A Molecular Biology and Phase II Study of Imetelstat (GRN163L) in Children with Recurrent High-Grade Glioma, Ependymoma, Medulloblastoma/Primitive Neuroectodermal Tumor and Diffuse Intrinsic Pontine Glioma.

This study consists of two parts: a Molecular Biology study and Phase II study, which will be conducted simultaneously.

**Molecular Biology:**
Children with recurrent or refractory medulloblastoma/primitive neuroectodermal tumor (PNET), ependymoma or high-grade glioma (HGG), for whom surgical resection is clinically indicated and who are amenable to surgical resection, will receive 1 (one) dose of imetelstat (GRN163L) as a 2-hour intravenous infusion at the recommended pediatric Phase II dose, 285mg/m², established in the Children’s Oncology Group (COG) Phase I single-agent pediatric study, at a target of 12-24 hours prior to the anticipated surgery during the Surgical Course. Any subject who requires surgery emergently is not eligible for this component of the trial. Following the pre-surgery imetelstat dose during the Surgical Course, the patients must demonstrate adequate coagulation parameters before surgery can be performed. After surgery, subjects will be treated with imetelstat at the recommended Phase II pediatric dose, 285mg/m², on Days 1 and 8 of each 21-day course starting at least 14 days after the pre-surgery imetelstat dose during the Surgical Course. Therapy may continue in the absence of disease progression or unacceptable toxicity for up to two years (34 courses). The following schematic summarizes the treatment plan and table describes the stratification plan.

**Molecular Biology Stratification**

<table>
<thead>
<tr>
<th>Stratum A</th>
<th>Stratum B</th>
<th>Stratum C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent or refractory medulloblastoma/PNET</td>
<td>Recurrent or refractory high-grade glioma</td>
<td>Recurrent or refractory ependymoma</td>
</tr>
</tbody>
</table>

**Phase II:**
Imetelstat (GRN163L) will be administered to children with recurrent or refractory medulloblastoma/PNET, HGG, ependymoma, or diffuse intrinsic pontine glioma (DIPG) on
Days 1 and 8 of every 21-day course as a 2-hour intravenous infusion at the recommended Phase II pediatric dose, 285mg/m². Therapy may continue in the absence of disease progression or unacceptable toxicity for up to two years (34 courses). The following schematic summarizes the treatment plan and table summarizes the strata that will be used in this trial.

### Phase II Stratification

<table>
<thead>
<tr>
<th>Stratum A</th>
<th>Stratum B</th>
<th>Stratum C</th>
<th>Stratum D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent or refractory</td>
<td>Recurrent or refractory</td>
<td>Recurrent or refractory</td>
<td>Recurrent or refractory</td>
</tr>
<tr>
<td>medulloblastoma/PNET</td>
<td>high-grade gliomas</td>
<td>ependymoma</td>
<td>diffuse intrinsic pontine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gliomas (DIPG)</td>
</tr>
</tbody>
</table>

**Objectives:**

**Primary Objectives**

**Molecular Biology:**

1. To test the ability of imetelstat (GRN163L) to inhibit telomerase activity by Telomere Repeat Amplification Protocol (TRAP) in tumor and peripheral blood mononuclear cells (PBMNCs) of children with recurrent or refractory medulloblastoma/PNET, HGG or ependymoma.

2. To characterize the pharmacokinetics of imetelstat in plasma, cerebrospinal fluid (CSF), and tumor tissue of children with recurrent or refractory HGG, medulloblastoma/PNET or ependymoma.

**Phase II:**

1. To estimate the sustained objective response rates (complete response (CR) plus partial response (PR), sustained for at least 6 weeks) to imetelstat administered intravenously on Days 1 and 8 of a 21-day course at the recommended Phase II pediatric dose, 285mg/m², in children with recurrent or refractory medulloblastoma/PNET, HGG, ependymoma or DIPG. Independent estimates of the objective response rates will be made for each of the four strata, three of which are histologically defined.

**Secondary Objectives**

**Phase II only:**

1. To assess evidence of telomerase expression by detection of hTERT mRNA and TERC RNA levels by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and telomerase activity by TRAP in archival tumor tissue (for medulloblastoma/PNET, HGG,
and ependymoma strata) and to explore association of telomerase positivity with objective response and progression-free survival (PFS).

