COG-ACNS2021: A Phase 2 Trial of Chemotherapy followed by Response-Based Whole Ventricular & Spinal Canal Irradiation (WVSCI) for Patients with Localized Non-Germinomatous Central Nervous System Germ Cell Tumor

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.

Rapid Central Review:

Pre-Enrollment Eligibility Screening
Prior to enrollment on this study, patients must be consented to and enrolled on APEC14B1, the COG Project:EveryChild Registry, Eligibility Screening, Biology, and Outcome Study, and sites must complete the appropriate APEC14B1-CNS generic forms and CNS Germ Cell Screening forms. RAPID CENTRAL IMAGING and RAPID CENTRAL TUMOR MARKER reviews will be performed under the APEC14B1-CNS sub-study to confirm eligibility. Please refer to the APEC14B1 Manual of Procedures (MOP) for instructions on accessing the APEC14B1-CNS forms.

The APEC14B1 Part A consent (Eligibility Screening) will cover the pre-enrollment eligibility screening (including imaging and tumor marker central reviews) for ACNS2021.

- To expedite the central review process, it is strongly recommended that sites submit all required materials on APEC14B1 and APEC14B1-CNS as soon as a diagnosis of germ cell tumor is suspected.
- Patients must be enrolled on APEC14B1 before slides or imaging are submitted. See Section 15.1.1 for details regarding the rapid central review and Section 16.0 for instructions on imaging submission.
- **Sites will receive notification by e-mail regarding central imaging review results within 3 business days of receipt of all required materials. Results from the central tumor marker review will also be available within 3 business days of receipt of all required materials.** The final screening eligibility determination prior to ACNS2021 enrollment will be made by one of the Study Chairs once the imaging and tumor marker review results are available. Notification of patient eligibility/ineligibility for ACNS2021 enrollment, based on imaging and tumor marker review results, will be sent to the e-mail addresses entered by the site during initial APEC14B1-CNS data entry in Rave. The information will also be available in Rave.

Mandatory Rapid Central Imaging Review
See Section 16.0. All patients must have RAPID CENTRAL IMAGING REVIEW on APEC14B1-CNS prior to enrollment on ACNS2021.

Mandatory Rapid Central Tumor Marker Review
All patients must have RAPID CENTRAL TUMOR MARKER REVIEW on APEC14B1-CNS prior to enrollment on ACNS2021.

___1. Timing
Patients must be enrolled prior to the start of treatment. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.**

___2. Protocol therapy must begin within 31 calendar days of definitive surgery or clinical diagnosis, whichever is later. If a biopsy only was performed, the biopsy date will be considered the date of definitive surgery. For patients who have a biopsy or incomplete resection at diagnosis followed by additional surgery, the date of the last resection will be considered the date of definitive surgery.

___3. Rapid Central Review

Mandatory rapid central review will be performed for all patients after study enrollment to confirm eligibility. **Materials for imaging review must be submitted within 7 days of study entry.** Results of rapid central review will be provided via e-mail within 72 hours of receipt of all required materials.

Materials to be submitted include imaging scans and details of AFP and hCGβ levels in the serum or CSF (see Section 15.1 for details).

This review will occur after enrollment but **results will preferably be available prior to starting therapy. If it is clinically necessary, patients may start chemotherapy before the results of rapid review are made available, but if patients are stable it is preferred that the treating physician await results of rapid central review.**

___4. Second-look Surgery

Second-look surgery is **required** for patients with residual primary tumor and with or without persistent tumor marker elevation at end of Induction. Investigators should ensure that patients considering participation in this study are aware of this surgical requirement.

If the local treating team believes there is a contraindication to second-look surgery (i.e., not feasible or safe), the protocol study team will arrange a call to discuss barriers to second-look surgery as this decision impacts study treatment. See Section 13.3 for details.

___5. **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: CBC with differential, 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.

___6. **Clinical Studies**

Clinical studies (e.g., auditory testing, pulmonary function tests), if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___7. **Disease/Staging Imaging**

Imaging studies must be obtained within 31 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary). CSF tumor markers and cytology must be within 31 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary). Serum tumor markers, AFP and hCGβ must be within 7 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___8. Age

Patients must be ≥ 3 years and < 30 years at the time of study enrollment.

