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TITLE: A Phase 1 Study of the ADAM-10 inhibitor, INCB007839 in Children with Recurrent/Progressive High-Grade Gliomas to Target Microenvironmental Neuroligin-3

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ABSTRACT & 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)

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1.0 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.

2.0 BACKGROUND

2.1 Study Disease

2.1.1 Pediatric Recurrent/Progressive High-Grade Glioma

Childhood brain tumors are the most common solid malignancy and the leading cause of cancer-related mortality in children.[1] The most aggressive type of pediatric central nervous system (CNS) tumors is high-grade glioma, including diffuse intrinsic pontine glioma (DIPG). Surgical resection, where possible, and radiotherapy may prolong survival, but at the time of recurrence or progression there are no effective treatments. Despite decades of clinical trials, there has been no substantial improvement with respect to therapeutic outcomes and most children eventually succumb to the disease.[2]

Therapies aimed at targetable pathways and mechanisms intrinsic to the glioma cell have translated to only limited success. Recent research shows that neuronal activity robustly promotes the growth of a range of molecularly and clinically distinct high-grade glioma (HGG) types, including adult glioblastoma (GBM), anaplastic oligodendroglioma, pediatric GBM, and DIPG.[3] A key mechanism of neuronal activity-regulated glioma growth is activity-regulated cleavage and release of the postsynaptic adhesion molecule Neuroligin-3 (NLGN3). ADAM (A Disintegrin and Metalloprotease) 10 is the protease responsible for neuronal activity-regulated neuroligin-3 cleavage and secretion into the glioma microenvironment. In this clinical trial, the use of an ADAM10 inhibitor is a therapeutic strategy to target elements of the tumor microenvironment that promote glioma progression.[3] The poor prognosis of high-grade gliomas in children, combined with the lack of effective therapies, emphasizes the importance of targeting this key microenvironmental mechanism promoting glioma growth.

2.1.2 Overview of neuronal activity and its role in glioma growth

Active neurons exert a robust mitogenic effect on normal neural precursor cells (NPCs) and oligodendrocyte progenitor cells (OPCs) in the juvenile and adult mammalian brain.[4] With this knowledge, it was hypothesized that neuronal activity may similarly promote the proliferation of HGG cells. Using optogenetic control of neuronal activity in patient-derived HGG models, it was demonstrated that neuronal activity does indeed promote circuit-specific HGG proliferation and growth.[3] To determine molecular mechanisms mediating the observed activity-regulated glioma growth, conditioned medium was examined from acute brain slices that were optogenetically stimulated, tetrodotoxin-silenced, or exhibited spontaneous neuronal activity. It was found that activity-regulated glioma mitogens were secreted into the conditioned media. Biochemical and proteomic analyses of this conditioned medium followed by sufficiency and necessity testing of the candidate factors identified brain-derived neurotrophic factor (BDNF), and unexpectedly, a secreted form of the synaptic protein neuroligin-3 (NLGN3) as the key mechanisms mediating activity-dependent glioma growth (Figure 1A). It was then determined that NLGN3 is cleaved in activity regulated fashion by the ADAM10 sheddase at the transmembrane domain, releasing the large N-terminal ectodomain (Figure 2). After binding to glioma cells via an as-of-yet unidentified binding partner that is currently being worked on, NLGN3 stimulated focal adhesion kinase (FAK) and downstream PI3K-mTOR pathway (Figure 1A), as well as numerous additional signaling and gene expression consequences. Among the gene expression changes that were observed following NLGN3 exposure is a feed-forward expression of NLGN3 itself in the glioma cell, together with

numerous other genes associated with synapse component.[3,5] Furthermore, it was observed that activity-regulated glioma proliferation and growth response to NLGN3 is a conserved mechanism across clinically and molecularly-distinct glioma types, including adult GBM, adult anaplastic oligodendroglioma, pediatric GBM and DIPG[3]. These findings indicated, for the first time, the important role of active neurons in the brain tumor microenvironment.

To test just how necessary NLGN3 is to HGG progression, patient-derived HGG were xenografted into NLGN3 knockout mice (back-bred onto an immunodeficient NOD-SCID-IL2R-gamma chain-deficient (NSG) strain to enable xenografting). It was found that HGG growth is strikingly and unexpectedly dependent on neuroligin-3 in the brain microenvironment. Xenografts of patient-derived pediatric GBM, DIPG, and adult GBM engraft, but fail to grow in brains lacking neuroligin-3 for up to six months (Figure 1B–C.)[5] Around six months, a subset of xenografts begin to grow through mechanisms that are currently being worked on. The requirement for neuoligin-3 in the microenvironment is conserved across glioma types, but does not extend to all cancers, as patient-derived breast cancer metastases grow well in the neuroligin-3 knockout brain.[5]

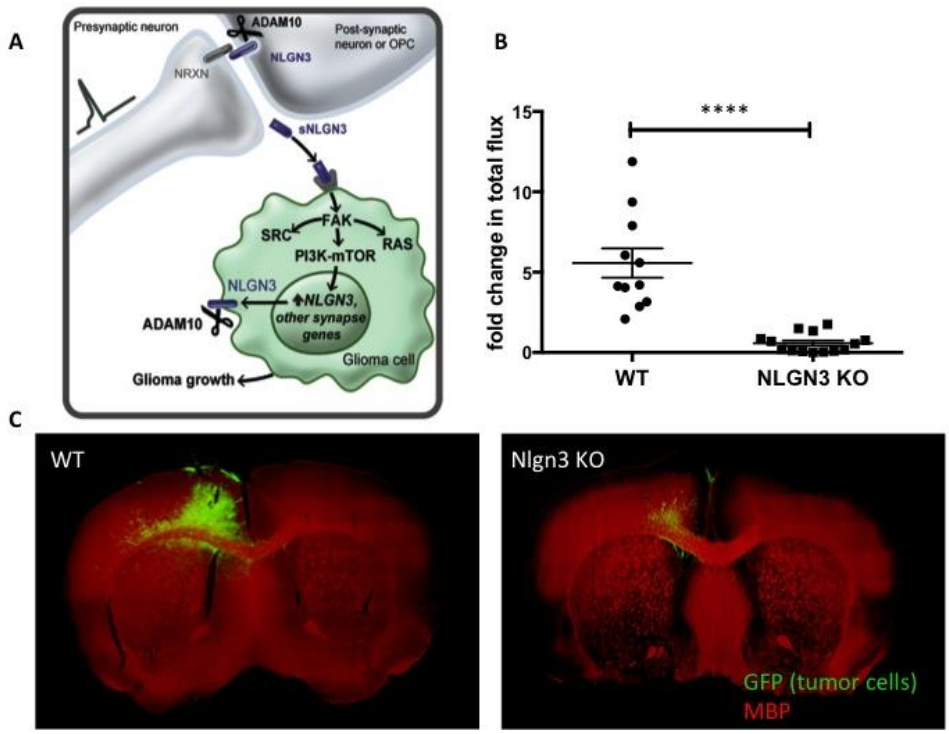


Figure 1. Neuronal activity regulates glioma growth through neuroligin-3.
(A) Schematic of neuroligin-3 (NLGN3) signaling to glioma. **(B–C)** Patient-derived pHGG cells (SU-pcGBM2 cells derived from a frontal cortex pediatric GBM) expressing GFP and firefly luciferase were xenografted into the premotor cortex of immunodeficient (NSG) *Nlgn3*$^{y/+}$ and *Nlgn3*$^{y/-}$ mice. Tumor growth was then monitored by *in vivo* bioluminescent imaging at multiple time points throughout a six-month period. **(B)** pHGG tumor growth in WT and NLGN3 knockout (KO) mice, as measured by fold change in photon emission with *in vivo* bioluminescent imaging (IVIS). Fold change from baseline is shown at 6 weeks after xenografting. Each dot represents one mouse. ****P < 0.0001, Student's two-tailed t-test. **(C)** Confocal micrographs of NLGN3 WT

(left) and NLGN3 KO (right) mouse brains bearing pHGG cells (green = GFP+ pHGG cells; red = myelin basic protein). Images represent tumor at six months. While tumor cells (green) engraft in the NLGN3 KO mouse, growth is strikingly stagnant. Figure adapted from Venkatesh et al., Nature, 2017.[5]

2.1.3 Overview of ADAM10 inhibition in pediatric high-grade gliomas

The inhibition of glioma growth observed in the neuroligin-3 deficient tumor highlights the potential to target this dependency for therapy. Having determined that ADAM10 is the enzyme responsible for activity-regulated NLGN3 cleavage and release into the glioma microenvironment (Figure 2), ADAM10 inhibition was tested as a therapeutic potential with the specific ADAM10 inhibitor GI254023X and found dramatic growth inhibition in a range of patient-derived HGG xenograft models (Figure 2f-i).[5] Due to the fact that GI254023X is not available for clinical use, blood brain barrier (BBB) penetration was then tested using INCB007839 (brand name Aderbasib), an ADAM 10/17 inhibitor that has progressed through a phase 1/2 clinical trial (NCT01254136) for breast cancer. Through these experiments, it was found that INCB007839 penetrates brain tissue to a reasonable degree, achieving > 100 ng/ml (~240 nM) concentration for ~4 hours.[5] Accordingly, proof-of-principal *in vivo* testing of INCB007839 in a patient-derived orthotopic xenograft model of pediatric GBM demonstrates robust growth inhibition (Figure 3a–d).[5]

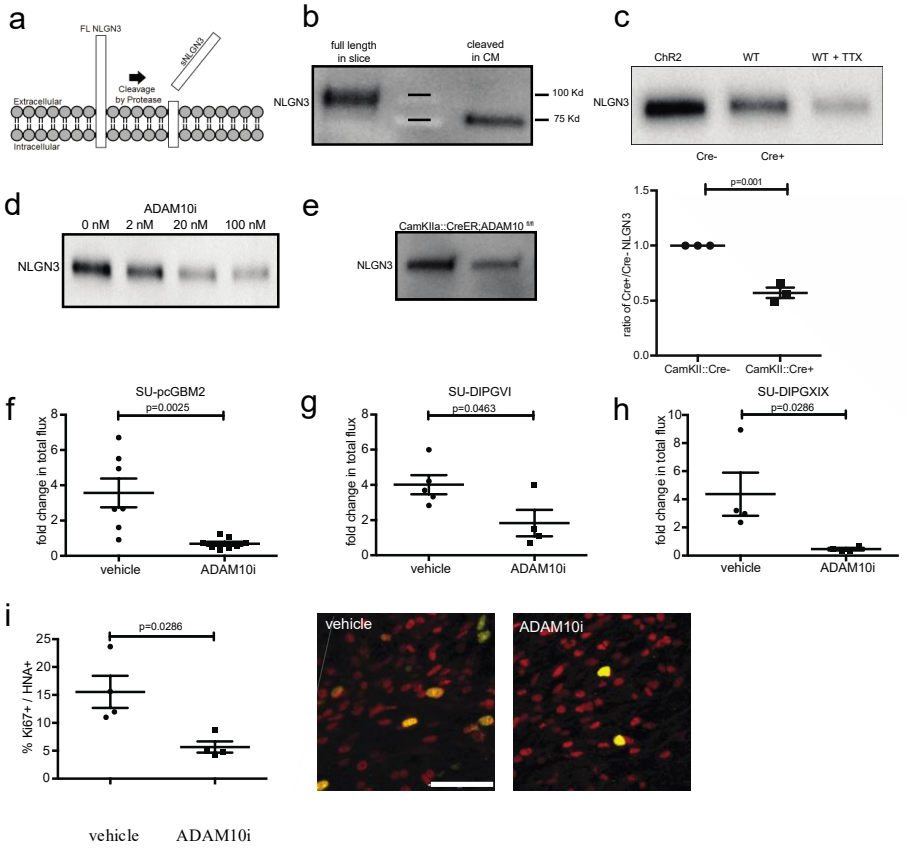


Figure 2. ADAM10 mediates activity-regulated NLGN3 secretion into the tumor microenvironment.

