

Single-arm, Open-label Phase II Efficacy Study of First-in-class HIF2-Alpha Inhibitor, PT2385, for Patients with Recurrent Glioblastoma

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A Protocol of the Adult Brain Tumor Consortium (ABTC)

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Version

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1.0 OBJECTIVES

Primary Objective

To estimate the efficacy of PT2385 as measured by radiographic response rate (by Response Assessment in Neuro-Oncology, RANO, criteria) in patients with recurrent glioblastoma

Secondary Objectives

1. To estimate the efficacy of PT2385 as measured by progression free and overall survival in patients with recurrent glioblastoma
2. To determine the safety of oral PT2385 in patients with recurrent glioblastoma

Exploratory Objectives

1. To describe the pharmacokinetic and pharmacodynamic properties of PT2385 in patients with recurrent glioblastoma
2. To describe baseline intratumoral hypoxia using novel, advanced MR-based neuroimaging sequences in patients with recurrent glioblastoma
3. To explore genetic polymorphisms involved in the metabolism of PT2385

2.0 BACKGROUND AND RATIONALE

2.1 Glioblastoma

Although the recent addition of temozolomide (TMZ) to radiation therapy for the treatment of glioblastoma (GBM) has resulted in improved outcomes, the estimated 2year survival with maximal therapy remains only 27% (Stupp, et al., 2005; Stupp, et al., 2009). Almost all GBMs progress, with a median time to progression of approximately 7 months. The prognosis is very poor for patients who have progressive/recurrent GBM. There is currently no standard therapy for recurrence. Salvage chemotherapies are largely ineffective, with progression-free survival at 6 months (PFS6) rates of 10-15%. Bevacizumab therapy at recurrence is associated with a high response rate, but not

significantly increased survival. Survival after failure of bevacizumab administered for GBM recurrence is very poor with a median survival of 4-6 months and PFS 6 of 0 (Reardon, et al., 2012). Hence, new therapies for recurrent GBM are urgently needed.

Hypoxia is a prominent feature of the tumor microenvironment in GBM. Pseudopallisading necrosis, one of the defining histologic characteristics of GBM, represents hypoxic tumor cells migrating away from dysfunctional vasculature (Rong, Durden, Van Meir, & Brat, 2006). This hypoxic environment promotes the self-renewal properties of glioma stem cells (GSCs) and may even drive non-stem cells toward a stemlike phenotype (Heddleston, Li, Hjelmeland, & Rich, 2009). Furthermore, hypoxia has been implicated as a potential mechanism of resistance to radiation therapy, a critical aspect of GBM treatment. However, to date few therapeutic agents have been developed which successfully modulate hypoxia pathways and improve outcomes in GBM.

2.2 PT2385

Rationale for the Therapeutic Target and Pathway

Several biochemical pathways mediate the cellular effects of hypoxia. Most importantly are the roles of the hypoxia inducible factors (HIFs). While HIF1-alpha (HIF1a) has been perhaps most widely studied in a variety of cancer models, HIF2a is potentially a more appealing target in GBM. HIF2a drives expression of numerous genes involved in angiogenesis (i.e. VEGFA), proliferation (i.e. cyclin D1), cell survival (e.g. class III betatubulin), and immune evasion (i.e. CD73). In contrast to HIF1a which is expressed in both GSCs and normal neural progenitors, HIF2a is specific and selective for GSCs (Li et al., 2009). In fact, the effects of hypoxia on the GSC phenotype has been shown to be directly mediated by HIF2a (Seidel et al., 2010). Dual labeling immunofluorescence studies show that HIF2a is co-expressed in cells expressing stem-cell markers (i.e. CD133) in perivascular locations and around areas of necrosis (Li et al., 2009). Furthermore, HIF2a and not HIF1a has been shown to regulate genes involved in mediating hypoxia-induced stemness (i.e. MAML3, NFATc2), promoting CD133 expression, and increasing neurosphere formation (Seidel et al., 2010). HIF2a is associated with CDH5-mediated neovasclogenesis in stem cell populations (Mao, Xue, Wang, Zhang, & Yan, 2013). HIF2a has been linked to over-expression of class III beta-tubulin, a survival factor that rescues cells from programmed cell death and has been linked to chemoresistance (Bordji, Grandval, Cuhna-Alves, Lechapt-Zalcman, & Bernaudin, 2014), aggressiveness (Katsetos, Dráberová, Legido, Dumontet, & Dráber, 2009), and poor prognosis (Ferrandina et al., 2006; Zhang et al., 2012). In conclusion, targeting HIF2a represents an opportunity to focus on a fundamental component of GBM (e.g. hypoxia) and potentially target the stem-like cell population which is purported to contribute to glioma heterogeneity, resistance to current therapies, and disease recurrence.

Preclinical Data in GBM

PT2385 is a first-in-class, orally administered potent and selective small molecule (383.34 Da) inhibitor of HIF2a. PT2385 has been shown to inhibit HIF2a-mediated signaling by disrupting the formation of the HIF2a:ARNT heterodimer in cells. Thus, in tumors where HIF2a is activated, PT2385 blocks the transcription of several genes involved in oncogenesis, including angiogenesis (e.g. VEGFA), proliferation (e.g. cyclin D1), immune evasion (e.g. CD73), metabolism (e.g. glucose transporter 1), and cell survival (e.g. class III beta-tubulin) (Chen et al., 2016; Wallace et al., 2016).

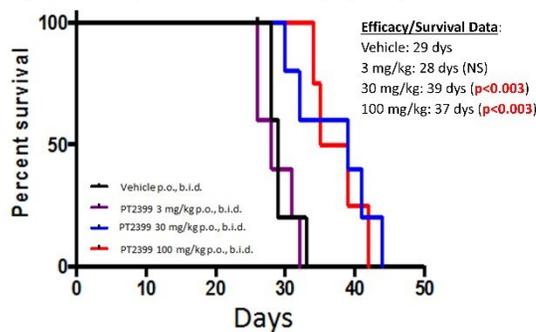
Table 1: Activity of PT2399 in orthotopic patient-derived xenograft models of GBM

Model	Vehicle Tumor Volume	Treated Tumor Volume	Growth Inhibition	Survival
1. R644 (GBM)	156 ± 11	91 ± 11	40%	No advantage
2. R777 (GBM)	123 ± 11	34 ± 22	72%	8 day improvement (28% over vehicle, p<0.003)
3. R548 (GBM)	NT	NT	NT	14.5 day improvement (45% over vehicle, p=0.006)
4. R533 (GBM)	NT	NT	NT	5.5 day improvement (12% over vehicle, p=0.001)

Caption: PT2399 is a structural analog distributed by Peloton Therapeutics for preclinical testing. All testing performed using orthotopic patient-derived xenograft (PDX) models including R644 (*p16^{INK4A}* deleted, CDK4 amplified), R777 (*PTEN* null, *PDGFRα* amplified, *p16^{INK4A}* deleted), and R548 (*PTEN* null, *EGFR* *viii* mutant). NT: not tested.

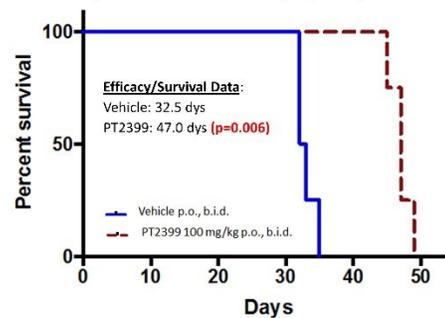
PT2385 is a first-of-its-kind agent and is unlike anti-VEGF or other existing targeted agents. Its mechanism of action is well upstream of existing anti-VEGF agents with more widespread cellular actions. Unlike anti-VEGF agents, PT2385 has no effect on rat blood pressure or heart rate at 5-times maximal efficacious exposure supporting its unique cellular action at the level of HIF2a. This activity translates to anti-tumor efficacy in mouse xenograft models of GBM (Table 1).

Figure 1a: Activity of PT2399 in an orthotopic primary GBM PDX model



Caption: Activity of PT2399 (structural analog of PT2385 for preclinical testing) in an orthotopic PDX model of GBM (R777: *PTEN* null, *PDGFRα* amplified, *p16^{INK4A}* deleted).

Figure 1b: Activity of PT2399 in an orthotopic primary GBM PDX model



Caption: Activity of PT2399 (structural analog of PT2385 used for preclinical testing) in an EGFR VIII mutant orthotopic PDX model of GBM (R548: *PTEN* null, *EGFR* *viii* mutant).

PT2399, a close structural analog of PT2385 with comparable brain uptake and the tool molecule used by external collaborators for preclinical testing, was evaluated in 4 orthotopic patient-derived xenograft (PDX) models of GBM. Survival benefit was observed in 3 of 4 models tested (Table 1, Figure 1a & 1b) with an average survival advantage ranging 12-45% (all $p < 0.001$). Growth inhibition has also been observed in an orthotopic renal cell carcinoma brain metastasis model (personal correspondence: Maher and Bachoo, University of Texas at Southwestern Medical Center).

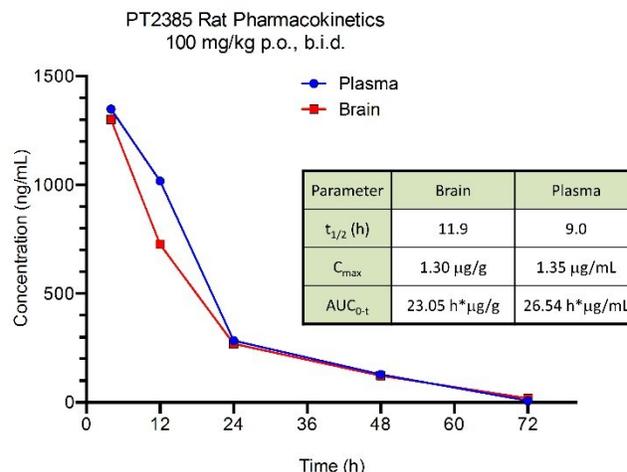


Figure 2: Rat brain & plasma PK after 3 days dosing of PT2385 (100 mg/kg)

Blood Brain Barrier Penetration

An important component of the development of novel drugs for treatment of GBM is the ability to cross the blood brain barrier (BBB). PT2385 has favorable characteristics for blood brain penetration in humans including low molecular weight (383 Da), low water solubility (log D value in octanol/water pH 7.4 is 2.19; < 3 being favorable), and high brain/plasma ratio in rats (ratio 0.9, Fig 2).

