

**COG-ACCL2031: A Phase 3 Randomized, Placebo-Controlled Trial Evaluating Memantine (IND# 149832) for Neurocognitive Protection in Children Undergoing Cranial Radiotherapy as Part of Treatment for Primary Central Nervous System Tumors**

***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. Timing  
Patients must be enrolled before study drug treatment begins. **Study drug is recommended to begin at least 2 weeks prior to planned initiation of RT**, but may begin as long as 4 weeks prior to RT. If the prior is not feasible, then the **first dose of study drug must be given no later than the start of radiation therapy.**
- \_\_\_ 2. Randomization  
Stratified randomization will take place only after a patient is enrolled via OPEN. This study is double-blinded and placebo-controlled. The treatment (memantine or placebo) will be randomly assigned based on the statistical design of the trial (see [Section 9.1](#)). See [Section 5.1](#) for information regarding emergency unblinding.
- \_\_\_ 3. Regarding Concomitant Enrollment on another Children's Oncology Group or other Therapeutic Trial  
The research team recognizes that patients who participate in this study may also be enrolled on other cooperative group or therapeutic protocols with alternative specified follow-up schedules. Adherence to directed testing on such therapeutic protocols should be prioritized over participation in this trial, ACCL2031.

The study team encourages any patients who are also enrolling on a therapeutic trial to be evaluated by the investigator from that trial to determine if exclusion criteria exist that would prevent such patients from co-enrolling on ACCL2031.

In cases of concomitant enrollment on a therapeutic trial, patients are permitted on ACCL2031 at the discretion of the principal investigator. Imaging and other follow-up data collected outside of the specified window for this trial may be unevaluable.

- \_\_\_ 4. Laboratory Studies  
**All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.**

**The following laboratory studies must be repeated prior to the *start of protocol therapy* if >7 days have elapsed from their most recent prior assessment: bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.**

**If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.**

- \_\_\_ 5. Disease/Staging Imaging  
**Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).**

- \_\_\_ 6. Age  
≥4 and <18 years at time of study entry
- \_\_\_ 7. Weight  
Patients must weigh 15 kg or greater at time of study entry.
- \_\_\_ 8. Diagnosis  
Newly diagnosed or recurrent primary brain tumors that have not received prior cranial radiotherapy.
- \_\_\_ 9. Treatment Plan  
Planned focal, cranial or craniospinal radiation treatment for a primary brain tumor.  
**Reminder: See Section 3.1.4** for timing requirements.
- \_\_\_ 10. Language  
The patient must have receptive and expressive language skills in English, French or Spanish since the neurocognitive function and QOL assessment instruments are available in these languages only.
- \_\_\_ 11. Organ Function Requirements

- Adequate renal function defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m<sup>2</sup> or
  - 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.		

- 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*

- \_\_\_ 12. The patient must be able to undergo Magnetic Resonance Imaging.

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

## EXCLUSION CRITERIA

- \_\_\_ 1. Life expectancy of less than 18 months
- \_\_\_ 2. Pre-existing conditions
  - a. Any contraindication or allergy to memantine.
  - b. Intractable seizures while on adequate anticonvulsant therapy, defined as more than one seizure per month for the past 2 months or since initiating anticonvulsant therapy.
  - c. Co-morbid systemic illnesses, psychiatric conditions, social situations, or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or would limit compliance with the study requirements.
  - d. Patients with a motor, visual, or auditory condition that precludes computerized neurocognitive assessments are not eligible to participate.
  - e. Patients with any medical condition or taking medications that lead to alterations of urine pH towards the alkaline condition (e.g., renal tubular acidosis, carbonic anhydrase inhibitors, sodium bicarbonate).
- \_\_\_ 3. Personal history of prior cranial or craniospinal radiotherapy is not allowed.  
**Note:** Prior anti-cancer therapy including surgery, chemotherapy, targeted agents are allowed as per standard of care clinical treatment guidelines. Please see [Section 4.1](#) for the concomitant therapy restrictions for patients during treatment.
- \_\_\_ 4. Pregnancy and Breastfeeding
  - a. Female patients who are pregnant are excluded since fetal toxicities and teratogenic effects have been noted for the study drug. A pregnancy test is required for female patients of childbearing potential.
  - b. Lactating females who plan to breastfeed their infants.
  - c. Sexually active patients of reproductive potential who do not agree to use an effective contraceptive method for the duration of their study participation.

## TREATMENT PLAN:

**Radiation therapy will proceed according to standard of care** at the discretion of the treating radiation oncologist or the therapeutic protocol on which the patient is co-enrolled. For this protocol, data regarding radiation delivered (as per standard of care) and the doses to brain regions of interest will be requested for inclusion in the analytic data set. See [Section 16.0](#) for Radiation Therapy Plan Submission Guidelines and [Section 15.0](#) for Imaging Studies Required.

Participants will be randomized 1:1 to receive memantine or identical looking placebo and stratified according to the statistical plan.

Memantine or placebo will begin after randomization and prior to initiation of radiotherapy. Study drug will be taken daily for 24 weeks total. Matching placebo liquid containing inert substances will be prescribed in the same dose escalation manner to participants randomized to the placebo control group.

This trial will follow published dosing for pediatric patients described previously ([Section 2.3](#)). Planned target memantine dose is approximately 0.4 mg/kg/day up to a maximum dose of 10 mg PO twice daily. Dose will increase on a weekly basis in 0.1 mg/kg/day up to 6 mg per day increments until target dose achieved. A minimum of 1 week of treatment with previous dose should be observed before increasing the dose.

Memantine or placebo will be supplied for the study and available in oral solution formulation. **Do not use commercial memantine supply.**

See section 5.1 for emergency unblinding instructions

## TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

**SPECIMEN REQUIREMENTS:****Biology Specimen Banking for Consenting Patients**

From patients who consent, the following samples will be obtained at the indicated time points:

Sample	Amount	<i>Time Points</i>			
		Baseline	End of RT	6 ± 1 Months	12 ± 3 Months
<b><u>Germline DNA (Blood)</u></b> Blood drawn into EDTA (purple top) tubes <b><i>Ship at Room Temperature</i></b>	4 mL blood	X			
<b><u>Serum</u></b> 10 mL blood drawn into red top tube. Centrifuge, aliquot, freeze (~3-5 mL) serum <b><i>Ship Frozen with Dry Ice</i></b>	10 mL blood to aliquot: ~3-5 mL Serum	X	X	X	X
<b><u>Urine</u></b> Collected in a standard urine cup and processed within 2 hours. <b><i>Ship Frozen with Dry Ice</i></b>	3-10 mL	X	X	X	X

Note: This trial has a protocol supplied patient medication diary that is required to be provided to the patient. See Appendix VII