(A) Schematic depicting neuroligin-3 (NLGN3) cleavage. **(B)** NLGN3 Western of slice lysate and conditioned medium (CM). **(C)** NLGN3 Western of CM from optogenetically-stimulated *Thy1::ChR2* slices or WT slices at baseline neuronal activity +/-tetrodotoxin (TTX**). (D)** NLGN3 Western of CM from optogenetically-stimulated *Thy1::ChR2* slices +/- indicated concentration of ADAM10 inhibitor. **(E)** NLGN3 Western and quantification of slice CM from *CamKIIa*::Cre^{ER};*ADAM10*$^{fl/fl}$ mice. **(F–H)** Orthotopic xenograft growth (fold change in photon flux) following systemic administration of GI254023X or vehicle control for **(F)** SU-pcGBM2 (*n*=7 control, *n*=8 treated mice), **(G)** SU-DIPG-VI (*n*=5 control, *n*=4 treated mice), **(H)** SU-DIPG-XIX (*n*=4 control, *n*=4 treated mice) xenografts. **(I)** *In vivo* proliferation index of SU-pcGBM2 cells in vehicle control and ADAM10i treated mice (*n*=4 mice/group). Representative confocal images (Ki67^{+}, green; human nuclear antigen, HNA^{+} red) of SU-pcGBM2 xenografts in vehicle-treated or ADAM10i-treated mice (*n*=4 mice/group). Scale bar=50µm. Figure adapted from Venkatesh et al., Nature, 2017.[5]

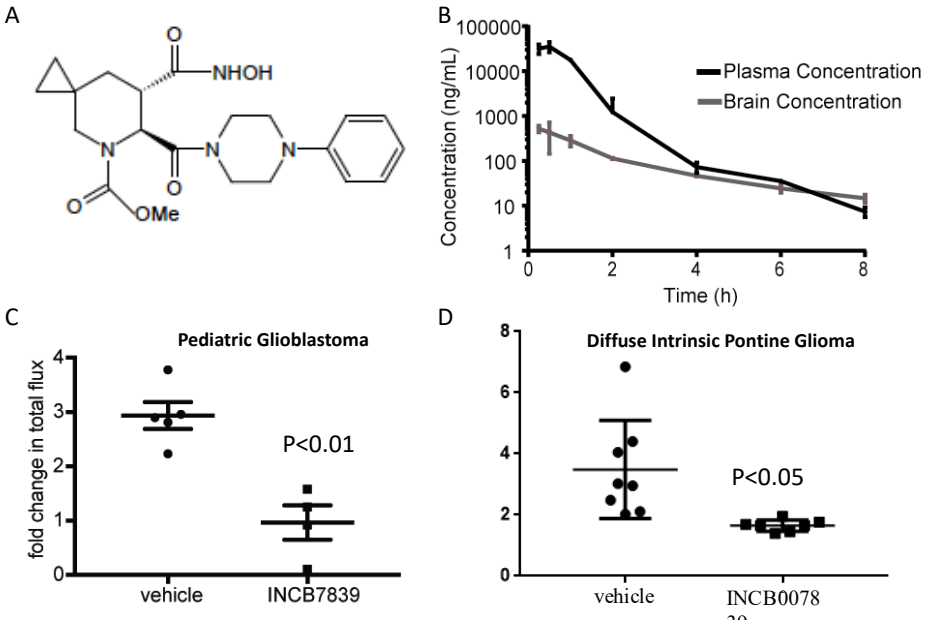


Figure 3. INCB007839 inhibits pediatric high-grade glioma growth.
(A) Molecular structure of INCB007839. **(B)** Brain and serum levels of INCB007839 at various time points following a single 50 mg/kg dose of INCB007839 as assessed by liquid chromatography-tandem mass spectrometry. **(C)** Patient-derived pGBM cells (SU-pcGBM2) expressing GFP and firefly luciferase were xenografted into the premotor cortex of immunodeficient (NSG) *Nlgn3*$^{+/+}$ (n=5) and *Nlgn3* $^{-/-}$ (n=4) mice. Tumor growth was then monitored by *in vivo* bioluminescent imaging (IVIS). Data shown are at the 2-week time point. **(D)** As in C, but in the SU-DIPG-VI xenograft model, xenografted to the pons, data shown are at the 1-week time point. Figure (B, C) adapted from Venkatesh et al, Nature, 2017.[5] D represents new data.

Lastly, survival analysis was completed in the SU-DIPG-VI xenograft model. Mice were xenografted at 7 weeks of age and treated with INCB007839 at a dose of 40 mg/kg. Treatment started at Week 18 and completed at Week 21. As seen in Figure 4, survival was improved with

treatment of INCB007839 compared to control.

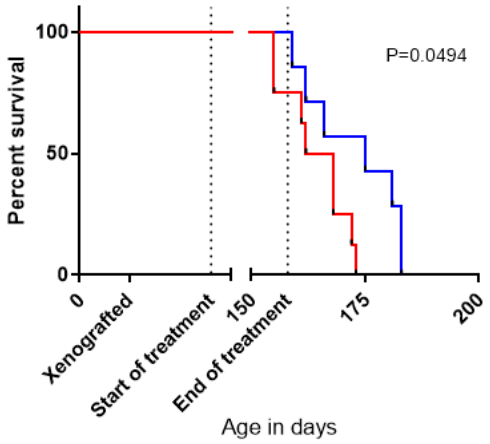


Figure 4. INCB007839 improves survival in an orthotopic xenograft model of DIPG. Log-rank analysis of SU-DIPG-VI orthotopic xenograft mouse model survival following treatment with INCB007839 (40 mg/kg; blue) or vehicle control (red) daily, 5 days a week for four weeks.

2.2 Investigational Agent: INCB007839 (Aderbasib™)

2.2.1 Preclinical Studies

2.2.1.1 *Anti-tumor activity*

INCB007839 is a selective inhibitor of the enzyme activity of the ADAM family of zinc-dependent metalloproteases, specifically ADAM10/ADAM17. INCB007839 was originally studied in breast cancer as ADAM metalloproteinases (also referred as sheddases) affect ErbB signaling.[6] The ErbB family of receptor tyrosine kinases (RTKs) is composed of EGFR (HER1 or ErbB1), HER2 (neu or ErbB2), HER3 (ErbB3), and HER4 (ErbB4).[7-9] Several ligands, including epidermal growth factor (EGF), transforming growth factor α (TGF-α), and four heregulin (HRG)/neuregulin (NRG) family members to name a few, bind to the ErbB family of RTKs. This ligand binding has been shown to lead to receptor dimerization, receptor phosphorylation, and subsequent activation of multiple downstream signaling cascades, including Ras/MAPK, PI3K/Akt and STATs that are essential for promoting cell growth, survival, and resistance to apoptosis. Dysregulation of this ErbB signaling pathways has been observed in numerous solid tumors, including breast, gastric, colon, non-small cell lung cancer, and prostate. ADAM inhibition restores this regulation. Xenograft studies in breast cancer and other solid tumors suggest that INCB007839 treatment, as a monotherapy, results in tumor growth inhibition. Furthermore, tumor growth inhibition was shown to coincide with significant reductions in cell proliferation in breast cancer cell lines.

The preclinical data described in the pediatric glioma section above is the only pediatric data described in the literature using INCB007839. Due to the finding that ADAM10 mediates activity-regulated NLGN3 secretion into the tumor microenvironment, INCB007839 was used to alter NLGN3 release in pediatric brain high-grade gliomas. Figure 3 shows INCB007839 inhibiting growth in pediatric high-grade gliomas (patient-derived orthotopic xenograft models of DIPG and pGBM).

2.2.1.2 *Animal Toxicity*

In toxicokinetic studies of INCB007839, INCB007839-related microscopic changes were noted in spleen, liver, bile duct, and thymus at the higher doses, all of which recovered following cessation of drug. Inhibition of long bone growth was observed with genetic ADAM10 deletion in mice.[10]

2.2.1.3 *Preclinical Pharmacology*

The pharmacokinetics of INCB007839 following intravenous (IV) and oral doses have been determined in mice, rats, beagle dogs, cynomolgus monkeys, and chimpanzees. Across species, INCB007839 exhibited an elimination half-life ranging from 1.6 hours in mice to 6.7 hours in chimpanzees after oral doses. In all species, oral INCB007839 was rapidly absorbed with a time to reach maximum concentration observed between 0.1 and 2 hours. The average bioavailability was determined at 51%, 18%, and 30% in rats, dogs, and chimpanzees, respectively. The CNS distribution of INCB007839 was determined in rats after an IV bolus dose of 1 mg/kg followed by a 2 mg/kg/hour IV infusion for 4 hours. The total brain to plasma partition coefficient (Kp) was 0.17 ± 0.23. INCB007839 was not highly protein bound with free fractions in mouse, rat, dog, and cynomolgus monkey determined at 10 µM to be 36%, 41%, 79%, and 55%, respectively. INCB007839 is not a potent inhibitor of CYP3A4. There was no significant metabolism of INCB007839 by any of the five major P450 (CYP) isozymes, and therefore the pharmacokinetic profile is not expected to be significantly affected by drugs that inhibit or induce CYP450 isoenzymes.

2.2.2 Adult Clinical Trials

2.2.2.1 *Healthy Volunteer Studies*

Four single and multiple-dose studies have been completed with INCB007839 in 112 healthy volunteers (INCB 7839-101, -102, -105, -120). In these studies, adverse events (AEs) were mild and self-limited, and included headache, diarrhea, abdominal cramps, maculopapular rash, somnolence, flushing, Grade 2 elevation of alanine aminotransferase, and upper respiratory tract infections. One subject experienced a serious adverse event (SAE) of DVT that was considered possibly related to study medication; this subject was subsequently found to have antithrombin III deficiency.

2.2.2.2 *Phase 1 Study using INCB007839 as Monotherapy*

In study INCB 7839-201 (also identified as NCT00820560), an open-label dose escalation study that enrolled 41 patients with advanced, previously treated solid tumors (including colorectal cancer, hormone refractory prostate cancer, breast cancer, or cancer of the head-and-neck), doses between 100 mg (immediate release, IR) twice a day (BID), and up to 500 mg (sustained release, SR) BID were explored. Of the AEs judged at least possibly related to study drug, 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 was declared to be DVT, although a clear dose-related relationship was not evident. There was a total of 9 thrombotic events occurring during the study including mild superficial thrombophlebitis (n=1, at dose of 300 mg SR BID plus warfarin prophylaxis), DVT (n=4, at dose of 300 mg SR BID), vena cava thrombosis with renal insufficiency in a patient with squamous cell cancer of the head and neck (n=1, at dose of 100 mg SR BID), atrial thrombosis in patient with breast cancer (n=1, at dose of 300 mg SR BID), and pulmonary embolism in patients with hormone-refractory prostate cancer (n=2, one subject at dose 200 mg SR BID and other subject at 500 mg SR BID plus warfarin prophylaxis). Several patients had complicating factors, such as the presence of advanced disease. The study was amended to include low dose warfarin as the primary component for thrombosis prophylaxis. Among 16 subjects taking either warfarin, aspirin, or both, two thrombotic events occurred (one patient developed superficial thrombophlebitis and one experienced a pulmonary embolism). In this study, there is no clear relationship between thrombosis events and the dose administered. Formal efficacy analysis was not conducted in this trial.

2.2.2.3 *Phase 1/2 Studies using INCB007839 in Combination Therapy*

Study INCB007839-202 (also identified as NCT00864175) is a phase 1/2 study using INCB007839 + trastuzumab + docetaxel (added at cycle 3 or later) for patients with previously untreated metastatic HER2+ breast cancer. The most frequently reported events occurring in ≥ 10% of patients were emesis, pyrexia, anorexia, pain, diarrhea, dyspnea, asthenia, headache, cough, arthralgia, vascular events, abdominal pain, and back pain; the majority of these events were not serious. Warfarin, as well as low dose aspirin in some patients, was used for thrombosis prophylaxis. The overall event rate of thrombosis in the study so far is 10% (7 of 65 patients reported); similar, if not less than the estimated rate of 10–17% in women with metastatic breast cancer receiving multi-drug therapy.[11,12] Efficacy data has not been reported.

Study INCB007839-204 (also identified as NCT01254136) is a phase 1/2 study using INCB007839 + trastuzumab + vinorelbine in patients with metastatic HER2+ breast cancer. Emerging data suggests the regimen is tolerable, however, further data is not available.

