Protocol Abstract and Schema

This is a phase I/II study to determine: 1) the maximum tolerated dose (MTD) or recommended phase II dose of ABT-888 in combination with radiation therapy, and 2) the efficacy of administering ABT-888 concurrently with radiation therapy, followed by maintenance therapy with ABT-888 and temozolomide (TMZ), in children with newly diagnosed diffuse intrinsic pontine glioma (DIPG).

This study consists of two parts: the phase 1, dose-finding component of the trial to estimate the MTD or recommended phase II dose of ABT-888 in combination with radiation therapy, and the phase 2 component of the study to evaluate the efficacy of ABT-888 and radiation therapy, followed by maintenance therapy with ABT-888 and TMZ, in children with newly diagnosed DIPG. Upon completion of ABT-888 and radiation therapy, patients enrolled in the Phase I study will continue with maintenance therapy with ABT-888 at 25 mg/m^2 bid and TMZ at 135 mg/m^2/day for 5 days every 28 days, the recommended phase II doses determined from PBTC-027. After Phase I is completed, all patients will receive radiation and ABT-888, at the MTD/recommended phase II dose determined from the Phase I study, followed by maintenance therapy with ABT-888 at 25 mg/m^2 bid and TMZ at 135 mg/m^2/day for 5 days every 28 days, the recommended phase II doses determined from PBTC27.

Since PBTC-027 enrolled patients who commonly received multiple prior chemotherapy treatments, and patients for PBTC-033 will be newly diagnosed, chemotherapy-naïve, and presumably have intact bone marrow reserve, we hypothesize that children for this clinical trial may tolerate higher combination doses of ABT-888 and TMZ compared to the children studied on PBTC-027. Therefore, during the maintenance therapy phase of both the Phase I and Phase II studies, intra-patient dose escalation of TMZ will be studied. Each patient will start maintenance therapy with ABT-888 at 25 mg/m^2 bid and TMZ at 135 mg/m^2/day for 5 days every 28 days. The TMZ dose will be escalated to 175 mg/m^2/day and then to 200 mg/m^2/day for 5 days every 28 days if no minimal toxicity is observed after each course.

The primary endpoints for the Phase I study will be toxicity and safety monitoring of ABT-888 in combination with radiation therapy and will include DLTs and toxic death. Dose-modifying toxicities for maintenance therapy will also be monitored to guide intra-patient dose escalation of TMZ and to terminate intra-patient dose escalation if excessive toxicity is observed (see section 5.1.3). The primary endpoint for the Phase II study will be the evaluation of the treatment efficacy as measured by 1-year overall survival (OS), with 1-year progression-free survival (PFS) and best tumor responses observed prior to tumor progression as the secondary measures of treatment efficacy.

PARP activity, non-homologous end-joining (NHEJ) activity, and γ–H2AX level in peripheral blood monocytes (PBMCs) will be quantified pre-treatment, 2 weeks after starting ABT-888 and irradiation, during the last week of ABT-888 and irradiation, and during the first course of maintenance therapy, as surrogate measures of intra-tumoral PARP inhibition and unrepaired double-stranded DNA breaks (DSB). In atypical pontine gliomas that are biopsied, PARP activity and DNA repair protein status will be studied either in frozen tumor material or FFPE samples as described in section 9.1.3. These molecular data will be correlated retrospectively

with efficacy measures outlined above. Pharmacokinetic studies of ABT-888 on day 1 and day 4 of ABT-888 and radiation treatment will also be performed. These PK studies will be required for Phase I and optional for Phase II of the study.

To differentiate pseudoprogression from true early progressive disease, quantitative MR measures of relative cerebral blood volume (rCBV), permeability (Ktrans, vp, and ve values), and apparent diffusion coefficient (ADC) will be obtained at diagnosis and during the first six months after starting protocol therapy and correlated with disease outcome, including whether such metrics differentiate patients with pseudoprogression from those with true early progressive disease.

Urine biomarkers will be employed to study the feasibility of a novel, non-invasive method to detect the presence, progression and response to therapy of pediatric brain tumors.

Schema:
Phase I Study
ABT-888 will be given twice daily on Monday through Friday, for 6-7 weeks, during daily radiation therapy (see table below). The first dose of ABT-888 should ideally be given 60-120 minutes prior to timing of radiation treatment. For patients who require sedation for radiation treatment and must remain NPO in the morning, ABT-888 should be given nightly prior to sleep, with the day time dose given shortly after the child awakens from sedation, adhering as closely to an every 12 hour schedule as possible.

