Protocol Abstract and Schema

A Phase I Trial of Pomalidomide for children with recurrent, progressive or refractory CNS tumors

DESCRIPTION AND RATIONALE

Central nervous system (CNS) tumors are the most common solid tumors among children. Although overall survival is estimated to be over 70% at 5 years, the outcomes for children with aggressive variants or recurrent/progressive disease are much lower.[1,2] In fact, with rare exception, once a child with a malignant brain tumor has suffered a recurrence, survival outcomes diminish tremendously. A variety of treatment strategies have been employed, including biologically targeted agents, high dose chemotherapy with autologous hematopoietic cell rescue, re-irradiation, and anti-angiogenic agents, but none have significantly improved outcome. Novel targeted therapies and immune modulating agents offer the potential for improved outcomes in these patients. Most recently, a number of immune modulating therapies have been explored in both pediatric and adult malignancies, including CNS tumors.[3-6] One group of agents that possesses both anti-angiogenic and immune modulating properties include the IMiDs, a group of drugs with structural characteristics similar to thalidomide. These agents, which include lenalidomide and pomalidomide, have multiple pharmacologic properties and potential anti-tumor effects including anti-angiogenesis, immune-modulation, anti-inflammatory properties and cytotoxic activity. The complete and exact antitumor mechanisms of action are unclear and may be multipronged and disease-dependent.[7] The IMiDs have shown significant efficacy in patients with multiple myeloma and myelodysplastic syndrome, and their activity against hematologic and non-hematologic malignancies, autoimmune diseases, and fibrotic disorders are being evaluated due to their tolerability, multiple mechanisms of action and efficacy data in a variety of tumor models and patients.[7-10] (See protocol document for references).

SCHEMA

Description

- This is a multicenter, Phase I dose escalation trial of pomalidomide for children with recurrent, progressive or refractory central nervous system (CNS) tumors to determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D), to evaluate toxicities and to characterize the pharmacokinetics (PKs) of pomalidomide in a pediatric population. The rolling 6 design is incorporated. Once the MTD or RP2D has been reached, expansion cohorts will be implemented where enrollment will be stratified based on age (<12 years vs. ≥12 years) and steroid use (not on steroids or [on physiologic doses alone] versus those taking therapeutic doses of steroids).

Schema

There will be one stratum for all patients during the initial dose escalation. Once the MTD or RP2D is defined, expansion cohorts will be filled as described above to include a minimum of 4 patients in each of the 4 steroid/age cohorts.

Pomalidomide will be administered orally once daily for 21 consecutive days followed by a 7 day rest period (28 days=one course). There will be no intra-patient dose escalation. The pomalidomide dose will be increased by approximately 33% increments in subsequent cohorts.

Only DLTs observed during the dose-finding period of therapy (course 1) will be used to guide dose escalation. Courses are repeated every 28 days and can continue for up to 26 courses unless any of the off-treatment criteria are met (see Section **Error! Reference source not found.**). The starting dose of pomalidomide will be 1.9 mg/m^2, (dose level 1) which is approximately 80% of the adult RP2D (4 mg orally daily). Patients will be followed for all adverse events (AEs) for 30 days after the last dose of study drug or until they begin a new therapy, whichever occurs first. Patients will also be followed for development of a second or secondary malignancy for 2 years from the last dose of study drug provided the subject has not withdrawn study consent, has been lost to follow-up or died.

Dosing of pomalidomide will be initiated at Dose level 1 and dose escalation is planned until the MTD is reached or a Phase 2 dose can be recommended. In the event that Dose level 1 (1.9 mg/m^2) is found to be too toxic, a de-escalation to Dose level 0 (1.3 mg/m^2) is possible. If all proposed dose levels (below in Table 1) are studied without reaching an MTD, considerations to further escalate will be discussed with the PBTC study team, CTEP and Celgene. Further dose escalation will be considered through the amendment process if there is no MTD identified and PKs reveal relevant escalating serum concentrations with escalating doses of drug.

Table 1
Pomalidomide Dosing Regimen

Dose Level	Dose (mg/m^2)
0	1.3 mg/m^2
1*	1.9 mg/m^2
2	2.6 mg/m^2
3	3.4 mg/ m^2
4	4.4 mg/m^2
*Starting dose	

OBJECTIVES

Primary Objectives

- To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of pomalidomide, in children from ≥ 3 years to < 21 years of age with recurrent, progressive or refractory CNS tumors when given once daily for 21 consecutive days of a 28-day course.

- To describe the toxicity profile and dose-limiting toxicities of pomalidomide in children from ≥ 3 years to < 21 years of age with recurrent, progressive or refractory CNS tumors**.**

- To characterize the pharmacokinetics of pomalidomide when administered orally in children from ≥ 3 years old to < 21 years of age with recurrent, progressive or refractory CNS tumors and study the association of PK parameters with age and steroid use.

