Protocol Abstract and Schema

A Phase 1 and Phase II 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 MEK1 and 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 (See section 2.3).

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 will be repeated every 28 days and continue 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 maximum tolerated 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 the biology of their tumor. Patients will be assigned to the following strata based on NF-1 status and presence or absence of BRAF alterations, specifically BRAF V_600E mutations and/or BRAF KIA1540 fusion as assessed by IHC and FISH respectively.
<table>
<thead>
<tr>
<th>Stratum 1</th>
<th>Stratum 2</th>
<th>Stratum 3</th>
<th>Stratum 4</th>
<th>Stratum 5</th>
<th>Stratum 6</th>
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<tbody>
<tr>
<td>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</td>
<td>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</td>
<td>Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (WHO I or II), with or without tissue</td>
<td>Patients with non NF-1 associated progressive, recurrent or refractory optic pathway glioma (OPG) with or without tissue available for BRAF evaluation.</td>
<td>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.</td>
<td>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</td>
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**Eligibility Criteria**

**Eligibility Criteria for Screening:**

Screening consent

Participant is willing to sign a screening consent and provide pre-trial tumor material for BRAF testing.

- All patients who are candidates for enrollment in Stratum 5 based on their tumor histology must be pre-screened.
- Screening may be applied to potential Stratum 1 and 2 patients when patient accrual is close to pre-specified interim analysis or final sample size thresholds in either stratum. The OBC will notify sites when/if it becomes necessary to screen patients for BRAF aberrations for Stratum 1 and 2.

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.

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 \( \geq 3 \) but \( \leq 21 \) 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 1 or 2: Non NF-1, non-optic pathway Pilocytic Astrocytoma

Note: All patients with non NF-1 associated optic pathway glioma with or without tissue must be enrolled on stratum 4.

Eligibility for Treatment Criteria

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 following 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.

- **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. BRFV600E 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. BRFV600E 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.

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 entering this study.

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 BSA \( \geq 0.55 \text{m}^2 \).

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 \( \leq 16 \) years of age) \( \geq 60 \) assessed within two weeks prior to registration

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 \( \geq 1,000/\mu L \) (unsupported)
- Platelets \( \geq 100,000/\mu L \) (unsupported)
- Hemoglobin \( \geq 8 \text{ g/dL} \) (may be supported)
- Total bilirubin \( < 1.5 \) times upper limit of normal for age
- AST(SGOT)/ALT(SGPT) \( \leq 2.5 \times \) institutional upper limit of normal for age
- Creatinine clearance or radioisotope GFR \( \geq 70 \text{ ml/min/1.73m}^2 \) or a serum creatinine based on age as follows:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Maximum Serum Creatinine (mg/dL)</th>
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<tr>
<td>( \leq 5 )</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt; 5 but ( \leq 10 )</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10 but ( \leq 15 )</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;15</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- Sodium, Potassium within the institutional limits of normal
- Calcium and Magnesium above the institutional lower limit of normal
- Albumin \( \geq 3 \text{g/dL} \)

Cardiac Function
Adequate cardiac function defined as:

- LVEF \( \geq 50\% \)
- QTc interval \( \leq 450 \) msecs

Hypertension

- Patients, 3-17 years of age must have a blood pressure that is \( \leq 95\text{th percentile for age, height and gender at the time of registration.} \)
  - 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 \( \geq 18 \) years of age must have a blood pressure that is \( < 140/90 \text{ mm of Hg} \) 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 are not eligible for the study.

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

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 are excluded.

Required use of a concomitant medication that can prolong the QT interval.

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