2. To estimate the stratum-specific PFS distributions of children with recurrent or refractory medulloblastoma/PNET, HGG, ependymoma or DIPG treated with imetelstat.

Molecular Biology and Phase II:
1. To characterize the plasma and CSF pharmacokinetics of imetelstat in children with recurrent or refractory medulloblastoma/PNET, HGG, ependymoma or DIPG.

2. To assess evidence of telomerase expression by detection of hTERT mRNA and TERC RNA levels by qRT-PCR, telomerase activity by TRAP, and telomere length by telomere terminal restriction fragment (TRF) analysis in PBMNCs prior to treatment with imetelstat and to assess evidence of telomerase inhibition by TRAP and telomere shortening by TRF analysis serially on treatment with imetelstat.

3. To compare incidence of Alternative Lengthening of Telomeres (ALT) mechanism in pediatric medulloblastoma/PNET, HGG, or ependymoma as determined by three different assays 1) ATRX/DAXX nuclear localization by immunofluorescence (IF) assay; 2) telomere-specific signal by fluorescence in situ hybridization (FISH); and 3) telomeric terminal restriction fragment (TRF) analysis by Southern blot and to assess correlation of these methods for ALT detection.

4. To assess whether ALT status is associated with objective response rates for children with recurrent or refractory medulloblastoma/PNET, HGG, or ependymoma treated with imetelstat.

5. To describe MRI characteristics and diffusion changes of recurrent or refractory medulloblastoma/PNET, HGG, ependymoma and DIPG tumors prior to and after treatment with imetelstat to assess for an early diffusion indicator of response.

6. To measure telomere length of tumors in children with recurrent or refractory medulloblastoma/PNET, HGG, or ependymoma and to assess association of tumor length with tumor response to imetelstat treatment.

PATIENT SELECTION

Eligibility Criteria:

Molecular Biology Study:
- Tumor: Subjects must have a histologically confirmed diagnosis of medulloblastoma/PNET, ependymoma or HGG (such as anaplastic astrocytoma, glioblastoma, gliosarcoma, or anaplastic oligodendroglioma) that is recurrent or refractory to conventional therapy.

- Subjects must have clinical indications for surgical resection and be amenable to receiving imetelstat prior to tumor resection. Subjects who require emergent surgery are not eligible for the Molecular Biology study.
Subjects must provide, fresh flash frozen tumor samples (target 50 mg tissue; as low as 20 mg is adequate) from the time of diagnosis or previous recurrence for the assessment of tumor telomerase activity by the TRAP assay.

**Phase II Study:**
- Tumor: Subjects must have recurrent or refractory disease with a histological diagnosis from either the initial presentation or at the time of recurrence. The requirement for histologic verification is waived for subjects with DIPG (stratum D). The following diagnoses are eligible and will be treated in separate strata (A-D):
  - recurrent or refractory medulloblastoma/PNET
  - recurrent or refractory high-grade glioma, (such as anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma, anaplastic oligodendroglioma)
  - recurrent or refractory ependymoma
  - recurrent or refractory DIPG (diagnosis by imaging characteristics acceptable; no histologic confirmation required)

- Slides from either initial diagnosis or relapse must be available for central pathology review for Strata A-C. Tissue slides must be sent per Section 10.1. If tissue slides are unavailable, the study chair must be notified prior to study enrollment.

- All subjects must have bi-dimensionally measurable disease in the brain and/or spine, defined as at least one lesion that can be accurately measured in at least two planes in order to be eligible for this study. Subjects who are enrolled on the Molecular Biology trial and who have measurable disease after the surgical resection and meet all other eligibility criteria for the Phase II study will be counted towards the accrual of the Phase II study.

