# Protocol Abstract and Schema

## *PBTC-042: Phase I study of CDK 4-6 inhibitor PD-0332991 (palbociclib; IBRANCE) in children with recurrent, progressive or refractory central nervous system tumors*

### *Description*

This is a multicenter, Phase I trial for children with Retinoblastoma Protein 1 (Rb1) positive recurrent, progressive or refractory central nervous system tumors.
In the recent years there have been several clinical trials in adults with cancer utilizing small molecule inhibitors targeting cell cycle regulatory genes such as CDKs (cyclin-dependent kinase). In normal cells, these kinases are kept under control by a gene, however, this gene is frequently deleted in cancers and these two kinases are uncontrollably activated which drives the cell to divide and form cancer. This trial is using PD-0332991 (palbociclib; IBRANCE), a selective CDK inhibitor, to be evaluated in children with CNS tumors.

PD-0332991 (Pfizer Corporation, USA) is an orally active, water soluble, cell-permeable highly specific inhibitor of CDK4 and 6. It is designed to shut down the activity of molecules, CDK4 and 6 that drive cell division. PD-0332991 is expected to work only if the cancer cells demonstrate expression of the tumor suppressor retinoblastoma (Rb1) protein which is needed to control cell growth even if CDK4/6 is inhibited. A screening test for presence or absence of Rb1 will therefore be performed in all types of CNS tumors except diffuse pontine glioma (DIPG), medulloblastoma, or Atypical Teratoid Rhabdoid Tumor (ATRT) to confirm eligibility for this trial.

### *Rationale:*

Survival for children with recurrent CNS tumors is dismal and novel therapeutic options need to be developed in order to improve outcome. Cancer initiation and progression is dependent on deregulation of the components and phases of the cell cycle. Ample evidence exists on alterations of CDKs, Cyclins, cell cycle inhibitors, and checkpoint proteins in pediatric CNS tumors. The presence of specific mutations in the proteins involved in G1-S phase transition of the cell cycle in these tumors is particularly relevant for the use of a specific CDK4/6 inhibitor like PD-0332991. Furthermore, it is likely that over 60% of pediatric CNS tumors are likely to have intact Rb-protein, a pre-requisite for the efficacy of this cell cycle inhibitor. PD-0332991 has not been tested in children with cancer thus far. A Phase I study is therefore needed to assess the toxicity, MTD, pharmacokinetics, and preliminary evidence of efficacy of this agent in this patient population. Since myelosuppression is the predominant side effect of this agent, the Phase I study will first evaluate the toxicities in children who have not been heavily pre-treated previously.

With the MTD identified in less-heavily pre-treated patients (stratum I), this phase I study will be expanded to include heavily pre-treated patients (defined as those who have received more than 4 prior regimens (either myelosuppressive chemotherapy or biologic) ± craniospinal irradiation ± myeloablative chemotherapy plus stem cell rescue) in a separate cohort (stratum II). Treatment of these patients will be initiated at 50 mg/m$^2$/day (one dose level below the potential MTD in stratum I) as the starting dose level. Stratum II is likely to mostly include patients with recurrent medulloblastoma, other central PNETs, ATRT, and germ cell tumors. Recent genomic studies of medulloblastoma and ATRT have demonstrated that Rb1 protein is intact in these tumors. Therefore, patients with medulloblastoma or ATRT will not be required to have their tumors screened for Rb1 expression.

### *Schema*

This is a dose escalation trial of PD-0332991 to determine the maximum tolerated dose in children with recurrent brain tumors. PD-0332991 is taken orally once a day for 21 days followed by a week rest. One course is therefore equivalent to 28 days. Therapy may continue for up to two years (26 courses) in the absence of disease progression or unacceptable toxicity.

Dosing is based on BSA calculated at the beginning of each course. The starting dose is 50 mg/m$^2$ for stratum I and stratum II. PD-0332991 dose escalations will be performed according to the table below until the maximum tolerated or recommended Phase II dose is reached. Since myelosuppression is the main dose limiting toxicity (DLT) of this drug, patients who have been more heavily pretreated are likely to experience hematologic toxicity with this agent. Therefore, patients will be divided into two strata; stratum I- patients who have received either focal radiotherapy (RT) only or focal RT ± ≤ 4 prior myelosuppressive chemotherapy and/ or biologic therapy regimens or stratum II- those who have received > 4 prior regimens (either chemotherapy or biologic agent), ± craniospinal irradiation, and ± myeloablative chemotherapy plus bone marrow or peripheral blood stem cell rescue. Enrollment to Stratum I is currently ongoing and has accrued 12 patients at dose level 1 (n=3), 2 (n=3), and 3 (n=6). Two patients enrolled at dose level 3 were inevaluable for DLT. Of the 10 evaluable patients, 2 of 4 patients at dose level 3 experienced a DLT of grade 4 neutropenia. Hence the MTD was exceeded at dose level 3, and 3 additional patients have been enrolled at dose level 2. The maximum tolerated dose (MTD) for stratum I is expected to be dose level 2 (75 mg/m$^2$/day for 21 days). Since the possibility of myelosuppression is expected to be more in patients enrolled in stratum II (heavily pretreated patients), we consider it more prudent to commence enrollment of patients at dose level 1 which is 50 mg/m$^2$/day. An MTD will be separately determined for this stratum.