Secondary Objectives

- To explore the preliminary efficacy of pomalidomide in this patient population as defined by radiographic response rate, duration of response, and Event-Free Survival (EFS) within the confines of a Phase 1 study. *For the purposes of this study, long-term stable disease will be considered a response (defined as stable disease for ≥ 6 courses).

- To investigate a relationship between pomalidomide dose and exposure with radiographic response and changes in immune function (for example, T-cell subsets NK cell activity, Granzyme B and circulating levels of IL-12, IL-2, IL-15 and GM-CSF.

PATIENT SELECTION

All patients must meet the following inclusion and exclusion criteria. NO EXCEPTIONS WILL BE GIVEN.

Eligibility Criteria

- Patients: Patients must have received standard therapy (or generally accepted upfront therapy if no standard exists) and have no known curative therapy.

- Tumor Diagnosis: Patients with a histologically confirmed diagnosis of a primary CNS tumor that is recurrent, progressive or refractory to standard therapy. Refractory disease will be defined as the presence of persistent abnormality on conventional MRI imaging that is further distinguished by histology (biopsy or sample of lesion) or advanced imaging, OR as determined by the treating physician and discussed with the primary investigator prior to enrollment. All tumors must have histological verification at either the time of diagnosis or recurrence except for patients with diffuse intrinsic brain stem tumors or optic pathway gliomas. Patients with Neurofibromatosis type-I (NF-1) associated CNS tumors are eligible if they meet all other eligibility criteria.

- Disease Status: Patients must have evaluable disease on MRI imaging.

- Age: Patient must be ≥ 3 years and < 21 years of age at the time of enrollment.

- BSA: Patients must have BSA > 0.55m^2 at the time of enrollment.

  In the event of de-escalation from dose level 1 to dose level 0 patients with BSAs in the range 0.58-0.65m^2, inclusive, are not eligible. This is due to limited capsule size and overlapping doses, meaning patients at dose level 0 with these BSAs (0.55-0.65) would receive the same exact dose they would have received at dose level 1, which is not a de-escalation and is potentially unsafe

- Prior Therapy: Patients must have recovered from clinically significant, acute, treatment-related toxicities of prior therapies. For those acute baseline adverse events attributable to prior therapy, recovery is defined as a toxicity Grade ≤ 2, using CTCAE v.4.0, unless otherwise specified in the Inclusion and Exclusion Criteria.

- Myelosuppressive Chemotherapy: Patients must have received their last dose of known myelosuppressive anticancer therapy greater than 28 days prior to study enrollment or > 42 days if nitrosourea.

- Investigational Agent: Patients must have received their last dose of any other investigational agent greater than 28 days prior to enrollment (with exception of FLT as described below in protocol section □).

- Biologic agent (anti-neoplastic): Patients must have received their last dose of any other biologic agent greater than 7 days prior to 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 and discussed with the PI.

- Monoclonal antibody treatment and agents with known prolonged half-lives:
  At least three half-lives must have elapsed prior to enrollment.

  Note: A list of the half-lives of commonly used monoclonal antibodies is available on the PBTC webpage under Generic Forms and Templates.

- Immunomodulatory therapy: Greater than 28 days must have elapsed since last dose of an immune modulating agent, including vaccine therapy.

  Agents that potentially fit into more than one category or do not clearly fit into any category listed above should be discussed with the study PI prior to enrollment.

- Radioisotopes: Administration of the radioisotope, ^{18}-FLT, which is being concurrently investigated on an imaging study within the PBTC, is allowed > 72 hours prior to initiation of pomalidomide on this study. Any adverse events related to the FLT must have resolved completely.

- Radiation: Patients must have had their last fraction of:
  - Craniospinal irradiation, total body irradiation (TBI), or ≥ 50% radiation of pelvis > 3 months prior to enrollment.
  - Focal irradiation > 6 weeks prior to enrollment.
  - Local palliative XRT (small port) ≥ 4 weeks.

- Bone Marrow Transplant: Patient must be:
  - ≥ 6 months since allogeneic bone marrow transplant prior to enrollment.
  - ≥ 3 months since autologous bone marrow/stem cell prior to enrollment.
  - ≥ 3 months since Stem Cell Transplant or Rescue without TBI with no graft vs. host disease prior to enrollment.

- No graft versus host disease.

- Anti-Convulsants: Patients on anticonvulsant therapy may continue these at the discretion of their treating physician. However, it is recommended that anticonvulsant levels be checked periodically as clinically indicated if possible since it is not clear if pomalidomide has an effect on metabolism or clearance of these agents (See Section **Error! Reference source not found.**).

- Alternative Supplements: Patients on alternative supplements should strongly be encouraged to discontinue them prior to enrollment. If they opt to continue, they may enroll on study as long as they have been receiving the supplement for at least 30 days, there is NO evidence of hepatic, renal or other organ dysfunction, administration is approved by the PI, and administration is documented in the study diary.