Cumulatively, these data suggest that INCB007839 has an adverse event profile consistent with the adult metastatic cancer study population. INCB007839 appears to exhibit a pro-coagulant effect in some adult patients, as evidenced by a potential increase in DVT incidence, whether used alone or in combination with trastuzumab. The mechanism of this effect is unknown.

2.2.2.4 *Clinical Pharmacokinetics*

INCB007839 pharmacokinetics was evaluated in healthy volunteers receiving the drug orally as immediate release (IR) tablets or as sustained release (SR) tablets. Following fasting administration of the INCB007839 IR tablets, the drug was rapidly absorbed with a time to reach

maximum concentration within 1 to 2 hours post-administration. The plasma INCB007839 concentrations were decreasing in a biphasic manner with a terminal half-life of approximately 10–14 hours. Following fasting administration of the INCB007839 SR tablets, the drug was absorbed more slowly with a time to reach maximum concentration shifting to 2 to 4 hours post-administration. Between the single dose range of 50 to 600 mg and the multiple doses range of 50 to 200 mg twice of day in adults, INCB007839 exhibited a linear pharmacokinetic profile, with maximum concentrations and AUC increasing in a proportional manner. In addition, the simulation of repeated INCB007839 single-dose pharmacokinetic profile was accurately predicting the steady-state pharmacokinetic profile. The effect of food was tested using the SR formulation of INCB7983. Following administration of the SR INCB007839 after high-fat, high calorie meal, the drug exhibited a much slower absorption profile with a time to reach maximum concentration between 6 to 8 hours. Moreover, the INCB007839 maximum concentration and AUC were increased by approximately 100% and 80%, respectively, compared to the values obtained after fasted administration of SR INCB007839. The primary routes of elimination of INCB007839 are urinary excretion of unchanged INCB007839, glucuronidation, and hydrolysis to the carboxylic acid metabolite.

2.2.3 Pediatric Clinical Trials

No pediatric studies of INCB007839 have been conducted to date.

2.3 **Rationale for proposed pediatric study**

Pediatric patients with recurrent/progressive high-grade gliomas have a very poor prognosis. Therapeutic agents to date have had limited success when targeting mechanisms intrinsic to the glioma cell. The use of an ADAM10 inhibitor like INCB007839 is a promising therapeutic strategy to target elements of the tumor microenvironment that promote glioma progression, and therefore represents a novel therapeutic strategy.

Overall, INCB007839 is a safe and tolerable drug in adult patients with advanced cancer. In addition, the preclinical data described above suggests that INCB007839 inhibits growth in pediatric high-grade gliomas and DIPG. This study will allow a more detailed description of the safety and tolerability of INCB007839 in pediatric patients with recurrent/progressive high-grade gliomas and also obtain preliminary data regarding the efficacy of this treatment approach.

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

Limited preclinical data suggest that ADAM10 deletion may be associated with abnormal bone growth; the potential effect of INCB007839 on bone development will therefore be monitored in this study by knee X-rays (that capture the tibial growth plate), and knee MRI if clinically indicated.

2.4 Correlative Studies Background

2.4.1 Rationale for Pharmacokinetic Studies

2.4.1.1 *Hypothesis*

The pharmacokinetics and tolerability of INCB007839 in pediatric patients with recurrent/progressive high-grade glioma will be similar as compared to prior studies of INCB007839 in the adult population.

2.4.1.2 *Preclinical and Clinical Data*

Pharmacokinetic studies will be essential for evaluating and interpreting toxicity and outcomes as there are no previous pediatric studies with INCB007839. Though it is hypothesized that the pharmacokinetics and tolerability will be similar between pediatrics and adults, there may be differences based on patients' previous treatment, age, weight, body habitus, and other co-factors. Additionally, evaluating plasma C_{max} and AUC and comparing to preclinical animal models will aid in understanding lack of efficacy, if present. Pharmacokinetic studies will be assessed pre-treatment and post-treatment during Course 1. Based on the previously observed $t_{1/2}$ life of this agent, samples will be collected after a single dose of INCB007839 for up to 48 hours post-administration, on Days 1 and 2 of Course 1. Thus, the second dose of INCB007839 scheduled on Day 1 and the two doses scheduled on Day 2 will be held. Because the drug administration along with food will likely increase the inter-patient variability in the absorption process, the drug should be taken as much as possible without food (1 hour before or 2 hours after meals). Because it was shown in adults that the single-dose pharmacokinetic profile was able to accurately predict the steady-state pharmacokinetic profile, no other required pharmacokinetic samples will be collected in this study beyond 48 hours after the first dose. Cerebrospinal fluid collection is optional.

2.4.2 Rationale for Other Correlative Studies

2.4.2.1 *Hypothesis*

Neuroligin-3 cleavage and secretion will be blocked with the use of INCB007839; we hypothesize that it is feasible to measure this in cerebrospinal fluid (CSF) samples from patients. HER2 and HER2 extracellular domain are also blocked; we hypothesize it is feasible to follow these in serum to monitor ADAM10 inhibitor pharmacodynamics. We will explore changes in these parameters with toxicity and outcome to determine if these may correlate with anti-tumor effects.

2.4.2.2 *Preclinical and Clinical Data*

Sources of NLGN3 include both normal brain and the glioma itself. NLGN3 expression in glioma cells is regulated by NLGN3 exposure and shedding is also mediated by ADAM10. ADAM10 inhibition should block neuroligin-3 cleavage and secretion from both normal brain and from glioma cells based on preclinical data as stated above and as published.[5] Changes in NLGN3 secretion may be measurable in CSF samples. Optional CSF samples would allow researchers to monitor this exploratory measure as a potential pharmacodynamic biomarker.

HER2 cleavage is mediated by ADAM10, and serum levels of the HER2 extracellular domain have been found to reflect ADAM10 inhibition. We will therefore test HER2 extracellular domain serum levels at Day 1 pre-dose and at Day 14 ± 2 days of Course 1.

2.4.3 Rationale for Amendment v3.0 (Protocol Version Date March 30, 2021), Anticoagulation

Given the increased risk of thromboses in adult patients with cancer and the risk of bleeding in patients with CNS tumors, we initially opted not to include prophylactic anticoagulation and to reconsider as necessary if thrombosis was observed in this trial. One patient (16 years old) with multiply recurrent high-grade glioma and a history of multiple intratumoral hemorrhages suffered a Grade 5 venous sinus thrombosis 9 days after initiating study drug (and approximately 7 days after placement of a ventriculoperitoneal shunt for symptomatic hydrocephalus). Because the study drug carries a known risk of thrombosis, attribution was assessed as possibly related to study drug. Given the severity of this event, we are amending the protocol to revise the eligibility criteria and to institute thrombosis prophylaxis, as the risk:benefit in this population appears to favor this.

2.4.4 Rationale for Amendment v4.0 (Protocol Version Date August 2, 2022), Response to report of PRES

One patient enrolled on this study experienced posterior reversible encephalopathy syndrome (PRES) in the setting of hypertension, gliomatosis cerebri, seizure activity, and disease progression. The study was placed on temporary hold to accrual while further investigation took place including the study team, the PBTC Steering Committee, the PBTC Toxicity Monitoring Committee, and the PBTC DSMB. Per information provided by the drug supplier, Incyte Pharmaceuticals, in other trials using this investigational agent, no other reports of PRES have been reported as at least possibly attributed to INCB007839. There have been 4 reports of hypertension at least possibly related to INCB007839. As a result of the event that occurred on study and following discussions with the above groups, CIRB, and FDA, the risks of PRES and hypertension have been added as Rare/Serious potential adverse effects of INCB007839.

3.0 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 3 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 Histological 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) > 95th 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., ≥ 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.

3.3 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study. NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

3.4 Treatment at the Primary Institution

All experimental protocol therapy should be dispensed and all on-treatment imaging studies should be obtained at a PBTC or study-participating institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA certified laboratory of the investigator's choice with the exception of the dose finding period. Imaging utilized to determine eligibility may be performed at an outside institution if all required imaging sequences are included and the study is deemed of adequate quality by the treating team. All required physical examinations, laboratory parameters need to be performed at the primary PBTC or study-participating institution during the dose finding period of the protocol.

3.5 Criteria to Start Treatment

- Subjects must start therapy within 7 days of enrollment.
- Laboratory values must be no older than 7 days prior to the start of therapy. If a test that is repeated post-enrollment and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If rechecks are still outside the limits for eligibility, the patient may not receive protocol therapy and will be considered off study.
- If, in the opinion of the treating physician, a patient's neurologic condition significantly worsens within 72 hours prior to treatment, the patient should not start treatment and should be taken off study.

4.0 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. Documentation requirements per registration type are outlined in the table below.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval;
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at [redacted].

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

4.2.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB prior to March 1, 2019. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted].

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.2 Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and

- Compliance with all protocol-specific requirements (PSRs).

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the *By Lead Organization* folder to expand, then select *Pediatric Brain Tumor Consortium (PBTC)* and protocol number *PBTC-056*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.6 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 **Patient Enrollment**

4.3.1 OPEN/IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with the CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted].

5.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 List of Biomarker Assays in Order of Priority

This section contains the collection, shipping, and handling information for all planned biomarker and exploratory correlative studies, and neuropathology review. The table below identifies the tests, sample type and amount, analyzing laboratory , and whether it is required or optional. For additional details, please review the associated section below.

Priority	Biomarker Name (Section #)	Biomarker Assay	Biomarker Type and Purpose	Mandatory or Optional	Timing	Specimen	Quantity Needed	Laboratory
1	Pharmacokinetics (PK) (Section 5.2.1)	Plasma PK assay	Phase 1 primary objective	M	C1D1 pre-dose and 1, 4, 8, 24, and 48 hours post-dose	Blood	2 mL	CRO/ Stewart Laboratory
2	Pharmacokinetics (PK) (Section 5.2.2)	CSF PK assay	Exploratory to characterize drug CSF disposition	O	Single time-point (pre-dose, anytime post-dose) or serial (pre-dose, 4 and 8 hours post-dose)	CSF	0.5 mL	CRO/ Stewart Laboratory
3	Serum levels of extracellular Her2 (Section 5.3.3)	HER2 ECD ELISA assay	Exploratory to assess ADAM10 cleavage of HER2 in serum as a biomarker of enzyme activity	M	Pre-dose, C1D14	Blood	2 mL	Monje Laboratory
4	NLGN3 in CSF (Section 5.3.4)	CSF Western blot against NLGN3	Exploratory to monitor ADAM10 inhibition of NLGN3 shedding	O	Before and during therapy *	CSF	0.5–1 mL	Monje Laboratory
5	PBTC CRB Biobanking (Section 5.3.1)	TBD	Exploratory for future research	O	Baseline	Unstained FFPE slides	20 slides	CHLA
6	PBTC CRB Biobanking (Section 5.3.1)	TBD	Exploratory for future research	O	Baseline	Blood (PBMCs)	5 mL	CHLA
7	PBTC Central Pathology Review (Section 5.3.2)	N/A	Exploratory to confirm diagnosis for PBTC CRB storage	O	Baseline	H&E stained slide	1 slide	CHLA

* CSF samples will be collected at the time of biopsy if biopsy is performed pretreatment. CSF samples will be collected at the time of lumber puncture or shunt tap as clinically indicated post-treatment.

5.2 Pharmacokinetic Studies

5.2.1 Plasma Pharmacokinetic Studies

Mandatory serial plasma pharmacokinetic (PK) studies will be conducted in all patients enrolled in this protocol during Course 1 on Days 1 and 2 of INCB007839 therapy.

5.2.1.1 *Serial Sampling Strategy*

Beginning on Day 1 of Course 1, serial whole blood samples for INCB007839 pharmacokinetic studies will be collected at the following timepoints (patients should take the first dose 1 hour before or at least 2 hours after eating):

- Pre-dose
- 1 hour (± 15 min) after first dose
- 4 hours (± 15 min) after first dose
- 8 hours (± 1 hour) after the dose
- 24 hours (± 2 hours) after the dose
- 48 hours (± 4 hours) after the dose

Patients will be asked to **hold** the second INCB007839 dose on Day 1 and the two INCB007839 doses on Day 2 of Course 1 so that pharmacokinetic studies can be performed to gain a baseline of INCB007839 disposition.