Studies in animals demonstrated the oral bioavailability to be 40% in rats and ~90% in dogs. The volume of distribution is greater than the total body water in mice, rats, dogs, and monkeys with a t_{max} between 0.5-2 hours and terminal half-life of 9 and 12 hours in rat plasma and brain, respectively. Plasma protein binding of PT2385 was 82% for human plasma protein with half-life of approximately 14 hours. The drug undergoes oxidative metabolism via CYP2C19 and CYP3A4 and O-glucuronidation (UDP-glucuronosyltransferase-2B7 isoenzyme) to form an inactive glucuronide conjugate (PT2639). PT2385 induced concentration-dependent increases in CYP2B6 and CYP3A4 mRNA cultured human hepatocytes with half-maximal effective concentrations (EC_{50} values) ranging from 10.3 to 33.5 μM (4-13 $\mu\text{g/mL}$) for CYP2B6 and from 9.3-41.2 μM (3.616 $\mu\text{g/mL}$) for CYP3A4.

Prior and Ongoing Clinical Trials with PT2385

As of August 15, 2016, PT2385 had been studied in 70 subjects, 16 healthy volunteers and 54 patients with ccRCC. Fifty-one patients have been enrolled in Part 1 of Study PT2385-101, the first-in-human study of PT2385; 26 patients were enrolled in the dose-escalation portion of Part 1, which has now completed enrollment and all dose-limiting toxicity evaluation periods. The dosages evaluated in the dose-escalation portion ranged from 100 to 1800 mg b.i.d. No dose-limiting toxicities were observed; no patients died during the study and no patients were discontinued from the study because of adverse events (AEs). The 800 mg b.i.d. dosage was selected as the recommended phase

2 dose based on an assessment of safety, pharmacokinetic, and pharmacodynamic data (Courtney et al., 2016). Twenty-five patients were enrolled in the dose expansion portion of Part 1 at a dosage of 800 mg b.i.d.

The most commonly reported AEs among the 51 patients enrolled in Part 1 were anemia, fatigue, peripheral edema, nausea and lymphocyte count decreased. Most AEs have been mild to moderate in severity and were reported as National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 to 2. The most common Grade 3/4 toxicities included anemia (5), decreased lymphocyte counts (5), hypoxia (5), and hypophosphatemia (3). One patient had a complete response (CR), four patients had a partial response (PR), and 17 patients had stable disease for more than 16 weeks. The longest duration of treatment has been 537 days for a patient in the 200 mg b.i.d. dosage group and 468 days for a patient treated at the 800 mg b.i.d dose.

In Part 2 of the study, PT2385 (800 mg b.i.d. orally) is being evaluated in combination with nivolumab (Opdivo®) (3 mg/kg intravenously once every two weeks). Three patients with ccRCC have been treated with the combination of PT2385 and nivolumab. There were 10 reported AE's; photophobia was the only event reported in more than one patient (2). All AE's in Part 2 were reported as Grade 1, with the exception of one Grade 3 AE of pleural effusion, which also met SAE criteria. The event of pleural effusion was considered not related to PT2385, but related to progressive disease.

Study PT2385-102 evaluated the effect of food on the pharmacokinetics of PT2385 in 16 healthy female volunteers in a crossover study. The presence of food had a mild effect (19% to 37% increase) on the exposure to PT2385 in this study; little to no effect was observed in exposure to PT2639 (the primary metabolite of PT2385) in the presence of food. The most common adverse events were headache, venipuncture site bruising, and nausea.

2.3 Rationale

Based on preclinical efficacy as a single-agent, favorable blood brain barrier penetrating properties, and acceptable safety profile with an established recommended phase II dose, we propose a phase II efficacy study of PT2385 in recurrent GBM. This study will provide the first-ever experience of PT2385 in GBM and provide the initial clinical experience of targeting this novel therapeutic pathway.

Bevacizumab-naïve patients have been specifically selected for this study. PT2385 is unlike other agents currently approved for the treatment of recurrent GBM. Though PT2385 potentially inhibits tumor production of VEGF, its action is well upstream of VEGF with widespread cellular action on cyclin D1, CD73, GLUT1, and others. Clinically, VEGF tyrosine kinase inhibitors are associated with hypertension; however, such findings could not be recapitulated in preclinical models of PT2385 treated rats (Fig 3). To avoid any potential impact of bevacizumab on tumor associated hypoxia, in this first experience of PT2385 in GBM, we propose to study this agent in bevacizumab-naïve patients at first recurrence.

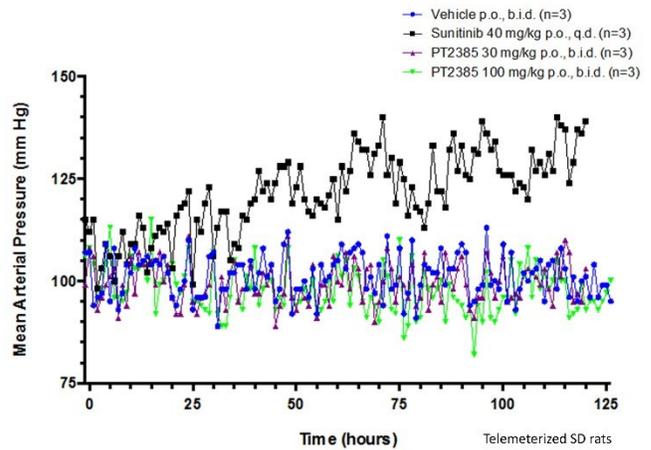


Figure 3: HIF-2 α Antagonism does NOT recapitulate anti-angiogenic effects in rats

Radiographic response has been specifically selected as the primary endpoint in this study and is supported by recent Cancer Treatment and Evaluation Program (CTEP)-approved trials ongoing within the Adult Brain Tumor Consortium (ABTC) including ABTC 1402. Overall and progression-free survival data will be gathered as secondary endpoints to inform subsequent drug development in this population.

Overall, this study will provide an initial experience of the clinical activity of PT2385 in GBM as a single agent. If positive, subsequent studies will determine the safe and effective dose of PT2385 which can be combined with radiation and/or temozolomide as a new therapeutic approach in the newly diagnosed setting.

In a condition with a dismal prognosis and limited therapeutic options, PT2385 is an extremely attractive agent for study. It targets a signaling pathway that is highly relevant for GBM and for which no similar agents are currently undergoing testing. Pharmacologic properties (i.e. molecular weight <400 Da, low water solubility) support ideal properties for blood brain penetration which is supported in preclinical studies. This agent shows promising activity in preclinical orthotopic PDX models of GBM and is an ideal first-in-class agent to investigate. In this study, we propose the first-ever experience with this agent in patients with recurrent GBM.

2.4 Correlative Studies Background

Pharmacokinetic Assessment

Pharmacokinetics:

In the existing experience in the single-arm phase I study of PT2385 in patients with renal cell carcinoma (RCC), pharmacokinetic data suggests that a small subset of patients may rapidly metabolize PT2385 into its inactive metabolite, thus limiting exposure to drug. To

further explore this variability, pharmacokinetic data will be assessed. Plasma concentrations of PT2385 and PT2639 will be determined by validated liquid chromatography/mass spectrometry methods. All PK studies and analyses will be funded by Peloton Therapeutics and contracted by Peloton Therapeutics through an external vendor which has been feasible in the ongoing phase 1 study in RCC. All PK studies and analyses will be performed by Peloton Therapeutics.

Pharmacogenomic Assessment:

PT2385 is metabolized by the polymorphic CYP2C19 (PMID 10971203) and CYP3A4 (PMID 16509759), suggesting the potential for CYP2C19 and CYP3A4 polymorphisms to influence the metabolism of PT2385 and potentially contribute to patient-to-patient variability in drug metabolism. Data from the phase 1 study in ccRCC are being gathered to explore potential explanations but a genomic target and validated assay do not currently exist. The primary objective of the study proposed is to determine the radiographic response rate and the study is designed to achieve this objective. Whole blood samples will be collected for sequencing of genes that may be involved in regulating PT2385 metabolism. Samples will be stored by Peloton Therapeutics for future pharmacogenomics analysis.

Pharmacodynamic Assessment

Pharmacodynamic markers to be assessed may include, but are not limited to, levels of erythropoietin (EPO) and vascular endothelial growth factors (e.g. VEGF, soluble VEGF). These markers have demonstrated the most promise based on data from the phase I study in ccRCC. Plasma concentrations of EPO and VEGF will be determined by commercially available ELISA contracted through an external vendor and funded by Peloton Therapeutics. This process has been feasible in the phase 1 study in ccRCC. All PD studies and analyses will be performed by Peloton Therapeutics.

Hypoxia Imaging

Patient selection is a critical component of the therapeutic development of targeted agents. While hypoxia is central to the pathogenesis of GBM, biologic response to agents that target hypoxia pathways may vary based on the degree of hypoxia present, the reliance on hypoxic pathways, and other factors. As such, critical to the development of the proposed agent is the exploration of imaging and other methods to inform patient selection. While several modalities hold promise in imaging hypoxia, no clinically available gold standard currently exists. Two innovative hypoxia and pH-weighted MR-based imaging sequences have been recently developed by a collaborator through the ABTC (Ellingson/UCLA). These sequences and associated endpoints are an exploratory component of this study. The sequences will not be used to evaluate radiographic response or progression (i.e. PFS) and are not designed as companion or integral biomarkers in this study. Importantly, tumor hypoxia and acidity are hypothesized to be potential drivers of HIF2a expression and may not change as a result of HIF2a inhibition; however, pre-treatment levels of hypoxia and acidity may predict patients that respond from inhibition of HIF2a. The proposed advanced imaging will be performed at baseline to explore the degree of hypoxia present at treatment

initiation. The objective for this correlative imaging component of the study is to describe the hypoxia signature of these tumors at baseline and explore possible correlations with clinical outcomes.

