

## Abstract and Schema

This is Phase I and Surgical study for children with retinoblastoma protein 1 (Rb1) positive recurrent or refractory central nervous system tumors.

Brain tumors are the leading cause of cancer-related death in children. Though cures for some are possible using conventional therapeutic approaches, outcome for highly malignant and recurrent brain tumors remains poor, despite aggressive multimodal therapy. Improved understanding of the inherent tumor biology and genomic landscape of brain tumors has spurred development of novel therapeutics aimed at targeted inhibition of important cancer-promoting pathways.

Aberrant cell cycle regulation and activation of the PI3K/Akt/mTOR pathway represent two highly important mechanisms of malignant potential in pediatric brain tumors. Joint inhibition of CDK4/6 and mTOR is promising due to strong biologic rationale, non-overlapping single-agent toxicities, and preliminary clinical experience in adults that suggests tolerability of this combination. Additionally, increased exposure of RAD001 in the presence of ribociclib, as observed in pharmacokinetic profiling of samples from adults receiving the combination, suggest that lower doses of both drugs may also be used in the pediatric population.

Ribociclib is an orally available cyclin-dependent kinase (CDK) inhibitor targeting cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway, with potential antineoplastic activity. Overexpression of CDK4/6, as seen in certain types of cancer, causes cell cycle deregulation. Ribociclib specifically inhibits CDK4 and 6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Inhibition of Rb phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth.

Everolimus is an inhibitor of selective mammalian target of rapamycin (mTOR), the effects of which specifically target the mTOR-raptor signal transduction complex 1 (mTORC1). The PI3K/AKT/mTOR pathway is dysregulated in the majority of human cancers and is the object of many targeted agents. Inhibition of mTORC1, an essential regulator of global protein synthesis downstream on the PI3K/AKT/mTOR pathway, reduces tumor cell proliferation, glycolysis and angiogenesis.

Both ribociclib and everolimus will be supplied by Novartis for PBTC-050 study.

### **Schema:**

This is Phase I and Surgical Study of ribociclib and everolimus given in combination in children with recurrent or refractory malignant brain tumors.

### Phase I

The primary objective of the Phase I component is to estimate the MTD and/or the recommended phase II dose (RP2D) of ribociclib and everolimus in children. Ribociclib and everolimus will be given in combination either in oral with drug-in-capsule versus liquid formulation or via gastric tube (liquid formulation). Ribociclib will be administered once a day for 21 days on/7 days off on a 28-day cycle and everolimus will be administered once a day for 28 days. One course is therefore equivalent to 28 days. Therapy may continue for up to a year (13 courses) in the absence of disease

progression or unacceptable toxicity. Patients who have at least clinically and radiographically stable disease at the end of course 13 may be able to participate in the extended therapy for up to an additional 13 courses (total maximum duration of treatment is 26 courses).

Dose Escalation Schedule Table

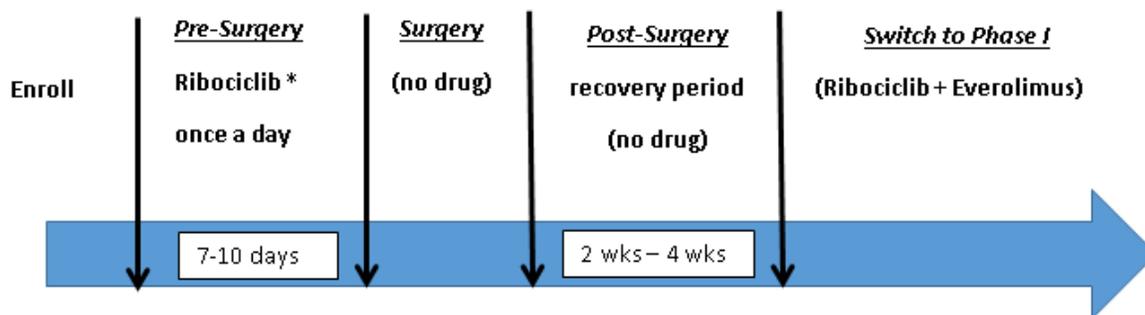
Dose Level	Ribociclib (mg/m <sup>2</sup> /day PO days 1-21)	Everolimus (mg/m <sup>2</sup> /day PO days 1 x 28)	BSA Restriction
-1	75 mg/m <sup>2</sup> /day	1 mg/m <sup>2</sup> /day	BSA ≥ 0.55m <sup>2</sup>
- 0.5*	120 mg/m <sup>2</sup> /day	1 mg/m <sup>2</sup> /day	BSA ≥ 0.75m <sup>2</sup>
0	75 mg/m <sup>2</sup> /day	1.2 mg/m <sup>2</sup> /day	BSA ≥ 0.55m <sup>2</sup>
<b>1(starting dose)</b>	<b>120 mg/m<sup>2</sup>/day</b>	<b>1.2 mg/m<sup>2</sup>/day</b>	<b>BSA ≥ 0.75m<sup>2</sup></b>
2	170 mg/m <sup>2</sup> /day	1.2 mg/m <sup>2</sup> /day	BSA ≥ 0.45m <sup>2</sup>
3	170 mg/m <sup>2</sup> /day	1.5 mg/m <sup>2</sup> /day	BSA ≥ 0.45m <sup>2</sup>

