

Protocol Abstract and Schema

A Phase I Clinical Trial of AZD2171 in Children with Recurrent or Progressive Central Nervous System (CNS) Tumors

Description:

A pediatric phase I trial AZD2171 will be performed in children and adolescents with recurrent or refractory tumors of the central nervous system, to determine the maximum tolerated dose (MTD). While the pediatric MTD dose of 32mg/m²/day was tolerated over the first 6 weeks of therapy in the initial cohort of patients, ongoing toxicity assessment suggests that this dose is not tolerated in many patients at this dose level (3 patients experienced DLTs among the 5 patients treated as part of the expanded cohort at this dose level). We are therefore proposing to expand the cohort of pediatric patients treated at the 20mg/m²/day dose (the dose that appears tolerable in adults and is being tested further in that patient population). AZD2171 will be administered by mouth once daily for 28 consecutive days in two strata: a) Stratum I: those who are not receiving enzyme inducing anticonvulsant drugs (EIACD) and b) Stratum II: those who are receiving enzyme inducing anticonvulsant drugs (EIACD).

Pharmacokinetic studies are required for study enrollment and protocol therapy with this amendment.

Primary Objectives:

- 1.1 To evaluate the safety of the 20mg/m² dose of oral AZD2171 administered once daily to children and adolescents with recurrent or refractory primary CNS tumors.
- 1.2 To describe the toxicity profile and dose-limiting toxicities of AZD2171 administered once daily to children and adolescents with recurrent or refractory primary CNS tumors.
- 1.3 To characterize the pharmacokinetics of 20 mg/m²/day dose of AZD2171 in children and adolescents.

Secondary Objectives:

- 1.1 To explore correlations among changes in plasma, serum and urine levels of proteins associated with angiogenesis including VEGF and VEGFR in patients who receive AZD2171 at different dose levels.
- 1.2 To obtain preliminary evidence of biologic activity of AZD2171 by evaluating alterations in tissue perfusion, tumor blood flow and metabolic activity using MR perfusion and diffusion imaging as well as PET analysis and correlating these findings with changes in tumor size by standard MRI.
- 1.3 To continue the PBTC investigation to explore associations between imaging assessments of antiangiogenesis effects and outcome measures such as response or PFS within the confines of a Phase I trial.

Inclusion Criteria

- Age: Patient must be ≤ 21 years of age at registration.
 - A total of 12 patients will be treated in Stratum I at the 20mg/m²/day dose. Six of these patients will be ≤12 years of age and the other 6 will be > 12 years (See section 13.2 for details). The accrual to Stratum II will not be constrained by the same age restriction as very few patients are expected to be enrolled onto that stratum.

- Tumor: Patients with a histological confirmed diagnosis of a primary CNS tumor (including histologically benign brain tumors (e.g. low-grade glioma)) that is recurrent, progressive, or refractory to standard therapy. All tumors must have histologic verification at either the time of diagnosis or recurrence. Patients with intrinsic brain stem or diffuse optic pathway tumors do not require histological confirmation of disease but should have clinical and/or radiographic evidence of progression.
- Neurological Score: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.
- Performance Score: Karnofsky Performance Score (KPS for >16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 yrs of age) ≥ 60 assessed within two weeks prior to registration.
- Patients at increased risk for compromised Left Ventricular Ejection Fraction (LVEF) must have a Karnofsky/Lansky score ≥ 70. Patients who have one of the following risk factors are considered at increased risk for compromised LVEF:
 - *Prior treatment with anthracyclines;*
 - *Prior treatment with trastuzumab;*
 - *A New York Heart Association classification of II controlled with treatment (refer to Appendix XIV);*
 - *Prior central thoracic radiation therapy (RT), including RT to the heart;*
 - *History of myocardial infarction within 12 months*
- Patient must be able to swallow tablets.
- Prior/Concurrent Therapy: Patients must have no known curative therapy available. Patients will be eligible regardless of the number of prior therapies except for those with prior treatment with AZD2171, as long as other eligibility criteria are met.
 - *Patient must have recovered from the significant acute toxicities of all prior therapy before entering this study and meet all other eligibility criteria specified 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 study registration.
 - Received their last dose of nitrosourea at least six (6) weeks prior to study registration.
 - Received their last dose of other investigational or biologic agent > seven (7) days prior to study registration.
 - If the investigational or biologic agent has a prolonged half-life (>48 hours) then these patients must be discussed with the study chair prior to registration.

