A Phase I study of the ADAM-10 inhibitor, INCB007839 in children with recurrent/progressive high-grade gliomas to target microenvironmental neuroligin-3

Abstract and Schema

This is a multicenter phase 1 trial of INCB007839 for children with recurrent or progressive high-grade gliomas, including but not limited to diffuse intrinsic pontine glioma (DIPG) and other diffuse midline gliomas (DMGs), after upfront therapy.

INCB007839 is an inhibitor of the ADAM (A Disintegrin and Metalloprotease) 10 and 17 proteases. Neuronal activity regulates glioma growth through neuroligin-3 (NLGN3). ADAM10 is the protease responsible for NLGN3 release into the tumor microenvironment and represents a promising therapeutic target. Pre-clinical studies of INCB007839 in patient-derived pediatric high-grade gliomas (glioblastoma and DIPG) revealed that INCB007839 inhibits pediatric high-grade glioma growth and improves overall survival. *In vivo* testing also demonstrated that INCB007839 penetrates brain tissue sufficient to achieve its pharmacodynamic effect of ADAM10 inhibition. Further pre-clinical studies in other animals revealed minimal toxicity, including non-adverse to mild increases in serum hepatobiliary enzymes, protein, calcium, cholesterol values, along with minimal decreases in RBC mass parameters; all parameters recovered.

INCB007839 has been evaluated in phase 1 and phase 2 clinical trials for previously treated solid tumors and breast cancer. Of the adverse events noted, the majority were mild-to-moderate in severity, the most frequent being fatigue, nausea, anorexia, diarrhea, emesis, abdominal pain, anemia, and constipation. The dose-limiting toxicity for monotherapy with INCB007839 in phase 1 clinical trials was declared to be deep venous thrombosis (DVT). Out of 41 patients, there were 9 thrombotic events including mild superficial thrombophlebitis (n=1), DVT (n=4), vena cava thrombosis with renal insufficiency in a patient with squamous cell cancer of the head and neck (n=1), atrial thrombosis in patient with breast cancer (n=1), and pulmonary embolism in patients with hormone-refractory prostate cancer (n=2). Overall, INCB007839 does exhibit a pro-coagulant effect in some adult patients, resulting in an increased incidence of DVT, whether used alone or in combination. The mechanism of this effect is unknown, and there is no clear relationship between the frequency of thrombosis and the dose administered.

The primary objectives of this study are to: (1) evaluate the safety and tolerability of INCB007839 administered daily to children with recurrent/progressive high-grade gliomas; (2) determine the maximum tolerated dose (MTD) and/or recommended phase 2 (RP2D) dose of INCB007839; and (3) characterize the pharmacokinetics of INCB007839.

The adult RP2D is 200 mg orally (PO) twice a day (BID). Given this recommended dose, we propose to test the pediatric equivalent based on a typical adult size of 1.67 m^2. Thus, this clinical trial will start at 120 mg/m^2 and de-escalate to 80 mg/m^2 if not tolerable. INCB007839 will be administered orally, twice a day each day for 28-day cycles. Treatment may continue up to 26 courses (approximately 2 years) in the absence of disease progression or unacceptable toxicity.

Dose Level	Dose of INCB007839 (mg/m^2/dose, PO, BID)	BSA Range
0	80 mg/m^2/dose BID	0.55–2.80 m^2
1*	120 mg/m^2/dose BID	0.70–2.50 m^2

* Starting dose (adult RP2D)

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 To evaluate the safety and tolerability of INCB007839 in children with recurrent/progressive high-grade gliomas, including diffuse intrinsic pontine glioma (DIPG), diffuse midline glioma (DMG), glioblastoma (GBM), and anaplastic astrocytoma.

1.1.2 To estimate the maximum tolerated dose (MTD) and/or recommend Phase 2 dose (RP2D) of INCB007839 administered orally in children with recurrent/progressive high-grade glioma.

1.1.3 To characterize the plasma pharmacokinetics of INCB007839 administered on this schedule in children with recurrent/progressive high-grade glioma.

