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Activity of a first-in-class oral HIF2-alpha inhibitor, PT2385, in patients with first recurrence of glioblastoma

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Abstract

Introduction: Hypoxia inducible factor 2-alpha (HIF2α) mediates cellular responses to hypoxia and is over-expressed in glioblastoma (GBM). PT2385 is an oral HIF2α inhibitor with in vivo activity against GBM.

Methods: A two-stage single-arm open-label phase II study of adults with GBM at first recurrence following chemoradiation with measurable disease was conducted through the Adult Brain Tumor Consortium. PT2385 was administered at the phase II dose (800 mg b.i.d.). The primary outcome was objective radiographic response (ORR = complete response + partial response, CR + PR); secondary outcomes were safety, overall survival (OS), and progression free survival (PFS). Exploratory objectives included pharmacokinetics (day 15 C_{min}), pharmacodynamics (erythropoietin, vascular endothelial growth factor), and pH-weighted amine- chemical exchange saturation transfer (CEST) MRI to quantify tumor acidity at baseline and explore associations with drug response. Stage 1 enrolled 24 patients with early stoppage for ≤ 1 ORR.

Results: Of the 24 enrolled patients, median age was 62.1 (38.7-76.7) years, median KPS 80, MGMT promoter was methylated in 46% of tumors. PT2385 was well tolerated. Grade ≥ 3 drug-related adverse events were hypoxia (n = 2), hyponatremia (2), lymphopenia (1), anemia (1), and hyperglycemia (1). No objective radiographic responses were observed; median PFS was 1.8 months (95% CI 1.6-2.5) and OS was 7.7 months (95% CI 4.9-12.6). Drug exposure varied widely and did not differ by corticosteroid use (p = 0.12), antiepileptics (p = 0.09), or sex (p = 0.37). Patients with high systemic exposure had significantly longer PFS (6.7 vs 1.8 months, p = 0.009). Baseline acidity by pH-weighted CEST MRI correlated significantly with treatment duration (R^2 = 0.49, p = 0.017). Non-enhancing infiltrative disease with high acidity gave rise to recurrence.

Conclusions: PT2385 monotherapy had limited activity in first recurrent GBM. Drug exposure was variable. Signals of activity were observed in GBM patients with high systemic exposure and acidic lesions on CEST imaging. A second-generation HIF2α inhibitor is being studied.

Trial registration: ClinicalTrials.gov NCT03216499.

Keywords: Amine imaging; Glioblastoma; Hypoxia; Hypoxia-inducible factor.