be assigned to either: Regimen A (RT without Carboplatin and Maintenance without Isotretinoin), Regimen B (RT with Carboplatin and Maintenance without Isotretinoin), Regimen C (RT without Carboplatin and Maintenance with Isotretinoin) or Regimen D (RT with Carboplatin and Maintenance with Isotretinoin). Randomization will be stratified on the basis of location and dissemination. Five strata will be defined: (1) M0 Medulloblastoma with >1.5 cm2 residual; (2) M+ Medulloblastoma; (3) M0 Supratentorial PNET with <1.5 cm2 residual; (4) M0 SPNET with >1.5 cm2 residual; (5) M+ SPNET. **Patients with a history of clinical depression, soybean allergy or paraben allergy will be randomly assigned to Regimen A or B and will not receive Isotretinoin.** Please document this in the medical record.
- \_\_\_ 4. Age greater than or equal to 3 and less than 22 years at the time of diagnosis.
- \_\_\_ 5. Newly diagnosed, previously untreated: (1) M0 Medulloblastoma with >1.5 cm2 residual; (2) M+ Medulloblastoma; (3) M0 or M+ Supratentorial PNET. Patients with anaplastic medulloblastoma are eligible regardless of M-stage or residual tumor. See Appendix II for M-Staging.
- \_\_\_ 6. All patients with M4 disease are not eligible.
- \_\_\_ 7. Cranial and Spinal MRI
  - A pre-operative MRI scan of the brain with and without contrast. **NOTE: CT scans are NOT sufficient for study eligibility since radiation therapy planning and response will be based on MRI scans only.**
  - Post-operative head MRI scan with and without contrast (preferably within 72 hours post-surgery). For patients who undergo stereotactic biopsy only, a post-operative MRI is not required. For patients with M2 and M3 disease, a post-op MRI is strongly encouraged, but not mandatory.
  - Spinal MRI imaging with and without gadolinium is required within 10 days of surgery if done preoperatively or within 28 days of surgery if done post-operatively. For posterior fossa tumors, preoperative MRI scans are preferred because surgically-induced inflammation/blood can be difficult to distinguish from tumor.
- \_\_\_ 8. Evaluation of Lumbar CSF Cytology

Lumbar CSF cytology examination must be obtained pre-operatively or within 31 days following surgery. The optimal time for obtaining CSF is prior to surgery or 1-3 weeks following surgery. Ventricular CSF (either pre- or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M3). Patients who are categorized as M1 must have either an intra-operative positive CSF (via lumbar puncture at the end of the procedure) or a positive lumbar CSF obtained > 7 days post-operatively (to rule out surgically induced false positives).
- \_\_\_ 9. Performance status: Karnofsky/Lansky  $\geq$ 50%, and life expectancy > 8 weeks.
- \_\_\_ 10. No previous chemotherapy or radiation therapy.
- \_\_\_ 11. Concomitant Medications Restrictions
  - Patients taking Accutane (Isotretinoin) for acne must discontinue drug use for this indication prior to enrollment. Corticosteroids should not be used during chemotherapy administration as an antiemetic because of their effect on the blood-brain barrier.

- **Isotretinoin is contraindicated in patients with parabens allergy as the capsule is preserved with the agent and patients with soybean allergy since Isotretinoin is suspended in soybean oil. These patients will be randomly assigned to Regimen A or B and will not receive Isotretinoin.**
- No other experimental therapy is permitted while on study.

\_\_\_ 12. Organ Function Requirements:

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

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
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
$\geq 16$ 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  $< 1.5 \times$  upper limit of normal (ULN) for age, and
  - SGOT (AST) or SGPT (ALT)  $< 2.5 \times$  upper limit of normal (ULN) for age.
  - For patients on anti-seizure medications, SGOT (AST) or SGPT (ALT) must be  $< 5 \times$  ULN.
- Adequate bone marrow function defined as:
  - ANC  $> 1,000/\mu\text{L}$
  - Platelets  $> 100,000/\mu\text{L}$  (untransfused)
  - Hemoglobin  $> 8 \text{ g/dl}$  (may be transfused)

\_\_\_ 13. Pregnancy - There is information indicating a risk of fetal or teratogenic toxicity with this treatment. Fetal toxicities and teratogenic effects of Isotretinoin (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosome abnormalities, multiple anomalies, pancytopenia, and low birth weight. Female patients who are post-menarchal must have a negative pregnancy test. Lactating female patients must agree not to breast-feed while on this trial. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

**REQUIRED OBSERVATIONS:**

**Required Observations, Pre-Treatment and During Radiation Therapy for Regimens A & C**

- CBC with diff, platelets
- Physical/Neuro exam, weight
- Electrolytes, Ca, Creatinine, BUN, magnesium, phosphorus, SGOT (or SGPT), bilirubin
- Serum Creatinine, Creatinine Clearance or GFR
- Audiogram (See Section 5.2.4 for Grading Scale)
- MRI of the Head (T2-weighted imaging and T1-weighted imaging pre- and postcontrast) and Spine with and without Contrast #
- Lumbar CSF cytology @
- Pregnancy Test (For Females who are Post-Menarchal)
- Neuropsychological Evaluation (Section 19.0) §
- QoL Evaluation (Section 19.0) \*
- Central Pathology Review (Section 15.0)
- Biology Studies (Section 16.0)

