COG-ACNS1821: A Phase 1/2 Trial of Selinexor (KPT-330) and Radiation Therapy in Newly-Diagnosed Pediatric Diffuse Intrinsic Pontine Glioma (DIPG) and High-Grade Glioma (HGG)

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. Prior to pre-enrollment (Step 0), a reservation must be made. 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 and no later than 31 calendar days after the date of radiographic diagnosis or definitive surgery as per Section 3.3.7. **Patients who are started on protocol therapy on a Phase 2 study prior to study enrollment will be considered ineligible**.
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment

___2. **To expedite the central review process, it is strongly recommended that sites submit tissue on APEC14B1 and commence the enrollment process as soon as diagnosis of HGG is suspected**.

___3. **Pre-Enrollment Eligibility Screening (Step 0)**
DIPG patients: Prior to enrollment on ACNS1821 (Step 1), DIPG patients must enroll on HGG Pre-Enrollment Eligibility Screening (Step 0). (Please see Section 3.1.1 for the Pre-Enrollment Eligibility Screening Criteria.) DIPG patients will not undergo the rapid central pathology and molecular reviews that are mandatory for HGG patients so enrollment on APEC14B1 is not mandatory. However, DIPG patients must complete Step 0 prior to enrollment on Step 1. Please refer to the APEC14B1 Manual of Procedures (MOP) for instructions on accessing the HGG Pre-Enrollment Eligibility Screening (Step 0) form.

HGG patients: Prior to enrollment on a COG treatment study for HGG, patients will be screened to determine which of the available treatment studies they may be eligible to enroll on. Screening will occur through APEC14B1, *The Project:EveryChild Protocol: A Registry, Eligibility Screening, Biology, and Outcome Study*. An overview of the currently available HGG treatment studies is provided in the APEC14B1 Manual of Procedures (MOP). Please refer to the APEC14B1 MOP for instructions on accessing the HGG Pre-Enrollment Eligibility Screening (Step 0) form.

Patients must be consented and enrolled on APEC14B1 Part A – Eligibility Screening and are highly recommended to consent to the NCI's CCDI Molecular Characterization Initiative (CCDI-MCI). Enrollment on APEC14B1 must be followed by enrollment on the HGG Pre-Enrollment Eligibility Screening (Step 0) on the same day to complete the RAPID CENTRAL PATHOLOGY and RAPID CENTRAL MOLECULAR REVIEWS. The APEC14B1 Part A consent will cover the Pre-Enrollment Eligibility Screening (including pathology and molecular central reviews) for the HGG treatment study. See Appendix II, Section 3.1.1, Section 14.0, and Section 15.0.

___4. Pre-Enrollment Eligibility Screening Criteria

- Age
  Patients must be ≥ 12 months and ≤ 21 years of age at the time of enrollment on Step 0.
  Please note:
  - **This age range includes pre-screening for all HGG patients. Individual treatment protocols may have different age criteria.**
  - Non-DIPG patients with tumors that do not harbor an H3K27M-mutation and are ≥ 18 years of age will not be eligible to enroll on ACNS1821 (Step 1).
- Diagnosis
  Patient is suspected of having localized, newly diagnosed HGG, excluding metastatic disease, OR patient has an institutional diagnosis of DIPG.

Please note: there are specific radiographic criteria for DIPG patient enrollment on ACNS1821 (Step 1), see Section 3.3.2.1.

- Consent
  For patients with non-pontine tumors: Patient and/or their parents or legal guardians have signed informed consent for eligibility screening on APEC14B1 Part A.
  For patients with DIPG: Patient and/or their parents or legal guardians have signed informed consent for ACNS1821.
- Mandatory Specimen Submission
  For patients with non-pontine tumors only, the specimens obtained at the time of diagnostic biopsy or surgery must be submitted through APEC14B1 ASAP, preferably within 5 calendar days of definitive surgery.
  Please note: See the APEC14B1 Manual of Procedures for a full list of detailed instructions for submitting required materials and for shipping details.

___5. Mandatory Rapid Central Pathology Screening Review for Strata DMG/HGG Only
See Appendix II and Section 14.0. All patients with non-pontine tumors must have RAPID CENTRAL PATHOLOGY SCREENING REVIEW ON APEC14B1 PRIOR TO STUDY ENROLLMENT ON ACNS1821 STEP 1 in order to avoid discordant diagnosis criterion for treatment on ACNS1821. Required samples from the time of diagnosis must be submitted on APEC14B1 to the BPC ASAP, preferably within 5 calendar days of surgery to allow for the pre-screening part of the protocol prior to enrolling on ACNS1821 Step 1.

___6. **Laboratory & Clinical Studies**
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to Step 1 *enrollment* unless otherwise indicated.

Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility.

If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 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 re-check is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

A pre- and post-operative brain or spine MRI with and without contrast must be obtained prior to enrollment (see Section 16.1). The requirement for post-operative MRI is waived for patients who undergo biopsy only and for Stratum DIPG patients enrolled without a biopsy.

___7. Age
Patients must be ≥ 12 months and ≤ 21 years of age at the time of enrollment.

___8. Diagnosis
Patients must have newly-diagnosed DIPG or HGG (including DMG).

- Stratum DIPG
  - Patients with newly-diagnosed typical DIPG, defined as tumors with a pontine epicenter and diffuse involvement of at least 2/3 of the pons on at least 1 axial T2-weighted image, are eligible. No histologic confirmation is required.
  - Patients with pontine tumors that do not meet radiographic criteria for typical DIPG (e.g., focal tumors or those involving less than 2/3 of the pontine cross-sectional area with or without extrapontine extension) are eligible if the tumors are biopsied and proven to be high-grade gliomas (such as anaplastic astrocytoma, glioblastoma, high-grade glioma NOS, and/or H3 K27M-mutant) by institutional diagnosis.
- Stratum DMG (with H3 K27M mutation)
  - Patients must have newly-diagnosed non-pontine H3 K27M-mutant HGG without *BRAFV600* or *IDH1* mutations **as confirmed by Rapid Central Pathology and Molecular Screening Reviews performed on APEC14B1 (see Section 3.1) or through the CCDI-MCI**.
    Note: Patients need not have either measurable or evaluable disease, i.e., DMG patients may have complete resection of their tumor prior to enrollment. Primary spinal tumors are eligible for enrollment. For rare H3 K27M-mutant HGG in non-midline structures (e.g., cerebral hemispheres), these patients will be considered part of Stratum DMG.

- Stratum HGG (without H3 K27M mutation)
  - Patients must have newly-diagnosed non-pontine H3 K27M-wild type HGG without *BRAF*^{V600} or *IDH1* mutations **as confirmed by Rapid Central Pathology and Molecular Screening Reviews performed on APEC14B1 (see Section 3.1) or through the CCDI-MCI**.

    Please note:
    - Patients who fall in this category and who are ≥ 18 years of age are not eligible due to another standard-of-care regimen (radiation/temozolomide) that is available (see Section 2.1 and Section 3.3.8.1).
    - Patients need not have either measurable or evaluable disease, i.e., HGG patients may have complete resection of their tumor prior to enrollment. Primary spinal tumors are eligible for enrollment.

___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 https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

___10. Prior Therapy

Patients must not have received any prior therapy for their CNS malignancy except for surgery and steroid medications.

___11. Concomitant Medications Restrictions

- Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
- Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.

___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
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
≥ 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. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Adequate Pancreatic Function Defined As:
  - Serum amylase ≤ 1.5 x ULN
  - Serum lipase ≤ 1.5 x ULN
- 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.

- Central Nervous System Function Defined As:
  - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

___13. Timing

Patients must be enrolled and protocol therapy must begin no later than 31 days after the date of radiographic diagnosis (in the case of non-biopsied DIPG patients only) or definitive surgery, whichever is the later date (Day 0). For patients who have a biopsy followed by resection, the date of resection will be considered the date of definitive diagnostic surgery. If a biopsy only was performed, the biopsy date will be considered the date of definitive diagnostic surgery.

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

EXCLUSION CRITERIA:

___1. Patients ≥18 years of age who have H3 K27M-wild type HGG.
___2. Patients who have an uncontrolled infection.
___3. Patients who have received a prior solid organ transplantation.
___4. Patients with Grade > 1 extrapyramidal movement disorder.
___5. Patients with known macular degeneration, uncontrolled glaucoma, or cataracts.
___6. Patients with metastatic disease are not eligible; MRI of spine with and without contrast must be performed if metastatic disease is suspected by the treating physician.
___7. Patients with gliomatosis cerebri type 1 or 2 are not eligible, with the exception of H3 K27M-mutant bithalamic tumors.
___8. Patients who are not able to receive protocol specified radiation therapy.
___9. Pregnancy and Breast Feeding

- Female patients who are pregnant are ineligible since there is yet no available information regarding human fetal or teratogenic toxicities.
- Lactating females are not eligible unless they have agreed not to breastfeed their infants. It is not known whether selinexor is excreted in human milk.
- 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 two effective methods of birth control (including a medically accepted barrier method of contraception, e.g., male or female condom) for the duration of their study participation and for 90 days after the last dose of selinexor. Abstinence is an acceptable method of birth control.

REQUIRED OBSERVATIONS:

Required Observations in Selinexor/Radiotherapy

a. History: Perform at baseline and weekly during Selinexor/Radiotherapy.
b. Physical exam with vital signs: Perform at baseline and weekly during Selinexor/Radiotherapy.
c. Height, weight: Perform at baseline and weekly during Selinexor/Radiotherapy.
d. Neurologic exam: Perform at baseline and weekly during Selinexor/Radiotherapy.
e. Performance status: Perform at baseline.
f. CBC, differential: Perform at baseline and every two weeks during Selinexor/Radiotherapy.
g. Electrolytes including Na, K, Cl, HCO3, glucose, Ca, PO4, Mg: Perform at baseline and every two weeks during Selinexor/Radiotherapy.
h. Creatinine, ALT, bilirubin: Perform at baseline and every two weeks during Selinexor/Radiotherapy.
i. Urinalysis: Perform at baseline.
j. Pregnancy test: Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use 2 effective methods of birth control including a medically accepted barrier method of contraception (e.g., male or female condom). Abstinence is an acceptable method of birth control. Pregnancy testing is required prior to tumor imaging per institutional guidelines.
k. Snellen eye chart: Perform at baseline. If a decline in visual acuity occurs or other visual symptoms occur, the patient should be referred to an ophthalmologist for an examination.
l. Specimens for biobanking (in consenting patients): See Section 15.2.

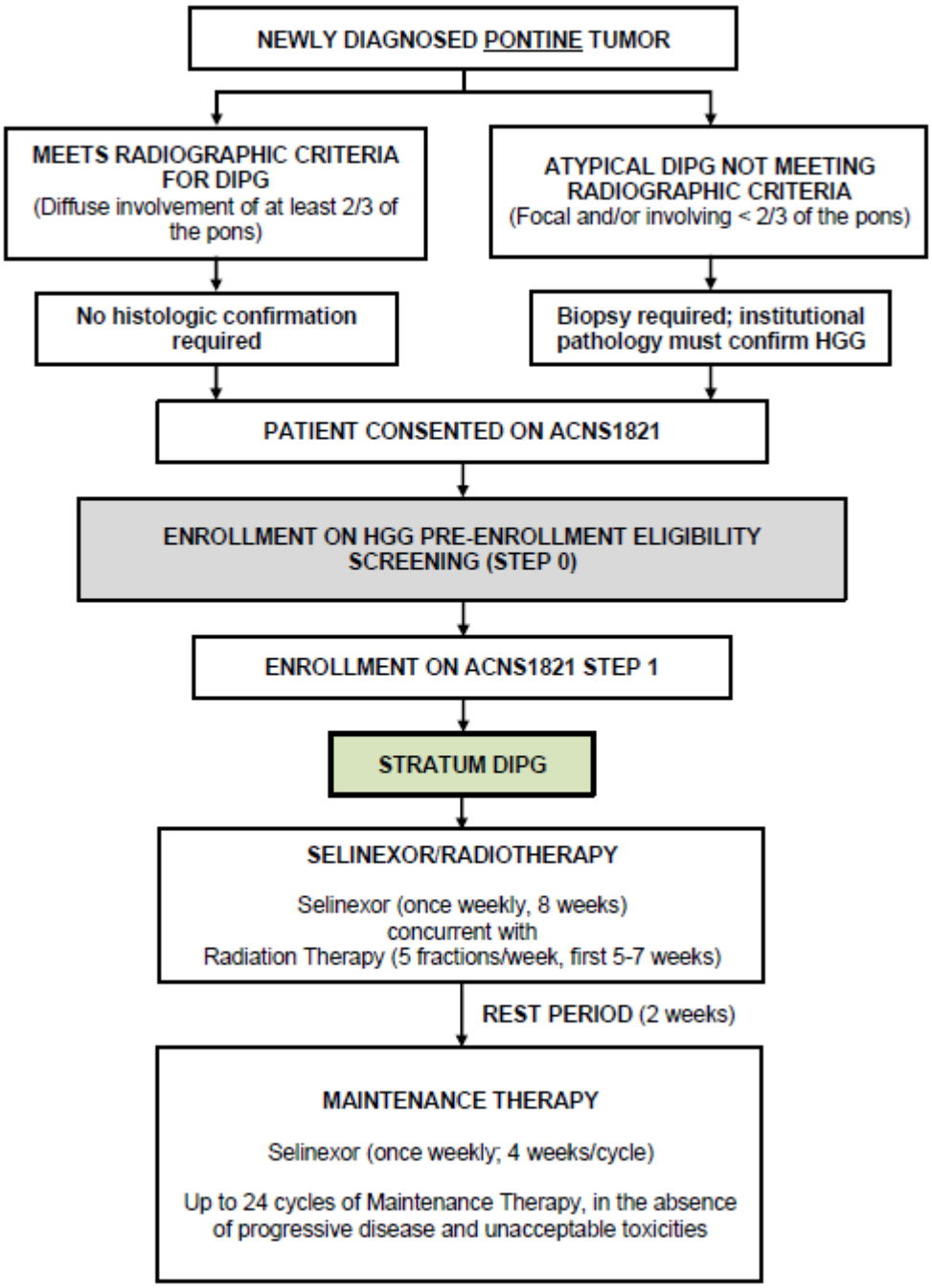
TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:
Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix VI

BIOLOGY REQUIREMENTS:
See Section 15.1
Peripheral blood, 10 mL, Streck tube
Frozen tumor, 3 x 100 mg pieces, If snap frozen tissue is not available, FFPE blocks or scrolls will be accepted.
CSF, 5 mL if available

TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA: STRATUM DIPG



EXPERIMENTAL DESIGN SCHEMA: STRATUM DMG AND STRATUM HGG