Société de Neuro-Oncologie Bretonne

E.1 : ESSAI TARGET

Full title	A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Clinical Efficacy AZD4547 in Patients with Relapsed/Refractory glioma positive for an FGFR fusion
Acronym	TARGET
Coordinating Investigator	Marc SANSON Department: Neurology Pitié-Salpêtrière Hospital
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	3% of GBM and IDHwt gliomas have a highly oncogenic FGFR-TACC gene fusion that confers high sensitivity to FGFR inhibitors to tumor cells, in vitro and in vivo. Preclinical data shows that expression of FGFR-TACC fusions confers sensitivity to FGFR inhibitors (including AZD4547) to GBM models (Fig. 1) .AZD4547 (AstraZeneca) is a potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases. Preclinical data have shown some CNS penetration (Table 1). It has shown a strong anti-tumor effect in animal models of FGFR-gene addiction, including FGFR-fusions (Fig. 1). Some of the important adverse events are hyperphosphatemia, and ocular complications (see below).
Primary objective and assessment criterion	To assess the efficacy of AZD4547 by measuring the rate of Progression Free Survival at 6 months (PFS6) in recurrent malignant glioma patients with FGFR-TACC fusion.
Secondary objectives and assessment criteria	- To characterize the safety, tolerability and PK of AZD4547 in glioma patients - To further assess the anti-tumor activity of AZD4547 for patients with recurrent glioma with FGFR-TACC fusion based on Overall Response Rate for patients with a measurable residue. - To further assess the anti-tumor activity of AZD4547 for patients with recurrent glioma with FGFR-TACC fusion based on the duration of PFS - To further assess the anti-tumor activity of AZD4547 for patients with recurrent glioma with a FGFR-TACC fusion based on Overall Survival AZD4547
Exploratory objectives	- To elucidate the mechanism of response and resistance (primary and secondary) by exploratory biomarker analysis
Experimental design	This is a phase II study in patients diagnosed with a FGFR3-TACC3 or FGFR1-TACC1 fusion positive glioma presenting with a recurrence of the disease after chemotherapy and radiotherapy. RNA will be systematically screened for the presence of FGFR-TACC in each of the 11 participating centers, and IHC for FGFR3 hyperexpression. We also encourage a wide use

	of FGFR3 IHC in non participating centers in order to identify additional potential candidates who can be referred to one of the 11 centers for assessment of FGFR-TACC expression by RNA analysis. Patients will receive AZD4547 at a dose of 80mg bd on a continuous schedule, until disease progression. With the following hypothesis: P0: PFS6=15%, P1: PFS6=35%, with alpha=5% and power=80%, an initial cohort of 12 patients will be treated. If objective anti-tumor effects are observed, the cohort will be expanded to include a total number of 38 subjects. Grade II gliomas are also eligible but they will constitute an extra small cohort.
Population involved	Patients 18 years or over
Inclusion criteria	1. Recurrent glioma after standard treatment, expressing the FGFR3-TACC3 or FGFR1-TACC1 fusion gene as confirmed by RT-PCR sequencing. 2. First recurrence occurring more than three months from the end of the radiotherapy or occurring outside the irradiated volume. 3. World Health Organisation performance status 0-2 (KPS>50) with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks. 4. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. If a patient declines to participate in any voluntary exploratory research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study 5. Aged at least 18 years. 6. Patients should be using adequate contraceptive measures which should be maintained during the whole duration of AZD4547 treatment and at least 7 days after treatment suspension. Females should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening: - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments. - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not

	tubal ligation
Exclusion criteria	1. Treatment with any of the following: - Nitrosourea within 6 weeks before the first dose of study treatment - Any investigational agents or study drugs from a previous clinical study within 30 days before the first dose of study treatment - Any other chemotherapy, anticancer immunotherapy or anticancer agents within 4 weeks before the first dose of study treatment, except hormonal therapy. - Potent inhibitors or inducers of CYP3A4 or 2D6 or substrates of CYP3A4 within the required washout period as specified in the section 7.3 - Prior treatment in this or another AZD4547 study, or prior randomisation in a study in which AZD4547 is/was under investigation. Prior treatment with any FGFR inhibitor. 2. Major surgery (excluding placement of vascular access) within 14 days before the first dose of study treatment 3. With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment 4. As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required 5. Any of the following cardiac criteria: - Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's correction.Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT

	syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval - History of myocardial infarction, unstable angina, stroke or transient ischemic attack within the last 6 months 6. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: - Absolute neutrophile count <1.5 x 10^9/L - Platelet count <100 x 10^9/L - Haemoglobin <90 g/L - Alanine aminotransferase >2.5 times the upper limit of normal (ULN) - Aspartate aminotransferase >2.5 times ULN Total bilirubin >1.5 times ULN - Creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN - Corrected calcium >ULN - Phosphate >ULN 7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD4547 8. History of hypersensitivity to active or inactive excipients of AZD4547 or drugs with a similar chemical structure or class to AZD4547 9. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements 10. Any of the following ophthalmological criteria: - Current evidence or previous history of retinal pigmented epithelium detachment (RPED) - Previous laser treatment or intra-ocular injection for

	treatment of macular degeneration - Current evidence or previous history of dry or wet age-related macular degeneration - Current evidence or previous history of retinal vein occlusion (RVO) - Current evidence or previous history of retinal degenerative diseases (eg, hereditary) - Current evidence or previous history of any other clinically relevant chorioretinal defect 11. Contraindications to MRI
Treatment being tested	*AZD4547 a selective anti FGFR1,2,3*
Benchmark treatment	AZD4547 will be administered orally at 80mg bd on a continuous schedule.
Other procedures added by the research	As part of the translational research and in order to assess drug penetration, a lumbar puncture will be performed in a subset of patients. AZD4547 concentrations in the CSF will also be measured in recurrent patients who are candidates for surgery.
Risks added by the research	Risk D
Practical procedure	Patients with IDH1 wild type glioma will be systematically screened for the presence of an FGFR3-TACC3/ FGFR1-TACC1 gene fusion on the initial tumor sample in each of the participating centers using RT-PCR analysis of tumor RNA, and FGFR3 expression by IHC. They will then be proposed to enter the trial at recurrence. AZD4547 will be administrated at 80mg bd (160 mg/d) until recurrence according to RANO criteria. Additional patients ie from non participating centres may be pre-screened through the wide use of FGFR3 IHC and positive cases will be further analysed by RT-PCR and the patient may be referred to one of the 11 participating centres.
Number of subjects chosen	12 patients with grade III-IVglioma at the first phase 26 patients with grade III-IV glioma at the second phase Patients with grade II gliomas will be also included but they will not be taken into account for efficacy calculation. We assume that grade II will represent 4 to 7 supplementary patients.
Number of centres	Approximately 11 centers (France, Italy, UK) International
Research period	- Inclusion period: 2 years - Participation: 13 months max 3 years and 1 month in total
Number of inclusions expected per centre	Approximately 0.2 patients

and per month	
Statistical analysis	Intermediate analysis PFS6months after 12 patients for futility
Funding source	AstraZeneca
Data Safety Monitoring Board anticipated	Yes