# Post-op MRI should be done within 72 hours of surgery. For patients who undergo stereotactic biopsy only, postop MRI is not required. For patients with M2 and M3 disease, a post-op MRI is encouraged, but not mandatory. Spinal MRI is required within 28 days of surgery if done post-operatively and within 10 days of surgery if done pre-op. (If MRI scan is performed within 10 days prior to surgery, then only a post-contrast examination is required). A pre-operative spinal MRI scan is preferable for patients with posterior fossa tumors because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

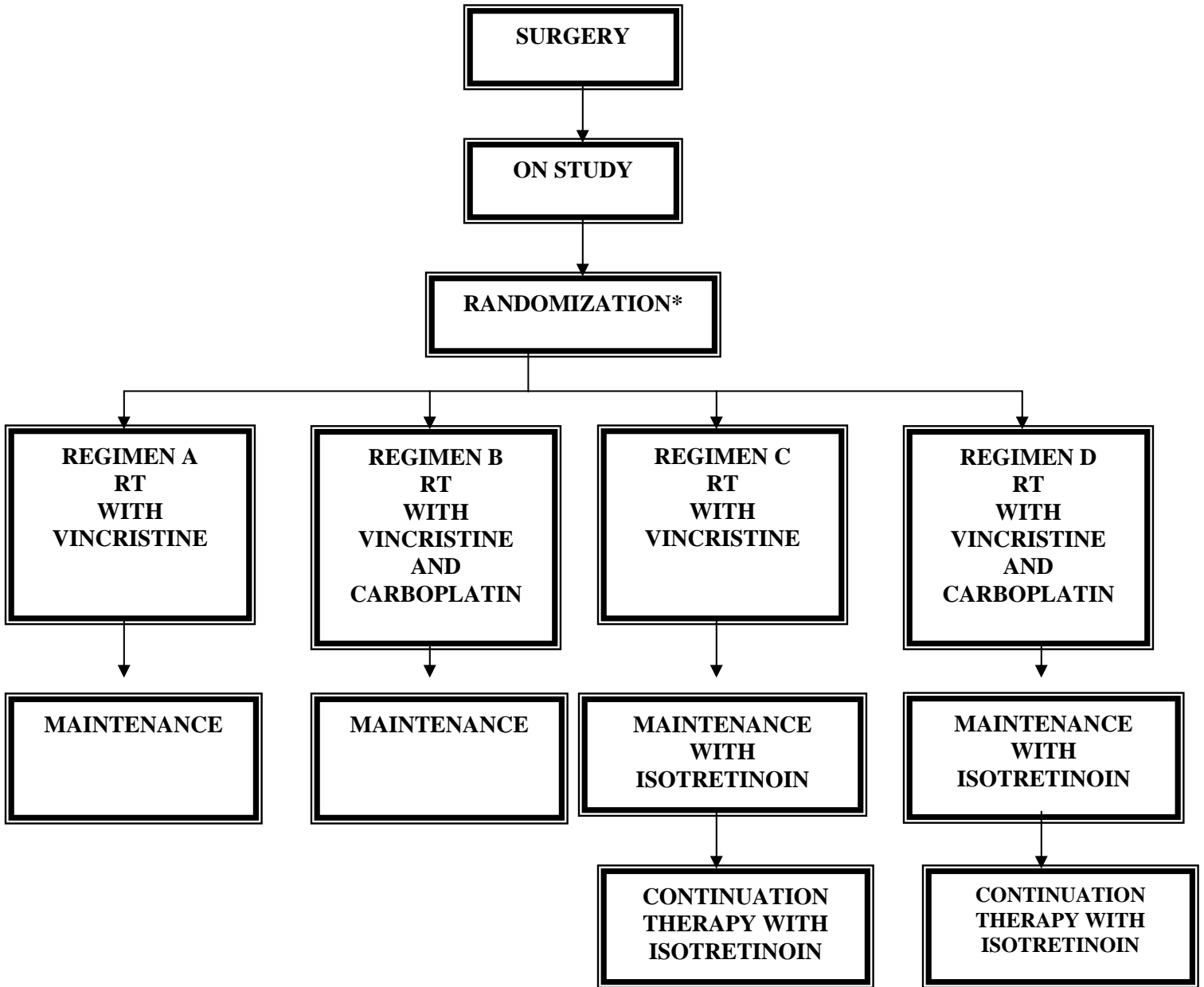
@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M3).

§ Obtain within 1 month of starting RT.

\* Obtain prior to the start of RT.

**TREATMENT PLAN:**

**EXPERIMENTAL DESIGN SCHEMA**



**\* Patients with a history of clinical depression or an allergy to parabens or soybeans will be randomly assigned to Regimen A or B without Isotretinoin.**

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0.

**SPECIMEN REQUIREMENTS:**

Consider ACNS02B3

**CENTRAL REVIEW REQUIREMENTS:**

Pathology Review

- Paraffin Blocks OR
- 2 H&E slides
- 4 unstained slides

Neuroradiological Review

- Send MRI scans to QARC
- Also, see Section 17.3

QARC Review

- See Section 18.8