Fast pH-weighted Molecular Magnetic Resonance Imaging (MRI) using Amine CEST-EPI: The chemical exchange between amine and amide protons in bulk water has been shown to be pH dependent using an imaging method called chemical exchange saturation transfer (CEST) imaging. In a recently set of published studies by Dr. Ellingson and colleagues, pH-weighted imaging was shown to have high spatial correspondence between regions of tumor acidity, elevated choline on MRS, elevated lactate on MRS, and elevated ^{18}F -FDOPA uptake (Figure 4, Harris et al., 2015; Harris et al., 2016). Results also suggested patients with acidic lesions (**Figure 4D**) were more likely to progress earlier after starting radiochemotherapy (**Figure 4F**), while patients with non-acidic lesions (**Figure 4E**) were more likely to respond favorably to therapy. Further, if tumors became less acidic during treatment they were also more likely to have a favorable PFS (Harris et al., 2015). Together, these results suggest characterization of intratumoral pH may be an important biologic feature that should be quantified in GBM patients, particularly for therapies that focus on manipulating the microenvironment, metabolism, or oxygenation.

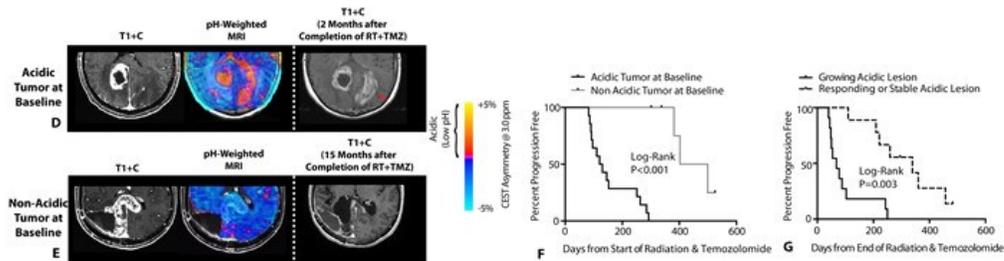


Figure 4: Amine CEST-EPI Imaging

Fast Hypoxia-Weighted MRI using Multi-Echo Spin-and-Gradient Echo (ME-SAGE)-EPI:

Recently, investigators have demonstrated the ability to estimate simultaneous T2 and T2* maps using multi-echo spin-and-gradient echo planar imaging (ME-SAGE)-EPI. Using a combination of T2, T2* and relative cerebral blood volume (rCBV), Magnetic Resonance (MR) estimates of relative oxygen extraction fraction (rOEF) can be acquired (Hirsch et al., 2014; He et al., 2007; Toth et al., 2013). Pilot results suggest these rOEF maps show measurable changes as a result of radiotherapy (**Figure 5**) (Toth et al., 2013). Thus, we will

acquire rOEF maps prior to HIF2a inhibition in order to explore whether patients with relatively hypoxic tumors respond favorably to PT2385. Using a combined multi-echo CEST-SAGE-EPI acquisition we will simultaneously estimate both pH and rOEF in the current study.

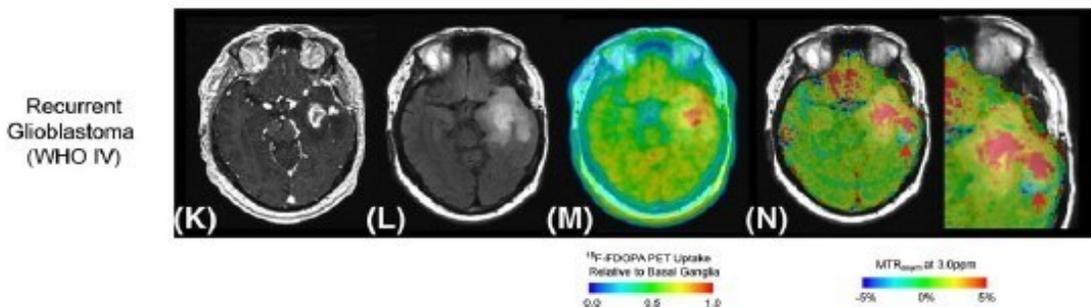


Figure 5: Hypoxia Weighted CEST-EPI-MTR Imaging showing (K) post-contrast T1-weighted image of a centrally ringenhancing recurrent GBM, (L) fluid attenuated inversion recovery (FLAIR) image of this lesion with surrounding edema, (M) FDOPA-PET demonstrating central regions of increase dopamine uptake, and (N) hypoxia-weighted CEST-EPI-MTR sequences showing regions of hypoxia extending beyond the centrally enhancing necrotic focus into region of FLAIR abnormality.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Patient Sample

Sample Size:

Minimum: 24 patients / Maximum: 35 patients

Accrual Rate:

3-5 patients per month

Gender:

Male and female

Age:

Patients must be at least 18 years of age.

Race:

Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

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	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	3	0	0	5
White	7	15	2	3	27
More Than One Race	0	0	0	0	0
Total	10	20	2	3	35

3.2 Eligibility Criteria

1. Patients must have histologically confirmed glioblastoma that is progressive or recurrent following radiation therapy and temozolomide according to the Response Assessment in Neuro-Oncology (RANO) criteria with:
 - a) New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.
 - b) Increase by $\geq 25\%$ in the sum of the products of perpendicular diameters between the postradiotherapy scan with the smallest tumor measurement and a scan at least 12 weeks from completion of RT+TMZ, on stable or increasing doses of corticosteroids.

Note: clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.

2. Tumor O(6)-methylguanine-DNA-methyltransferase (MGMT) methylation status must be available. Results of routinely used methods for MGMT methylation testing (e.g. methylation-specific polymerase chain reaction, MSPCR, or quantitative PCR) are acceptable.

3. Patients must have a tumor tissue form indicating availability of archived tissue from a previous surgery for glioblastoma, completed and signed by a pathologist. See Section [9.5.5](#).
4. Patients must have measurable (defined by at least 1 cm x 1 cm) contrast-enhancing disease by MRI imaging within 21 days of starting treatment.
5. Patients must be able to undergo MRI of the brain with gadolinium. Patients must be maintained on a stable or decreasing dose of corticosteroid regimen (no increase for 5 days) prior to this baseline MRI.
6. Patients must be in first recurrence of glioblastoma following radiation therapy and temozolomide.
7. Patients must have recovered from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:
 - 12 weeks from the completion of radiation.
 - 6 weeks from a nitrosourea chemotherapy
 - 3 weeks from a non-nitrosourea chemotherapy
 - 4 weeks from any investigational (not FDA-approved) agents
 - 2 weeks from administration of a non-cytotoxic, FDA-approved agent (e.g., erlotinib, hydroxychloroquine, etc.)
8. Patients must be 18 years of age or older.
9. Patients must have a Karnofsky Performance (KPS) Status \geq 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
10. Patients must have the following organ and marrow function:

Absolute neutrophil count	\geq 1,500/mcL
Platelets	\geq 100,000/mcL
Hemoglobin	\geq 9 g/dL
Total bilirubin	\leq institutional upper limit of normal
AST (SGOT)/ALT (SGPT)	\leq 4 \times institutional upper limit of normal
Creatinine	\leq institutional upper limit of normal
OR	
Creatinine clearance	\geq 60 ml/min/1.73m ² for patients with creatinine levels above institutional normal
APTT or PTT	\leq 1.5 x institutional upper limit of normal

11. Patients must be able to provide written informed consent.
12. Women of childbearing potential must have a negative serum pregnancy test prior to study start. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and through 30 days after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and through 30 days after the last dose of study drug.
13. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for \geq five years.
14. Patients must be able to swallow tablets.

3.3 Ineligibility Criteria

1. Patients receiving any other investigational agents are ineligible.
2. Patients must not have received prior anti-VEGF therapy including bevacizumab (i.e. patients must be bevacizumab naïve)
3. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to PT2385 are ineligible.
4. Patients on enzyme-inducing anti-epileptic drugs (EIAED) are not eligible for treatment on this protocol. Patients may be on non-enzyme inducing anti-epileptic drugs or not be taking any anti-epileptic drugs. Patients previously treated with EIAED may be enrolled if they have been off the EIAED for 10 days or more prior to the first dose of PT2385.
5. Patients with a history of bleeding diathesis are ineligible.
6. Patients who have not recovered to $<$ CTCAE grade 2 toxicities related to prior therapy are ineligible.

7. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, clinically significant cardiac disease, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.
8. Pregnant women are excluded from this study because the effects of PT2385 on a fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with PT2385, breastfeeding should be discontinued if the mother is treated with PT2385.
9. HIV-positive patients on combination antiretroviral therapy are ineligible due to potential drug-drug interactions with PT2385.

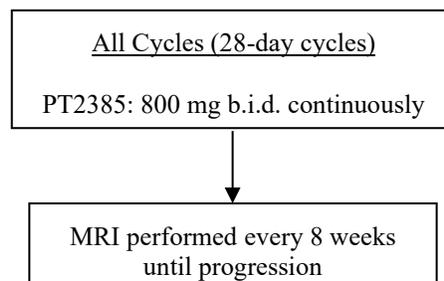
4.0 TREATMENT PLAN

This is a Phase II, open-label, multicenter efficacy study of PT2385 as monotherapy in patients with recurrent glioblastoma. All subjects must have had histological confirmation of glioblastoma by either biopsy or resection that is progressive or recurrent following radiation therapy + temozolomide.

4.1 Treatment Schema

The goal of this study is to estimate the efficacy of PT2385 as measured by radiographic response in recurrent GBM.

Following enrollment, patients will receive PT2385 at the recommended phase II dose of 800 mg twice daily, continuously in 28-day cycles until progression or unacceptable toxicity. Patients will be followed by routine blood work, and general and neurological examination. A brain MRI will be performed prior to every odd-numbered cycle (every 8 weeks). Response will be assessed by RANO criteria (Section [8.1](#)).



Blood samples to characterize the plasma pharmacokinetics and pharmacodynamics of PT2385 will be obtained from all patients at baseline and in Weeks 1, 2, and 4 of the first

cycle (see Sections [9.5.1](#) and [9.5.2](#)). A blood sample for pharmacogenomic assessment will also be obtained at baseline (Section [9.5.3](#)).

Patients at qualified sites will have simultaneous pH- and hypoxia-weighted MRI performed at baseline (Section [9.5.4](#)).

Patients will continue receiving PT2385 until they meet the criteria for disease progression or other criteria for going off treatment (Section [10.0](#)). Standard of care treatment options will exist for patients who suffer tumor progression or recurrence on treatment. All patients will be followed for progression-free and overall survival. Overall survival will be assessed as the date from treatment start to death from any cause.