- Steroids: Patients must be on a stable or decreasing dose of corticosteroids for 5 days prior to enrollment. Patient may be taking therapeutic doses of steroids during the initial dose escalations and prior to defining an RP2D. This should be recorded in the database. Once the RP2D has been established, enrollment may be limited based on steroid use. *Physiologic replacement doses will be defined on this protocol as no more than 0.75 mg/m^2/day of dexamethasone or equivalent of steroids. Doses higher than this will be considered therapeutic.

- Inclusion of Women and Minorities: Both males and females of all races and ethnic groups are eligible for this study.

- Clinical Status: Patients should have no significant worsening in clinical status for a minimum of 7 days prior to enrollment.

- Neurologic Status: Patients must be able to swallow whole capsules.

  Patients should undergo a repeat MRI prior to enrollment if there is a significant worsening or new neurologic symptoms in the interval between the eligibility scan and start of protocol therapy. *The repeat scan will act as a new baseline and the eligibility scan for these patients.

- Performance Status: Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 14 days of enrollment must be ≥ 50.

- Organ Function: Patients must have organ and marrow function as defined below:

  - Absolute neutrophil count > 1,000/mm3

  - Platelets > 100,000/ mm3 (unsupported, defined as no platelet transfusion within 7 days and recovery from nadir)

  - Hemoglobin ≥ 8 g/dL (may receive transfusions)

- Total bilirubin ≤ 1.5 times institutional upper limit of normal (ULN)
- ALT (SGPT) < 3 x institutional upper limit of normal
- Albumin ≥ 3 g/dL
- Serum creatinine based on age/gender as noted in Table 2. Patients that do not meet the criteria in Table 2 but who have a 24-hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 ml/min/1.73 m2 are eligible.

Table 2

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.		

- Pulmonary Function - Oxygen saturation as measured by Pulse oximetry must be ≥ 93% on room air.

- Growth Factors: Patients must be off all colony-stimulating growth factor(s) for at least 1 week prior to enrollment (i.e. filgrastim, sargramostim). Two weeks must have elapsed if patients received PEG formulations.

- Pregnancy Status: Pregnant or breast-feeding patients are excluded. Female patients of childbearing potential must have a negative serum or urine pregnancy test at the time of enrollment. This protocol defines the following childbearing potential risk categories as:

  - Female child/young adult of childbearing potential as a female who has:

    - Achieved menarche and/or breast development, in Tanner stage 2 or greater

      Onset of fertility typically occurs within 3-12 months after menarche. Menarche varies considerably from person to person, and thus no age cut off can be attributed. One of the primary tools used to follow a girl's progress through puberty is the Tanner staging system, which describes the pattern of development of the secondary sex characteristics. Tanner stage 2 corresponds to the beginning of breast development, which is the first visible sign of puberty in girls. Breast development is estrogen stimulated, and since ovulation cannot occur without estrogen, Tanner stage 2 will be a

reliable marker for the definition of fertility.

- Has not undergone a hysterectomy or bilateral oophorectomy, or has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

* Note: Amenorrhea following cancer therapy does not rule out childbearing potential.

- Pregnancy Prevention: Patients of childbearing or child fathering potential must use medically acceptable form(s) of birth control as stated within the pomalidomide Pregnancy Risk Minimization Plan, which includes abstinence, while being treated on this study. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

***Please see Protocol Appendix E, F, G, and H for further information and requirements in regards to pregnancy risk, education and testing as described briefly below.**

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Error! Reference source not found. (must be completed and signed by a trained counsellor (experienced in provision of age-appropriate counselling) at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the patient records.

Error! Reference source not found. will be given to each patient receiving pomalidomide study therapy and or their parent/guardian. The patient and or parent/guardian must read this document prior to the patient starting pomalidomide study treatment and each time they receive a new supply of study drug.

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- 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.

Exclusion Criteria

- 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.

- Prior Cancer Diagnosis:
  - Patients with a history of any other malignancy will not be eligible.
  - Patients with radiation-induced gliomas will not be eligible.

- Thrombosis or Known Coagulopathy: Patients with a history of non-central line related thrombosis, more than one prior central-line related thrombosis, or known coagulopathy will not be eligible due to the potential risk of thrombosis with this family of agents. Patients with a first degree family member with a known coagulopathy will be excluded, and therefore, obtaining a family history is essential when possible. Patients actively on anticoagulation therapy are not eligible.

- Current Therapy: Patients who are receiving any other anti-cancer or investigational drug therapy are excluded.

- Concomitant medications: Patients taking a known moderate to potent inhibitor of CYP1A2 are excluded. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Therefore, use of CYP1A2 inhibitors may increase pomalidomide exposure. Please see Protocol Appendix I **Error! Reference source not found.**for a list of common moderate and potent inhibitors of CYP1A2.

- 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.

- Prior Treatment: Patients who have received pomalidomide in the past are not eligible. Patients who have prior treatment with other IMiDs (thalidomide, lenalidomide) ARE eligible if they meet all other eligibility criteria and did not have "significant toxicity" associated with lenalidomide or thalidomide use. A "significant" toxicity will be defined as one that required a dose reduction or discontinuation due to toxicity.