

Abstract and Schema

Phase 1 and Pharmacokinetic 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. (See section 2.1)

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).

This is a multicenter, phase 1 and pharmacokinetic trial to determine 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.

Schema:

This is a dose escalation trial of AZD6244 administered orally twice daily for 28 consecutive days. Courses will be repeated every 28 days and continue for 13 courses or until one of the Off-treatment criteria have been met.

The starting dose for patients is 33mg/m²/dose, BID for a total daily dose of 66mg/m²/day. Dose escalations will be performed according to the Table below until the MTD or the recommended phase two dose (RP2D) is identified. The nomogram for dosing AZD6244 is located in Appendix VIII.

Dose Level	Dose
0	25 mg/m ² /dose, BID (total daily dose 50 mg/m ² /day)
1*	33 mg/m ² /dose, BID (total daily dose 66 mg/m ² /day)
2	43 mg/m ² /dose, BID (total daily dose 86 mg/m ² /day)
3	56 mg/m ² /dose, BID (total daily dose 112 mg/m ² /day)
4	73mg/m ² /dose, BID (total daily dose 146 mg/m ² /day)
5	95 mg/m ² /dose, BID (total daily dose 190 mg/m ² /day)

*Starting dose level.

1.1 Primary Objectives

- 1.1.1 To estimate the maximum tolerated dose (MTD) or recommend a Phase II dose of AZD6244 in children with recurrent or refractory low-grade glioma.
- 1.1.2 To describe the toxicity profile and define the dose limiting toxicity of AZD6244 in children with recurrent or refractory low-grade glioma.

1.2 Secondary Objectives

- 1.2.1 To characterize the inter- and intra-patient variability in AZD6244 pharmacokinetics administered on this schedule and to assess the influence of patient specific covariates (including concomitant drug therapy) on AZD6244 pharmacokinetics.
- 1.2.2 To evaluate the feasibility of collecting pre-trial tumor samples and the feasibility of using immunohistochemical assays to identify BRAF aberrations in available tumor specimens.
- 1.2.3 To determine if pre-trial tumor samples show the biochemical signature that indicates activation of the MAPK pathway.
- 1.2.4 To describe MRI characteristics of the tumors before and after treatment and to explore the diffusion changes in the tumors before and after treatment to determine if there is an early diffusion indicator of response.
- 1.2.5 Within the constraints of a Phase I trial, to document antitumor activity of treatment with AZD6244, as measured by objective responses and PFS.
- 1.2.6 To explore the pharmacogenetic polymorphisms in AZD6244 metabolizing enzymes and transporters and relate these polymorphisms to AZD6244 pharmacokinetics.

2 PATIENT SELECTION

2.1 Eligibility Assessment Timelines

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

2.2 Criteria to Start Treatment

- 2.2.1 Patients must start therapy within 7 working days of registration.
- 2.2.2 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 48 hours prior to the start of therapy. If the recheck is still outside the limits for eligibility, the patient may not receive protocol therapy.

All patients must meet the following inclusion and exclusion criteria. **NO EXCEPTIONS WILL BE GIVEN.**

2.3 Inclusion Criteria

Both men and women of all races and ethnic groups are eligible for this study.

2.3.1 Age

Patient must be ≥ 12 but ≤ 21 years of age at registration.

2.3.2 Tumor

Patients with a histologically confirmed diagnosis of low grade gliomas (WHO Grades I & II). Patients with optic pathway gliomas are eligible with clinical and/or radiographic evidence of progression.

2.3.3 Neurological Status

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

2.3.3.1 Patients must be able to swallow capsules.

2.3.4 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.

2.3.5 Prior Therapy

The patient has received prior therapy with radiation prior to study registration. Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

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

2.3.5.2 Biologic agent: Patient must have recovered from any toxicity potentially related to the agent and received their last dose of the biologic agent ≥ 7 days prior to study registration.

- 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. The duration of this interval should be discussed with the study chair.
- For biologic agents that have a prolonged half-life, the appropriate interval since last treatment should be discussed with the study chair prior to registration.

2.3.5.3 Monoclonal antibody treatment:

At least three half-lives must have elapsed prior to registration. Such patients should be discussed with the study chair prior to registration.

2.3.5.4 Radiation: Patients must have:

- Had their last fraction of local irradiation to primary tumor ≥ 12 weeks 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) or total body irradiation > 3 months prior to registration

2.3.5.5 Bone Marrow Transplant: Patient must be:

- ≥ 6 months since allogeneic bone marrow transplant prior to registration
- ≥ 3 months since autologous bone marrow/stem cell prior to registration

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

2.3.5.7 Growth factors 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.

2.3.6 Organ Function: Documented within 14 days of registration and within 7 days of the start of treatment.

2.3.6.1 Bone Marrow:

- Absolute neutrophil count $\geq 1000/\mu\text{l}$ (unsupported)
- Platelets $\geq 100,000/\mu\text{l}$ (unsupported)
- Hemoglobin ≥ 8 g/dL (may be supported)

2.3.6.2 Renal: Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m² or a serum creatinine based on age as follows:

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

2.3.6.3 Hepatic:

- Bilirubin < 1.5 times upper limit of normal for age
- SGPT/SGOT (ALT/AST) ≤ 2.5 times institutional upper limit of normal for age

2.3.6.4 Electrolytes:

- Sodium: ≥ 130 and ≤ 145 mmol/L
- Potassium: 3.4- 4.8 mmol/L
- Calcium: ≥ 7 mg/dL
- Magnesium: ≥ 0.7 mmol/L

2.3.6.5 Nutrition: Albumin ≥ 3 g/dL

2.3.7 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.

2.3.8 Pregnancy Prevention

The effects of AZD6244 on the developing human fetus at the recommended therapeutic dose 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, 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 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.

2.3.9 Informed Consent

Signed informed consent according to institutional guidelines must be obtained.

2.4 Exclusion Criteria

- 2.4.1** 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 or would likely interfere with the study procedures or results.
- 2.4.2** Patients receiving any other anticancer or investigational drug therapy.
- 2.4.3** Patients with uncontrolled seizures are not eligible for the study.
- 2.4.4** Previous MEK inhibitor use such as PD-0325901; CI1040; AS73026; GDC 0973; ARRY43182; GSK110212.
- 2.4.5** Prior treatment with a BRAF inhibitor
- 2.4.6** Patients with QTc interval >450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (*e.g.*, heart failure, hypokalemia, family history of long QT interval syndrome) including heart failure that meets New York Heart Association (NYHA) class III and IV definitions (see Appendix IV) are excluded.
- 2.4.7** Required use of a concomitant medication that can prolong the QT interval. See Appendix V for a table of medications with the potential to prolong the QTc interval. A comprehensive list of agents with the potential to cause QTc prolongation can be found at <http://www.azcert.org/medical-pros/drug-lists/browse-drug-list.cfm?alpha=A>
- 2.4.8** Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.
- 2.4.9** History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD6244.