___9. Diagnosis

Patients must be newly diagnosed with localized primary CNS NGGCT of the suprasellar and/or pineal region by pathology and/or serum or CSF elevation of AFP above institutional normal or > 10 ng/mL or hCGβ > 100 mIU/mL **as confirmed by Rapid Central Marker Screening Review on APEC14B1-CNS**. Suprasellar, pineal and bifocal tumors are included. Basal ganglia or other primary sites are excluded. Please see exclusion criteria in Section 3.3.7.

- Patients with any of the following pathological elements are eligible: endodermal sinus (yolk sac), embryonal carcinoma, choriocarcinoma, malignant/immature teratoma and mixed GCT (i.e., may include some pure germinoma) if malignant elements listed above are present. Patients with only mature teratoma are excluded. Patients with pure germinoma admixed with mature teratoma are excluded (would be eligible for pure germinoma protocols).

___10. Imaging

Patients must have eligibility confirmed by Rapid Central Imaging Review performed on APEC14B1-CNS as described in Section 3.1.2. See Section 16.1 for required time points and Section 16.2, Section 16.3, Table A, and Table B for scan requirements and additional details for the Rapid Central Imaging Review.

Imaging studies must be obtained within 31 days prior to study enrollment and start of protocol therapy. (**Note:** for patients that have had surgery and post-operative imaging performed, it is the post-operative MRI that must be obtained within 31 days prior to enrollment.)

- Brain MRI
  Patients must have a cranial magnetic resonance imaging (MRI) with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative brain MRI with and without gadolinium. The post-operative brain MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative brain MRI is recommended but not required.
- Spine MRI
  Patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment. Spine MRI with and without gadolinium is recommended.

___11. CSF

- CSF Cytology
  Lumbar CSF must be obtained prior to study enrollment unless medically contraindicated. If a patient undergoes surgery and lumbar CSF cytology cannot be obtained at the time of surgery, then it should be performed at least 10 days following surgery and prior to study enrollment. False positive cytology can occur within 10 days of surgery.
- CSF Tumor Markers
  Patients must have **RAPID CENTRAL TUMOR MARKER REVIEW** CSF tumor markers obtained prior to enrollment unless medically contraindicated. Ventricular CSF obtained at the time of CSF diversion procedure (if performed) is acceptable for tumor markers but lumbar CSF is preferred. In case CSF diversion and biopsy/surgery are combined, CSF tumor markers should be collected first.

___12. 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:
  - 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 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.*
- Central Nervous System Function Defined As:
  - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
  - Patients must not be in status epilepticus, coma or assisted ventilation prior to study enrollment.

___13. Timing

Protocol therapy must begin within 31 calendar days of definitive surgery or clinical diagnosis, whichever is later. If a biopsy only was performed, the biopsy date will be considered the date of definitive surgery. For patients who have a biopsy or incomplete resection at diagnosis followed by additional surgery, the date of the last resection will be considered the date of definitive surgery.

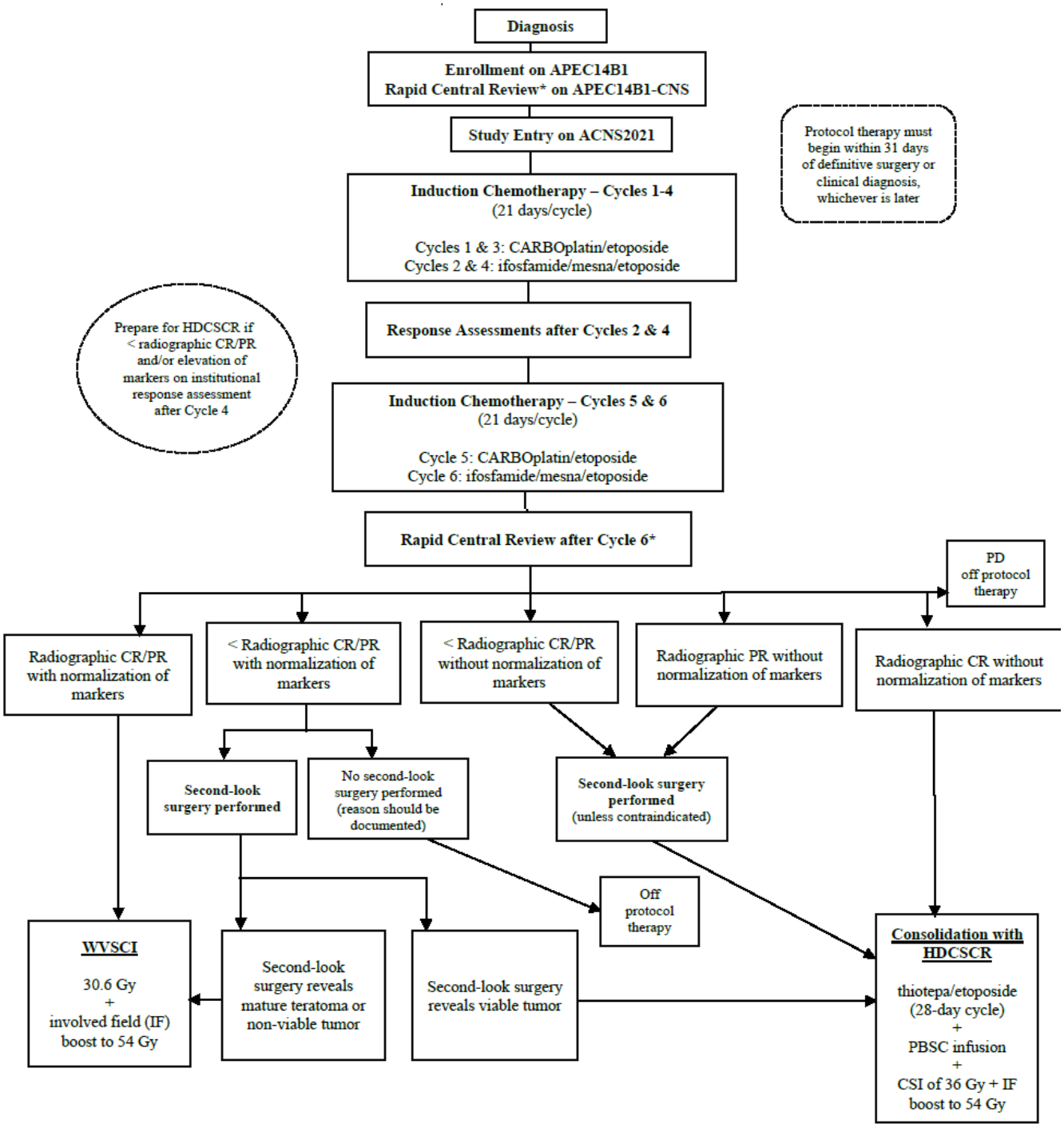
Assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

___1. Patients with tumors located outside the ventricles (i.e., basal ganglia, thalamus).
___2. Patients with only mature teratoma and non-elevated markers upon tumor sampling at diagnosis.
___3. Patients who have received any prior tumor-directed therapy for their diagnosis of NGGCT other than surgical intervention and corticosteroids.
___4. Patients with metastatic disease (i.e., MRI evaluation, lumbar CSF cytology or intraoperative evidence of dissemination).
___5. Pregnancy and Breastfeeding

- Female patients who are pregnant, since fetal toxicities and teratogenic effects have been noted for several of the study drugs.
  Note: Serum and urine pregnancy tests may be falsely positive due to HCGβ-secreting germ cell tumors. Ensure the patient is not pregnant by institutional standards.
- 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.

EXPERIMENTAL DESIGN SCHEMA



*Rapid central review for this study includes a review of imaging and tumor markers. See Section 10.4 for radiographic and tumor marker definitions.

CR: Complete Response
PR: Partial Response
PD: Progressive Disease
WVSCI: Whole ventricular & spinal canal irradiation
HDCSCR: High-dose chemotherapy with stem cell rescue
CSI: Craniospinal irradiation

REQUIRED OBSERVATIONS:

Required Observations – CARBOplatin/Etoposide, Cycles 1, 3 & 5

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

a. Medical history and physical exam (with vital signs, height, weight, and neurologic exam): Perform prior to the start of each cycle.
b. Performance status: Perform prior to the start of each cycle.
c. CBC with platelets and differential: Perform prior to the start of each cycle, and weekly during Induction.
d. BUN, Calcium, PO4, Magnesium, Sodium, Potassium: Perform prior to the start of each cycle, and weekly during Induction (if clinically indicated).
e. Serum Creatinine: Perform all at baseline. Serum Creatinine to also be done prior to the start of each cycle. Creatinine Clearance and GFR to be done if Serum Creatinine is abnormal prior to the start of each cycle.
f. ALT, albumin, total and direct bilirubin: Perform prior to the start of each cycle.
g. Audiogram or BAER: Perform at baseline and prior to the start of each cycle.
h. Endocrine function: Perform at baseline. Endocrine evaluation includes: Tanner stage and serum cortisol (8 AM), TSH with reflex free T4, IGF-1 and IGF-BP3, LH, FSH, and Estradiol (female patients)/Testosterone (male patients).
i. Banking studies (optional, consent required): See Section 15.2 for details.

TREATMENT PLAN:

All patients with newly diagnosed localized primary CNS NGGCT will receive 6 cycles of Induction chemotherapy. Based on rapid central review of tumor response assessment at end of Induction, patients will proceed to second-look surgery or directly to treatment with either WVSCI or HDCSCR + CSI. **The results of rapid central review must be received and reviewed by the treating physician prior to proceeding to the next phase of treatment.** In addition, this protocol requires pre-treatment review of radiotherapy plans (see Section 17.12).

For patients with less than a radiographic CR/PR with or without persistent tumor marker elevation, second-look surgery will be **required**. If the local treating team believes there is a contraindication to second-look surgery, the study team will arrange a call to discuss barriers to second-look surgery as this decision impacts study treatment. See Section 13.3 for details regarding second-look surgery. Note that some patients with clinical suspicion of growing teratoma syndrome may require second-look surgery early (before the end of Induction). These patients will resume Induction chemotherapy after surgery and complete the remaining cycles (for a total of 6 cycles of Induction chemotherapy) before rapid central review at the end of Induction and proceeding to the next phase of treatment. Patients who develop PD (whether by tumor imaging or marker response) or who have less than CR/PR with normalization of markers following Induction and do not undergo second-look surgery will be removed from protocol therapy.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

RAPID CENTRAL REVIEW REQUIREMENTS:

See Section 16.0

OPTIONAL BIOLOGY REQUIREMENTS:

Specimen Schedule and Requirements

All samples for banking should be shipped to the Biopathology Center (see Section 15.2.1.4 for shipping instructions). Samples should be collected as outlined below:

Sample	Amount	Container	Taken at the following time points:
Peripheral blood	10 mL per timepoint	Streck RNA Complete (10 mL) tubes **preferred**. Purple top EDTA tubes may be used if Streck RNA Complete tubes are not available.	• Pre-treatment/diagnosis • After Induction Cycles 2 and 4 • Prior to start of Consolidation (for HDCSCR patients) • Prior to start of RT • End of therapy • Relapse or progression
Snap-frozen tumor tissue	20 mg pieces (any amount)	Cryovial or tube	• Pre-treatment/diagnosis • Relapse or progression
Formalin Fixed Paraffin Embedded (FFPE) tumor tissue	10 unstained paraffin sections (5 µm thickness **preferred**) on glass slides (charged, unbaked) 1 stained H&E	N/A	• Pre-treatment/diagnosis • Relapse or progression
CSF	10 mL per timepoint*	Cryovial or tube	• Pre-treatment/diagnosis • After Induction Cycles 2 and 4 (if positive at baseline) • Prior to start of Consolidation (for HDCSCR patients) • Prior to start of RT • End of therapy • Relapse or progression

*All diagnostic CSF samples will follow the recommended volume for CSF cytology evaluation, since the supernatant after the removal of cell pellet will be used for research studies. If patient is less than 3 years old, all subsequent CSF samples will be 1-3 mL.

Note: A minimum of 5 mL of blood is required if using 10 mL Streck RNA Complete tubes to maintain sample integrity. Streck RNA Complete tubes are not provided for blood collection on this study. In all cases, blood draw volumes should strictly adhere to institutional limitations, taking other blood draws into consideration.