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 Step 1 enrollment, a reservation must be made. See protocol Section 3.2.3.

___2. Pre-Enrollment Eligibility Screening
DIPG patients: Prior to enrollment on ACNS1821 (Step 1), DIPG patients must be enrolled on APEC14B1, *the COG Project:EveryChild Registry, Eligibility Screening, Biology, and Outcome Study,* and consented to Part A (to ensure our ability to utilize imaging reports for eligibility diagnosis). DIPG patients will not undergo the rapid central pathology and molecular reviews that are mandatory for HGG patients, therefore specimens for pre-enrollment eligibility screening are NOT required to be submitted for this strata.

HGG patients: 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*, Part A, and sites must complete the appropriate CNS/HGG screening forms. RAPID CENTRAL PATHOLOGY and RAPID CENTRAL MOLECULAR reviews will be performed to confirm eligibility. Please refer to the APEC14B1 Manual of Procedures (MOP) for instructions on accessing the CNS/HGG screening forms.

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). The APEC14B1 Part A consent will cover the CNS/HGG 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.

Once the CNS/HGG Pre-Enrollment Eligibility Screening results are known, all eligibility criteria for the appropriate treatment study, including patient consent, must be met prior to enrollment on Step 1 of that treatment study.

- **To expedite the central review process, it is strongly recommended that sites submit all required materials on APEC14B1 and MCI (if applicable) as soon as diagnosis of HGG is suspected**.

- Samples from the time of diagnosis (see Section 3.1.1.4) must be submitted on APEC14B1 to the COG Biopathology Center (BPC) ASAP, preferably within 5 calendar days of surgery to allow for the CNS/HGG Pre-Enrollment Eligibility Screening prior to consent and enrollment on Step 1 of the treatment trial. **Patients must be enrolled on APEC14B1 before slides are shipped to the BPC.**

  IMPORTANT NOTE: Delay of specimen submission (> 5 calendar days after surgery) will **significantly** slow down the central review process and will not guarantee central review completion within the 31-day window from surgery to initiation of protocol therapy. It is **strongly** suggested that sites submit required specimens no later than 5 days after diagnostic surgery to meet the timing requirements outlined in Section 3.2.5.

- **Sites will receive notification by e-mail regarding central histopathology review results within 7 calendar days of receipt of all required materials at the BPC. Sites may use one of three options to obtain required targeted gene sequencing results for molecular review: 1) Participation in APEC14B1-MCI, with submission of whole exome test results; 2) Submission of clinical (CAP/CLIA certified or equivalent) local targeted sequencing results for all three required genes (*BRAF*^{V600}, *IDH1*, *IDH2*), or 3) Targeted central molecular testing through CNS/HGG screening. Central molecular review results will be available within 24 calendar days of receipt of all required materials at the BPC (up to 30 calendar days total after surgical resection). For patients consenting to CCDI-MCI for molecular testing or relying on local targeted sequencing results, sites need to upload reports for central review as soon as they are available.** The final screening eligibility determination will be made by one of the Study Pathologists once the histopathology and molecular results are available. Notification of patient eligibility/ineligibility for Step 1 enrollment on a treatment trial, based on histopathologic and molecular phenotyping results, will be sent to the e-mail addresses entered by the site during initial CNS/HGG pre-enrollment eligibility screening registration. The information will also be available in RAVE. (Note: The BPC is not responsible for sending results to sites).

- Radiotherapy planning should begin as soon as possible at the local sites in order to permit commencement of radiotherapy within 31 calendar days of definitive surgery (see Section 17.0).

___3. Pre-Enrollment Eligibility Screening Criteria

The following criteria must be met prior to initiating CNS/HGG Pre-Enrollment Eligibility Screening.

- Age

  Patients must be ≤ 25 years of age at the time of enrollment on APEC14B1 Part A CNS/HGG pre-enrollment eligibility screening.

  Please note:
  - This required age range applies to the pre-enrollment eligibility 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: Patients and/or their parents or legal guardians must have signed informed consent for eligibility screening on APEC14B1 Part A.

  For patients with DIPG: Patients and/or their parents or legal guardians must have signed informed consent for ACNS1821.

- Mandatory Specimen Submission

  For patients with non-pontine tumors <u>only</u>, 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.

___4. 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 under 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.

Sites will be notified by e-mail of the rapid central pathology review within 7 calendar days of receipt of all required samples at the BPC. Notification of histopathologic eligibility/ineligibility will be sent to the e-mail addresses that were entered by the site during initial CNS/HGG Pre-Enrollment Screening registration.

To expedite the central review process, it is strongly recommended that the site submit tissue through APEC14B1 and commence the process of enrollment as soon as a diagnosis of high-grade glioma is suspected. See Section 3.1.1 Pre-Enrollment Eligibility Screening Criteria.