After the first INCB007839 dose on Day 1, the next dose must be administered on Day 3 AFTER the collection of the 48-hour sample.

Table 2. Mandatory PK sampling schedule

Course / Day	# of doses administered per day	PK sampling timepoints
Course 1 Day 1	One dose (AM)	- Pre-dose - 1 hour (± 15 min) after first dose - 4 hours (± 15 min) after first dose - 8 hours (± 1 hour) after first dose
Course 1 Day 2	No doses (hold)	24 hours (± 2 hours) after first dose
Course 1 Day 3	Two doses* (AM and PM)	48 hours (± 4 hours) after first dose

* The first INCB007839 dose on Day 3 of Course 1 must be administered **after** the 48-hour sample has been collected.

5.2.1.2 *Collection and Handling of Specimens*

- **Before the start of the pharmacokinetic studies:**

Sites should contact the Stewart Laboratory at St. Jude Children's Research Hospital at [redacted] to request a Pharmacokinetic Kit for each patient enrolled on the study. The Pharmacokinetic Kit will provide the material to enable collection of samples.

- **During the pharmacokinetic studies:**

At each time point, 2 mL of blood will be collected into appropriate BD Vacutainer tubes with K_2EDTA. When applicable, the sterile discard volume should be returned to the patient after the blood has been obtained. Samples should be centrifuged within 30 minutes of collection at room

temperature for 2 minutes at 10,000 rpm. For facilities equipped with lower-speed centrifuges, samples may be centrifuged at 1,000 to 1300 x *g* for 10 minutes. Immediately after centrifugation, transfer the plasma supernatant to an individually labeled screw-top tube. Samples should be labeled with the PBTC study number, PBTC Accession Number, sample type, collection date, corresponding study timepoint (e.g., C1D1), and collection time on the corresponding sample label and affixed to the screw-top tube. Within 1 hour of sample collection, store plasma samples at -80°C until shipment.

The Pharmacokinetic Data Collection Form (DCF) located on the PBTC-056 Protocol Webpage should be completed with the exact date and time that the sample was drawn and the exact date and time that the drug was administered. All the information on the DCF should be filled out, and the DCF must be included in the shipment with the pharmacokinetic specimens collected.

Important remarks:

- For children less than 13 kg or for children with subcutaneous ports, contact Dr. Clinton Stewart or his designee [redacted] for a reduced sampling strategy.
- As much as possible, patients are asked to take INCB007839 without food (1 hour before or 2 hours after meals). If the drug is taken along with food, this must be reported in the Pharmacokinetic DCF.
- Further information regarding the sample collection, processing and shipping will be found in the Pharmacokinetic Collection, Processing & Shipment Manual available on the PBTC-056 Protocol Webpage.

5.2.1.3 *Shipping of Specimens*

Samples should be shipped for delivery Monday through Thursday with a generous amount of dry ice enclosed to safeguard against shipping delays. Weekend and holiday deliveries should be avoided. Samples should be shipped within 30 days of the last sample being taken. The site should use the PBTC-056 PK FedEx account details, located on the PBTC-056 Protocol Webpage. Ship all pharmacokinetic samples along with the completed Pharmacokinetic DCF to:

Stewart Laboratory
[redacted]

5.2.2 Cerebrospinal Fluid (CSF) Pharmacokinetic Studies

In consenting patients for whom CSF is accessible, single or serial CSF pharmacokinetic studies will be conducted.

5.2.2.1 *Serial CSF Studies*

Ventricular CSF (0.5 mL) should be obtained at the following timepoints:

- Pre-dose
- 4 hours (± 30 min) after drug administration
- 8 hours (± 30 min) after drug administration.

Simultaneous plasma samples should be obtained at the time of all the CSF sample collections.

5.2.2.2 *Single CSF Studies*

CSF samples may be collected at any time after study enrollment where CSF is collected as part of the best clinical practice (e.g., those requiring CSF diversion or VP shunt revision during therapy, or research participants requiring shunt externalization for infection, or at the time of lumbar puncture or shunt tap as clinically indicated post-treatment).

A simultaneous plasma sample should be obtained at the time of the CSF sample collection.

5.2.2.3 *Collection and Handling of Specimens*

- **Before the start of the pharmacokinetic studies:**

Sites should contact the Stewart Laboratory at St. Jude Children's Research Hospital at [redacted] to request a Pharmacokinetic Kit for each patient enrolled on the study. The Pharmacokinetic Kit will provide the material to enable collection of samples.

- **During the pharmacokinetic studies:**

At each time-point, collect 0.5 mL of CSF in a screw-top tube along with concomitant plasma sample. Record the exact time that the CSF and plasma samples were obtained along with the exact time of drug administration on the CSF Pharmacokinetic DCF located on the PBTC-056 Protocol Webpage. Samples should be labeled with the PBTC study number, PBTC Accession Number, sample type, collection date, corresponding study timepoint (e.g., C1D1), and collection time. Samples should be stored at -80°C until shipped. All the information on the DCF should be filled out, and the DCF must be included in the shipment with the pharmacokinetic specimens collected.

Further information regarding the sample collection, processing and shipping will be found in the Pharmacokinetic Collection, Processing & Shipment Manual available on the PBTC-056 Protocol Webpage.

5.2.2.4 *Shipping of Specimens*

Samples should be shipped for delivery Monday through Thursday with a generous amount of dry ice enclosed to safeguard against shipping delays. Weekend and holiday deliveries should be avoided. Samples should be shipped within 30 days of the last sample being taken. The site should use the PBTC-056 PK FedEx account details, located on the PBTC member website. Ship all pharmacokinetic samples along with the completed Pharmacokinetic DCF to:

Stewart Laboratory

[redacted]

5.3 Exploratory Correlative Studies

5.3.1 PBTC Central Review and Biorepository (PBTC CRB) Pathology and Exploratory Correlative Studies

The Pathology Central Review and Biorepository (PBTC CRB)'s function is to collect, distribute, and store specimens for pathology review and planned correlative studies which support the laboratory objectives of this protocol. **If the patient does not consent to participation in the repository, other correlative study samples should be submitted following the guidelines in the appropriate correlative study section.**

The CRB will also serve as a central repository for specimens collected for future research and leftover specimens (tumor tissue or blood) returned to the repository following the planned analysis from patients who consent to future research studies. These samples will be stored in the repository for undefined future studies which support the mission of the PBTC. **If the patient does not consent to future research, remaining correlative study samples will be destroyed once the PBTC-056 analysis is complete.**

5.3.1.1 *PBTC CRB Submission Guidelines*

If the patient consents to provide slides for submission to the repository at the time of participation in a PBTC trial the following should be submitted:

- Tumor material

Slides from the original and/or recurrent surgery should be prepared for storage. The site should provide up to twenty (20) unstained sections cut at 4 µm in thickness on (+) slides from the most representative section. Fewer unstained sections may be submitted based on size and availability of tissue. Preference is for tissue that has not previously been frozen. The corresponding pathology report(s) including immunohistochemical, special stains, and molecular/genetic results are to be uploaded to the PBTC using the secure File Upload system. These reports will be made available to the pathologist via a link in ProtoLab.

Suitability of sections would be established by preparing one (1) H&E to ensure that the sections meet the following criteria:

- histologically representative of the reported lesion
- contain at least 60% viable tumor
- no more than 40% necrosis

- Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs may be collected by processing a 2–5mL whole blood specimen with Ficoll or collecting the specimen in a BD Vacutainer™ CPT™ Cell Preparation Tube with Sodium Citrate or similar tube which is available locally. Once separated, all pellets must be snap frozen and stored at least at -20°C prior to dry ice shipment

5.3.1.2 *Specimen Collection*

- Processing by Ficoll tube
  1. Collect 2–5mL of fresh blood into an EDTA tube.
  2. Transfer blood into a sterile 50 mL tube and add double the amount of PBS. MIX GENTLY.
  3. Set up another tube containing half of its total volume of Ficoll. For example, if there is 15 mL of blood + PBS, then use 7.5 mL of Ficoll (2:1 ratio).
  4. At very slow pace (approx. 2 mL/minute), layer the blood + PBS mixture onto the Ficoll so that the solutions DO NOT MIX. Spin the blood/Ficoll at 750 g in slow mode for 30 minutes @ 25°C. After spin you will see four distinct layers: plasma (top layer), white fluffy ring (2nd layer), Ficoll (3rd layer), and blood (bottom layer).
  5. Remove plasma layer down to about 1 mL above the white fluffy ring and discard.
  6. Collect the entire white fluffy ring. If ring is hard to see, also take extra liquid above. Then discard everything else.
  7. Place this fraction of white blood cells into a fresh 50 mL sterile tube with 20 mL of PBS. Spin down for 10 minutes @ 25°C, 750 x g in fast mode. Remove the supernatant. Add back to pellet 1 mL of PBS and spin for 5 min. at 4°C at 10,000 rpm. Remove supernatant.
  8. Freeze the pellet of WBCs in a 2 mL cryovial and store at -80°C until shipment. Cryovials larger than 2 mL cannot be accepted by the PBTC CRB.
  9. Please ensure that the labeling system used is designed to withstand temperatures down to -80°C. Samples should be stored at -80°C until shipment. For short term storage (2–3 weeks) -20°C is acceptable. NOTE 4°C IS NOT ACCEPTABLE STORAGE.

If it is not possible to collect the PBMC by Ficoll gradient then separation of PBMC can be conducted using CPT tube separation as an alternative. However, the PBMC pellet MUST BE frozen immediately and stored at -80°C.

- *Collection and Processing by CPT tube*
  1. Peripheral blood should be collected in a BD Vacutainer CPT™ Cell Preparation Tube with Sodium Citrate or similar tube which is available locally. 8 mL and 4 mL CPT tubes can be obtained from Fisher Scientific (Cat# 02-685-125, 02-688-81) or Becton-Dickinson (BD No.362761, 362760). The 8 mL tubes have a 6 mL minimum draw and the 4 mL tubes have a 3 mL minimum draw.
  2. Centrifuge the CPT™ tube at 1500 x g for 30 minutes at room temperature (20°C to 25°C). DO NOT APPLY THE BREAK ON THE CENTRIFUGE. Use acceleration 5, brake 0 ("slow mode").
  3. It may be necessary to spin the tube longer to ensure that all of the red blood cell

components have been separated from the plasma layer through the polyester gel barrier.
4. The tube should be removed immediately from the centrifuge. The mononuclear layer and plasma lie above the polyester gel plug.
5. Using a sterile pipette, remove as much of the plasma component (upper half of the CPT tube) without disturbing the mononuclear layer if possible and discard.
6. Transfer mononuclear cell layer (and some residual plasma layer) to a labeled 15 mL conical centrifuge tube and add 5 mL sterile room temperature magnesium or calcium-free phosphate buffered saline (PBS) to fill the conical tube and recap.
7. Centrifuge at 450 x g for 10 minutes at room temperature (20°C to 25°C). Use acceleration 9, brake ("fast mode").
8. Remove supernatant, being careful not to aspirate the cellular pellet at the bottom of the tube.
9. Add 1 mL of sterile PBS to the pellet and gently re-suspend by pipetting up and down. Transfer the entire suspended pellet to the labeled 2 mL cryovial. Cryovials larger than 2 mL cannot be accepted by the PBTC CRB.
10. Centrifuge the cryovial at 450 x g for 5 minutes (or spin down the microcentrifuge tube at 1300 x g for 5 minutes) at room temperature. Discard the supernatant. Store the cell pellet cryovial frozen at -80°C. For short term storage (2–3 weeks) -20°C is acceptable.

5.3.1.3 *Handling of Specimens*

All samples should be labeled with the following:

- Patient PBTC Accession #
- PBTC study #
- Collection date
- Slide number (For slides only; designate as "PBTCR #" where the # is assigned from 1 to 20 or the highest number of unstained sections prepared, sequentially) **or** "PBTCR H&E" for the H&E stained section.

Slides, scrolls, and Formalin Fixed, Paraffin Embedded (FFPE) tumor material should be shipped at room temperature. PBMCs should be shipped with a generous amount of dry ice enclosed to safe guard against shipping delays.