\*Dose reduction if toxicities clearly attributable to Everolimus

### Surgical Cohort

The primary objective of the Surgical Cohort is to characterize ribociclib concentrations in tumor and plasma in children with refractory or recurrent CNS tumors undergoing neurosurgical procedures. Patients will take ribociclib alone at the pediatric MTD (350 mg/m<sup>2</sup>/day) for 7 – 10 days prior to surgery. Following tumor resection and within 2-4 weeks of post-surgery period, patients enrolled on the surgical study will be switched over to the phase I study and be treated with ribociclib and everolimus combination at the assigned dose level.

If the starting dose of ribociclib is intolerable or if DLTs of the starting dose of ribociclib are clearly attributable to the study drug, the dose will be dose de-escalated to 280 mg/m<sup>2</sup>/day.



\* Ribociclib must be initiated within 7 days of enrollment

## **Inclusion Criteria:**

**All subjects must meet the following inclusion and exclusion criteria.** No exceptions will be given. Imaging studies to establish eligibility must be done within 3 (three) weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment. Subjects enrolled on the surgical study, will be re-assessed following guidelines in Section 10.1 of the protocol prior to starting the combination of ribociclib and everolimus.

## **Eligibility for Screening (Phase I and surgical study)**

All subjects must meet the following screening criteria without exception.

### *Tumor*

- Patients with a histologically confirmed diagnosis of HGG, medulloblastoma, CNS embryonal tumor (NOS), Ependymoma, or ATRT that is recurrent, progressive or refractory.
- Patients with recurrent DIPG with typical radiographic appearance who have undergone biopsy are eligible provided there is histologic confirmation of malignant glioma WHO II-IV. Rb1 screening for these patients is required only if adequate tissue is available.
- Patients with recurrent brainstem tumors with an atypical presentation who have undergone biopsy are eligible provided there is histologic confirmation of malignant glioma WHO II-IV. These patients must undergo Rb1 screening. These patients must have radiographic evidence of progression.
- Patients with secondary malignant gliomas will be eligible for this study but should conform to all other eligibility requirements. Patients with low-grade gliomas are excluded.

### *Pre-trial tumor tissue availability:*

Formalin fixed paraffin embedded tumor tissue (preferably from the most recent recurrence) must be available to assess Rb1 protein status prior to enrollment on Phase I or surgical study. If the subject has results from prior Rb1 IHC testing in a CLIA-certified laboratory the requirement for screening to assess Rb1 protein status is waived. In these cases, patients will not be required to sign a screening consent.

Patients with recurrent diffuse intrinsic brain stem glioma (DIPG) that has an atypical presentation must also submit the tumor tissue for Rb1 protein status confirmation or provide previous testing results from a CLIA certified laboratory. Patients who have been biopsied for atypical DIPG but do not have sufficient tissue for Rb1 screening are not eligible.

### *Age*

Patient must be  $\geq 1$  but  $\leq 21$  years of age at the time of enrollment.

### *BSA*

- Patients enrolled on dose level -1 must have  $BSA \geq 0.55m^2$
- Patients enrolled on dose level -0.5 must have  $BSA \geq 0.75m^2$
- Patients enrolled on dose level 0 must have  $BSA \geq 0.55m^2$
- Patients enrolled on dose level 1 must have  $BSA \geq 0.75m^2$
- Patients enrolled on dose level 2 and 3 must have  $BSA \geq 0.45m^2$

### *Screening Consent*

Patients who are candidates for enrollment for the phase I or surgical studies must sign a screening consent and provide pre-trial tumor material for Rb1 testing unless testing is not needed due to diagnosis or the availability of prior Rb1 IHC results. The screening consent is to be obtained according to institutional guidelines.

### *Potential Eligibility for Study Enrollment*

Patients screened for this trial should be expected to meet the criteria for treatment as outlined below.