- *Radiation: Patients must have:*
 - had their last fraction of craniospinal irradiation or total body irradiation > 3 months prior to registration
 - had their last fraction of focal irradiation to evaluable sites of disease >4 weeks prior to registration
- *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
 - *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 Neulasta®.*
- The following laboratory values must be assessed within two (2) weeks of registration and again (if necessary) to be within seven (7) days prior to the start of therapy.
 - *Bone Marrow:*
 - Absolute neutrophil count ≥ 1000/μl (unsupported)
 - Platelets ≥ 75,000/μl (unsupported)
 - Hemoglobin ≥ 8 g/dL (may be supported)
 - *Renal: Serum creatinine ≤ 1.5 times upper limit of institutional normal for age or GFR ≥ 70 ml/min/1.73m².*
 - *Hepatic:*
 - Bilirubin ≤ 1.5 times upper limit of normal for age
 - SGPT (ALT) ≤ 2.5 times institutional upper limit of normal for age
 - *Metabolic: Urine dipstick or urinalysis with < 1+ protein*
 - Nutrition: Albumin ≥ 3 g/dL
- No overt renal, hepatic, cardiac or pulmonary disease.
- Female patients of childbearing potential must have negative serum or urine pregnancy test. Patient must not be pregnant or breast-feeding.
- Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.
- Signed informed consent which includes consent to the required Pharmacokinetic studies according to institutional guidelines must be obtained.

Exclusion Criteria

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that, in the investigator's opinion, would compromise the patient's ability to tolerate AZD2171 or likely interfere with the study procedures or results.
- Patients receiving any other anticancer or investigational drug therapy.
- Patients, ages 1-17, with uncontrolled hypertension, (defined as systolic and/ or diastolic BP at > 95th

percentile for age, height and gender). 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 \leq the 95th percentile for age, height and gender prior to patient registration. Ensure patient is at rest prior to repeat BP measurement. Patients \geq 18 years of age will be excluded if the BP is $>140/90$. If a BP reading prior to registration is $> 140/90$, it must be rechecked and documented to be $\leq 140/90$ prior to patient registration. Ensure the patient is at rest prior to the repeat BP measurements.

- Patients with prior treatment with AZD2171.
- Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.
- Patients found to be at increased risk for compromised LVEF (see 4.1.5 above) will be considered ineligible if they have the following conditions:
 - *QTc prolongation >500 msec or other significant ECG abnormality noted within 14 days of treatment*
 - *A New York Heart Association classification of III or IV and a Karnofsky/Lansky <70 . (NOTE: patients classified as class II controlled with treatment may continue with increased monitoring).*
 - *Conditions requiring concurrent use of drugs which may cause QTC prolongation. These drugs are prohibited during studies with AZD2171 (refer to Appendix XV for a listing of these agents).*

Rationale:

AZD2171 is an orally available, highly potent, subnanomolar inhibitor of the VEGF receptor tyrosine kinase (both VEGFR1 and VEGFR2). Interestingly, this molecule also inhibits signaling through c-kit, which has also been implicated in the pathogenesis of certain central nervous system tumors^{6,7} With the current amendment, we are proposing to expand the cohort of patients treated with AZD2171 at the dose of $20\text{mg}/\text{m}^2$ in children, adolescents, and young adults with recurrent or progressive central nervous system tumors.

Schema:

This is a Phase I trial of AZD2171 administered orally once daily for 28 consecutive days. Courses will be repeated every 28 days and continue for 26 courses or until one of the off-study criteria have been met. Patients will be stratified according to those not receiving enzyme inducing anticonvulsant drugs (EIACD) (Stratum I) or those receiving EIACD (Stratum II).

<i>Stratification Scheme</i>	
<i>Stratum I</i>	<i>Stratum II</i>
Must not be receiving EIACD	Receiving EIACD

Prior to version 8.0, the starting dose for patients, which varied by strata, was $20\text{mg}/\text{m}^2$ for stratum I and $15\text{mg}/\text{m}^2$ for stratum II. Dose escalations were performed separately in Strata I and II. The MTD for Stratum I was determined to be $32\text{mg}/\text{m}^2$ based on the original design using the CRM .

<i>AZD2171 Dose Escalation Table</i>		
Dose Level	Stratum I Patients not on enzyme- inducing anticonvulsant drugs Daily Dose (mg/m²)	Stratum II Patients taking enzyme- inducing anticonvulsant drugs Daily Dose (mg/m²)
-1	12	10
0	15	12
1*	20	15
2	25	20
3	32	25
4		32

*starting dose

While the pediatric MTD dose of 32mg/m²/day was tolerated over the first 6 weeks of therapy in the initial cohort of patients, ongoing toxicity assessment suggests that this dose is not tolerated in many patients at this dose level (3 patients experienced DLTs among the 5 patients treated as part of the expanded cohort at this dose level). We are therefore proposing to expand the cohort of pediatric patients treated at the 20mg/m²/day dose (the dose that appears tolerable in adults and is being tested further in that patient population). Nomogram for dosing AZD2171 is located in Appendix VII.