5.3.1.4 *Shipment of Specimens*

The sample collection, shipping dates and tracking number(s) must be documented in the eCRF. Samples collected for the repository should be sent to the PBTC CRB via FedEx by completing the internet form at http://www.fedex.com/us/ and requesting FedEx to email [redacted]. FedEx user ID and password for pathology shipping can be found on the PBTC-056 Protocol Webpage. Samples are to be shipped to:

PBTC CRB
[redacted]

[redacted]

5.3.2 Pathology Central Review

Retrospective central pathology review will be completed from the slides submitted to the PBTC CRB if the patient consents to the CRB. Pathologist review of slides submitted to the PBTC CRB will include the following elements:

- Examination of H&E stained slides: For each subject, one (1) H&E stained slide per one representative block from the brain tumor, removed either at initial diagnosis or relapse, should be submitted for review.
- Review of the corresponding pathology report(s) of the immunohistochemical, special stains, and molecular/genetic results from current and/or original primary tumor
- If necessary, review of immunohistochemical or special stained slides. Slides submitted to the PBTC CRB will be digitized to 40X. H&E stained sections will be retained and filed at the CRB. Original immunohistochemical or special stain slides will be returned to the submitting institution.

5.3.3 Serum Pharmacodynamics Study: HER2 ECD

Serum pharmacodynamic studies are mandatory and will be obtained from all patients enrolled on this study.

5.3.3.1 *Collection of Specimens*

The blood samples for INCB007839 pharmacodynamic (PD) studies will be collected at the following timepoints:

- Pre-dose
- Course 1 Day 14 (± 2 days)

5.3.3.2 *Handling of Specimens*

At each time point, 2 mL of blood will be collected into appropriate BD Vacutainer red-top tube. The Pharmacodynamic Data Collection Form (DCF) should be completed with the exact time that the sample is drawn as well as the exact time that the drug is administered. The PD DCF is located on the PBTC-056 Protocol Webpage.

Instructions for serum processing:

1) Allow vacutainer to fill completely.
2) Gently invert the vacutainer approximately 5 times to allow complete mixing of additive.
3) Allow sample to clot at room temperature.
4) Centrifuge to separate the clot from the serum (refrigerated centrifuge is recommended but not required).
    a. Spin at 1200 x g for 10 minutes.
5) Remove the stopper of the vacutainer.
6) Using a pipette, aliquot serum into screw top tube for shipping.
7) Samples should be labeled with the PBTC Study #, PBTC Patient Accession #, collection date, and the Course, Day, and Time information for each sample. Store samples at -80°C

until shipment.

5.3.3.3 *Shipping of Specimens*
At the start of the study, each participating institution will receive a Pharmacodynamics (PD) Kit from Dr. Michelle Monje for the collection of samples.

Samples should be shipped for delivery Monday through Thursday with a generous amount of dry ice enclosed to safeguard against shipping delays. Weekend and holiday deliveries should be avoided. Sites should contact the Monje Laboratory at Stanford University, at [redacted] to request a Pharmacodynamics Kit for each patient enrolled on the study.

Samples should be shipped within 30 days of the last sample being taken. The site should use the PBTC-056 PK FedEx account details located on the PBTC-056 Protocol Webpage. Ship all pharmacodynamic samples on dry ice, along with a completed Pharmacodynamics DCF to:

Monje Laboratory
[redacted]

Samples must be shipped from the site to the respective laboratory within 30 days of last sample collection in order to receive cost reimbursement. The sample collection and shipping dates must be documented in the eCRF.

5.3.4 Exploratory Pharmacodynamics Study: NLGN3 in CSF samples
In consenting patients, this exploratory correlative study will monitor CSF NLGN3 levels by western blot in optional lumbar punctures or ventricular/Ommaya taps before and after initiation of therapy.

5.3.4.1 *Collection & Handling of Specimens*
CSF samples will be collected after study enrollment at the time of any lumbar puncture or shunt tap from an Ommaya as clinically indicated.

5.3.4.2 *Shipping of Specimens*
Undiluted, frozen CSF samples should be shipped for delivery Monday through Thursday with a generous amount of dry ice enclosed to safeguard against shipping delays. Weekend and holiday deliveries should be avoided.

Samples should be stored at -80°C and shipped as soon as possible. The site should use the PBTC-056 FedEx account details, located on the PBTC-056 Protocol Webpage. Ship all CSF samples on dry ice to:

Monje Laboratory
[redacted]

5.3.4.3 *Site Performing Correlative Study*
Michelle Monje laboratory at Stanford University.

5.4 Neuroimaging Studies

Patients will have MRI brain (for primary brain HGG) or MRI spine (for primary spinal cord HGG) with and without contrast performed at the following timepoints:

- Prior to therapy
- After Courses 2, 4, and 6
- After Courses 9, 12, 15, 18, 21, and 24 (approximately every 12 weeks)
- Post-therapy (after Course 26)

MRI spine should be performed prior to therapy and at the same time points as standard MRI brain, if clinically indicated. For primary spinal HGG, brain imaging should only be performed as clinically indicated. See Section 11 for details.

Standard MR imaging will include Sagittal T1 MPRAGE, axial DWI, axial T2 FLAIR, axial T2, and post gadolinium sagittal T1 MPRAGE (with reconstructions) images. The standard MR parameters are listed on the PBTC NIC web page located at http://www.childrenshospital.org/research/centers-departmental-programs/pediatric-brain-tumor-consortium-neuroimaging-center under Neuroimaging Studies/ Specific MR Imaging Sequences-Open PBTC Protocols. There is also a link to the same PBTC-NIC webpage from the PBTC-056 Protocol Webpage.

Volumetric analyses will be done at the Neuroimaging Center (NIC, Children's Hospital Boston) via the Vitrea (Vitrea™) workstation, from the axial T2 FLAIR and T1-weighted post-contrast brain images.

5.4.1 Neuroimaging Review

Local review of MR imaging studies will be performed at each site and central review of the MR imaging studies will be conducted through the PBTC Neuroimaging Center (NIC). NIC review will include assessment of response to therapy (as feasible). The director and one neuroradiologist of NIC will review the imaging studies at study completion. If the local and central review are not in agreement, the NIC neuroradiologist will confer with the participating site to determine why there is a discrepancy via conference call.

For patients whose MRI scans suggest a response, a confirmation scan should be obtained approximately 8 weeks later. This scan, as well as the baseline and best response scans, will be electronically transferred to the PBTC Neuroimaging Center (NIC) for central review at the

completion of the study. All patient specific data are stripped from the images and replaced with PBTC Accession numbers prior to transmitting the images to the NIC. All image data transfer is accomplished using PGP (pretty-good-privacy) 128-bit encryption which meets industry standard for secure communication.

6.0 TREATMENT PLAN

Treatment can be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Alternative therapies such as cannabinoids (cannabis oil, THC, etc.) will not be allowed.

Timing of protocol therapy administration and response assessment studies are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures from protocol directed therapy and/or disease evaluations for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable and should be documented. Contact a Study PI and the responsible Protocol Coordinator if there are any questions.

6.1 Agent Administration

This is a phase 1 dose finding trial in pediatric patients with recurrent/progressive high-grade glioma, including DIPG and other diffuse high-grade gliomas.

Given that the adult RP2D was 200 mg PO BID, we plan to evaluate the safety and tolerability of approximate pediatric equivalent dose based on a typical adult size of 1.67 m^2. Thus, we propose to start at 120 mg/m^2 and de-escalate to 80 mg/m^2 if this dose is not tolerable.

INCB007839 is administered orally (PO), twice a day each day for 28-day cycles. A medication diary will be required to ensure appropriate drug administration (Appendix C). The patient will be requested to maintain the medication diary documenting each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

Given the known risk of thrombosis associated with INCB007839, DVT prophylaxis is required with low molecular weight heparin (LMWH, e.g., enoxaparin at 1 mg/kg/day [can be divided BID] with a maximum dose of 40 mg/day), with a goal of anti Xa level of 0.3–0.5 units/mL. DVT prophylaxis should continue throughout the duration of treatment and for 2 weeks after cessation of study drug, except as noted below.

- If a contraindication to DVT prophylaxis occurs (e.g., a new injury at risk of bleeding, planned invasive procedures, allergy to pork products, etc.), the study drug should be held at the time of LMWH cessation. LMWH should be held in these instances per institutional standards or the treating physician's discretion if no guidelines exist. If the temporary risk of anti-coagulation resolves, patients may restart INCB007839 with concurrent LMWH at the discretion of the treating physician.

Table 3. Dose De-escalation Schedule

Dose Level	INCB007839 dose (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

Patients on Dose Level 0 who have a BSA of 0.55–1.0 m^2 will only receive the AM dose.
* Starting Dose

Table 4. Course 1 Dosing Schedule

BID Dosing*	Day 1	Day 2	Day 3–28
AM Dose	Yes	No	Yes
PM Dose	No	No	Yes

*Patients will be asked to hold the second dose on Day 1 and the two doses on Day 2 of Course 1 for plasma PK studies. The AM dose on Day 3 must be administered AFTER the collection of the PK sample (48-hour).

6.1.1 INCB007839

INCB007839 is supplied as 100 mg sustained release tablets. Patients will receive INCB007839 orally twice a day each day for 28-day cycles. Patients may continue to receive INCB007839 on study for up to 26 courses (approximately 2 years) in the absence of disease progression or unacceptable toxicity. Enrolled patients will be followed after completion of study therapy for 2 years or death, whichever occurs first. Delays between courses for reasons other than toxicity may occasionally occur, however, dosing should follow the treatment plan as closely as possible. Discuss and document any protocol deviations with the Study Chair. Duration of therapy is defined in Section 6.4.

Dosing should be adjusted based on body surface area (BSA) calculated at the beginning of each course of therapy. The dose prescribed should be rounded to the nearest deliverable dose based on the BSA adjustment and the available pill size. Dosing tables which reflect this approach are available in Appendix B. Patients will be provided with a medication diary for INCB007839, instructed in its use, and must bring the diary as well as the remaining pill bottles with them to each appointment. The medication diary is in Appendix C.

As much as possible, INCB007839 should be taken without food (1 hour before meals or 2 hours after), with water rather than other fluids. Dosing is every 12 hours (± 2 hours), but if a dose is not given within 4 hours, consider it missed. If a dose is missed, it should be documented in the diary and the next scheduled dose should be taken as scheduled. Patients who vomit a dose of INCB007839 should NOT be re-dosed, and appropriate anti-emetic therapy should be implemented prior to the next scheduled dose.

6.1.2 Criteria to start subsequent courses

A course may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in Section 3.1.9, and 3.1.14 if applicable.

- If a patient does not meet these parameters at the end of the dose-finding period, then

INCB007839 should be held until parameters meet the criteria. If parameters are not met within 7 days of the scheduled course to begin, this is a dose-limiting toxicity (see Section 6.2) and dose reduction is indicated.

- If a patient does not meet these parameters at the end of subsequent courses (i.e., Course 2 and onward), then INCB007839 should be held until parameters meet the criteria. If parameters are not met within 7 days of the scheduled course to begin, this will require a dose modification (see Section 7.0).
- If INCB007839 is held for any reason other than toxicity (e.g., planned procedure), it can be restarted (with concurrent anti-coagulation) at the same dose and with counting of course days continuing (e.g., if INCB007839 is held on Days 13–16 of a course due to a shunt revision, restart INCB007839 and LMWH on Day 17 and continue counting course days for a 28-day course).

6.2 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the events listed in this section that are at least possibly related to the investigational agent and that occur during the dose-finding period regardless of expectedness.

- Any INCB007839-related adverse event during the first course of therapy that leads to a dose reduction or results in the permanent cessation of therapy will be considered dose limiting. All dose modifications in all courses are to follow the guidelines provided.
- Any INCB007839-related adverse event during the first course of therapy that results in a delay of treatment > 7 days.