### **Eligibility Criteria: Prior to Study Enrollment**

(applicable for Phase I and surgical cohort)

#### *Rb1 Status*

Patient has intact Rb1 protein confirmed either from previous results or screened tissue. All testing must be performed in a CLIA certified laboratory. DIPG patients with radiographically typical appearance will be waived from this requirement.

#### *Diagnosis*

##### Phase I (Stratum 1)

- Patients with Recurrent or Refractory CNS tumors

Patients with a histologically confirmed diagnosis of a primary CNS tumor that is recurrent, progressive, or refractory. All tumors must have histologic verification of HGG, medulloblastoma, CNS embryonal tumor (NOS), Ependymoma, or ATRT. Patients with low-grade gliomas are excluded.

- Patients with DIPG

Patients with progressive DIPG, as defined by progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.), OR an increase in the bi-dimensional measurement, taking as a reference the smallest disease measurement recorded since last treatment, OR the appearance of a new tumor lesion since diagnosis.

Please note:

- Patients with a radiographically typical DIPG, defined as a tumor with a pontine epicenter and diffuse involvement of more than 2/3 of the pons, are eligible without histologic confirmation.
- Patients with pontine lesions that do not meet these radiographic criteria will be eligible if there is histologic confirmation of malignant glioma WHO II-IV. These patients must have radiographic evidence of progression.

##### Surgical Study (Stratum 2)

- Patients must have recurrent or refractory disease with a histological diagnosis at either the time of diagnosis or at the time of recurrence of one of the following:
  - HGG
  - medulloblastoma,

- CNS embryonal tumor (NOS),
  - Ependymoma, or
  - ATRT
- Patients for whom surgical intervention is clinically indicated (gross total resection or sub-total resection) at recurrence and are amenable to receiving ribociclib for 7 – 10 days prior to resection
    - Note: Patients with DIPG are excluded from the surgical study.

#### *Age*

Patient must be  $\geq 1$  and  $\leq 21$  years of age at the time of enrollment.

#### *BSA*

- Patients enrolled on dose level -1 must have  $BSA \geq 0.55m^2$
- Patients enrolled on dose level -0.5 must have  $BSA \geq 0.75m^2$
- Patients enrolled on dose level 0 must have  $BSA \geq 0.55m^2$
- Patients enrolled on dose level 1 must have  $BSA \geq 0.75m^2$
- Patients enrolled on dose level 2 and 3 must have  $BSA \geq 0.45m^2$

#### *Prior Therapy*

Patients must have received prior therapy other than surgery and must have fully recovered from the acute toxic effects of all prior anti-cancer therapy ( $\leq$ Grade 1 with the exception of alopecia) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the defined eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

#### *Myelosuppressive chemotherapy*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

#### *Investigational/Biologic Agent*

- Biologic or investigational agent (anti-neoplastic):

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent  $\geq 7$  days prior to study enrollment.

- For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
- Monoclonal antibody treatment and agents with known prolonged half-lives: At least three half-lives must have elapsed prior to enrollment.

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

#### *Radiation*

Patients must have had their last fraction of:

- Craniospinal irradiation ( $>24Gy$ ) or total body irradiation  $> 12$  weeks prior to enrollment.
- Focal irradiation  $> 2$  weeks prior to enrollment

### Stem Cell Transplant

Patient must be:

- $\geq 3$  months since autologous bone marrow/stem cell transplant prior to enrollment

### Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study

### Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment.
- Patients with seizure disorders may be enrolled if seizures are well controlled on an anti-epileptic drug that is not a strong inducer or inhibitor of CYP3A4/5 are eligible.

### Performance Status

#### Phase I

- Karnofsky Performance Scale (KPS for  $> 16$  years of age) or Lansky Performance Score (LPS for  $\leq 16$  years of age) assessed within one week of enrollment must be  $\geq 50$ .

### Surgical Study

- Karnofsky Performance Scale (KPS for  $> 16$  years of age) or Lansky Performance Score (LPS for  $\leq 16$  years of age) assessed within one week of enrollment must be  $\geq 60$ .

Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

### Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count  $\geq 1.0 \times 10^9$  cells/L
- Platelets  $\geq 100 \times 10^9$  cells/L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin  $\geq 8$ g/dl (unsupported)
- Total bilirubin  $\leq 1.5$  times institutional upper limit of normal (ULN)
- ALT(SGPT)  $\leq 3$  x institutional upper limit of normal (ULN)
- AST (SGOT)  $\leq 3$  x institutional upper limit of normal (ULN)
- Albumin  $\geq 2$  g/dl
- Serum creatinine based on age/gender as noted in Table 6. Patients that do not meet the criteria in Table 6 but have a Creatinine Clearance or GFR (radioisotope or iothalamate)  $\geq 70$  ml/min/1.73 m<sup>2</sup> are eligible.

