COG-ACNS2321
A Phase II Trial Evaluating Chemotherapy followed by Response-Based Reduced Radiation Therapy for Patients with Central Nervous System Germinomas

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

Pre-Enrollment Eligibility Screening

___1. 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

___2. The APEC14B1 Part A consent (Eligibility Screening) will cover the pre-enrollment eligibility screening (including imaging and tumor marker central reviews) for ACNS2321.

___3. • 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 germinoma is suspected.

___4. • Imaging scans and details of AFP and hCGβ levels in the serum and CSF (unless LP is medically contraindicated) must be submitted to allow for Pre Enrollment Eligibility Screening on APEC14B1-CNS prior to consent and enrollment on ACNS2321. Central imaging and tumor marker reviews may take up to 3 business days after receipt of all required materials, therefore, required materials should be submitted as soon as possible to avoid treatment delays.

• See Section 15.1.1 for details regarding the rapid central review and Section 16.0 for instructions on scan submission.

___5. • 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 ACNS2321 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 ACNS2321 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.

___6. • Protocol therapy must begin within 31 calendar days of definitive surgery or clinical diagnosis, whichever is later. See Section 3.2.4 for details on timing of imaging.

Pre-Enrollment Eligibility Screening Criteria

The following criteria must be met prior to initiating the Germ Cell Tumor Pre Enrollment Eligibility Screening process.

___**7.** **Age**
Patients must be ≥ 3 years and < 30 years at the time of enrollment on screening.

___8. **Diagnosis**
Patients suspected of having newly diagnosed primary localized germinoma of the suprasellar and/or pineal region; germinoma of the basal ganglia and or/thalamic primary sites; metastatic germinoma are eligible.

___9. **Consent**
Patient and/or their parents or legal guardians have signed informed consent for APEC14B1 Part A – Eligibility Screening.

___10. **Mandatory Rapid Central Imaging Review** See Section 16.0. **All patients must have RAPID CENTRAL IMAGING REVIEW on APEC14B1-CNS prior to enrollment on ACNS2321.**

- To document tumor location and extent of disease, standard whole brain MRI with and without contrast (gadolinium) and spine MRI with contrast (gadolinium) must be submitted. See Section 16.1 for required time points for Rapid Central Imaging Review and Section 16.2, Section 16.3, Table A, and Table B for additional details required for the Rapid Central Imaging Review. See Table A and Table B for specific MRI sequences that are required. Failure to perform these specific required sequences may delay the review process and jeopardize enrollment.

- Scans must be submitted to IROC as soon as possible to avoid treatment delays. Review results will be available within 3 business days of receipt of all required and evaluable MRI images and reports. Repeat imaging may be required following central radiology review for patients with inadequate MRI imaging.

___11. **Mandatory Rapid Central Tumor Marker Review**
All patients must have RAPID CENTRAL TUMOR MARKER REVIEW on APEC14B1-CNS prior to enrollment on ACNS2321.

- Details of AFP and hCGβ levels in the serum and CSF (unless LP is medically contraindicated – see Section 3.3.6.2) must be submitted in Rave as soon as possible to avoid treatment delays. Review results will be available within 3 business days of receipt of all required materials.

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 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 who are started on protocol therapy prior to study enrollment will be **considered ineligible**.

___2. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___3. **Following patient eligibility confirmation and study enrollment, patients must begin treatment within 31 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.

Second-look Surgery Second-look surgery may be considered for patients with residual primary tumor at end of Induction (or when clinically indicated). Investigators should ensure that patients considering participation in this study are aware of this surgical recommendation. A post-operative MRI should be obtained within 72 hours of

surgery. **Radiotherapy must start within 6 weeks from the end of Induction or second-look surgery, whichever is later**.

___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: 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.

___5. **Clinical Studies**
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

___6. **Disease/Staging Imaging**
Imaging studies must be obtained within 31 days prior to 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).

Please note: **RAPID CENTRAL IMAGING and RAPID CENTRAL TUMOR MARKER** reviews performed under APEC14B1-CNS must be available prior to study entry on ACNS2321. Please see Section 3.1 for additional details regarding Pre□Enrollment Eligibility Screening.