1.2 Secondary Objectives

1.2.1 To make a preliminary assessment of efficacy via objective response and overall survival in children with recurrent/progressive high-grade glioma.

1.3 Exploratory Objectives

1.3.1 To assess and monitor ADAM10 inhibition of HER2 (human epidermal growth factor receptor 2) extracellular domain in serum and explore potential correlation with patient outcome.

1.3.2 To assess and monitor ADAM10 inhibition of neuroligin-3 (NLGN3) in cerebrospinal fluid (CSF).

1.3.3 To characterize the pharmacokinetics of INCB007839 in cerebrospinal fluid.

3 PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within three weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

3.1 Inclusion Criteria

3.1.1 Histologic diagnosis

Patients with recurrent/progressive high-grade gliomas, as defined by progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid wean, electrolyte disturbances, sepsis, hyperglycemia, etc.), **OR** a ≥ 25% increase in the bi-dimensional measurement, taking as a reference the smallest disease measurement recorded since diagnosis utilizing the MRI sequence best demonstrating tumor, **OR** the appearance of a new/metastatic tumor lesion(s) since diagnosis.

- Eligible diagnoses include but are not limited to the following: diffuse intrinsic pontine glioma (DIPG), H3K27M-altered diffuse midline glioma (DMG), glioblastoma multiforme, anaplastic astrocytoma and anaplastic oligodendroglioma. Spinal cord tumors are eligible with pathologic confirmation of the above.
- Please note: Patients with a radiographically typical DIPG at diagnosis, defined as a tumor with a pontine epicenter and diffuse involvement of more than 2/3 of the pons, are eligible without histologic confirmation.
- Patients with pontine lesions that do not meet these radiographic criteria will be eligible if there is histologic confirmation of pontine glioma WHO II-IV.
- Patients with diffuse or multi-focal disease are eligible; patients with leptomeningeal spread are eligible.

3.1.2 Age

Patients must be ≥ 3 but ≤21 years of age at the time of enrollment.

3.1.3 BSA

Patients must have a BSA ≥ 0.70–2.50 m^2 for dose 120 mg/m^2/dose BID.
Patients must have a BSA ≥ 0.55–2.80 m^2 for dose 80 mg/m^2/dose BID (Patients who have BSA 0.55–1.00 m^2 will only receive 100 mg AM dose).

3.1.4 Ability to Swallow

Patients must be able to swallow tablets whole.

3.1.5 Measurable disease

Patients must have measurable disease in two dimensions on MRI to be eligible (as defined within the protocol, Section 12.1.2).

3.1.6 Prior Therapy

- Patients must have failed at least 1 standard, tumor-directed treatment besides surgery and recovered from the acute treatment-related toxicities (defined as ≤ Grade 1) of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment on this study.

- Patients must be ≥ 28 days from any prior surgery at the time of study enrollment (with the exception of minor dental and dermatological procedures).

3.1.6.1 Chemotherapy

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

3.1.6.2 Investigational/Biologic Agent

- Biologic or investigational agent (anti-neoplastic):

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

  - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 28 days prior to study enrollment.

- Immunotherapies:

Patients who have received checkpoint inhibitors or other immunotherapies with a known potential for pseudoprogression and who have assumed tumor progression must be at least 12 weeks from prior immunotherapy AND have at least two MRI scans at least 4 weeks apart demonstrating further progression OR have a biopsy to confirm tumor progression OR have new site(s) of disease.

3.1.6.3 Radiation

Patients must have had their last fraction of:

- Craniospinal irradiation, whole brain radiation, total body irradiation or radiation to ≥ 50% of pelvis or spine ≥ 42 days prior to enrollment.
- Focal irradiation ≥ 14 days prior to enrollment.
- Local palliative irradiation to site other than primary tumor progression site ≥ 14 days prior to enrollment

3.1.6.4 Stem Cell Transplant

Patients must be:

- ≥ 6 months since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease
- ≥ 3 months since autologous stem cell transplant prior to enrollment

3.1.7 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 7 days prior to enrollment.
- Patients with seizure disorders may be enrolled if seizures are well controlled.

