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^2/day x 21 days)**	**Everolimus (mg/m^2/day x 28 days)**	**BSA Restriction**
-1	75 mg/m^2/day	1 mg/m^2/day	BSA≥0.55m^2
- 0.5*	120 mg/m^2/day	1 mg/m^2/day	BSA≥0.75m^2
0	75 mg/m^2/day	1.2 mg/m^2/day	BSA≥0.55m^2
1(starting dose)	**120 mg/m^2/day**	**1.2 mg/m^2/day**	**BSA≥0.75m^2**
2	170 mg/m^2/day	1.2 mg/m^2/day	BSA≥0.45m^2
3	170 mg/m^2/day	1.5 mg/m^2/day	BSA≥0.45m^2

*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^2/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^2/day.