**Stratum I and II - PD-0332991 (IBRANCE) Dosing Regimen and BSA Restrictions**

| Dose Level | Dose (mg/m$^2$) | BSA (m$^2$) |
|---|---|---|
| 1* | 50 | ≥ 1.20 |
| 2** | 75 | ≥ 0.93 |
| 3 | 95 | ≥ 0.70 |

*Starting dose for stratum II
** Current enrollment for stratum I

## OBJECTIVES

### Primary Objectives

- To determine the maximum tolerated dose (MTD)/Phase II recommended dose and describe toxicities related to PD-0332991 in children with Retinoblastoma Protein 1 (Rb1) positive recurrent, progressive, or refractory primary CNS tumors. MTD will be determined separately in less-heavily pre-treated vs. heavily pre-treated patients.
- To determine plasma pharmacokinetics of PD-0332991 in children with Rb1 positive recurrent, progressive or refractory primary CNS tumors

### Secondary Objectives

- To record preliminary evidence of efficacy of PD-0332991 in children with recurrent CNS tumors
- To evaluate CDK4/6, cyclin D1-3, Ink4a-ARF copy-number variations in available tumor tissue by array comparative, genomic hybridization (aCGH)

- To explore the potential relationships between the pharmacokinetics of PD-0332991 and pharmacodynamic response (e.g. percentage change in absolute neutrophil count (ANC), platelet counts)
- To explore the pharmacogenetic polymorphisms in PD-0332991 metabolizing enzymes and transporters and relate these polymorphisms to PD-0332991 pharmacokinetics

## PATIENT SELECTION

**Screening Criteria**
All subjects must meet the following criteria without exception.

- Screening Consent
    - Patients who are candidates for enrollment are willing to sign a screening consent and provide pre-trial tumor material for Rb1 testing. Screening applies to patients with all types of CNS tumors except DIPG, medulloblastoma, or ATRT.

- Tumor
    - Patients must have recurrent, progressive or refractory central nervous system (CNS) tumors. Patients with secondary malignant gliomas will be eligible for this study but should conform to the strict prior treatment exposure criteria irrespective of the number of individual tumors treated previously. Patients with low grade gliomas are excluded.

- Prior Therapy
    - Stratum I: Less-Heavily Pretreated Stratum
        - ❖ Patients who have received the following:
            - ▪ $\leq$ 4 prior treatment regimens* with either myelosuppressive chemotherapy or biologic agents and/or
            - ▪ focal radiotherapy

    - Stratum II: Heavily Pretreated Stratum
        - ❖ Patients who have received the following:
            - ▪ 4 prior treatment regimens* with either myelosuppressive chemotherapy or biologic agents and/or
            - ▪ craniospinal irradiation and/or
            - ▪ myeloablative chemotherapy with autologous stem cell rescue

*A treatment regimen is defined as a single agent (chemotherapeutic or biologic), or a sequential combination of therapies that can include radiotherapy (with or without concurrent radiosensitizer, chemotherapy, or biologic therapy) followed by maintenance therapy (either single or combination) given over a period of time at either diagnosis or relapse.

- Age
    - Patient must be $\geq$ 4 years and $\leq$ 21 years of age.

- Patient must be able to swallow capsules.

- 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. Only

patients with recurrent diffuse intrinsic brain stem glioma (DIPG), medulloblastoma, or ATRT can be enrolled without the need for available tumor tissue for Rb1 protein status confirmation.

- BSA:
  - Patients enrolled on dose level 1 (50mg/m2) must have BSA≥ 1.20m2
  - Patients enrolled on dose level 2 (75mg/m2) must have BSA≥0.93m2
  - Patients enrolled on dose level 3 (95mg/m2) must have BSA≥0.70m2

**Eligibility for Treatment Criteria**
All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given.

- Eligible Diagnosis
  - Tumor type:
    Histologically confirmed retinoblastoma protein (Rb1) positive primary recurrent, progressive, or refractory central nervous system tumors. Patients with low grade gliomas are excluded.

    Formalin fixed paraffin embedded tumor tissue (preferably from the most recent recurrence) must be available to assess Rb1 protein status prior to enrollment. Patients with recurrent diffuse intrinsic brain stem glioma (DIPG), medulloblastoma, or ATRT can be enrolled without the need for available tumor tissue for Rb1 protein status confirmation.

- Measureable Disease
  - Patients must have measurable disease (in 2-dimensions) on MRI scan of brain and/or spine to assess preliminary evidence of response.

- Age
  - Patient must be ≥ 4 years and ≤ 21 years of age at the time of enrollment.

- BSA:
  - Patients enrolled on dose level 1 (50mg/m2) must have BSA≥1.20m2
  - Patients enrolled on dose level 2 (75mg/m2) must have BSA≥0.93m2
  - Patients enrolled on dose level 3 (95mg/m2) must have BSA≥0.70m2

- Prior Therapy
  - Stratum I: Less-Heavily Pretreated Stratum
    - ❖ Patients who have received the following:
      - ▪ ≤ 4 prior treatment regimens* with either myelosuppressive chemotherapy or biologic agents and/or
      - ▪ focal radiotherapy.

  - Stratum II: Heavily Pretreated Stratum
    - ❖ Patients who have received the following:
      - ▪ > 4 prior treatment regimens* with either myelosuppressive chemotherapy or biologic agents and/or
      - ▪ craniospinal irradiation and/or
      - ▪ myeloablative chemotherapy with autologous stem cell rescue

*A treatment regimen is defined as a single agent (chemotherapeutic or biologic), or a sequential combination of therapies that can include radiotherapy (with or without concurrent radiosensitizer, chemotherapy, or biologic therapy) followed by maintenance therapy (either single or combination) given over a period of time at either diagnosis or relapse.

- Patients must have fully recovered from the acute treatment- related toxicities of all prior therapies prior to entering this study. For those acute baseline adverse events attributable to prior therapy, patients must meet organ function criteria (section ) in the Inclusion and Exclusion Criteria.
- Chemotherapy: Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to enrollment in the study or at least six (6) weeks for those receiving nitrosourea.
- Bone marrow/Stem Cell Infusion:
  - ≥ 3 months since autologous bone marrow/stem cell infusion prior to enrollment (stratum II only)
- Biologic therapy: Patients should have received their last dose of biologic agent ≥ 7 days prior to enrollment. In the event the patient has received another biologic agent and has experienced ≥ Grade 2 myelosuppression, then at least three (3) weeks must have elapsed prior to enrollment. If the investigational or biologic agent has a prolonged half-life then at least three (3) weeks interval is required. For patients on monoclonal antibodies including Bevacizumab, please refer to list of half-lives available on the PBTC webpage under Generic Forms and Templates.
- Radiotherapy:
  - Patients must have had their last fraction of:
    Focal irradiation > 2 weeks prior to enrollment
    Craniospinal irradiation > 3 months prior to enrollment (stratum II only)
- Corticosteroids: Patients who are receiving dexamethasone or other corticosteroids must be on a stable or decreasing dose for at least 1 week prior to enrollment. It is recommended that patients be off all steroid therapy or receive the least dose that will control their neurologic symptoms
- Growth factors: All colony forming growth factor(s) have been discontinued for at least one week prior to enrollment (filgrastim, sargramostim, and erythropoietin). For patients on long acting growth factors, the interval should be two weeks.

- 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 that are stable for a minimum of one week prior to enrollment.

- Patients must be able to swallow capsules.

- Performance Status
  Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 60.

- Organ Function
  Patients must have normal organ and marrow function as defined below:
  - Absolute neutrophil count >1,000/mm3
  - Platelets >100,000/ mm3 transfusion independent (no platelet transfusion one week prior to enrollment )
  - Hemoglobin ≥ 8g/dl
  - Total bilirubin ≤ 1.5 times upper limit of institutional normal (ULN) for age
  - AST (SGOT)/ALT(SGPT) < 3 x institutional upper limit of normal for age
  - Serum albumin ≥ 3g/dL
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m2 or a serum creatinine based on age/gender as follows:

| 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. | | |

- Pregnancy Status
  Female patients of childbearing potential must have a negative serum pregnancy test at the time of enrollment.

- Pregnancy Prevention
  Patients of childbearing or child fathering potential must agree to use adequate contraceptive methods while being treated on this study and for 97 days after completing therapy.

- Informed Consent
  Patient and/or guardian have the ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.

**Exclusion Criteria**

- Patients with any clinical significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) that is likely to interfere with the study procedures or results
- Patients with low grade gliomas and Rb1 negative tumors
- Patients with QTc interval of > 450 msec or those on medications known to prolong QTc interval (see **Error! Reference source not found.**)
- Prior treatment on a CDK inhibitor (e.g. Flavopiridol)
- Patients who are receiving drugs that are strong inducers or inhibitors of CYP3A4 (see**Error! Reference source not found.**)
- Patients who are receiving any other investigational therapy
- Patients who require enzyme inducing anti-convulsants to control seizures
- Patients with cataracts on ophthalmologic examination. The ophthalmology report from the institution should clearly specify the presence or absence of cataracts per slit lamp examination.