## Protocol Abstract and Schema

***PBTC-018: A Phase 1 Trial of CC-5013 in Pediatric Patients with Recurrent or Refractory Primary CNS Tumors***

***Description:***
A pediatric phase I trial of CC-5013 will be performed in children with recurrent or refractory tumors of the central nervous system, to determine the maximum tolerated dose (MTD) and safety profile of CC-5013 in this pediatric population. CC-5013 will be administered as capsules orally once a day for 21 days of a 28-day course.

***Primary Objectives:***

1. To estimate the MTD of oral CC-5013 administered to children with recurrent or refractory primary CNS tumors once daily for 21 days of a 28 day course
2. To describe the toxicity profile and define the dose-limiting toxicity of CC-5013 in children with recurrent or refractory primary CNS tumors

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***Secondary Objectives:***

3. To characterize the pharmacokinetics of CC-5013 in children and adolescents
4. To characterize the pharmacogenetics of CC-5013 in children and adolescents
5. To evaluate changes in circulating endothelial cells (CECs) and circulating endothelial cell precursors (CEPs) in patients treated with CC-5013, and to investigate the correlation between changes in CECs and CEPs, plasma, serum and urine levels of proteins associated with angiogenesis including thrombospondin, b-FGF, TNF-α, IL-12, IL-8 and VEGF, and correlate these changes with changes in MR perfusion and clinical outcome.
6. To evaluate changes in MR spectroscopy, MR perfusion and diffusion during treatment

***Eligibility Criteria:***

- **Age**: Patient must be ≤ 21 years of age.
- **Tumor**: Patients with a histological diagnosis of primary CNS tumor (including histologically benign brain tumors (e.g. low-grade glioma)) that is recurrent, progressive, or refractory to standard therapy. Patients with intrinsic brain stem or diffuse optic pathway tumors do not require histological confirmation of disease but should have clinical and/or radiographic evidence of progression.
- **Performance Score**: Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60
- Patient must be able to swallow capsules.
- **Prior/ Concurrent Therapy**:
    a. Patients must have no known curative therapy available.
    b. Patients must have recovered from any significant toxicity associated with prior therapy. Patients will be eligible regardless of the number of prior therapies, as long as other eligibility criteria are met.
    c. Patients must have:
        - received their last dose of known myelosuppressive anticancer chemotherapy or biological therapy at least three (3) weeks prior to study registration
        - received their last dose of nitrosourea or mitomycin-C at least six (6) weeks prior to study registration
        - received their last dose of other investigational agent or an anticancer drug known to not be myelosuppresive at least seven (7) days prior to study registration.

d. XRT: Patients must have had their last fraction of craniospinal irradiation ≥ 3 months prior to registration and their last fraction of local irradiation to primary tumor ≥ 4 weeks prior to registration. Patients must have recovered from toxic effects associated with any other radiation therapy.

e. Bone Marrow Transplant: ≥ 6 months since allogeneic bone marrow transplant and ≥ 3 months since autologous bone marrow/stem cell transplant prior to registration.

f. Growth factors: Off all colony forming growth factor(s) > 2 weeks prior to registration

- **Organ function**

  The following laboratory values must be assessed within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy. Lab values should be repeated within 48 hours of therapy if the patient has undergone significant clinical change.

  a. *Bone Marrow:* Absolute neutrophil count ≥ 1000/µl (unsupported); Platelets ≥ 100,000/µl (unsupported), Hemoglobin ≥ 8.0 g/dL (may be supported)
  b. *Renal*: Serum creatinine within upper limit of institutional normal for age or GFR ≥ 70 ml/min/1.73m$^2$.
  c. *Hepatic*: Bilirubin ≤ 1.5 times upper limit of normal for age; SGPT (ALT) < 2.5x institutional upper limit of normal for age and albumin ≥ 2 g/dL.
  d. No overt renal, hepatic, cardiac or pulmonary disease.

- Female patients of childbearing potential must have negative serum or urine pregnancy test. Patient must not be pregnant or breast-feeding.
- 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.
- Signed informed consent according to institutional guidelines must be obtained.

***Exclusion Criteria***

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- Patients with a body surface area (BSA) ≤ 0.4 m$^2$ are excluded.
- Patients with a first degree relative who had a venous thrombosis before age 50 yrs or an arterial thrombosis before age 40 yrs are excluded.
- Patients who have had a thromboembolic event that is not line-related are excluded.
- Patients with any significant medical illnesses that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- Patients with any disease that would obscure toxicity or significantly alter drug metabolism.
- Patients receiving any other chemotherapeutics or investigational agents.
- Patients with uncontrolled infection.
- Patients unable to swallow capsules.
- Patients with known hypersensitivity to anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

***Rationale:*** Pediatric patients with recurrent and refractory malignant CNS tumors have a very poor prognosis. Many tumors, including several types of childhood CNS tumors have shown a dependency on angiogenesis for tumor growth, demonstrating intense neovascularization and producing potent

angiogenic mediators. In addition, the degree of angiogenesis has been shown to inversely correlate with survival in pediatric patients with high-grade tumors.

Over the last decade, several mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these is the secretion by tumor cells of cytokines with angiogenic properties. Tumor cells can also release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (i.e. bFGF), or induce angiogenesis indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (i.e. TNF-α, bFGF).

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CC-5013 is a potent analog of thalidomide that exerts a broad spectrum of pharmacologic, antiangiogenic, and immunologic effects. CC-5013 has been shown to be more potent than thalidomide in stimulating proliferation of T cells following primary induction by T-cell receptor activation, and more potent than thalidomide in augmenting production of IL-2 and IFN-γ following TCR activation of PBMC (IL-2) or T-cells (IFN-γ). CC-5013 also exhibits dose-dependent inhibition of LPS-stimulated production of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 by PBMC, and increased production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC.

CC-5013 has been well tolerated in adult studies of patients with multiple myeloma and glioma. The dose-limiting toxicity appears to be myelosuppression. CC-5013 has not yet been studied in children.

***Schema:***

This is a dose-escalating trial of CC-5013 administered orally once daily for 21 days followed by a 7-day break. Courses will be repeated every 28 days and continue for 12 courses or until one of the off-study criteria have been met.