4.2 Treatment Requirements

All eligible patients who consent to this study must have a baseline (post-operative, if surgery is applicable) pre-treatment MRI showing measurable disease (i.e. 1 cm x 1 cm enhancement). This baseline scan must be done within 21 days prior to the initiation of treatment.

Prior to every cycle patients must have:

1) ANC \geq 1500/ μ l and platelets \geq 100,000 / μ l.

AND

2) All toxicities recovered to \leq grade 1 (or tolerable grade 2 for non-hematologic toxicity) or \leq baseline.

4.3 Drug Administration

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Treatment will be administered on an outpatient basis. Patients will be provided with medication diaries ([Appendix I](#)) and instructed in their use. Patients will be instructed to bring all unused medication and their diaries to each study visit for assessment of compliance.

4.3.1 PT2385 Administration

PT2385 will be administered on an outpatient basis as an oral dose of 800 mg twice daily. Patients should take the doses approximately the same time each day. Each dose should be taken 12 hours apart (\pm 2 hours). Tablets should be taken with 8 ounces of water and

may be taken with or without food. Tablets should be swallowed whole, not chewed or crushed.

Missed doses may be made up if taken within 4 hours after the scheduled administration time. Study drug may not be taken within 8 hours before the scheduled time for administration of the next dose. Patients who vomit after study drug administration should not retake that study drug dose but should resume taking study drug with the next scheduled dose.

Patients will be requested to record each dose of PT2385 on the Patient Medication Diary in [Appendix I](#).

4.4 General Concomitant Medication and Supportive Care Guidelines

Prohibited Concomitant Medications During Study

Patients may receive other medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, anti-neoplastic biological therapy or other investigational agents. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study.

PT2385 is primarily metabolized by UGT2B17, UGT2B7, UGT2B15, CYP2C19 and CYP3A4. Strong inhibitors of CYP2C19 and CYP3A4 should be avoided in patients receiving PT2385 ([Appendix II](#)).

PT2385 has been shown to induce the enzymes CYP3A4 and CYP2B6 in cultured human hepatocytes. Simcyp PBPK model simulations indicate weak-to-moderate CYP3A4 substrate midazolam DDIs (~50% reduction in midazolam AUC) at the clinically relevant PT2385 doses. Simulations also indicate that PT2385 is a weak CYP2B6 inducer (< 11% AUC reduction for CYP2B6 substrate bupropion at the clinically relevant PT2385 doses). PT2385 is not a potent inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 ($IC_{50} > 8.8 \mu\text{g/mL}$). It is unlikely to significantly inhibit these CYPs at the clinically relevant PT2385 concentrations ($C_{\text{max}} \sim 3.14 \mu\text{g/mL}$). A partial list of CYP3A4, CYP2B6, CYP2C9, and CYP2C19 substrates is provided in [Appendix III](#).

Patients taking medications metabolized by CYP3A4 and CYP2B6 should be monitored carefully for decreases in drug effect. Patients taking medications metabolized by CYP2C9 and CYP2C19 should be monitored for potential increases in drug effect.

Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. The lowest required steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

Anticonvulsants

No data exist regarding the interaction of PT2385 with enzyme-inducing anti-epileptic drugs (EIAEDs). For this study, patients may **not** be on EIAEDs; patients who require antiepileptic drugs (AED) may be on non-enzyme inducing anti-epileptic drugs (NEIAED). If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a ≥ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an EIAED drug must be used for a patient on study the patient will be removed from the protocol.

Herbal and Non-Traditional Medications

No data exist regarding the interaction of PT2385 with commonly used herbal or nontraditional medications. Patients should be instructed not to use such medications while receiving PT2385 therapy.

5.0 DOSING DELAYS/DOSE MODIFICATION FOR TOXICITY

Clinically significant adverse events or abnormal laboratory values assessed as unrelated to disease progression, intercurrent illness, or concomitant medications may require dose delay and/or dose modification. Such toxicities must have an attribution of possible, probable, or definite to PT2385 (see Section [9.2.2](#)). If multiple toxicities occur, dose modification decisions should be based on the most severe toxicity.

For patients experiencing toxicity meeting the criteria below, PT2385 will be stopped. If the patient recovers (\leq grade 1 [or tolerable grade 2 for non-hematologic toxicity] or \leq baseline) a dose reduction is required for subsequent doses. Skipped doses will not be made up. If there is any question or clarification required concerning a toxicity, the treating site should contact the ABTC Central Office to determine patient's toxicity status. The ABTC Central Office, with the Study Chair (who may consult with Peloton Medical), will make the final decision.

- Hematological toxicities will require dose modification if any of the following occur and complete blood counts and differentials were obtained according to the

mandated schedule (CBC, differential, and platelets drawn twice a week until the ANC \geq 1500/ mcL and platelets \geq 100,000/ mcL): grade 3 or 4 lymphopenia will not be considered a toxicity requiring dose modification.

- ANC of $<$ 500/ mcL
- Platelets $<$ 25,000/ mcL
- Febrile neutropenia
- Any hematological toxicity that prevents administration of \geq 80% of the planned PT2385 doses for that cycle

➤ Non-hematological toxicities will require dose modification if any of the following occur:

- Grades 3-4 severity (except nausea, vomiting, and diarrhea without sufficient prophylaxis; except alopecia; except grade 3 hyperglycemia; except grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement therapy; and except grade 3 neurologic toxicity responding within two weeks to steroids, anticonvulsants, or electrolyte correction; and except Grade 3 asymptomatic hypoxia. A subject's first episode of deep venous thrombosis [DVT] or pulmonary embolism [PE] will not require dose modification)

ANY TREATMENT RELATED TOXICITY (AS DEFINED ABOVE) CAUSING DELAY IN TREATMENT OF OVER 21 DAYS IN THE START OF A CYCLE WOULD RESULT IN TAKING THE PATIENT OFF TREATMENT.

5.1 Dose Modification for PT2385

The dose levels and the general approach to PT2385 dose modification on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly recorded on the case report form.

Dose reductions are required for any clinically significant toxicity as defined above. Dosing will stop until the toxicity has resolved to \leq grade 1 (or tolerable grade 2 for nonhematologic toxicity) or \leq baseline. After resolution, when dose reduction is permitted, the dose of PT2385 will be modified as stipulated below, with a maximum of 2 dose reductions. The maximum length of time that PT2385 can be held is 21 days. If treatment-related toxicity is not resolved in \leq 21 days, the patient will be removed from treatment. If there is any question, the ABTC Central Office and the Study Chair should be contacted. The ABTC Study Chair may consult with Peloton Medical as needed for any issues.

Dose Reduction Table for PT2385

Dose Level	PT2385
Starting dose	800 mg b.i.d.
First dose reduction	600 mg b.i.d.
Second dose reduction	400 mg b.i.d.

5.2 Major Events

Major Events are non-treatment-related grade 3 and 4 hematologic and non-hematologic toxicities. Treatment should be delayed for major events if PT2385 may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (\leq grade 1 [or tolerable grade 2 for nonhematologic toxicity] or \leq baseline). If toxicity is not resolved in \square 28 days, the patient will be removed from treatment. The ABTC Central Office should be consulted if you are not clear on whether to continue or delay treatment.

5.3 Use of Hematologic Growth Factors

During the first 28 days of treatment, granulocyte colony stimulating factor (G-CSF) should be administered only for severe or prolonged neutropenia or for neutropenic sepsis. There will be no constraint on the use of growth factors during subsequent treatment; however, prophylactic use is discouraged and adherence to the American Society of Clinical Oncology (ASCO) guidelines is recommended (JCO, 12, 1994: pp 2471-2508). Patients should receive all necessary supportive care, including blood products, transfusions, antibiotics, pain medications, bisphosphonates, and replacement hormonal therapies (insulin, thyroid hormones, estrogen/progesterone).

5.4 Toxicity Criteria

All toxicities will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 until March 31, 2018; CTCAE version 5.0 will be utilized beginning April 1, 2018. 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 web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). See also Section [9.2.2](#), Recording of Adverse Events.

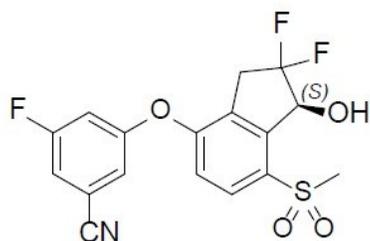
6.0 PHARMACEUTICAL INFORMATION

PT2385

Chemical Name: 3-(((1*S*)-2,2-difluoro-1-hydroxy-7-methanesulfonyl-2,3-dihydro-1*H*inden-4-yl)oxy)-5-fluorobenzonitrile

Other Names: PT2385, PT-2385, PT0002385 and CK 1558

Chemical Structure:



Molecular Formula: C₁₇H₁₂F₃NO₄S. **M.W.:** 383.34 g/mol

Chemical Properties: PT2385 has low solubility in water. The Log D value for PT2385 in octanol/water pH 7.4 is 2.19.

Pharmaceutical Properties: PT2385 is an anticancer agent that inhibits the function of HIF-2 α by disrupting the formation of the HIF-2 α :ARNT heterodimer with consequent impairment of hypoxic signaling in cancer cells.

Formulations: PT2385 is formulated as an immediate release tablet in a 200 mg strength. The excipients used in the formulation include United States Pharmacopeia or National Formulary grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, polysorbate 80 and magnesium stearate.

Storage: PT2385 tablets are to be stored at room-temperature conditions, 15°C to 30°C (59°F to 86°F).

Stability: Studies are ongoing to monitor the stability of PT2385 tablets.

Route of Administration: Oral, given with or without food. Each dose should be taken with 8 ounces (240 mL) of water.

6.1 Agent Ordering

The investigator or those named as sub-investigators on the Statement of Investigator Form 1572 agree to supply study drugs only to those patients enrolled in the study. The

investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by Peloton Therapeutics. The study site will maintain a dispensing log.

Once a site has submitted all required regulatory documents to ABTC and Peloton (Forms 1572, CVs, licenses, IRB protocol approval) an initial supply of drug can be ordered. An ABTC drug order form, which can be found on the ABTC website (ABTCConsortium.org), should be emailed to the ABTC Central Office to initiate sending drug. The ABTC Central Office will forward the drug order form to Peloton. Please allow a minimum of 7 days from the receipt of the drug order at Peloton for drug shipment.