Schema – Radiation Phase of Therapy							
Week	**1**	**2**	**3**	**4**	**5**	**6**	**Week 7-10**
ABT-888, BID	Twice daily, M-F, for 6-7 weeks						Rest/ Evaluation
Radiation Therapy	Daily, M-F, for 6-7 weeks						

Dose Level 1 of ABT-888 during radiation treatment will be approximately 80% of the dose that has been safely tolerated in adults (100 mg BID). It is also expected that the 150 mg bid dose level in adults will be declared tolerable shortly. Dose escalation/de-escalation will be done using a standard phase I, 3 + 3 design in increments of approximately 30% (see the table below). If the adult dose of 150 mg bid with radiation has been declared tolerable by the time this trial begins patient accrual, and the starting dose level of 50 mg/m^2 bid is also tolerated in children, we propose to proceed from dose level 1 directly to dose level 3 (85 mg/m^2 bid, equivalent to the adult dose of 150 mg bid). If dose level 3 is not tolerated, then we will de-escalate to dose level 2. If dose level 3 is tolerated, we will study dose level 4 only if supported by adult clinical data and PBMC PARP inhibition data from our ongoing trial.*

ABT-888 Dose Level During Radiation, for Phase I	
Dose Level	**ABT-888 dose (mg/m^2/dose BID), M-F**
0	35 mg/m^2/dose BID
1 (starting dose level)	50 mg/m^2/dose BID
2	65 mg/m^2/dose BID
3	85 mg/m^2/dose BID
4(pending supporting data)*	110 mg/m^2/dose BID

Upon completing radiation treatment and ABT-888, all patients from Phase I of the study will continue with maintenance therapy starting week 11, as outlined below.

Schema- Maintenance Phase of Therapy						
Each Course	**May receive a maximum of 10 courses**					
Day	1	2	3	4	5	6-28
ABT-888, BID	x,x	x,x	x,x	x,x	x,x	Rest/Evaluation
Temozolomide, once daily	x	x	x	x	x	Rest/Evaluation

Phase II Study

Phase II of the study will begin when the MTD/recommended phase II dose of ABT-888 in combination with radiation therapy has been determined from the Phase I study. Maintenance therapy will consist of ABT-888 and TMZ beginning at week 11 (3-4 weeks after the completion of radiation and ABT-888). Starting doses of maintenance therapy will be 25 mg/m^2 bid of ABT-888 and 135 mg/m^2/day of TMZ, for 5 days every 28 days, which are the recommended phase II doses from PBTC-027. Since this dose determination was based on children with refractory brain tumors, many of whom were heavily pre-treated, it is possible that children with newly diagnosed DIPG, who are chemotherapy naïve at entry, will tolerate higher doses of ABT-888 and TMZ during maintenance. In an effort to maximize the TMZ dose (and potentially the efficacy of the combination treatment) that can be administered with ABT-888 for each patient, **intra-patient dose escalation of TMZ will be studied only for patients with minimal hematologic toxicities in each course, defined as ≤ Grade 1 thrombocytopenia and ≤ Grade 2 neutropenia, and minimal non-hematologic toxicities not meeting the definition of dose-modifying toxicities in section 5.1.3.1,** after their first course of maintenance therapy at Dose Level 1. These patients' TMZ dose will be escalated for Course 2 to 175 mg/m^2/day (Dose Level 2), and subsequently (Course 3) to 200 mg/m^2/day of TMZ (Dose Level 3) if the toxicities observed after 1 course of protocol therapy at each dose level meet the above criteria.

Intra-Patient Dose Escalation during Maintenance Therapy (Days 1-5 per 28 day cycle)		
Dose Level	**ABT-888**	**TMZ Dose**
0	20 mg/m^2 BID	135 mg/m^2/day
1 (Starting Dose)	25 mg/m^2 BID	135 mg/m^2/day
2	25 mg/m^2 BID	175 mg/m^2/day
3	25 mg/m^2 BID	200 mg/m^2/day

1. OBJECTIVES

1.1 Phase I Primary Objectives

1. To identify the maximum tolerated dose or recommended Phase II dose of ABT-888 which can be safely administered concurrently with radiation therapy, followed by maintenance therapy with ABT-888 and TMZ, in patients with newly diagnosed DIPG.
2. To study the plasma pharmacokinetics (PK) of ABT-888 during ABT-888 and radiation therapy.
3. To study the feasibility of intra-patient dose escalation of TMZ during maintenance therapy with ABT-888 and TMZ.
4. To describe the toxicities associated with administering ABT-888 and radiation therapy, followed by ABT-888 and TMZ, in patients with newly diagnosed DIPG.
5. To estimate the proportion of newly diagnosed DIPG patients treated on protocol that are determined to have experienced pseudoprogression.

