ET-30. A PHASE I TRIAL OF AZD7451, A TROPOMYOSIN-RECEPTOR KINASE (TRK) INHIBITOR, FOR ADULTS WITH RECURRENT GLIOBLASTOMA MULTIFORME (GBM)

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BACKGROUND: We have shown that inhibition of TrkA both genetically and pharmacologically results in profound inhibition of glioma stem cell migration in vitro and in vivo. AZD7451 is the first in class of highly potent and selective Trk inhibitors and therefore may have significant anti-glioma cell invasive properties. METHODS: We conducted an open label phase I study of AZD 7451 mesylate, with a standard 3 + 3 dose escalation scheme, to determine the MTD and describe pharmacokinetics. The drug was administered as an oral solution (10 mg/ml) at 12 mg, 24 mg, 40 mg, and 60 mg daily. DL3 and DL4 were administered with divided twice daily dosing. Plasma concentrations of AZD7451 were measured with ultra-performance liquid chromatography and tandem mass spectrometry using samples obtained at baseline and various points through the first 4 week cycle of therapy. RESULTS: 14 patients were enrolled. There were no radiographic responses to therapy, and no patients achieved disease control beyond cycle 2. There were no DLTs. Unexpected treatment related toxicities included grade 1-2 thrombocytopenia and anemia. No neurological adverse events related to therapy were observed. All patients were evaluable for C1D1 pharmacokinetics. The majority of samples were below the limit of quantitation (LLOQ) of 0.5 ng/mL by ~4 h post-dose. AZD7451 T1/2 ranged from 20-50 min with once daily or BID dosing. No statistically significant increases in CMAX, AUCINF, T1/2, or volume of distribution were observed as dose increased. CONCLUSIONS: Based on the interim PK analysis for AZD7451 indicating poor oral bioavailability, short <60 min plasma T1/2 half-life, and rapid clearance kinetics, PK exposures are insufficient in humans to inhibit Trk at target plasma concentrations necessary for efficacy in preclinical models. The absence of DLTs or early efficacy signals in GBM patients is also consistent with poor AZD7451 exposures in humans.
NOW ENROLLING
Phase 2b study of IGV-001 in patients with newly diagnosed glioblastoma (NCT04485949)

OBJECTIVES

- PRIMARY OBJECTIVE: Progression-free survival
- SECONDARY OBJECTIVE: Overall survival
- SAFETY OBJECTIVE: Safety and tolerability

Key Inclusion Criteria
Patients who take part in the trial* must:
- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

Key Exclusion Criteria
Patients are not allowed to participate* in the trial if they have:
- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn’s disease)
- Heart disease or history of heart issues

*Additional criteria apply. Please refer to protocol 14379-201 for full inclusion and exclusion criteria. †Patients can participate if they had some skin cancers, superficial bladder cancer (cancer that was only on the surface of the lining of the bladder), or carcinoma in situ (cancer that had not spread) of the cervix or breast that had been cured.

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IGF-1R, insulin-like growth factor 1 receptor; KPS, Karnofsky Performance Scale; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

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