6.2 Agent Accountability

Each institutional investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from Peloton, using the NCI Oral Drug Accountability Record Form (Oral DARF).

Upon termination of the study the investigator or designee must complete a final inventory of supplies.

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) and ABTC policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov.

Site Registration Requirements – IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsu.org> and clicking on the RSS tab.

Site registration documents must be submitted to the Regulatory Submission Portal of the CTSU Member Web site (login is required). To access the Regulatory Submission Portal, the site staff must have an Active CTEP IAM account. Site staff can utilize the Regulatory Submission Portal at any time by clicking the “Regulatory submission” subtab under the “Regulatory” Tab, located at the top of all pages on the CTSU members’ website. (See Regulatory Submission Portal User Guide 12.6.16 on CTSU website (www.ctsu.org) for detailed instructions on how to use portal).

Patient Registration:

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). All site staff will use OPEN. OPEN is a web-based registration system available to users 9 a.m. to 4:30 p.m. Eastern Time. The system can be accessed by entering credentials at <https://www.ctsu.org> and clicking on the OPEN tab, or by entering credentials at the OPEN portal URL <https://open.ctsu.org>.

Prior to discussing protocol entry with the patient, site staff must check the ABTC website (ABTConsortium.org) for protocol status and slot availability.

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

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role (or equivalent) on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Upon completion of the registration process in OPEN, sites should contact the ABTC Central Office to confirm the patient's registration.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (<https://open.ctsu.org>). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.0 RESPONSE ASSESSMENT / SAFETY AND QUALITY ASSURANCE

8.1 Criteria for Response Assessment

Subjects with measurable disease will be assessed by the RANO (radiographic assessment in neuro-oncology) criteria (Wen et al., 2010). For the purposes of this study, subjects should be re-evaluated at the end of every 2 cycles (approximately every 8 weeks) with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below.

Measurable disease. Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal size of 1 cm x 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are >2 lesions (multifocal) at baseline, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered nonmeasurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and nonmeasurable lesions are assessed.

Complete Response – CR (requires *all* of the following):

- a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- b) No new lesions.
- c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- d) Subjects must be off corticosteroids (or on physiologic replacement doses only).
- e) Stable or improved non-enhancing (T2/FLAIR) lesions.
- f) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response – PR (requires *all* of the following):

- a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- b) No progression of non-measurable disease.
- c) No new lesions.
- d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
- f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. g) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease – SD (requires *all* of the following):

- a) Does not qualify for CR, PR, or progressive disease (PD).
- b) The designation of stable disease requires a minimum of 4-week duration.
- c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
- d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. e) Stable clinically.

Progressive Disease – PD (defined by *any* of the following):

- a) $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
- b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). c) Any new lesion.
- d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy,

cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.

- e) Failure to return for evaluation due to death or deteriorating condition.
- f) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

8.2 Assessment of Response

Assessment of response will begin with the MRI performed just prior to *every oddnumbered* treatment cycle. If during any scheduled MRI, the subject has a Complete Response or Partial Response, the MRI should be repeated prior to the next cycle. All scans are to be compared to the smallest measurement scan to date. The subject will then return to the every odd-numbered cycle schedule. This is required to confirm the duration of response. Subjects will be classified as responders if they have a minimum duration of response for 4 weeks at any time after the first cycle of PT2385. MRI scans of subjects showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

8.3 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, pregnancy testing (in women of childbearing potential), regular measurement of vital signs, and the performance of physical/neurological examinations; ECGs and other cardiac monitoring may be performed as necessary.

8.4 Quality Assurance

Neuropathology: The neuropathologic diagnosis of glioblastoma will be made at the respective institution. If any question arises regarding the accuracy of the neuropathologic diagnosis, slides (and pathological blocks, if necessary) will be reviewed by the central review pathologist. For protocols with “response” as an outcome, all patients with a documented complete response or partial response may have representative pathology slides undergo central review.

Neuroradiology: MRI scans of patients showing tumor response as assessed locally will be centrally reviewed by the ABTC Imaging Core at the UCLA Brain Tumor Imaging Laboratory by board-certified neuroradiologists who will independently assess tumor size and assess radiographic response.

Adherence to protocol therapy: Screening/baseline source documentation will be submitted/uploaded into CTEP’s iMedidata Rave system and will be reviewed by the ABTC Central Office. As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Table of Required Observations

PT2385 (28-Day Cycles)

	Baseline	Days 1-28 of every cycle	Cycle 1	Weekly During Cycle 1	Weekly During All Cycles	Pre-Odd Cycles (cycles 3+)	Pre-Even Cycles	Off Treatment	30 Days post-last dose
PT2385		6							
Glucocorticoids Dose Evaluation	1					5		8	
AE Evaluation	1			7		5	5	8,10	11
MRI	1,15					5		8	
H&P/Neuro Exam	1					5	5	8	
KPS	1					5	5	8	
Vital Signs with pulse oximetry	1,2			2,7		2,5	2,5	2,8	
CBC, Diff, Platelets	1				9,7	5,9	5,9	8	
Serum Chemistry	1,3			3,7		3,5	3,5	3,8	
APTT or PTT	1								
Serum Pregnancy Test	1,4								

Plasma Samples for Pharmacokinetics			12						
Plasma Samples for Pharmacodynamics			13						
Plasma Sample for Pharmacogenomics	14								
Archived Tumor Tissue	16								

- 1– All baseline measurements must be done within minus 21 calendar days of treatment administration unless otherwise specified.
- 2– Including blood pressure, respiratory rate, heart rate, temperature, weight, height: height is required at baseline only; weight is required at pre-odd cycle evaluations only. Patients with dyspnea or asymptomatic desaturation (oxygen saturation <92%), will be further evaluated as clinically indicated: evaluation may include chest x-ray, arterial blood gas analysis, pulmonary function testing including diffusion capacity, co-oximetry, as well as evaluation for specific causes of hypoxia/dyspnea.
- 3– Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
- 4– For women of child-bearing potential.
- 5– Within minus 5 calendar days of cycle start.
- 6– PT2385 is administered orally twice daily on Days 1-28 of each 28-day cycle (see Section [4.3.1](#)). Patients are required to keep a medication diary. 7– ± 1 day
- 8– Evaluations done within +7 days of off treatment date unless indicated: do not repeat: if MRI within minus 14 days of off-treatment date; if H&P/neuro, KPS, labs within minus 5 days of off-treatment date.
- 9– If ANC < 1500 or plts < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥1500 or plts ≥100,000) per protocol. If counts are recovered (ANC ≥1500 or plts ≥100,000) on day of scheduled drawing do not repeat until next protocol schedule day
- 10 – Adverse Events must be followed for at least 30 days from last dose of PT2385.
- 11– Perform within +14 days of the 30-day post-last dose date.
- 12– Plasma samples will be obtained for pharmacokinetics in Cycle 1 at Weeks 1, 2, and 4; see Section [9.5.1](#) for details.
- 13– Plasma samples will be obtained for pharmacodynamics in Cycle 1 at Weeks 1 and 4; see Section [9.5.2](#) for details.
- 14– A single whole blood sample will be collected at baseline for pharmacogenomics. See Section [9.5.3](#).
- 15– Baseline MRI at qualified sites will also include advanced MR imaging measurements in addition to standard anatomic sequences. See Section [9.5.4](#).
- 16– Archived tumor tissue from the most recent resection for glioblastoma will be collected from patients when sufficient tissue is available. See Section [9.5.5](#).

9.2 Adverse Events: Lists and Reporting Requirements

Patients will be evaluated for toxicity if they have received at least one dose of PT2385.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 9.2.1, below) and the characteristics of an observed AE (Section [9.2.2](#)) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting. Adverse Events will be collected for at least 30 days following the last dose of study drug.

All adverse events must be reported to the ABTC Central Office and the NCI in the manner described and per the requirements of the investigative site's Institutional Review Board.

Adverse events will be entered into CTEP's Medidata Rave database by the investigative site in a timely manner. See Section [12.0](#) – Records to be Kept.

9.2.1 Adverse Events and Potential Risks

A total of 110 patients have received PT2385 in Study PT2385-101. In Part 1, 26 patients were enrolled in the dose-escalation phase and 25 in the dose-expansion phase. Fifty patients have been enrolled in Part 2, and 9 patients in Part 3. As of October 22, 2017, the longest duration of treatment of any patient in PT2385-101 is 969 days for a patient in the 200 mg b.i.d. dose group. The longest duration of treatment of a patient at the 800 mg b.i.d. dose (the recommended phase 2 dose) is 859 days.

Part 1: No dose-limiting toxicities were observed during the dose-escalation portion of Part 1 of the study. As of October 22, 2017, no patients in Part 1 have died during the study and no patients were discontinued from the study because of adverse events. The most commonly reported AEs in 51 patients enrolled in the dose-escalation and expansion cohorts were anemia, fatigue, peripheral edema, nausea and back pain. Most AEs were mild to moderate in severity and were reported as Grade 1 to 2. The most common Grade 3/4 toxicities included anemia (5), decreased lymphocyte counts (4), hypoxia (5), and hypophosphatemia (4).

Part 2: In Part 2 of the study, ccRCC patients were enrolled at a dose of 800 mg b.i.d. orally and 3 mg/kg of nivolumab intravenously once every two weeks. As of October 22, 2017, 50 patients have been treated with the combination of PT2385 and nivolumab. The most commonly reported AEs were fatigue, anemia, nausea, arthralgia and back pain. Most AEs were reported as Grade 1 or Grade 2 in severity. The only Grade 3 or 4 toxicities reported in more than one patient included anemia (3), back pain (3), fatigue (2), hypoxia (2), pleural effusion (2), and lymphocyte count decreased (2).

Part 3: In Part 3 of the study, ccRCC patients were enrolled at a dosage of 800 mg b.i.d. orally in combination with cabozantinib (dose levels: 40 mg q.d. and 60 mg q.d.). The most commonly reported AEs were anemia, alanine aminotransferase increased, hypertension, and proteinuria. Most AE's were reported as Grade 1 or Grade 2 in severity. The only Grade 3 toxicity reported in more than one patient was hypophosphatemia.