1.2 Phase II Primary Objectives

1. To estimate the overall survival distribution for newly diagnosed patients with DIPG treated with the combination of ABT-888 and radiation therapy, followed by ABT-888 and TMZ, and compare to PBTC historical controls.
2. To study the feasibility of intra-patient dose escalation of TMZ during maintenance therapy with ABT-888 and TMZ.
3. To estimate the proportion of newly diagnosed DIPG patients treated on protocol that are determined to have experienced pseudoprogression.

1.3 Secondary Objectives

1. To estimate the progression free survival distribution and to summarize the best tumor responses observed prior to progression or recurrence.
2. To explore the plasma pharmacokinetics (PK) of ABT-888 during ABT-888 and radiation therapy.
3. To explore peripheral blood mononuclear cell (PBMC) PARP activity before and after treatment with ABT-888.
4. To explore quantifying non-homologous end-joining (NHEJ) activity or γ-H2AX levels (as surrogate markers of unrepaired DSBs) in PBMC before and after treatment with ABT-888.
5. To explore quantifying PARP activity and DNA repair protein levels in biopsied atypical pontine gliomas, if available.
6. To explore associations of molecular parameters from secondary aims 3, 4 and 5 with PFS and OS after conclusion of clinical trial.
7. To explore the quantitative MR measures of relative cerebral blood volume (rCBV), vascular permeability (Ktrans, vp, and ve values), and apparent diffusion coefficient (ADC) within the first six months of initiating protocol treatment to correlate with disease outcome and determine whether such metrics differentiate patients with pseudoprogression from those with true early progressive disease.
8. To explore the potential utility of urine biomarkers as a novel, non-invasive method of detecting and tracking changes in the status of pediatric brain stem gliomas.

PATIENT SELECTION

Eligibility Criteria

The eligibility criteria listed below are to be interpreted literally and cannot be waived. No exceptions will be given. All clinical and laboratory data required to determine eligibility of a patient enrolled on this trial must be available in the patient's medical or research record.

Age

Patients must be ≤ 21 years of age at registration

Tumor

Patients with newly diagnosed diffuse intrinsic pontine gliomas (DIPGs), defined as tumors with a pontine epicenter and diffuse intrinsic involvement of the pons, are eligible without histologic confirmation. Patients with brainstem tumors that do not meet these criteria or not considered to be typical intrinsic pontine gliomas will only be eligible if the tumors are biopsied and proven to be an anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma, anaplastic mixed glioma or fibrillary astrocytoma.

> *Note: Patients with juvenile pilocytic astrocytoma, pilomyxoid astrocytoma, gangliogliomas, or other mixed gliomas without anaplasia are not eligible. Patients with disseminated disease are not eligible, and MRI of spine must be performed if disseminated disease is suspected by the treating physician*

Neurological Status

Patients must be able to swallow oral medications to be eligible for study enrollment.

Performance Status

Karnofsky ≥50% for patients >16 years of age and Lansky ≥50 for patients ≤ 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Prior Therapy

Patients must have not received any prior therapy other than surgery and/or steroids.

Organ Function

Patients must have normal organ and marrow function documented within 14 days of registration and within 7 days of the start of treatment as defined below:

- Absolute neutrophil count ≥1,000/mm^3
- Platelets ≥100,000/ mm^3 (unsupported)
- Hemoglobin ≥10g/dl (unsupported
- Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m^2 or
  Serum creatinine based on age/gender as follows:

Table 1

Serum Creatinine for age/gender	
Age	**Maximum Serum Creatinine (mg/dL)**

	Male	Female
1 to < 2 years	0.6	0.6
2 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.		

- Total bilirubin ≤1.5 times upper limit of normal (ULN) for age
- ALT(SGPT) ≤5 x institutional upper limit of normal for age
- Albumin ≥2g/dl

Pregnancy Status

Female patients of childbearing potential must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test.

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.

Informed Consent

Signed informed consent according to institutional guidelines must be obtained. Assent, when appropriate, will be obtained according to institutional guidelines.

Exclusion Criteria

Concurrent Illness

Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.

Inability to Participate

Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

Seizures

Patients with active seizures or a history of seizure are not eligible for study entry