3.1.8 Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 2 weeks of enrollment must be ≥ 60, including ability to ambulate with or without assistance.

3.1.9 Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.0 x 10^9 cells/ L
- Platelets > 100 x 10^9 cells/ L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥ 8 g/dL (may receive transfusions)
- Total bilirubin ≤ 1.5 times institutional upper limit of normal (ULN)
- ALT (SGPT) and AST (SGOT) < 3 x institutional upper limit of normal (ULN)
- Albumin ≥ 2 g/dL
- Serum creatinine based on age/gender as noted in **Table 1**. Patients that do not meet the criteria in **Table 1** but have a 24-hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Table 1: **Serum Creatinine for age/gender**

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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.1.10 Corticosteroids

Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 7 days prior to enrollment.

3.1.11 Growth Factors

Patients must be off all colony-forming growth factor(s) for at least 7 days prior to enrollment (e.g. filgrastim, sargramostim or erythropoietin). Fourteen (14) days must have elapsed if patient received a long-acting formulation.

3.1.12 Pregnancy Prevention

Patients 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.

3.1.13 Informed Consent

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

3.1.14 HIV Positive Patients

HIV-positive patients are eligible if the following criteria are met:

- Stable on their antiretroviral agents
- Have CD4 counts above 400/mm^3
- Undetectable viral loads, and
- No need for prophylactic medications for an opportunistic infections

3.2 Exclusion Criteria

3.2.1 Pregnancy or Breast-feeding

Pregnant women or nursing mothers are excluded from this study. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

- Pregnant or breast-feeding women are excluded from this study due to risks of fetal and teratogenic adverse events as seen in animal studies.

3.2.2 Concurrent Illness

- Patients with any clinically significant unrelated systemic illness (e.g., serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with any other current malignancy.
- Patients with uncontrolled hypertension (i.e., a blood pressure (BP) > 95^{th} percentile for age, height, and gender; patients with values above these levels must have their blood pressure controlled with medication prior to starting study drug).
    - The normal blood pressure by height, age, and gender tables can be accessed in the Generic Forms section of the PBTC member's webpage.
    - Patients who are ≥ 18 years of age must have blood pressure that is < 140/90 mm of Hg at the time of registration.

3.2.3 Concomitant Medications

- Patients who are receiving any other anti-cancer, investigational or alternative (e.g. cannabinoids) drug therapy are ineligible.

3.2.4 Prisoners

Prisoners will be excluded from this study.

3.2.5 Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures and study restrictions.

3.2.6 Allergy

- Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition.

- Patients with a history of allergy to pork products due to contraindications with low molecular weight heparin (LMWH).

3.2.7 Thrombosis Risk

- Patients with a known coagulopathy or bleeding disorder (e.g., von Willebrand's disease) are not eligible.
- Patients with a history of non-central line related thrombosis or disorders that promote clotting (e.g., anti-thrombin III deficiency, Lupus anticoagulant) are not eligible.
- Significant family history of thrombosis (i.e. deep venous thrombosis or pulmonary embolus) in a first-degree relatives (i.e., parents or siblings) are not eligible.
- Estrogen containing contraceptives are not permitted due to thrombotic risk. Progestin-only contraception along with alternate forms of contraception are acceptable.
- Patients should be counseled to avoid smoking/tobacco products.
- If there is any contraindication to DVT prophylaxis, the patient is not eligible.

Family history must be documented to the best extent it is known.

3.2.8 Subjects with current or prior symptomatic intratumoral or intracranial hemorrhage are ineligible.

3.2.9 Subjects with asymptomatic evidence of new CNS hemorrhage of more than punctate size (i.e., $\geq$ 4 mm) and/or more than one punctate focus of hemorrhage (< 4 mm or not seen on more than one slice) on baseline MRI obtained within 14 days prior to study enrollment are ineligible.