Serious Adverse Events in Study PT2385-101: The serious adverse events reported in Part 1, Part 2, and Part 3 of the study, as of October 22, 2017, are listed in [Table 2](#), [Table 3](#), and [Table 4](#) respectively. Fifty-eight of the AEs reported for 33 patients met SAE criteria, of which only four were considered to be possibly related to PT2385 by Peloton.

Central Nervous System: No adverse CNS effects were observed in toxicity studies of PT2385 and the results of neurologic safety pharmacology testing (FOB) were negative for any effects. However, PT2385 is known to cross the blood-brain barrier and significant concentrations have been found in the brain. Three cases of Grade 2 aphasia with VHL-associated ccRCC in clinical study PT2385-202 after the data-cutoff date of October 22, 2017. These three case reports met “serious” criteria of important medical events, and SUSAR criteria. In the absence of confounding factors, Peloton assessed all three case reports as possibly related to PT2385. Prior to the above cases, there have been no previous reports of aphasia across the PT2385 clinical development program. The only other AEs in the Nervous system disorder SOC that have been reported in >10% of patients include dizziness and headache, all Grade 1 or Grade 2 in severity. Patients participating in clinical studies of PT2385 will be observed carefully for any potential CNS toxicities.

Table 2: Serious Adverse Events Reported in Part 1 of Study PT2385-101

System Organ Class/ Preferred Term	No. of Events	Dosage (mg b.i.d.)	Relationship	Treatment Discontinued Because of AE
Cardiac Disorders Atrial Fibrillation	1	800	Unrelated	No
Gastrointestinal Disorders Constipation	1	800	Unrelated	No
Small Intestinal Obstruction	1	800	Unlikely	No
Varices esophageal	1	800	Unrelated	No
General Disorders Chest Pain	1	800	Unrelated	No
Non-Cardiac chest pain	1	800	Unrelated	No
Infections and Infestations Pneumonia	2	400/400 800	Unrelated/Unlikely	No/No
Septic Shock	1	800/800	Unlikely	No
Urinary tract infection	2		Unrelated/Unrelated	No/No
Metabolism and Nutrition Disorders Dehydration	1	800	Unrelated	No
Hypercalcemia	1	800	Unrelated	No
Musculoskeletal and Connective Tissue Disorders Arthralgia	1	800	Unrelated	No
Back pain	1	200	Unrelated	No
Osteoarthritis	1	800	Unrelated	No
Pain	1	400	Unrelated	No
Pain in extremity	2	800/800	Unrelated/Unrelated	No/No

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Nervous System Disorders	2			
Dysarthria	1	800	Unlikely	No
Transient ischemic attack	1	800	Unlikely	No
Renal and Urinary Disorders	2			
Acute kidney injury	1	800	Unrelated	No
Hematuria	1	800	Unrelated	No
Respiratory, Thoracic and Mediastinal Disorders	3			
Hypoxia	2	1200/1200	Possibly/Unlikely	No/No
Pulmonary embolism	1	800	Possibly	No
Surgical and Medical Procedures	1			
Nephrostomy	1	800	Unrelated	No
Vascular Disorders	2			
Hypotension	1	800	Unrelated	No
Bleeding varicose vein	1	800	Unrelated	No

Table 3: Serious Adverse Events Reported in Part 2 of Study PT2385-101

System Organ Class/ Preferred Term	No. of Events	Dose of PT2385 (mg b.i.d.)	Relationship (PT2385 / nivolumab)	Treatment Discontinued Because of AE
Gastrointestinal Disorders	3			
Gastrointestinal hemorrhage	1	800	Unrelated/Unrelated	No
Constipation	1	800	Unrelated/Unrelated	No
Pancreatitis	1	800	Unrelated/Unrelated	No
General Disorders	3			
Death	1	800	Possibly/Possibly	Yes
Pain	2	800	Unrelated/Unrelated	No
Infections and Infestations	1			
Localized infection	1	800	Unrelated/Unrelated	No
Injury, poisoning and procedural complications	1			
Administration related reaction	1	800	Unrelated/Possibly	Yes
Investigations	3			
Blood creatinine increased	1	800	Unrelated/Unrelated	No
Blood bilirubin increased	1	800	Unrelated/Unrelated	No
Troponin T increased	1	800	Unrelated/Unrelated	No

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NCI # ABTC-1602

PI: R. Strowd

Metabolism and Nutrition Disorders Hyperkalemia	1 1	800	Unrelated/Unrelated	No
Musculoskeletal and Connective Tissue Disorders	3			
Musculoskeletal chest pain	1	800	Unrelated/Unrelated	No
Back pain	1	800	Unrelated/Unrelated	No
Musculoskeletal disorder	1	800	Unrelated/Unrelated	No
Nervous System Disorders Spinal cord compression	1 1	800	Unrelated/Unrelated	No
Renal and Urinary Disorders Acute kidney injury	1 1	800	Unrelated/Unrelated	No
Respiratory, Thoracic and Mediastinal Disorders	5			
Hypoxia	1	800	Possibly/Unrelated	No
Pleural effusion	4	800	Unrelated/Possibly	No
Surgical and Medical Procedures Craniotomy	1 1	800	Unrelated/Related	No

Table 4: Serious Adverse Events Reported in Part 3 of Study PT2385-101

System Organ Class/ Preferred Term	No. of Events	Dose of PT2385 (mg b.i.d.)	Relationship (PT2385 / cabozantinib)	Treatment Discontinued Because of AE
Cardiac Disorders Atrial Fibrillation	1 1	800	Unrelated/Unrelated	No
General Disorders Disease progression	1 1	800	Unrelated/Unrelated	No
Musculoskeletal and Connective Tissue Disorders Back pain	2 2	800	Unrelated/Unrelated	No
Respiratory, Thoracic and Mediastinal Disorders	2			
Dyspnea	1	800	Unrelated/Unrelated	No
Epistaxis	1	800	Unrelated/Related	No

9.2.2 Adverse Event Characteristics

Definition - Adverse Event (AE)

Adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Recording of Adverse Events - ABTC AE Form

- The investigator will monitor each patient closely for the development of adverse events and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.
- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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 web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). You must use one of the CTCAE criteria to define your event.

Adverse events not included in the CTCAE should be reported under “Other” within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New adverse events may be submitted to the CTEP Help Desk at ncictcaehelp@mail.nih.gov for annual evaluation by the CTCAE Change Management Committee.

- **Attribution of the AE:** The investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:
 - *Unrelated* – The AE is clearly not related to the investigational agent(s).
 - *Unlikely* – The AE is doubtfully related to the investigational agent(s).
 - *Possible* – The AE may be related to the investigational agent(s).
 - *Probable* – The AE is most likely related to the investigational agent(s).
 - *Definite* – The AE is clearly related to the investigational agent(s).
- All adverse events should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the investigator, constitute adverse events (even if not serious) should be followed.

9.3 Serious Adverse Events and Expedited Adverse Event Reporting

9.3.1 Definition – Serious Adverse Event (SAE)

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.

9.3.2 Expedited Adverse Event Reporting

➤ **Use CTEP-AERS Web Application and Document on ABTC AE Form**

- All SAEs must be documented on both the ABTC AE form and using the CTEPAERS Web Application within 24 hours of learning of the event.
- Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP web site (<https://eappsctep.nci.nih.gov/ctepaers>). In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the ABTC Central Office by telephone at 410-614-4400 or 410-955-3657 or 410-599-4610. Once Internet connectivity is restored, the 24-hour notification must be entered electronically into CTEP-AERS by the original submitter at the site.
- ABTC will be notified automatically when an SAE is reported through CTEPAERS (within 24 hours). All SAEs will be documented and tracked by the ABTC Central Office. Queries and follow up required for completing all SAEs will be conducted through the ABTC Central Office in a timely fashion. When an expedited report is required (7 or 15 days), a speedy resolution of queries will be expected in order to allow for on-time reporting to the FDA. ABTC is responsible for reporting all applicable SAEs to the FDA.

- CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) of the Adult Brain Tumor Consortium (ABTC), the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.
- The ABTC Central Office is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.
- Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. 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.

9.3.3 Other SAE Reporting

Any Serious Adverse Event, as described in Section [9.3.1](#), including death due to any cause, which occurs during this study must be **reported immediately (within 24 hours)** to the ABTC Central Office.

A phone call must be made to:

SERENA DESIDERI
ABTC DATA COORDINATOR
OFFICE: 410-614-4400
FAX: 410-614-9335
OR JOY FISHER, ABTC MANAGER: 410-955-3657 / 410-599-4610

These events also must be reported by the investigator to the appropriate Institutional Review Board (IRB).

Patients who are removed from study due to adverse events should be followed until the adverse event has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

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.

Any secondary malignancies that occur following treatment with PT2385 should be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- 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 Section [12.0](#).

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 reporting via CDUS unless otherwise specified.

9.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions (Section [12.4](#)).**

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.

9.5 Correlative Studies

9.5.1 Pharmacokinetic Assessment (All Patients)

This correlative study is mandatory for all patients.

Blood samples will be collected for the determination of PT2385 and its direct glucuronide metabolite (PT2639) plasma concentrations at the following time points:

- Cycle 1, Week 1, Day 1, Pre-dose 1: within 15 minutes prior to dose
- Cycle 1, Week 1, Day 1, 6 Hours Post-dose 1: 6 hours +/- 15 minutes post-dose
- Cycle 1, Week 3, Day 15, Pre-dose 1: within 30 minutes prior to dose
- Cycle 2, Week 1, Day 1, Pre-dose 1: within 30 minutes prior to dose

Details for the collection, processing, storage, and shipment of samples for the determination of PK effects are provided in the lab manual.

These time points have been selected based on experience from the ongoing phase 1 study in RCC where the pretreatment and 6 hour post-dose time points provide optimal assessment of trough and maximum observed plasma concentration (C_{max}). Week 2 and week 4 will provide data on steady state. Plasma concentrations of PT2385 and PT2639 will be determined by validated liquid chromatography/mass spectrometry methods contracted by Peloton Therapeutics through an external vendor.

9.5.2 Pharmacodynamics and Laboratory Biomarkers (All Patients)

This correlative study is mandatory for all patients.