6.2.1 Non-hematologic dose limiting toxicity is defined as:

- Any Grade 4 non-hematologic toxicity
- Any Grade 3 non-hematologic toxicity with the exception of:
    - Grade 3 nausea and vomiting of < 5 days and responsive to anti-emetic treatment
    - Grade 3 elevation of transaminases that returns to levels meeting eligibility criteria within 7 days of study drug interruption and does not recur upon restarting drug.
    - Grade 3 fever or infection of fewer than 5 days in duration
    - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation
- Any Grade 2 non-hematologic toxicity that persists for > 7 days and is considered medically significant or sufficiently intolerable by the patient that the toxicity requires treatment interruption
- Any deep venous thrombotic event (superficial phlebitis is excluded unless Grade 3 or 4 as above)
    - If a patient on this study has a thrombotic/thromboembolic event that is not related to the central line, treatment with INCB007839 will be discontinued and not restarted. Determination of attribution will be reviewed by the study team and discussed with PBTC Toxicity Committee and CTEP; and such events will be reported to the CTEP-AERS, PBTC DSMB, and the FDA as events of special interest in an expedited fashion. See special reporting requirements in Section 10.3. In this event, enrollment will be halted until fully reviewed. In addition, any patient experiencing a non-central line-related thromboembolic event should have the

studies listed below performed as soon as possible after the event.

- Patients with a venous thrombosis should have the following assessed as soon as possible after thrombosis is suspected/confirmed:
  - CBC
  - Antithrombin
  - Protein C
  - Protein S
  - Factor V Leiden
  - Prothrombin G20210A gene analysis
  - Fasting serum homocysteine
  - Lupus anticoagulant assays
  - Anticardiolipin level

- Patients with an arterial thrombosis should have:
  - CBC
  - Fasting serum homocysteine
  - Lupus anticoagulant
  - Anticardiolipin level
  - LDL, HDL, triglycerides

6.2.2 Hematologic dose limiting toxicity is defined as:

- Any Grade 4 hematologic toxicity with the exception of lymphopenia
- Grade 3 neutropenia with fever
- Requiring a platelet transfusion (threshold for transfusion is a platelet count of $< 50{,}000/\mu L$) on 2 separate days (following adequate initial platelet transfusion to $> 100{,}000/\mu L$) during a single course.

Management and dose modifications associated with the above adverse events are outlined in Section 7.

6.2.3 Dose-finding period

The dose-finding period begins with the initial dose of INCB007839 and ends on the last day of Course 1. Should there be a delay starting the subsequent course, dose-finding will complete on the start date of Course 2.

Management and dose modifications for toxicities which occur outside of the dose-finding period should also follow guidelines in Section 7, however, these will not be considered dose limiting for the purpose of dose finding.

6.2.4 Dose De-escalation

Dose de-escalation will proceed as follows:

- Course 1 will be started with an initial cohort of six (6) patients at 120 mg/m^2/dose BID (the dose levels to be tested are listed in Table 3). If more than 1 DLT is observed in 6 patients treated at Dose Level 1, de-escalation to Dose Level 0 will occur as outlined in

Section 9.1. Only DLTs observed during the dose finding period of therapy will be used to guide dose de-escalation. Patients treated at Dose Level 0 who have a DLT will discontinue study therapy.

- If thrombosis occurs outside of the DLT period, this will be discussed with study team to determine attribution to study drug, potential dose-association, as well as consideration of the risk/benefit ratio of prophylaxis in subsequent patients.

- Patients enrolled on Dose Level 1 who have a dose-modifying toxicity outside of the dose-finding period (e.g., in Courses 2 and onward) should have the dose of INCB007839 reduced on subsequent courses to Dose Level 0. Patients can begin the subsequent course at the lower dose when the toxicity has resolved to Grade 1 or baseline and laboratory parameters are met as defined in Section 3.1.9 and 3.1.14. Patients enrolled on Dose Level 0 who require a dose reduction will not receive further treatment on study and will be considered off treatment (see Section 6.4.2).

6.3 General Concomitant Medication and Supportive Care Guidelines

6.3.1 Steroids

Corticosteroids should be used at the lowest dose to control symptoms of edema and mass effect, and discontinued, if possible. Use of corticosteroids should be recorded in the RAVE database. Steroids should not be used to control other symptoms, e.g., nausea.

6.3.2 Anticonvulsants

Anticonvulsants should be used, if indicated. Use of anticonvulsants should be recorded in the RAVE database.

6.3.3 Growth Factors

Routine use of growth factors (e.g., G-CSF, GM-CSF, and erythropoietin) is not permitted. However, therapeutic use of G-CSF or GM-CSF in patients with serious neutropenic conditions, such as sepsis, may be considered at the investigator's discretion. Use of growth factors should be recorded in the RAVE database.

6.3.4 Anti-emetics

The use of anti-emetics will be at the investigator's discretion. Use of anti-emetics should be recorded in the RAVE database.

6.3.5 Febrile neutropenia

Febrile neutropenia should be managed according to the local institutional guidelines. Measures include laboratory testing, blood and urine cultures, and institution of broad-spectrum antibiotics.

6.3.6 Antihypertensive Medications

Hypertension should be managed, if indicated. Antihypertensives to maintain blood pressure below the 95th percentile for age, height, and gender (based on the normal blood pressure chart available in the Generic Forms section of the PBTC member's website) are allowed per the discretion of the treating physician according to institutional guidelines. Use of antihypertensive

medications should be recorded in the RAVE database.

6.3.7 Pneumocystis jiroveci pneumonia (PJP) prophylaxis

The use of medication (i.e., Bactrim) for PJP prophylaxis in patients on chronic steroids is recommended, but it is at the investigator's discretion.

6.3.8 Neurosurgical or other surgical procedures

If a neurosurgical procedure or other surgical procedure is required for a reason other than tumor progression (e.g., the onset of hydrocephalus), these procedures should be documented but will not constitute criteria for declaring the patient "off therapy". INCB007839 should be held after any surgical intervention (with the exception of minor dental or dermatological procedures) for at least 28 days after surgery. LMWH should be held as indicated for the surgical procedure but restarted as soon as deemed safe by the treating surgeon.

6.4 **Duration of Therapy**

In the absence of treatment delays due to adverse event(s), treatment on study may continue up to 26 courses (approximately 2 years) or until further disease progression, unacceptable toxicity, withdrawal of consent, or until one of the following Off Treatment criteria in Section 6.4.2 applies.

6.4.1 On Study Data Submission Schedule

Pre-treatment, on-study, and off-treatment data, as well as patient response data are to be recorded in the electronic data collection screens using the RAVE database. See the Required Data and Timetable for Submission form located on the PBTC-056 Protocol Webpage for the schedule. For assistance, contact the PBTC Protocol Coordinator listed on the cover page.

6.4.2 Off Treatment Criteria

At the discontinuation of treatment, the "Off Treatment Date" is to be recorded in the eCRF and is to be consistent with the reason given for going off treatment. The "Last Treatment Date" is defined as the last date that the patient received protocol based therapy. The reason for discontinuation of treatment must be documented by the attending investigator in the medical record and recorded in the eCRF.

Patients will be considered Off Treatment for the following reasons:

- Development of unacceptable toxicity as outlined in Section 6.2. See Section 10.3 and 10.4 for specific reporting requirements.
- Progressive disease (PD) as described in Section 12.2.
- Development of a medical or psychiatric illness that in the investigator's judgment renders the patient incapable of further therapy on this protocol or the treating physician determines continuation on this study is not in the patient's best interest.
- The patient, parent, or legal guardian refuses further treatment on this protocol. In this case the investigator should clarify if the family also wishes to withdraw consent for continued participation for data collection purposes.
- Completion of all protocol defined treatment
- Pregnancy
- Non-Compliance that in the opinion of the investigator does not allow for ongoing participation.

- Termination of the study by the sponsor
- Investigational agent manufacturer can no longer provide the study agent.
- Development of a non-central line related thrombosis

Patients who are off protocol therapy must be followed until an "Off Study Criterion" is met.

6.4.2.1 *Data Submission Schedule for Patients Off Treatment*

All patients must be followed for a minimum of 30 days from the last treatment date. Toxicities that are considered at least possibly related to study treatment and are ongoing at the end of day 30 of last treatment date will be followed until resolution or return to baseline, unless consent is withdrawn for further data submission or follow-up.

Patients who do not meet an off-study criterion will continue to be followed for 2 years from the last dose of protocol treatment for the monitoring of unexpected later developing toxicities or other morbidity and to document disease progression and survival. Data should be updated quarterly in the RAVE database. The requested follow-up data, including imaging uploads requested in Section 5.4, are to be submitted quarterly in the RAVE database from the date the patient went off treatment. Data to be recorded during this interval are the following:

- Any adverse events that are possibly, probably, or definitely related to the study drug (see Section 10 for specific reporting timelines)
- Dates of disease assessment and results of the associated disease assessments.
- Date of disease progression
- Date of commencement of new anticancer therapy
- Date of most recent contact
- Date of death

6.4.3 Criteria for Removal from Study

Patients who are off protocol therapy will be followed until they meet criteria for removal from study. The date and reason for the patient coming off study must be documented in the eCRF and the Operations, Biostatistics and Data Management Core (OBDMC) must be notified according to standard reporting guidelines (see Sections 10.3, 10.4, and 13.2, Data submission for Off Study, and the Required Data and Timetable Submission from located on the PBTC-056 Protocol Webpage).

Ongoing AEs, or AEs that emerge after the patient is removed from protocol therapy but within 30 days of the last dose of study treatment, must be followed and reported via Rave and CTEP-AERS (if applicable). Toxicities that are at least possibly related to the study treatment and are ongoing at the end of day 30 of last treatment date will be followed until resolution or return to baseline, whichever is longer.

- Patient determined to be ineligible.
    - If the patient was found to be ineligible after starting treatment, follow-up should continue for 30 days from the last administration of study drug or until any drug-related toxicity resolves or returns to baseline, whichever is longer.
- Patient did not initiate treatment on study.
- Parent, patient, or guardian withdraws consent for further required observations of data submission.
- Patient death while on study. The IRB, Study Chair, and OBDMC must be notified as per Section 10.3.
- Patient has started another anti-cancer therapy. Follow-up must still be completed for 30 days following the last treatment date.
- Patient has completed study follow-up which is defined as 2 years following last dose of INCB007839.
- Progressive disease
    - If PD occurs within less than 30 days of off-treatment date, then follow-up should continue until 30 days from off-treatment date.
    - If the off-treatment reason is toxicity and the patient is subsequently found to have PD, then follow-up should continue for 30 days from the off-treatment date or until the toxicity resolves or returns to baseline, whichever is longer.

6.4.3.1 *Data Submission for Patients Off study*

No data will be collected documenting treatment or reporting events or disease status that occur subsequent to the official "off study" date with the exception of adverse events with an attribution of possible, probable, or definite that occur after the "off study" date.

7.0 DOSING DELAYS/DOSE MODIFICATIONS

The Study Chair or Co-Chair must be notified of any dosage modifications, prior to the implementation of the dose modification. There is only one dose reduction planned for this study. Patients receiving INCB007839 80 mg/m^2 BID daily and who meet criteria for a dose reduction must be removed from protocol therapy.

7.1 Hematologic and Non-hematologic Adverse Events and Management

7.1.1 Dose Modification for Thromboembolic Toxicity

Thromboembolic event *	Management
Grade 1	Manage superficial thrombosis as per institutional standards, no change in dose needed.
Grade 2 **	Thromboembolic events should be managed as per institutional standards. Unless thrombosis is catheter-associated, discontinue INCB007839. If catheter-associated, hold INCB007839 until catheter-associated thrombosis is resolved.
Grade 3	Thromboembolic events should be managed as per institutional

Thromboembolic event *	Management
	standards. Discontinue INCB007839.
Grade 4	Thromboembolic events should be managed as per institutional standards. Discontinue INCB007839.
* Patients requiring a delay of > 14 days should go off protocol therapy. ** Please note: Grade 2 superficial thrombophlebitis should be considered a Grade 1 thromboembolic event and managed as per the Grade 1 management above.	

7.1.2 Dose Modification for Non-thromboembolic Toxicity

A patient who has a non-thromboembolic toxicity at 120 mg/m^2 or is delayed > 7 days from the planned start of the next course should be dose reduced to 80 mg/m^2 on subsequent cycles. A patient who has a non-thromboembolic toxicity at 80 mg/m^2 or is delayed > 7 days from the planned start the next course will not receive further treatment on study and will be considered off treatment (see Section 6.4.2.