Inclusion Criteria

___7. **Age**
Patients must be ≥ 3 years and < 30 years at the time of study enrollment.

___8. **Diagnosis**
Patients must be newly-diagnosed primary localized germinoma of the suprasellar and/or pineal region by pathology and/or serum and/or CSF hCGβ 5-50 mIU/mL AND institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists), including tumors with contiguous ventricular or unifocal parenchymal extension. No histologic confirmation required.

* Patients with EITHER (A) bifocal (pineal + suprasellar) involvement; OR (B) pineal lesion with diabetes insipidus (DI); AND hCGβ ≤ 100 mIU/mL in serum and/or CSF; AND institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists) in both serum and CSF. No histologic confirmation required.

- Patients with hCGβ 51-100 mIU/mL in serum and/or CSF and institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists) in both serum and CSF. Histologic confirmation of germinoma IS required.

- Patients with germinoma of the basal ganglia and or/thalamic primary sites are eligible.

- Patients with metastatic germinoma including non-contiguous disease or distant disease in the brain, ventricles, or spine are eligible.

- Patients with germinoma admixed with mature teratoma are eligible.

___9. Performance Level Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age (See Appendix II).

___10. **Imaging**
Patients must have eligibility confirmed by Rapid Central Imaging Review performed on APEC14B1-CNS as described in Section 3.1.1. 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.

___11. **Timing**
Patients must be enrolled, and protocol therapy must begin, no later than 31 days after definitive surgery or clinical diagnosis, whichever is later. See Section 3.2.43.

___12. CSF Patients must have eligibility confirmed by Rapid Central Tumor Marker Review performed on APEC14B1-CNS as described in Section 3.1.3.

___13. **CSF Cytology**
Lumbar CSF must be obtained prior to study enrollment (see Section 3.1) 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. Of note, lumbar CSF should not be performed prior to obtaining spine MRI, as this can make interpretation of the spine MRI less clear.

___14. **Tumor Markers**
Patients must have CSF tumor markers obtained prior to study enrollment (see Section 3.1) 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. Ideally serum and CSF tumor markers should be collected at the same time and processed without delay.

___15. **Organ Function Requirements**
Adequate Bone Marrow Function Defined As:
For patients with solid tumors: - 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: - For pediatric patients (age 3-17 years): 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
≥ 17 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.

OR - a 24-hour urine Creatinine clearance ≥ 70 mL/min/1.73 m2
OR - a GFR ≥ 50 mL/min/1.73 m2 . 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 or plasma creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

• For adult patients (age 18 years or older): Creatinine clearance ≥ 70 mL/min, as estimated by the Cockcroft and Gault formula or a 24-hour urine collection.

The creatinine value used in the calculation must have been obtained within 28 days prior to registration. Estimated creatinine clearance is based on actual body weight.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg}\dagger}{72 \times \text{creatinine}^* \text{ (mg/dl)}}$$

Multiply this number by 0.85 if the participant is a female.
† The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).
* Actual lab serum or plasma creatinine value with a minimum of 0.7 mg/dL.

___16. 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

___17. Adequate Pulmonary Function Defined As: - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination.

___18. Central Nervous System Function Defined As:
- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- CNS toxicity ≤ Grade 2
- Patients must not be in status epilepticus, coma or assisted ventilation prior to study enrollment.

___19. HIV
HIV-infected patients on effective anti-retroviral therapy with undetectable viral load are eligible for this study.

EXCLUSION CRITERA

___1. Patients with any of the following malignant pathological elements are not eligible: - endodermal sinus (yolk sac) - embryonal carcinoma, choriocarcinoma - malignant/immature teratoma and mixed GCT (i.e., may include some germinoma)

___2. Patients with only mature teratoma upon tumor sampling at diagnosis and negative tumor markers are not eligible.

___3. Patients who have received any prior tumor-directed therapy for their diagnosis of germinoma other than surgical intervention and corticosteroids are not eligible.

___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.
  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.

___5. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

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 VI.