**For both Molecular Biology and Phase II studies**
- Age: Subjects must be ≥12 months and ≤21 years of age
- Neurological Status: Subjects with neurological deficits should have deficits that are stable for a minimum of one (1) week prior to registration. A baseline detailed neurological exam should clearly document the neurological status of the subject at the time of registration on the study.
- Performance Status: Karnofsky ≥ 50% for > 16 years of age; Lansky ≥ 50% for children ≤ 16 years of age documented within 14 days of study registration and within 7 days of the start of study drug administration.
- Organ Function
  - Hemoglobin ≥8 g/dL (may receive blood transfusions),
  - Absolute neutrophil count > 1,000/µL,
  - Platelet count ≥ 100,000/µL (transfusion independent defined as no platelet transfusions with a 7-day period prior to enrollment).
• Serum bilirubin < 2.0 mg/dL (patients with Gilbert syndrome, serum bilirubin < 3.0 × ULN)
• ALT (SGPT) ≤ 2.5 × institutional ULN,
• AST (SGOT) ≤ 2.5 × institutional ULN,
• Alkaline phosphatase < 2.5 × institutional ULN
• Albumin ≥ 2 g/dL.
• Adequate coagulation defined as aPTT < 1.2 × ULN
• Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m² or a serum creatinine based on age/gender as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>1 to &lt; 2 years</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>2 to &lt; 6 years</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6 to &lt; 10 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10 to &lt; 13 years</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>13 to &lt; 16 years</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>≥ 16 years</td>
<td>1.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

- 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.

- Concurrent medications: Subjects on systemic anticoagulants are excluded from this study as the drug can cause minor, transient changes in aPTT.
- Pregnancy Status: Female subjects of childbearing potential must not be pregnant or breastfeeding. Female subjects of childbearing potential must have a negative serum or urine pregnancy test. (Pregnancy test must be repeated within 48 hours prior to the start of therapy).
- Pregnancy Prevention: Subjects of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.
- Prior Therapy: Subjects must have recovered from the acute toxicities of all prior therapy before entering this study. For those acute baseline adverse events attributable to prior therapy, recovery is defined as a toxicity Grade ≤ 2, using CTCAE v.4.0, unless otherwise specified in the Inclusion and Exclusion Criteria.
- Myelosuppressive chemotherapy: Subjects must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration or at least six (6) weeks if nitrosourea.
- Investigational / Biologic agent:
- Subjects must have received their last dose of investigational or biologic agent ≥ 7 days prior to study registration.
- In the event that a subject has received an investigational or biologic agent and has experienced ≥ Grade 2 myelosuppression, then at least three (3) weeks must have elapsed prior to registration.
- If the investigational or biologic agent has a prolonged half-life ($\geq 7$ days) then at least three (3) weeks must have elapsed prior to registration.
- Monoclonal antibody treatment: Subjects must have completed at least 3 half-life periods from the last dose of monoclonal antibody prior to registration.
  Note: A list of half-lives of commonly used monoclonal antibodies is available on the PBTC website under Generic Forms and Templates
- Radiation: Subjects must have received their last dose of radiation (XRT):
  - $\geq 2$ weeks prior to study registration for local palliative XRT (small volume)
  - $\geq 3$ months prior to study registration for craniospinal XRT
  - $\geq 6$ wks prior to study registration for other substantial bone marrow irradiation
- Bone Marrow Transplant: Subject must be $\geq 3$ months since autologous bone marrow/stem cell transplantation prior to registration.
- Corticosteroids: Subjects who are receiving a corticosteroid, such as dexamethasone, must be on a stable or decreasing dosage for at least 1 week prior to registration.
- Growth factors: At least 7 days since the completion of therapy with a hematopoietic growth agent (filgrastim, sargramostim, and erythropoietin) and 14 days for long-acting formulations.
- Informed Consent: Ability to understand and the willingness to sign a written informed consent document

**Exclusion Criteria**
- Current Therapy: Subjects must not be receiving any other investigational agents.
- Inability to Participate: Subjects with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.
- Agent Allergies: History of allergic reactions attributed to compounds of similar chemical or biologic composition to imetelstat.
- Known coagulopathy or bleeding diathesis
- Subjects with imaging evidence of any CNS hemorrhage, including punctate areas consistent with hemorrhage, on baseline MRI obtained within 14 days prior to study enrollment are not eligible.
- Use of systemic anticoagulant medications.
- Concurrent Illness:
  Uncontrolled intercurrent illness including, but not limited to, ongoing or active serious infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cirrhosis or psychiatric illness/social situations that would limit compliance with study requirements
- Pregnancy and Breastfeeding
  Pregnant women are excluded from this study because imetelstat is an investigational agent with unknown potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with imetelstat, breastfeeding should be discontinued if the mother is treated with imetelstat. These potential risks may also apply to other agents used in this study