8.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 10.1.

8.1 INCB007839 (NSC # 812570)

Product description: INCB007839 (Incyte Corporation)

Empirical Formula: $C_{21}H_{28}N_4O_5$

Molecular Mass: 416.47

Pharmacological Class: Novel inhibitor of EGFR signaling; an inhibitor of the ADAM10 and ADAM17 proteases; anti-tumor agent

Route of administration: Oral

Formulation: The tablets should be dispensed in the original containers.

One hundred (100) mg sustained release tablets are composed of compendial ingredients such as Lactose Monohydrate, Microcrystalline Cellulose, Dibasic Calcium Phosphate Dihydrate, Hypromellose, Sodium Citrate, and Magnesium Stearate. The hypromellose is the ingredient that provides sustained release and varying amounts and grades of this ingredient are used to achieve desired profile.

Storage requirements: Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F).

Solubility: Approximately 1–2 mg/ml in water

Stability: Drug substance is stable for at least 48 months at 25ºC/60%RH. The 100 mg sustained release tablets are stable for at least 24 months at 25ºC/60%RH.

8.1.1 Agent Ordering

INCB007839 may be requested by the principal investigator (or their authorized designee) at each participating institution. All regulatory documents, as required by the PBTC, must be current and up to date prior to requesting the study drugs. Drug request form can be found on the PBTC-056 Protocol Webpage. The form can be emailed to the agent distributor Catalent [redacted]. In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Any unused/expired study drug and containers may be destroyed according to the institutional standard operating procedure. The method and the record of destruction must be documented and maintained at the site.

8.1.2 Agent Accountability and Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent strength, formulation and ordering investigator on this protocol.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The primary aims of this study are to evaluate the safety and tolerability of INCB007839 and identify the maximum tolerated dose or the recommended phase 2 dose in children and young adults with recurrent/progressive CNS tumors. Based on this approach we propose to enroll 6 patients at Dose Level 1. If we observe no more than 1 DLT, enrollment on this dose level will be expanded to at least 12 subjects in order to obtain additional PK and safety information. If Dose Level 1 is not tolerable then we will de-escalate to Dose Level 0 and repeat the same process. If more than 3 DLTs are observed in 12 subjects at Dose Level 1, then the initially identified MTD based on 6 subjects will be considered unsafe and a dose de-escalation to Dose Level 0 will be considered.

We will use a design similar to the Rolling-6 design and open 6 slots initially on Dose Level 1. If we observe no-more than 1 DLT in these 6 subjects then we would expand this cohort to at least 12 patients for PK and additional safety information. If more than 1 DLT is observed on Dose Level 1 in 2–6 subjects, then further enrollment to Dose Level 1 will stop, the dose will be de-escalated to Dose Level 0 and the same approach will be repeated.

Based on the above-outlined de-escalation rules, if Dose Level 0 is found to be too toxic, then the trial will be closed to accrual and the merits of amending or closing the trial permanently will be reconsidered.

Accrual will be suspended for any Grade 5 AE which is at least possibly attributable to the study agent until a full assessment can be made. At that time, the toxicity data and all associated information will be reviewed by the study committee, the PBTC toxicity monitoring committee and DSMB, CTEP, and by the FDA prior to a deliberate decision to resume accrual.

Similarly, if a patient on this study has a thrombotic/thromboembolic event that is not related to the central line (except superficial phlebitis), treatment with INCB007839 will be discontinued and not restarted for that subject. Determination of attribution will be reviewed by the study team and discussed with PBTC Toxicity Committee and CTEP. A list of such events that will be reported to the CTEP-AERS, PBTC DSMB, and the FDA as events of special interest in an expedited fashion are in Section 10.3.

9.2 Sample Size/Accrual Rate

9.2.1 Projected Accrual Rages and Study Duration

If Dose Level 1 is determined to be safe then the study could be completed for the safety/tolerability assessment with 15 patients (including a few who may be inevaluable). The maximum sample size is ~28, in the event that we de-escalate to Dose Level 0 after 12 patients are treated at Dose Level 1.

The projected accrual rate is 1–2 patients per month, based on knowledge of the member institutions and their commitment to the Consortium. With 2 possible dose levels, the study duration is estimated to be 1.5–2 years from study activation, if both dose levels are investigated.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	1	0	0	**3**
White	6	9	4	2	**21**
More Than One Race	1	1	0	0	**2**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Total	10	12	4	2	28

9.2.2 Statistical Analysis of Pharmacokinetics/Pharmacogenetics

The plasma INCB007839 concentration-time data will be analyzed using non-compartmental and/or population-based compartmental methods. Individual pharmacokinetic parameters of interest such as the area under the curve after single dose from 0 to ∞ [$AUC_{0-\infty}$], maximum concentration [C_{MAX}], time to reach C_{MAX} [T_{MAX}], and apparent oral clearance [CL/F] will be calculated based on the Course 1 Days 1 and 2 pharmacokinetic samples.

9.3 Data Analysis

As part of routine analyses, toxicities will be summarized by dose level, by grade, and by attribution. These analyses will also take into account the actual dosage received by subjects to ensure that large deviations in dosage that will likely occur due to limitations in the formulation of the agent do not lead to safety concerns. Furthermore, at the end of the study, we will explore associations between PK parameters (such as Cmax and AUC) and higher grade toxicities that may help identify safety trends.

Because this is a phase 1 study, observations of objective responses are expected to be rare. Thus, these will be reported in a descriptive fashion. Similarly, the exploratory marker studies for HER-2 and neuroligin-3 will be summarized based on descriptive statistics and plots without formal inference.

10.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

- *Baseline Abnormalities*

Any baseline (pre-treatment) abnormalities observed during the initial physical examination should be recorded in the RAVE database.

- *Treatment or within 30 days of treatment*

Only record adverse events Grades 1 and 2 in the electronic case report forms (CRFs) if the attribution is at least **possibly** related to INCB007839. Record all adverse events Grades 3 through 4 and deaths), regardless of attribution on the electronic case report forms.

10.1 Comprehensive Adverse Events and Potential Risks List

10.1.1 Adverse Events List for INCB007839

COMMON, SOME MAY BE SERIOUS In 100 people receiving INCB007839, more than 20 and up to 100 may have:
• Thrombotic events including pulmonary embolism, DVT, and superficial thrombophlebitis • Nausea • Vomiting • Anorexia • Flatulence • Diarrhea • Headache • Dizziness • Drowsiness • Tinnitus • Fatigue • Fever • Dehydration • Pain • Bleeding from the nose • Dyspnea

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving INCB007839, from 4 to 20 may have:
• Rash • Abdominal pain • Constipation • Anemia • Hypoxia • Muscle weakness • Pancreatitis

RARE, AND SERIOUS In 100 people receiving INCB007839, 3 or fewer may have:
• Liver failure • Disseminated intravascular coagulation • Infection • Reversible posterior leukoencephalopathy syndrome (also known as Posterior reversible encephalopathy syndrome [PRES]) • Hypertension

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.4).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted]. Once internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The following must be copied on expedited reports (24-hour notification and the complete report) submitted via CTEP-AERS:

Study Chair:
Michelle Monje, MD, PhD
[redacted]

PBTC OBDMC:
Nina Butingan, MBS
[redacted]

Study Co-chair:
Katherine E. Warren, MD
[redacted]

Regulatory Affairs contact for IND Holder:
St. Jude Regulatory Affairs
[redacted]

The OBDMC will email and/or fax the SAE/CTEP-AERS report within 24 hours of their awareness of the event to Incyte Corporation via email to [redacted] or fax [redacted].

The IND holder, St. Jude Children's Research Hospital, shall notify the FDA of any event that is both a suspected unexpected serious adverse reaction (SUSAR) in accordance with FDA rules and regulations (21 CFR 312.32). Follow-up information to a safety report will be submitted, as requested.

The IND Sponsor or designee will submit a report of the suspected unexpected serious adverse event to the FDA. The FDA prefers these reports to be made on a MedWatch 3500A form, but alternative formats are acceptable (e.g., a summary letter). The report should describe the event as fully as possible. Supporting documentation (lab reports, summary notes, and autopsy report) should accompany the report. A fatal or immediately life-threatening suspected adverse event will be reported to the FDA within 7 calendar days of the receipt of the initial report by the IND sponsor. A non-fatal, non-life threatening unexpected, suspected, serious adverse event will be reported to the FDA within 15 calendar days of receipt of the initial report by the IND Sponsor.

The PBTC OBDMC will post all IND Safety Letters on the PBTC-056 webpage. Sites will be notified via email of the receipt of the IND Safety Letter(s) and instructed to submit these to their local IRB in accordance with the institution's requirements.

The IND Annual Report will be submitted by the IND holder as required by the FDA. This submission will be cross referenced according to local regulations to the Incyte/ INCB007839 at the time of submission.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

<u>Note</u>: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.4 Special Expedited Reporting Requirements for the Study

The following thromboembolic events (Grades 1–5) should be reported expeditiously through CTEP-AERS regardless of attribution of study drug:

- Arterial thromboembolism
- Superior vena cava syndrome
- Thromboembolic event
- Vascular disorder (other)
- Thrombotic thrombocytopenic purpura
- Myocardial infarction
- Visceral arterial ischemia
- Budd-Chiari syndrome
- Portal vein thrombosis
- Sinusoidal obstruction syndrome
- Ischemia cerebrovascular
- Stroke
- Transient ischemic attacks

The following events should follow the serious adverse events reporting requirements described in the table above:

- Superficial thrombophlebitis
- Phlebitis
- Vasculitis
- Hemorrhoids
- Phlebitis infective
- Intraoperative venous injury
- Vascular access complication
- Avascular necrosis

10.4 **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 **Pregnancy**

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators:

Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia)
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol. The Adverse Event eCRF should be updated with the appropriate description within 1 week of learning of the secondary malignancy.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11.0 STUDY CALENDAR

Data is to be submitted according to the Data submission timelines located on the PBTC-056 Protocol Webpage.

	Pre-therapy	Course 1	Courses 2–26	Completion/ Discontinuation of Treatment
INCB007839 (IND Agent) [A]		X	X	
Physical Assessments				
Medical history	X	Weekly	X	X
Physical exam	X	Weekly	X	X
Vital signs/height/weight/BSA	X	Weekly	X	X
Performance status	X	Weekly	X	X
Neurologic exam	X	Weekly	X	X
Laboratory Evaluations				
CBC with differential [B] WBC, HgB, Platelets, ANC, ALC	X	Weekly	X	X
Serum Chemistry [B] Sodium, Potassium, Bicarbonate, Chloride, Calcium, BUN, Creatinine, Glucose, Phosphorous, Magnesium, Albumin, Total Protein, SGPT(ALT), SGOT(AST), Total Bilirubin	X	Weekly	X	X
Anti-Xa Levels [C]		X	X	
Serum or Urine pregnancy test (for females of childbearing potential) [D]	X	X	X	
CSF cytology [E]	X			
Imaging Assessments				
Brain MRI (standard) with diffusion [F]	X		X	X
Spinal MRI [F]	X		X	X
Right knee X-ray [G]	X		X	X
Correlative Studies	**Refer to Sample Collection Schedule in Section 5.1**			

A. Dose as assigned.
B. To be done more frequently throughout the duration of treatment if required to monitor toxicities.
C. To be done once after starting low molecular weight heparin (e.g., enoxaparin) and as needed if there is a change in renal function.
D. Within 72 hours prior to starting treatment.
E. CSF will be collected if clinically indicated or patient agrees to optional pharmacokinetics or pharmacodynamics studies using CSF samples (Sections 5.2.2 and 5.3.4).
F. Patients will have MRI Brain (for primary brain HGG) or MRI spine (for primary spinal cord HGG) with and without contrast at the timepoints listed in Section 5.4. MRI Spine should be performed prior to therapy and at the same time points as standard MRI Brain, if clinically indicated. For primary spinal HGG, brain imaging should only be performed as clinically indicated.
G. Obtain pre-treatment X-ray (AP and lateral views, include tibial growth plate) of the right knee; to be repeated every 12 weeks. If abnormalities are detected on routine X-rays, MRI scan of both knees should be performed.