REQUIRED OBSERVATIONS:

Required Observations – Induction Chemotherapy Cycles 1-4

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

a. History: Perform prior to the start of each cycle

b. Physical Exam (vital signs, height, weight, and neurologic exam) Bilirubin, ALT & Creatinine: Perform prior to the start of each cycle

c. Performance Status: Perform prior to the start of each cycle

d. CBC (differential, platelets): Perform prior to the start of each cycle, and obtain weekly if clinically indicated

e. Electrolytes (including BUN, Calcium, PO4, Magnesium, Sodium, Potassium): Perform prior to the start of each cycle, and obtain weekly if clinically indicated

f. Serum or plasma Creatinine (Creatinine Clearance and GFR to be done if Serum Creatinine is abnormal): Perform prior to the start of each cycle

g. ALT, albumin, total and direct bilirubin: Perform prior to the start of each Cycle

h. Serum markers (hCGβ, AFP): Perform prior to the start of each cycle

i. Brain MRI with and without gadolinium[1]: Brain MRI should be repeated after Cycle 2 and end of Induction in all patients

j. Spine MRI: Repeat after cycle 2 and end of Induction in metastatic disease patients only

k. Audiogram or BAER

l. Endocrine Function[2]

m. CSF Cytology[3]: Obtain at baseline. If positive at baseline, obtain again at the end of Induction

n. CSF Markers (hCGβ, AFP)[3,4]: Obtain at baseline. If positive at baseline, obtain again at the end of Induction

o. Pregnancy test (for females of childbearing potential)

p. Banking studies [4]

1) *All patients must have a cranial MRI with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative cranial 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 cranial MRI is recommended but not required.*

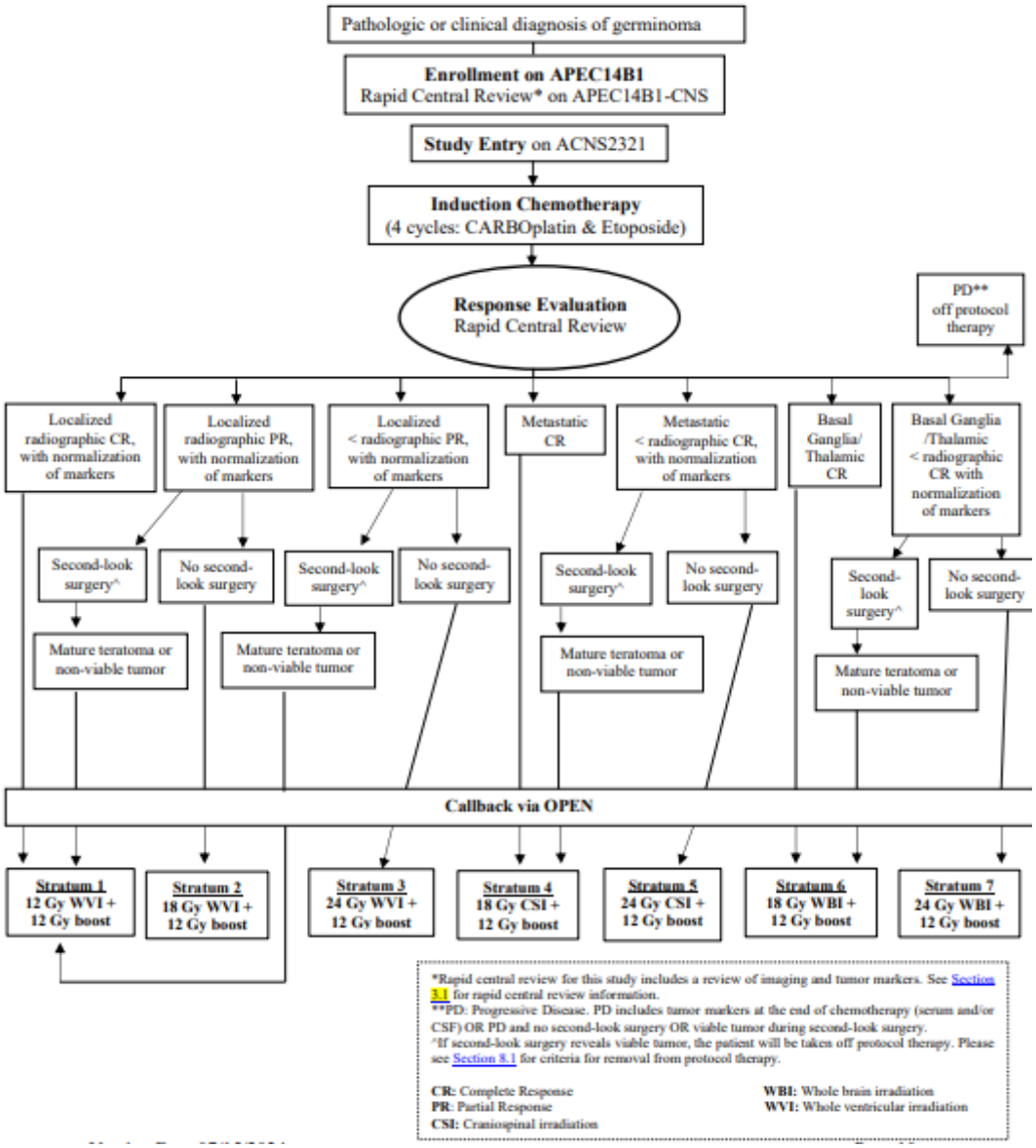
2) *Endocrine evaluation* includes: Tanner stage and serum cortisol (before 8 AM), prolactin, fasting lipid panel, fasting glucose, A1C, TSH with free T4, IGF1 and IGF-BP3, LH, FSH, and Estradiol (female patients)/Testosterone (male patients).*
**Testing is strongly encouraged but required only as clinically indicated.*