Rapid central review of the submitted specimens will occur via digital whole slide images scanned at the BPC. Unstained slide/FFPE scroll distribution will be coordinated by the BPC. All samples will undergo central pathology review. Difficult cases will be discussed among the study neuropathologists so as to achieve a consensus review diagnosis.

Once the central pathology results are known and diagnosis is confirmed as DMG/HGG, it is recommended that discussions regarding the possible treatment studies be initiated with the patient/family.

___5. Mandatory Rapid Central Molecular Screening Review for Strata DMG/HGG Only
See Appendix II, Appendix III and Section 15.0. All patients who have pathology confirmed by central pathology review must then have RAPID CENTRAL MOLECULAR SCREENING REVIEW ON APEC14B1 PRIOR TO STUDY ENROLLMENT ON ACNS1821 STEP 1 in order to avoid discordant diagnoses and to verify diagnosis criteria for treatment on ACNS1821.

Please note: The following elements are required for central pathology and molecular review:

Histopathology: Samples must be submitted for central histopathology review for all patients.

Immunohistochemistry: H3 K27M immunohistochemistry may be performed centrally at the Biopathology Center if not reported in the local clinical pathology report.

Targeted gene sequencing: Sites may use one of three options to obtain required targeted gene sequencing results for molecular review:

1. Participation in APEC14B1-MCI, with submission of whole exome test results for study screening, or
2. Submission of clinical (CAP/CLIA certified or equivalent) local targeted sequencing test results for all three required genes (*BRAF^{v600}, IDH1, IDH2),* or
3. Targeted central molecular testing through CNS/HGG screening.

Although all options meet minimum criteria for study screening, MCI testing is strongly encouraged as the preferred option for patients with adequate tissue as the most comprehensive molecular characterization will be provided by the MCI.

Acceptable local test results include:

- CAP/CLIA-certified results for H3 K27M **immunohistochemistry**
- CAP/CLIA-certified results for *BRAF^{v600}*, *IDH1* and *IDH2* **targeted sequencing**

Redacted copies of the laboratory report(s) containing these results must be uploaded to the "HGG Pre-Enrollment Report Upload" CRF in Rave so that the results can be included in our central molecular review.

If a site wishes to submit laboratory report results in lieu of samples, the BPC staff ***MUST*** be notified (during initial registration on screening) that test results will be provided via laboratory report(s). The laboratory reports will need to be uploaded as soon as they become available. If local targeted gene sequencing reports are not uploaded within two weeks of surgery, then there may not be sufficient time to submit samples if the reports are insufficient.

> Please note: samples ***must*** be submitted for any molecular testing that is ***not*** done locally. See the APEC14B1 MOP for a list of samples required for molecular testing. Central reviewers may request samples if the submitted reports are not sufficient.

For those sites who do not provide results from acceptable local tests, samples must be submitted for central testing/central review. The following tests will be performed through central testing.

- H3 K27M IHC staining, and review will occur at Nationwide Children's Hospital.
- Real time molecular characterization for *BRAF^{v600}*, *IDH1 and IDH2* will occur through NCI's CCDI Molecular Characterization Initiative (CCDI-MCI) or at the University of Washington in a CAP/CLIA certified laboratory.

The CCDI-MCI includes enhanced whole exome sequencing (WES), the RNA Archer Fusion-Plex assay, and the Illumina 850K EPIC DNA methylation array method on tumor and blood samples. For patients who do not consent, or who do not have sufficient tissue for CCDI-MCI, molecular characterization by targeted sequencing will occur at the University of Washington.

Results from CCDI-MCI on APEC14B1 will be available within 21 days of receipt of all required materials at the BPC. The CCDI-MCI results reports must be downloaded from the MCI portal by the site and then must be redacted and uploaded to the "HGG Pre-Enrollment MCI Upload" CRF in Rave as soon as they are available to the site. **Upload of these reports by sites in a timely manner is critical as the central reviewers will not have access to the MCI portal.** Results of the central review of the molecular reports will be available within 3 days of CCDI-MCI report upload into Rave. Results from the molecular review for eligibility/ineligibility will be sent to the e-mail addresses entered by the site during initial CNS/HGG Pre-Enrollment Eligibility Screening registration.

If central molecular screening is conducted at University of Washington, specimens will have targeted Next-Generation Sequencing (NGS) analysis for determination of mutations involving *BRAF^{v600}* and *IDH1 and IDH2*. These results will be directly provided by the central molecular review.

Results from the central molecular screening review will be available within 24 calendar days of receipt of all required samples at the BPC (up to 30 calendar days total after surgical resection). Patients will receive results from the treating physician. **Results from the molecular review for eligibility/ineligibility will be sent to the e-mail addresses that were entered by the site during initial CNS/HGG Pre-Enrollment Eligibility Screening registration.** (Note: The BPC is not responsible for sending results to sites.)

___6. Age

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

___7. 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 *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**.

    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.