12.0 MEASUREMENT OF EFFECT

Although the clinical benefit of INCB007839 has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be monitored for tumor response and symptom relief in addition to safety and tolerability. In addition to a baseline scan, confirmatory scans will also be obtained approximately 8 weeks following initial observation of an objective response.

12.1 Antitumor Effect Definitions

- Evaluable for Toxicity

Patients who receive at least 1 dose of INCB007839 and experience a DLT or are removed from treatment for study agent-related toxicity during the dose finding period (first 28 days of treatment) are evaluable for estimating the MTD.

Patients who receive approximately 85% (at least 45/53 of required doses; at least 23/27 required doses for patients enrolled on Dose Level 0 who have BSA 0.55–1.0 m^2) of prescribed therapy during the dose finding period will be considered evaluable for estimating the MTD, as long as no additional anti-cancer therapy or supportive care that would confound the interpretation of any observed toxicity or side effect is given. Patients must have completed all of the clinical and laboratory monitoring requirements specified by the protocol up to the time of disease progression for them to be considered evaluable for MTD. Patients receiving less than 85% of planned dosing during the dose-finding period for reasons other than toxicity will be considered inevaluable and will be replaced.

Patients who do not have DLT and who have completed all therapy during the dose finding period but who failed to comply with *all* the specified clinical and laboratory monitoring requirements for the first course may be considered inevaluable for estimating the MTD and replaced.

- Evaluable for Efficacy

All patients who receive at least 1 dose of the agent will be considered evaluable for efficacy analyses and will be assessed based on the tumor response criteria described below.

12.1.1 Disease Parameters

In order to completely document the assessment of response, the measurements of the longest tumor dimension, and its perpendicular, of all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Tumor response criteria are determined by changes in size using the longest tumor dimension and its perpendicular. FLAIR, T2 or post contrast T1 weighted images may be used—whichever gives the best estimate of tumor size.

Since many tumors contain non-enhancing components (or, in some cases, the tumor may not

enhance at all), both the enhancing and the non-enhancing components must be evaluated—on post contrast T1 weighted images and on FLAIR/T2 weighted images, respectively. Increase in enhancement on T1 weighted images without accompanying increase in disease bulk on T2 or FLAIR images is not considered tumor progression. In turn, enlarging areas of non-enhancing tumor (defined as mass effect/tissue thickening) are evidence of tumor progression. Conversely, decrease in enhancing tumor component without decrease in overall FLAIR/T2 extent may represent change in tumor permeability (commonly observed with antiangiogenic therapies) rather than represent tumor response.

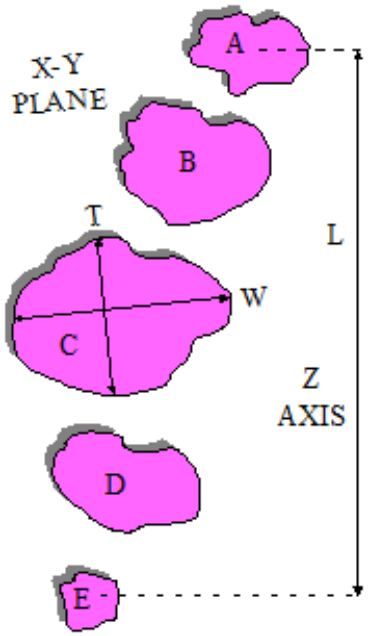
12.1.2 Method

The following section describes the methodology. (See Figure 5 for illustration.

- For MRI imaging (preferred), the longest measurement of the tumor (or width, W) should be determined. It can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups. Longest diameter of target lesion(s) should be selected in the axial plane only for CT.

- The measurement (transverse (T)) perpendicular to the width in the selected plane should be determined. NOTE: A measurable lesion should have a minimal transverse measurement that is at least twice the combined thickness of the image slice and the inter-slice gap. For example, with a 4 mm slice and a 0.4 mm gap, minimal measurable lesion diameter is 8.8 mm. Smaller lesions would not be measurable for study purpose.

- Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted and changes in extent/thickness assessed on follow up studies.



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

Figure 5. Tumor size measurement based on cross-sectional imaging

12.2 Tumor Response Criteria

12.2.1 Complete Response (CR)

Complete disappearance on MR of all evaluable tumor and mass effect, on a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses), accompanied by a stable or improving neurologic examination, and maintained for at least 8 weeks.

12.2.2 Partial Response (PR)

Greater than or equal to 50% reduction in tumor size by bi-dimensional measurement, as compared with the baseline measurements, on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination, and maintained for at least 8 weeks.

12.2.3 Stable Disease (SD)

Neurologic exam is at least stable and maintenance corticosteroid dose not increased, and MR imaging meets neither the criteria for PR nor the criteria for Progressive Disease. If this category is to be reported as of possible clinical benefit, Stable Disease status must be maintained for 8 weeks.

12.2.4 Progressive Disease (PD)

Progressive Disease (PD): Progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.), OR a greater than 25% increase in the bi-dimensional measurement, taking as a reference the smallest disease measurement recorded since the start of protocol therapy, OR the appearance of a new tumor lesion.

Increasing doses of corticosteroids required to maintain stable neurological status should be strongly considered as a sign of clinical progression unless in the context of recent wean or transient neurologic change.

12.2.5 Progression-free Survival (PFS)

Interval of time between date of initiation of protocol treatment and minimum date of documentation of PD, second malignancy, death due to any cause, or date of last follow-up.

12.2.6 Duration of Response

- Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

- Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the Pediatric Brain Tumor Consortium's (PBTC) data safety monitoring plan.

13.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at [redacted].

Users may also contact OBDMC to get help with study specific issues including clinical forms, data entry, data query, data sign-offs and/or uploading of regulatory and other required documents. For complete OBDMC contact details, click on the OBDMC Contact Information link that is available in the Members' Area of the PBTC website (http://www.pbtc.org/).

13.2.1 Method

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study and the data will be released to an unauthorized third party without the prior written approval of the Pediatric Brain Tumor Consortium (PBTC).

The PBTC Protocol Coordinators, other authorized representatives of the sponsor, regulatory representatives, PBTC auditors, representatives of the IRB or the pharmaceutical collaborator supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Source documents which are the original records of clinical findings, observations or activities in a clinical trial are to be maintained at each participating site. Sites must upload all source documentation which supports the eligibility, DLT, or dose finding and evaluability of the participant to the PBTC via the RAVE database. In the event the patient experiences unexpected events, additional source documentation may be requested to complete the event review. These documents may include but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda and radiographic images.

Study participant study related data, which is for purposes of statistical analysis and scientific reporting will be transmitted to the Pediatric Brain Tumor Consortium electronically via the RAVE database. This will not include the participant's contact or identifying information. Rather, research participants and their research data will be identified by a unique study identification number assigned at the time of screening or registration. The study participant's contact information will

be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

The study data entry and study management systems used by clinical sites and by the PBTC will be secured and password protected. At the end of the study, all study data is maintained on a secure server.

After the study is completed, the data collected will be maintained on a server and may be used by other investigators, including those outside the study. With the participant's approval and as approved by local IRBs, biological samples labeled only with the participant's protocol specific identification number will be stored at the PBTC Central Review and Biorepository and could be made available to other investigators for future unspecified research. Investigators conducting future studies will not have access to the key for stored data collected while the participant is on study. Clinical data will be de-identified before it is shared with other investigators.

If the participant agrees to submit a repository sample, those samples contain genetic information that may be used for research related to brain tumors and their treatment. They may also be used to develop tests/assays to improve diagnosis and treatment of these diseases in the future. Genetic research may consist of the analysis of one or more genes or the analysis of genetic markers throughout the genome.

14.0 REFERENCES

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APPENDIX A PERFORMANCE STATUS CRITERIA

MODIFIED LANSKY SCORE (Score as 0 – 100)

A. Normal Range

100 = Fully active
90 = Minor restrictions in physically strenuous play
80 = Restricted in strenuous play, tires more easily, otherwise active

B. Mild to moderate restriction

70 = Both greater restrictions of and less time spent in active play
60 = Ambulatory up to 50% of time, limited active play with assistance/supervision
50 = Considerable assistance required for any active play; fully able to engage in quiet play

C. Moderate to severe restriction

40 = Able to initiate quiet activities
30 = Needs considerable assistance for quiet activity
20 = Limited to very passive activity initiated by others e.g., TV)
10 = Completely disabled, not even passive play
0 = Unresponsive, coma

KARNOFSKY SCALE

100 = Normal; no complaints
90 = Able to carry on normal activities; minor signs or symptoms of disease
80 = Normal activity with effort
70 = Cares for self. Unable to carry on normal activity or to do active work
60 = Requires occasional assistance but able to care for most of his/her needs
50 = Requires considerable assistance and frequent medical care
40 = Disabled; requires special care and assistance
30 = Severely disabled; hospitalization indicated though death not imminent
20 = Very sick. Hospitalization necessary. Active support treatment necessary.
10 = Moribund
0 = Dead

APPENDIX B DOSING TABLES FOR INCB007839

Dose Level 1: 120 mg/m^2/dose BID
BSA Restriction: 0.70–2.5 m^2

	Total Daily Dose (mg)	BSA range (m^2)		Tablets Required (based on 100 mg tablets)	
		Low	High	AM	PM
INCB007839 Dose Level 120 mg/m^2 BID	200	0.70	1.00	1	1
	300	1.01	1.45	2	1
	400	1.46	1.87	2	2
	500	1.88	2.50	3	2

Dose Level 0: 80 mg/m^2/dose BID
BSA Restriction: 0.55–2.80 m^2

	Total Daily Dose (mg)	BSA range (m^2)		Tablets Required (based on 100 mg tablets)	
		Low	High	AM	PM
INCB007839 Dose Level 80 mg/m^2 BID	100	0.55	1.00	1	0
	200	1.01	1.56	1	1
	300	1.57	2.18	2	1
	400	2.19	2.80	2	2

APPENDIX C MEDICATION DIARY

Patient ID: _____ **Drug:** INCB007839

Course Number: _____ **Start Date:** ____/____/____ **Total Daily Dose:** _____ mg
End Date: ____/____/____

A total of _____ 100 mg tablets are dispensed for Course ___

1. Complete one form for **each** course of treatment.
2. You will take INCB007839 twice a day orally or as directed. INCB007839 should be taken without food (1 hour before meals or 2 hours after), with water rather than other fluids. Store the INCB007839 tablets at controlled room temperature (20°C–25°C, also known as 68°F–77°F).
3. Low molecular weight heparin (LMWH, e.g., enoxaparin at 1 mg/kg/day [can be divided BID] with a maximum dose of 40 mg/day) should be given throughout the duration of treatment with INCB007839 and for 2 weeks after cessation of INCB007839, except in the event of toxicity as noted in Section 6.1.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. INCB007839 dosing is every 12 hours (± 2 hours), but if dose is not given within 4 hours consider it missed. If a dose is missed, it should be documented in the diary and the next scheduled dose should be taken as scheduled. Patients who vomit a dose of INCB007839 should NOT be re-dosed.
6. Please bring this form and your bottles of INCB007839 when you return for each appointment. All medication bottles (including empty ones) are to be brought to clinic at each appointment.

Day	Date	**INCB007839 AM dosing**	**INCB007839 PM dosing**	**LMWH (total daily dose)**	**Comments**
		# of 100 mg tablets	**# of 100 mg tablets**	Drug name & units: _____	
1					
2					
3					
4					
5					
6					
7					
8					
9					

Day	Date	INCB007839 AM dosing	INCB007839 PM dosing	LMWH (total daily dose)	Comments
		# of 100 mg tablets	# of 100 mg tablets	Drug name & units: _____	
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Day	Date	INCB007839 AM dosing # of 100 mg tablets	INCB007839 PM dosing # of 100 mg tablets	LMWH (total daily dose) Drug name & units: _____	Comments
29		**No INCB007839 dosing.** **Record LMWH dose if applicable or use a new diary if starting a new course.**			
30					
31					
32					
33					
34					
35					
36					
37					
38					
39					
40					
41					
42					

The medication diary has been reviewed, and the INCB007839 tablets have been counted.

Signature: _____ Date: _____

APPENDIX D PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov