Protocol Abstract and Schema

A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma

Description and Rationale:
Low grade gliomas are among the most common primary CNS neoplasms of childhood. Recent studies demonstrate constitutive activation of the BRAF oncogene by multiple mechanisms. The most common mechanism observed is a genetic fusion which results in loss of the regulatory domain of BRAF; this fusion gene is described in the majority of JPA specimens examined. Alternate mechanisms of activation, such as the BRAF V600E mutation have also been described in low grade glioma. BRAF is a component of the Ras/Raf/MAP kinase signaling cascade, and constitutive activation of BRAF results in increased MAP kinase signaling, with subsequent cellular proliferation. We propose that inhibition of the MAP kinase MEK1 and 2 will have antitumor effects in BRAF activated tumors.

AZD6244 is an orally available small molecule inhibitor of the MAP kinase MEK1 and 2. Preclinical studies demonstrate that it results in MEK1and 2 inhibition (measured by ERK1 and 2 phosphorylation). An initial Phase 1 study in adult patients also suggests that treatment with AZD6244 inhibits ERK phosphorylation in PBMC and in post treatment tumor specimens at tolerable doses.

PBTC-029 began as a multicenter, phase 1 and pharmacokinetic trial to estimate the MTD and/or select a recommended phase 2 dose of AZD6244 in children 12 years or over with recurrent or refractory low grade glioma following radiation and/or chemotherapy and was later amended to include unirradiated patients as young as 3 years old.

Schema:
Phase 1 was a dose escalation trial of AZD6244 administered orally twice daily for 28 consecutive days. Courses are repeated every 28 days and continued for 26 courses or until one of the Off-treatment criteria have been met.

The starting dose for patients was 33mg/m^2/dose, BID for a total daily dose of 66mg/m^2/day.

Dose levels 1, 2 and 0 were investigated in Phase 1, and 25 mg/m^2/dose, BID was established as the MTD as well as the Phase II recommended dose in both age strata investigated (age ≥12 years, and age < 12 years).

Phase II Stratification Schema:
The primary objective of the phase II component of the study is to assess the efficacy of AZD6244, administered at 25 mg/m^2/dose, BID, as measured by objective response (CR+PR) rate in a single arm Phase II study in patients stratified based on histology or the biology of their tumor. Patients will be assigned to the following strata based on NF-1 status, histology and presence or absence of BRAF alterations, specifically BRAF^{V600E} mutations and/or BRAF KIA1540 fusion as assessed by IHC and FISH respectively.

Stratum 1	Stratum 2	Stratum 3	Stratum 4	Stratum 5	Stratum 6
Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **with** pre-trial tumor material available and **with** a BRAF aberration, excluding patients with optic pathway glioma	Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **with** pre-trial tumor material available and **without** BRAF aberration, excluding patients with optic pathway glioma	Patients with NF-1 associated progressive, recurrent or refractory low-grade glioma (WHO I or II), **with or without** tissue	Patients with non NF-1 associated progressive, recurrent or refractory optic pathway glioma (OPG) **with or without** tissue available for BRAF evaluation.	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than pilocytic astrocytoma or optic pathway glioma). These patients' tumors must have BRAF aberrations which will be determined by screening prior to enrollment on the treatment protocol.	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than OPG) with tissue available for BRAF analyses who cannot be classified into Stratum 1, 2 or 5 due to inadequate tissue quality, assay failure, etc.

Re-treatment Schema:
The Re-treatment Study will allow patients who were enrolled on PBTC-029 or PBTC-029B and had prolonged stable disease or sustained response, to go back on AZD6244 at the time of progression and evaluate response, progression-free survival and the impact of other variables on outcome. This information will be useful in determining the optimal duration of therapy with AZD6244 in patients with low grade gliomas. Furthermore, it will allow an evaluation of the safety of treatment beyond 2 years.

PATIENT SELECTION

Eligibility Assessment Timelines

- Imaging evaluations necessary to establish eligibility for study entry must be done within three (3) weeks prior to registration.
- All other evaluations necessary to establish eligibility for study entry must be done within two (2) weeks prior to registration.

Criteria to Start Treatment

- Patients must start therapy within 7 calendar days of registration.
- Laboratory values must be no older than seven (7) days prior to the start of therapy. If a test that is repeated after registration and prior to therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If laboratory values still fail to meet eligibility criteria, the patient may not receive protocol therapy.
- All patients must meet the following inclusion and exclusion criteria. **NO EXCEPTIONS WILL BE GIVEN**.

Eligibility Criteria for Screening on Phase II Study:

- Screening consent

Participant is willing to sign a screening consent and provide adequate pre-trial tumor material for BRAF testing (both for BRAF V^{600E} mutation and BRAF KIAA1549 fusion assessments).

  - Stratum 5
    - All patients who are candidates for enrollment in Stratum 5 based on their tumor histology must be pre-screened.
  - Stratum 2
    - Screening will also be applied to potential 2 patients.

- Patients with Prior BRAF Testing

Patients whose prior BRAF testing was performed at another lab (CLIA/CAP certified or otherwise) must send additional tumor material to BWH for confirmation (see Section 9.1.1 for tissue requirements).

However, to preserve available tumor material, patients whose tumor material has previously undergone BRAF analysis at the Lindeman and Ligon Labs at Brigham and Women's Hospital using the same procedures as described in this protocol, will not be required to submit additional tumor material for analysis. These patients must have both the BRAFV600E mutation and BRAF KIAA1549 fusion assessments done and if only one test was previously conducted; additional tissue will be required for the second test.

- Age: Patient must be ≥ 3 but ≤ 21 years of age at registration

- Diagnosis

Patient must have one of the following:

- For Stratum 5: Non NF-1 associated LGG (other than Pilocytic Astrocytoma or Optic

Pathway Glioma)
- For Stratum 2: Non NF-1, non-optic pathway Pilocytic Astrocytoma

Eligibility for Treatment Criteria for Phase II Study:

- Tumor

Non NF-1 Non-Optic Pathway Pilocytic Astrocytoma:

- Patients with sporadic (non NF-1 associated), histologically diagnosed progressive, recurrent or refractory non-optic pathway pilocytic astrocytoma who have pre- treatment tumor tissue available for BRAF analysis.

NF-1 Associated LGG:

- NF-1 patients with radiographic evidence of a progressive, recurrent or refractory low grade glioma, with or without pre-treatment tumor tissue.

Non NF-1 Optic Pathway Glioma:

- Patients with progressive, recurrent or refractory optic pathway glioma, with or without pre-treatment tumor tissue.

Non NF-1 LGG (other than Pilocytic Astrocytoma or Optic Pathway Glioma):

- Patients with histologically diagnosed progressive, recurrent or refractory non NF-1 associated LGG (other than Pilocytic Astrocytoma or Optic Pathway Glioma). These patients must have BRAF aberrations as documented by the Lindeman and Ligon Labs at Brigham and Women's Hospital using the same procedures as described in this protocol.

Patients will be assigned to one of 6 strata prior to enrollment. All BRAF assessments used for stratification below must be done at the Lindeman and Ligon Labs at Brigham and Women's Hospital using the same procedures as described in this protocol. Assessments for both BRAF V^{600E} mutation and BRAF KIAA1549 fusion are required for patients who will enroll on strata 1, 2 and 5.

- Stratum 1: Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma with pre-trial tumor material available and with a BRAF aberration i.e. $BRAF^{V600E}$ mutation and/or BRAF KIAA1549 fusion as determined by IHC and FISH, respectively. Patients with optic pathway glioma are excluded.
- Stratum 2: Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma with pre-trial tumor material available and without a BRAF aberration i.e. $BRAF^{V600E}$ mutation and/or BRAF KIAA1549 fusion as determined by IHC and FISH, respectively. Patients with optic pathway glioma are excluded.
- Stratum 3: Patients with Neuro-fibromatosis 1 (NF-1) associated progressive, recurrent or refractory low grade glioma (WHO Grade I & II), with or without tissue
- Stratum 4*: Patients with non-NF1 associated progressive, recurrent or refractory optic pathway glioma with or without tissue available for BRAF evaluation.
- Stratum 5: Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma other than pilocytic astrocytoma or optic pathway glioma with a documented BRAF aberration identified in pre-trial tumor material.

- Stratum 6: Patients with non-NF-1 associated progressive, recurrent or refractory low grade glioma (other than OPG) with tissue available for BRAF analyses who cannot be classified into Stratum 1, 2 or 5 due to inadequate tissue quality, assay failure, etc.