___8. 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.

___9. Prior Therapy

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

___10. 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.

___11. 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.

___12. 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 or equivalent/age-appropriate/best possible measure of visual acuity: 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

OPTIONAL BIOLOGY REQUIREMENTS:

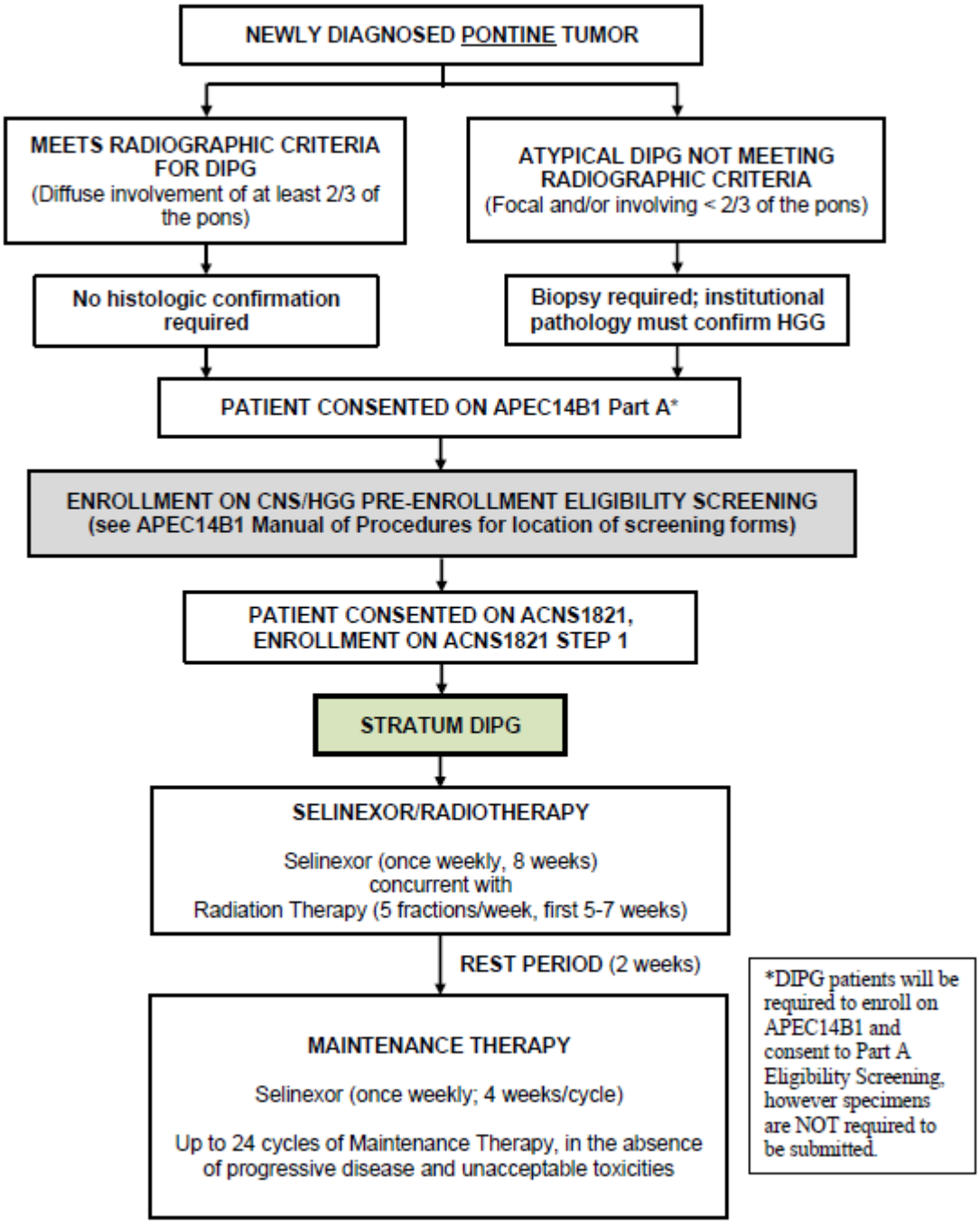
See Section 15.2.1 – 15.2.1.1
Peripheral blood, 10 mL, Streck tube
Frozen tumor, 3 x 100 mg pieces, If snap frozen tissue is not available, FFPE blocks or scrolls will be accepted.
CSF, 5 mL if available

TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA: STRATUM DIPG

Dose-Finding Phase

Amendment #3
As of Amendment #3, The dose-finding phase has been completed. The RP2D dose for the Efficacy Phase was determined to be DL3 of **Selinexor: 55 mg/m2/dose (maximum 120 mg/dose).**

The starting dose level for selinexor will be 35 mg/m2 weekly.



EXPERIMENTAL DESIGN SCHEMA: STRATUM DMG AND STRATUM HGG