In the phase I study in RCC, target engagement as measured by diminution of EPO expression is rapid, pronounced, and sustained starting at 6 hours post-dose #1. Based on this experience, plasma samples for analysis of PD effects (biomarkers) in this study will be collected at the following time points:

- Cycle 1, Week 1, Day 1, Pre-dose 1: Within 15 minutes prior to dose
- Cycle 1, Week 1, Day 1, 6 Hours Post-dose 1: 6 hours +/- 15 minutes post-dose □
- Cycle 2, Week 1, Day 1, Pre-dose 1: Within 30 minutes prior to dose

Details for the collection, processing, storage, and shipment of samples for the determination of PD effects are provided in the lab manual.

Plasma concentrations of EPO and VEGF will be determined by commercially available ELISA and contracted through an external vendor by Peloton Therapeutics.

9.5.3 Pharmacogenomic Assessment (All Patients)

This correlative study is mandatory for all patients.

A single whole blood sample will be collected at baseline for sequencing of genes that may be involved in regulating PT2385 metabolism. Details for the collection, processing, storage, and shipment of samples for the determination of PG effects are provided in the lab manual. Samples will be stored by an external vendor contracted by Peloton Therapeutics for pharmacogenomics analysis.

PT2385 is metabolized by the polymorphic CYP2C19 (PMID 10971203) and CYP3A4 (PMID 16509759), suggesting the potential for CYP2C19 and CYP3A4 polymorphisms to influence the metabolism of PT2385 and potentially contribute to patient-to-patient variability in drug metabolism. Data from the phase 1 study in RCC are being gathered to explore potential explanations but a genomic target and validated assay do not currently exist.

9.5.4 Exploratory pH and Hypoxia MRI (All Patients at Select Sites)

The following correlative imaging will be performed at baseline on all patients at sites with advanced imaging capabilities as defined below.

Simultaneous pH- and hypoxia-weighted MRI using multi-echo amine chemical exchange saturation transfer spin-and-gradient echo echo planar imaging (ME-aCEST-SAGE-EPI):

The correlative imaging components of the study are purely exploratory. The purpose is to investigate whether baseline imaging phenotypes derived from pH- and hypoxiaweight imaging predict patients that will respond from inhibition of HIF2a. We hypothesize that patients with acidic or hypoxic tumors will likely express high levels of HIF2a, making these patients particularly amenable to HIF2a inhibitor treatment.

In this study we will perform a single image acquisition to simultaneously quantify pH and hypoxia using a custom multi-echo amine chemical exchange saturation transfer spin-and-gradient echo echo planar imaging (ME-aCEST-SAGE-EPI) technique. We will quantify (1) the magnetization transfer ratio asymmetry at the amine proton off-resonance frequency ($MTR_{asym} @ 3ppm$) as a measure of tumor acidity and (2) R_2' or $rOEF$ estimates ($rOEF = R_2' / (c * rCBV)$) as a measure of tissue hypoxia. These studies will be performed only at baseline, prior to treatment initiation, to explore whether baseline acidity or hypoxia predict patients that will respond to HIF2a inhibition.

Simultaneous pH- and hypoxia-weighted MRI will be performed at baseline only with Siemens 3T MR systems, which are available at 7 of the 11 ABTC sites. Thus, correlative

imaging data will be restricted to those patients enrolled at these sites. Based on prior enrollment data and experience within the ABTC, we anticipate that at least 25 patients (if the study proceeds to full enrollment) or 16 patients (i.e. if early stoppage criteria are met) to be analyzable for this exploratory objective. Of note, this study is not designed to validate these imaging sequences, as all correlative imaging is strictly exploratory and optional. Acidity and hypoxia imaging scans are purely investigational and will NOT be used for efficacy measurements. Efficacy will be determined by radiographic response and PFS using RANO criteria alone.

Prior to patient enrollment, all sites able to perform simultaneous pH- and hypoxiaweighted MRI will receive this sequence from Dr. Ellingson at UCLA through communications with Siemens Healthcare. This sequence is approximately 10-15 minutes long and will be placed into the imaging protocol prior to contrast agent administration. Raw imaging data will be transmitted electronically via the standing protocol of the Adult Brain Tumor Consortium to Dr. Ellingson at UCLA for data processing and imaging analysis.

9.5.5 Archival Tumor Tissue for IDH1 Mutational Status and HIF Expression (All Patients)

Archived tumor tissue from the most recent resection for glioblastoma will be collected from patients, when sufficient tissue is available. If sufficient tissue is not available from the most recent surgery, then tissue from an earlier surgery is acceptable, if available, including from the initial resection at diagnosis.

At the time of registration, prior to beginning treatment, a tumor tissue form indicating availability must be completed and signed by a pathologist. This form provides written documentation of the availability of tissue for this study and the pathologist's agreement to send it as described below.

10 unstained slides, preferentially from the most recent tumor resection, will be requested. The associated pathology report from the institution of collection should be shipped with the slides.

Details for the collection and shipment of tissue samples are provided in the lab manual.

9.5.5.1 IDH Mutational Status

If IDH1 mutational status testing was performed and reported previously, testing will not need to be repeated. For patients with reported IDH1 test results, the previous IDH1 test report should be submitted. Results of routinely used methods for IDH1 testing are acceptable (i.e. immunohistochemistry, DNA-based methods). Results should include at least IDH1-R132 status; results of less common IDH gene mutation is not required.

Immunostaining for IDH1-R132H will be performed on all available tumor tissue using established methods. Briefly, tumor slides will be evaluated by the neuro-pathologist. Sections will be stained and scored according to previously described methods using an anti-human IDH1-R132H antibody (Capper et al., 2010) and reported as IDH1-R132H mutant positive or negative.

9.5.5.2 HIF Expression

Tumor tissue samples will be analyzed for HIF-2 α and HIF-1 α expression, and for the presence of other elements of the HIF pathway.

10.0 OFF TREATMENT/OFF STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The investigator may discontinue any subject's participation for any reason, including adverse event or failure to comply with the protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason must be stated on the case report form, and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for adverse events (AEs) for at least 30 days from the last dose of PT2385.

10.1 Off Treatment Criteria

1. **Disease Progression:** Remove patient from protocol therapy at the time progressive disease is documented. Disease progression is defined as: Progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued.
2. **Adverse Event:**
 - Intercurrent illness that prevents further administration of treatment
 - Patients who experience unacceptable toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.
3. **Patient Withdrawal:** Patient's refusal to continue treatment: in this event, document the reason for withdrawal.

4. **Non-Compliance:** Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.)
5. **Physician Decision:** If at any time the treating physician feels constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.
6. **Protocol Defined Delay:**
 - Patients who experience a treatment-related toxicity causing a delay in treatment >21 days
 - Delay in protocol >28 days for major events or other non-treatment related delays
 - Patients who require >2 dose reductions
 - Patients who must be put on an enzyme-inducing anti-epileptic drug (EIAED) during the study
7. **Death**

10.2 Off Study Criteria

Patients will only be off study at the time of death. All patients will be followed for survival every 2 months for the first two years from the off treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit). Please note that additional survival status reports will be required twice yearly for ABTC Central Office reporting.

11.0 STATISTICAL CONSIDERATIONS

Primary Objectives

To estimate tumor objective response rate. The tumor response includes complete response (CR) and partial response (PR) per RANO criteria.

Secondary Objectives

1. To determine the safety of oral PT2385 800 mg twice daily in patients with recurrent glioblastoma
2. To estimate overall survival
3. To estimate progression-free survival

Exploratory Objectives

1. To describe the pharmacokinetic and pharmacodynamic properties of PT2385 in patients received PT2385 800 mg twice daily, continuously in 28-day per cycle.
2. To describe baseline intratumoral hypoxia using MR-based neuroimaging sequences.

Sample size justification

This is a single-arm, open label, multi-institutional, non-randomized safety and efficacy study in patients with first recurrence of GBM. The primary endpoint is tumor radiographic response (PR+CR). The study hypothesizes the single agent of PT2385 will achieve at least 20% radiographic response rate. The 20% response rate is considered clinically meaningful compared to a null hypothesis of 5% response rate (Taal et al., 2014).

The sample size estimation is based on a 2-stage design (minimax) with 85% statistical power and a false positive rate at 5%. At the first stage, 24 patients will be enrolled onto the study. The trial will be stopped and accept the null hypothesis if the response rate is less than or equal to 1/24. Otherwise, the study will continue to stage 2. The probability of early stopping for futility is 0.661 when the null is true and 0.033 when a true response is 20%. Eleven additional patients will be enrolled on the second stage of the trial. If 5 out of 35 patients have an objective response, the study will reject the null hypothesis to conclude PT2385 is effective to treat patients with first recurrence of glioblastoma.

Analysis Plan

General considerations:

The primary efficacy analysis will be performed on the Intent-to-Treat (ITT) population which is defined as all subjects who were enrolled onto the study. The primary safety analysis will be performed on the safety population who received at least one dose of study drug.

Objective response rate

To estimate tumor objective response rate, the proportion of patients who had objective partial response (PR) or complete response (CR) during the course of the treatment will be estimated along with 95% confidence intervals using the exact binomial method.

Overall Survival

To estimate overall survival, survival time is defined as the time from the date of treatment start to the date of death occurrence /or censored at the time of last known

alive. Survival probability and median time survival will be estimated using KaplanMeier method along with 95% confidence interval.

Progression-free Survival

To estimate progression-free survival (PFS), progression-free survival time is defined as the date of treatment start to the date progression was deemed. Probability of PFS and median of PFS will be estimated using Kaplan-Meier method along with 95% confidence interval.

Date of progression will not be imputed for patients with missing tumor assessment(s) during planned tumor assessment. Patients who died without a reported progression, with complete scheduled imaging scans will be considered to have progressive disease on the date of death. Patients who did not have disease progression or died with more than two missing planned MRI scans will be censored at the date of last tumor assessment.

Safety/Toxicity

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for scoring toxicity and adverse events until March 31, 2018; CTCAE version 5.0 will be utilized beginning April 1, 2018. The severity and frequency of toxicity will be tabulated using descriptive statistics. The proportions of subjects who experienced grade 3 or above toxicities will be estimated, along with 95% confidence intervals by each type of toxicity.

Pharmacokinetics

Pharmacokinetic analyses are generally in descriptive nature and they will be performed with Phoenix® WinNonlin® software. PK parameters, including area under the curve (AUC), and maximum concentration (Cmax) at 6 hours post-dose, will be determined for PT2385 and PT2639 (i.e. primary inactive metabolite). Each PK parameter will be summarized descriptively (n, arithmetic mean, standard deviation, minimum, median, maximum, and coefficient of variation). Geometric means will be reported for AUC and Cmax parameters. For PK analysis, PT2385 and PT2639 plasma concentrations that are below the limit of quantitation of the assay will be censored during analysis. Standard clinical trial monitoring and data management practices will be used to ensure the integrity of study data.