3) *Lumbar CSF cytology 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 markers must be obtained unless medically contraindicated. If possible determine CSF markers and serum markers on the same day. If lumbar CSF markers are contraindicated, ventricular CSF markers are acceptable. In case CSF diversion and biopsy/surgery is combined, ventricular CSF should be collected first.*

4) *Banking studies (optional, consent required): See Section 15.2 for details.*

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



TOXICITIES AND DOSAGE MODIFICATIONS:

"See Section 5.0"

REQUIRED RAPID CENTRAL REVIEW:

___1. Mandatory rapid central imaging and tumor marker review will be performed at study entry to confirm the extent of the disease, and at the end of Induction Cycle 4 to determine response. Imaging scans and details of AFP and hCGβ levels in the serum and/or CSF will be reviewed on both occasions.

___2. Study Entry:
Biomarker results (AFP and hCGβ levels) will be submitted via Rave, and material for imaging review must be submitted as soon as possible. (See Section 16.0 for scan submission details.) Results of rapid central review will be provided via e□mail within 3 business days of receipt of all required materials.

___3. **End of Induction:**
Biomarker results (AFP and hCGβ levels) will be submitted via Rave, and material for imaging review must be submitted as soon as possible after completion of Cycle 4 of Induction therapy. (See Section 16.0 for scan submission details.) Results of rapid central review will be provided via e-mail within 3 business days of receipt of all required materials.

OPTIONAL STUDIES FOR BIOBANKING:

Specimens for Biobanking
In consenting patients, please submit samples for banking for future biology studies as outlined below. Sites are encouraged to submit samples even if not all are available (e.g., if only peripheral blood is available, please submit the peripheral blood sample).

If a patient has consented to optional banking on APEC14B1 and has submitted tumor and/or CSF at the time of diagnosis under that protocol, these samples do not need to be duplicated for the optional specimen banking on ACNS2321. If tumor tissue was not submitted for APEC14B1, then please submit tissue for ACNS2321.

If a patient has not submitted blood in a Streck Cell-Free DNA tube via APEC14B1, then they are strongly encouraged to submit blood in a Streck Cell-Free DNA tube for APEC14B1, using an APEC14B1 transmittal form. It is preferred that this blood be collected prior to treatment start, but it can still be collected after treatment has begun. See APEC14B1 MOP for details.

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 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)	N/A	• Pre-treatment/diagnosis • Relapse or progression

Sample	Amount	Container	Taken at the following time points:
	1 stained H&E		
CSF	10 mL per timepoint*	Cryovial or tube	• Pre-treatment/diagnosis • After Induction Cycle 4 (if positive markers or cytology at baseline) • Prior to start of RT (if positive markers or cytology at baseline) • End of therapy (if positive markers or cytology at baseline) • 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 younger 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.