*Clarification: Stratum 4 was specifically designed for patients with hypothalamic/optic pathway gliomas. The intent is that if there is any optic chiasm invasion regardless of where the tumor is originating from (chiasm vs. hypothalamus vs. other location), the patient should be enrolled on Stratum 4, regardless of whether the tumor has been biopsied or not. Obviously, there are some tumors that include part of the hypothalamus and clearly do **NOT** include the chiasm at all. In these situations, and if the tumor is a biopsy proven pilocytic astrocytoma, these patients should be enrolled on Stratum 1 or 2 (depending upon BRAF status).

- Patients must have bi-dimensionally measureable disease defined as at least one lesion that can be accurately measured in at least two planes in order to be eligible for this study.

- Prior Therapy

Patients must have received prior therapy other than surgery and must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, biologic therapy or radiotherapy prior to study entry.

- Myelosuppressive chemotherapy: Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three weeks prior to study registration or at least six weeks if nitrosourea.

- Biologic agent: Patient must have received their last dose of the biologic agent ≥ 7 days prior to study registration.
  - For biologic agents that have a prolonged half-life, at least three half-lives must have elapsed prior to registration

- Monoclonal antibody treatment: At least three half-lives must have elapsed prior to registration**.**

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 local irradiation to primary tumor ≥12 months prior to registration; **investigators are reminded to review potentially eligible cases to avoid confusion with pseudo-progression**.
  - Had their last fraction of craniospinal irradiation (>24Gy) > 3 months prior to registration

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

- Growth factors: Patients must be off all colony-forming growth factor(s) for at least 1 week prior to registration (filgrastim, sargramostim, erythropoietin) and at least 2 weeks for long-acting formulations.

- Age: Patient must be ≥ 3 but ≤ 21 years of age at registration.

- BSA: Patients must have a BSA ≥0.55m^2.

- Neurological Status: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.

- Patients must be able to swallow capsules

- Performance Status

Karnofsky Performance Scale (KPS for > 16 yrs. of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration (See APPENDIX A).

- Organ Function

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

  - Absolute neutrophil count ≥1,000/µL (unsupported)
  - Platelets ≥100,000/µL (unsupported)
  - Hemoglobin ≥ 8 g/dL (may be supported)
  - AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal for age
  - Total bilirubin < 1.5 times upper limit of normal for age
  - Albumin ≥ 3g/dL
  - Serum Sodium and Potassium within the institutional limits of normal
  - Serum Calcium and Magnesium above the institutional lower limit of normal
  - Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m^2 or a serum creatinine based on age as follows:

Table 1

Age (years)	Maximum Serum Creatinine (mg/dL)
≤5	0.8
> 5 but ≤ 10	1
>10 but ≤15	1.2
>15	1.5

- Cardiac Function: Adequate cardiac function defined as:
  - LVEF ≥55%
  - QTc interval ≤450 msecs

- Hypertension
  - Patients, 3-17 years of age must have a blood pressure that is ≤ 95th percentile for age, height and gender at the time of registration.
    - 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 ≥18 years of age must have a blood pressure that is <140/90 mm of Hg at the time of registration.

Note: If a BP reading prior to registration is above the 95th percentile for age, height and gender it must be rechecked and documented to be ≤ the 95th percentile for age, height and gender prior to patient registration.

- Pregnancy Status

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

- Pregnancy Prevention

The effects of *AZD6244* on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for four weeks after dosing with *AZD6244* ceases. Women of child-bearing potential must have a negative pregnancy test prior to entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Please note that the *AZD6244* manufacturer recommends that adequate contraception for male patients should be used for 16 weeks post-last dose due to sperm life cycle.

- Informed Consent

Ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.

Exclusion Criteria

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), likely interfere with the study procedures or results.

- Patients who are receiving any other anticancer or investigational agents.

- Patients with uncontrolled seizures

- Previous MEK inhibitor use such as PD-0325901; CI1040; AS73026; GDC 0973; ARRY43182; GSK110212.

- Prior treatment with a BRAF inhibitor such as Vemurafenib or Dabrafenib (Previous treatment with Sorafenib is allowed)

- Patients with other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) that meets New York Heart Association (NYHA) class II or above (APPENDIX B)

- Required use of a concomitant medication that can prolong the QT interval. See APPENDIX C for a table of medications with the potential to prolong the QTc interval.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD6244.

Eligibility Criteria for Enrollment on the Re-Treatment Study

- Patients must have recurrence or progression of their low-grade glioma after coming off treatment with AZD6244 on PBTC-029 or PBTC-029B, with or without having received additional anti-tumor therapy following discontinuation of AZD6244. The progression must be unequivocal and sufficient to warrant re-treatment in the opinion of the investigator. Progression will be defined as either PD that meets the study definitions of progressive disease by MRI (Section 12.1.4) or vision deterioration thought to be related to tumor in patients with optic pathway tumors.

- Patients must have received treatment on PBTC-029 or PBTC-029B for a minimum of 12 courses with at least stable disease, or had a sustained response (PR/CR) but remained on treatment < 12 courses.

- Patients must have bi-dimensionally measureable disease defined as at least one lesion that can be accurately measured in at least two planes.

- Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, biologic therapy or radiotherapy prior to study entry.

  - Myelosuppressive chemotherapy: Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three weeks prior to registration on the Re-treatment Study or at least six weeks if a nitrosourea.

  - Biologic agent: Patient must have received their last dose of the biologic agent ≥ 7 days prior to study registration.
    - For biologic agents and monoclonal antibody treatment, at least three half-lives must have elapsed prior to registration.
  - Other Investigational Agents (not fitting into one of the above specified categories): Patients must have received their last dose of any other investigational agent greater than 28 days prior to enrollment.

  - Radiation: Patients must have:
    - Had their last fraction of local irradiation to the primary tumor ≥12 months prior to registration; **investigators are reminded to review potentially eligible cases to avoid confusion with pseudo-progression**.
    - Had their last fraction of craniospinal irradiation (>24Gy) > 3 months prior to registration

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

  - Growth factors: Patients must be off all colony-forming growth factor(s) for at least 1 week prior to registration (filgrastim, sargramostim, erythropoietin) and at least 2 weeks for long-acting formulations.

- Neurological Status: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.

- Patients must be able to swallow capsules

- Performance Status: Karnofsky Performance Scale (KPS for > 16 yrs. of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration

- Organ Function
  - Absolute neutrophil count >1,000/µL (unsupported)
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  - AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal for age
  - Total bilirubin < 1.5 times upper limit of normal for age
  - Albumin ≥ 3g/dL
  - Serum Sodium and Potassium within the institutional limits of normal
  - Serum Calcium and Magnesium above the institutional lower limit of normal
  - Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m2 or a normal serum creatinine based on age as follows:

Table 2

Age (years)	Maximum Serum Creatinine (mg/dL)
≤5	0.8
> 5 but ≤ 10	1
>10 but ≤15	1.2
>15	1.5

- Cardiac Function: Adequate cardiac function defined as:
  - LVEF ≥55%
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- Hypertension
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- Pregnancy Status: Female patients of childbearing potential must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test.

- Pregnancy Prevention
  The effects of AZD6244 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for four weeks after dosing with AZD6244 ceases. Women of child-bearing potential must have a negative pregnancy test prior to entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Please note that the AZD6244 manufacturer recommends that adequate contraception for male patients should be used for 16 weeks post-last dose due to sperm life cycle.

- Informed Consent: Ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.

- **Exclusion Criteria**
  - Patients taken off treatment for progressive disease on PBTC-029 or PBTC-029B
  - Patients previously treated with a MEK inhibitor other than AZD6244.
  - Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), likely interfere with the study procedures or results
  - Patients who are receiving any other anticancer or investigational agents.
  - Patients with uncontrolled seizures
  - Patients with other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) that meets New York Heart Association (NYHA) class II or above
  - Required use of a concomitant medication that can prolong the QT interval.
  - History of allergic reactions attributed to AZD6244 or compounds of similar chemical or biologic composition.

- **Inclusion of Women and Minorities:** Both males and females of all races and ethnic groups are eligible for this trial.

- **Other:** All patients must have current and past smoking status recorded in the RDC database.

- **Treatment at Primary Institution**

All experimental protocol therapy should be administered/dispensed and all imaging studies obtained at the primary institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA certified laboratory of the investigator's choice.