Pharmacodynamics

The plasma concentration level of each exploratory Pharmacodynamic marker (i.e. EPO, VEGF) will be summarized descriptively (arithmetic mean, standard deviation) at each sample collection time point (pretreatment, 6-hours post-dose, steady state, progression). Their changes from baseline will be presented using standard descriptive statistics and

graphic summaries. Possible association between changes of concentration and clinical outcomes could be explored using statistical modeling techniques.

Hypoxia Imaging

Hypoxia imaging is strictly exploratory. The objective is to describe tumoral hypoxia using advanced MR-based sequences prior to treatment initiation in patients with recurrent GBM. Advanced MRI imaging including CEST and rOEF will be postprocessed as per standard protocols including motion and inhomogeneity correction prior to analysis. Post-processing will be performed by Dr. Ben Ellingson (UCLA, ABTC Imaging Core).

Measurements of Acidic Tumor Volume: Relative pH assessed using MTR_{asym} at 3ppm will be calculated by first performing B_0 homogeneity correction, then calculating the difference in signal intensity between positive and negative offset frequencies divided by the signal intensity with no saturation, $(S_{+3ppm} - S_{-3ppm})/S_0$, for each image voxel. Acidic tumor will be defined as having $MTR_{asym} @ 3ppm > 5\%$ as determined empirically (Harris et al., 2015). Both mean $MTR_{asym} @ 3ppm$ and volume of acidic tumor within contrast enhancing and/or T2 hyperintense tumor regions will be used as exploratory measures of tumor acidity.

Measurements of Hypoxic Tumor Volume: The blood oxygenation-based reversible transverse relaxation rate, R_2' , has been shown to be directly proportional to relative oxygen extraction fraction (rOEF), scaled by the relative cerebral blood volume (rCBV) (Hirsch et al., 2014; Toth et al., 2013). In the current study we will estimate R_2' using T_2 and T_2^* measurements obtained from the ME-SAGE component of the acquisition [$R_2' = (1/T_2^*) - (1/T_2)$]. If available, we will use rCBV measurements from dynamic susceptibility contrast (DSC) perfusion MRI to estimate $rOEF$ ($rOEF = R_2'/(c * rCBV)$, where c is a constant relating to the specific static magnetic field strength). Both mean R_2' and estimates of $rOEF$ within contrast enhancing and/or T2 hyperintense tumor regions will be used as exploratory measures of tumor hypoxia.

Baseline tumor acidity and hypoxia will be defined both as continuous (e.g. mean $MTR_{asym} @ 3ppm$, mean R_2' , etc.) as well as categorical variables (i.e. acidic/hypoxic vs non-acidic/hypoxic) based on $>50\%$ of tumor having an acidic signature ($>3\% MTR_{asym} @ 3ppm$) or hypoxic signature ($R_2' > 5 s^{-1}$).

Descriptive statistics including the proportion of acidic/hypoxic and non-acidic/hypoxic lesions will be estimated with 95% confidence intervals. Fisher's exact test or other nonparametric analysis methods will be used to explore potential correlations between tumor acidity/hypoxia (imaging categorical variable) and tumor radiographic response.

12.0 STUDY ADMINISTRATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

12.1 Investigator's Study File

The Investigator's Study File must contain all essential documents as required by ICH E6, including IRB and governmental approvals with correspondence, informed consent forms, patient enrollment and identification logs, drug accountability records, staff *curriculum vitae*, authorization forms and other appropriate documents/correspondence etc.

12.2 Source Data/Documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include for example, patient hospital/clinic records, original laboratory reports, ECG read-outs, MRI reports, pathology and special assessment reports, etc.

Source documents are part of the study documents and must be maintained, and direct access to source documents made available upon request, for monitoring visits, IRB review, audits or inspections. All source documents used to verify answers on CRFs will be uploaded to RAVE, including all documentation to prove eligibility criteria was met.

12.3 Document Retention and Archiving

The Investigator must keep all study documents on file for at least 5 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to local regulations.

These files must be made available for inspection, upon reasonable request, to authorized representatives of Sponsor or regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

12.4 Data Collection/Reporting

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eappsctep.nci.nih.gov/iam>). In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

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. 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 listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions please contact the CTSU Help Desk at 1-888-823-5923 or ctscontact@westat.com.

- All data are due within 14 days of evaluation time point. Please see Section [9.1](#) for evaluation time points. Note: Source documentation to verify each CRF must be uploaded into Rave.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION [9.3](#)

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.5 Study Monitoring

The ABTC Study Monitor (Sponsor) will remotely monitor the Investigator and study team on a regular basis throughout the study to verify the adherence to Good Clinical Practice (GCP), the protocol and the completeness, consistency and accuracy of the data being entered into the CRFs. The Study Monitor will also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Study Monitor will only conduct target on-site monitoring (See ABTC Monitoring plan for details). If on sight monitoring is necessary, the Investigator shall ensure that the study monitor has direct access to all required study data (source documents) during

the visits. This includes all patient records needed to verify the entries in the CRFs, regulatory documents, pharmacy records or any other documents of concern.

The Investigator agrees to cooperate with the Study Monitor and ABTC to ensure that any deviations or issues detected in the course of monitoring visits are resolved.

12.6 Audits and Inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP and regulatory requirements. These audits may also be conducted for quality assurance to ensure that complete and accurate data are submitted and that adverse events, complications and/or adverse reactions are being identified and reported.

The study may also be inspected by health authority inspectors, after appropriate notification. In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

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14.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The investigator is responsible for the retention of the patient log and patient records.

ABTC # 1602

NCI # ABTC-1602

PI: R. Strowd

APPENDIX I – PATIENT MEDICATION DIARY

PT2385 DIARY (PT2385 twice every day in 28-day cycles)

Patient Name _____ (*initials acceptable*) **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **PT2385** _____ mg (___ tablets) **twice per day on Days 1- 28 of every 28-day cycle**. Take doses about 12 hours apart at approximately the same times each day.
Take PT2385 with 8 ounces of water. PT2385 may be taken with or without food. Tablets should be swallowed whole, do not chew or crush.
2. Record the date and the time you took each PT2385 dose.
Record missed or skipped dose(s). If you miss a dose you may make up that dose if you take it within 4 hours of the time you normally take it. There must be at least 8 hours before the next dose.
If you vomit a dose, do not re-take the study drug. Take the next dose at the time that you normally take the next scheduled dose.
3. Bring this form and any remaining PT2385 tablets when you return for each appointment.

Week	Day	Date	Time of dose morning dose	# of 200 mg tablets	Time of dose evening dose	# of 200 mg tablets	Comments
1	1						
	2						
	3						
	4						
	5						
	6						
	7						
2	8						
	9						
	10						
	11						
	12						
	13						
	14						
3	15						

Single-arm, Open-label Phase II Efficacy Study of First-in-class HIF2-Alpha Inhibitor, PT2385, for Patients with Recurrent Glioblastoma

ABTC # 1602

NCI # ABTC-1602

PI: R. Strowd

	16						
	17						
	18						
	19						
	20						
	21						
4	22						
	23						
	24						
	25						
	26						
	27						
	28						

Patient's Signature _____

Date _____

Nurse's Signature _____

Date _____

APPENDIX II – PARTIAL LIST OF STRONG CYP2C19 AND CYP3A4 INHIBITORS

CYP2C19 Inhibitors	CYP3A4 Inhibitors
esomeprazole	indinavir
lansoprazole	nelfinavir
omeprazole	ritonavir
pantoprazole	clarithromycin
cimetidine	itraconazole
fluoxetine	ketoconazole
	nefazodone
	saquinavir suboxone
	telithromycin

Consult a frequently updated medical reference for possible changes.

APPENDIX III – PARTIAL LIST OF SUBSTRATES OF CYP3A4, CYP2B6, CYP2C9, AND CYP2C19

CYP3A4 Substrates	CYP2B6 Substrates	CYP2C9 Substrates	CYP2C19 Substrates
clarithromycin	artemisinin	ibuprofen	esomeprazole
erythromycin	bupropion	naproxen	lansoprazole
quinidine	efavirenz	tolbutamide	omeprazole
alprazolam	ketamine	glipizide	pantoprazole
diazepam	meperidine	losartan	phenytoin
midazolam	methadone	irbesartan	amitriptyline
cyclosporine	nevirapine	glyburide	carisoprodol
indinavir	propofol	glipizide	citalopram
nelfinavir	selegiline	celecoxib	clopidogrel
ritonavir	sorafenib	fluoxetine	cyclophosphamide
cisapride		rosiglitazone	imipramine
chlorpheniramine		tamoxifen	labetalol
terfenadine		valproic acid	nilutamide
amlodipine		zafirlukast	progesterone
diltiazem			propranolol
nifedipine			teniposide

ABTC # 1602

NCI # ABTC-1602

PI: R. Strowd

atorvastatin lovastatin simvastatin estradiol testosterone carbamazepine codeine fentanyl haloperidol ondansetron			voriconazole
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Consult a frequently updated medical reference for possible changes.

APPENDIX IV – PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD
Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **PT2385**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

PT2385 interacts with certain specific enzymes in the liver.

- The enzymes in question are **CYP2C19 and CYP3A4**, and PT2385 is broken down by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

PT2385 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

PT2385 must be used very carefully with other medicines that use certain liver enzymes to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP2C19 and CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at _____.

<p>STUDY DRUG INFORMATION WALLET CARD</p> <p>You are enrolled on a clinical trial using the experimental study drug PT2385. This clinical trial is sponsored by the NCI. PT2385 may interact with drugs that are processed by your liver. Because of this, it is very important to:</p> <ul style="list-style-type: none">➤ Tell your doctors if you stop taking any medicines or if you start taking any new medicines.➤ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.➤ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	<p>PT2385 interacts with specific liver enzymes called CYP2C19 and CYP3A4 and must be used very carefully with other medicines that interact with these enzymes.</p> <ul style="list-style-type: none">➤ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP2C19 and CYP3A4.➤ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.➤ Your study doctor's name is _____ and can be contacted at _____.
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