Table 6

Serum Creatinine for age/gender		
Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1

10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

### *Corticosteroids*

Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to enrollment.

### *Growth Factors*

Patients must be off all colony- forming growth factor(s) for at least 1 week prior to enrollment (i.e. filgrastim, sargramostim or erythropoietin). 2 weeks must have elapsed if patients received long-acting formulations.

### *Pregnancy Status*

Female patients of childbearing potential must have a negative serum or urine pregnancy test.

### *Pregnancy Prevention*

Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control while being treated on this study.

“Women of child-bearing potential” is defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Combination of any of the two following (a+b or a+c or b+c)
  - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Female patients must agree not to breastfeed their infants while on study.

Patients of child fathering potential (defined as > Tanner stage 2) must use a condom during intercourse while taking the drug during treatment, for 8 weeks after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men during intercourse with a male or female partner in order to prevent delivery of the study drug via semen.

### *Informed Consent*

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines. Assent, when appropriate, will be obtained according to institutional guidelines.

## **Exclusion Criteria**

### *Surgery*

Patients who are otherwise deemed clinically unsuitable for surgical resection (applicable for surgical study only)

### *Breast feeding*

Patients who are breast feeding

### *Concurrent Illness*

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with any other current malignancy, except patients with a secondary brain tumor if the patient's first malignancy has been in remission for at least 5 years from the end of treatment.

### *Concurrent Therapy*

- Patients who are receiving any other anticancer or investigational or/and anti-neoplastic therapies, including chemotherapy, immunotherapy, target therapy, biological response modifiers.
- Previous treatment with CDK4/6 inhibitors (such as PD-0332991, abemaciclib) and/or mTOR inhibitors (such as sirolimus, temsirolimus or everolimus).
- Patients who are currently receiving treatment with agents that are known to cause QTc prolongation or induce Torsades de Pointes
- Known need for major surgery within 14 days of the first dose of ribociclib and everolimus. Please note: Gastrostomy, insertion of a G tube, Ventriculo-peritoneal shunt, endoscopic ventriculostomy and central venous access are NOT considered major surgery.

### *Concomitant Medications*

Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to enrollment

- Known strong and moderate inducers or inhibitors of CYP3A4/5, including enzyme inducing anti-convulsant drugs (EIACDs), grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Herbal preparations/medications (except for vitamins) including, but not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop

using all herbal medications and dietary supplements at least 7 days prior to enrollment.

### *Cardiac disease*

Clinically significant active cardiac disease, uncontrolled heart disease and/or a history of cardiac dysfunction including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to screening
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Documented cardiomyopathy
- Patient has a Left Ventricular Ejection Fraction (LVEF) <50% as determined by echocardiogram (ECHO)
- History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of screening
- Long QT syndrome or known family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
  - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
  - Concomitant use of medication(s) with a known risk to prolong the QT interval and/or days prior to starting study drug) or replaced by safe alternative medication.
- 12-lead Electrocardiogram (ECG):
  - QTc >450 msec
- Hypertension defined as:
  - Patients 1-12 years of age with blood pressure that is > 95th percentile for age, height and gender at the time of enrollment.
    - The normal blood pressure by height, age and gender tables can be accessed in the Generic Forms section of the PBTC members' webpage.
  - Patients who are  $\geq$  13 years of age with blood pressure > 130/80 mm of Hg at the time of enrollment.

\* Note: If a BP reading prior to enrollment does not meet parameters, blood pressure should be rechecked and documented to be within eligibility range prior to patient enrollment.

### *Bleeding Disorder*

Patient is currently receiving warfarin or other coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed as long as patient has adequate coagulation defined as: aPTT INR  $\leq$  1.5 x upper limit of normal.

### *Allergy*

Patient has a known hypersensitivity to ribociclib or any of its excipients as described below:

- The capsules contain only the drug substance without any excipients.
- The film-coated tablets consist of drug substance and compendial quality colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating is a mix of compendial quality iron oxides, lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum. Patients allergic to peanut and soy are not permitted to take the film-coated tablet formulation.
- The oral solution consists of ribociclib succinate in water with an orange flavoring agent and common excipients such as preservatives, sweetener and pH modifier

### *Inability to Participate*

Patients with inability to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.