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Phase 1/2 study of investigational hypoxia-targeted drug, TH-302, and bevacizumab (bev) in recurrent glioblastoma (GBM) following bev failure

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BACKGROUND: Despite vascular dependence, GBM is resistant to antiangiogenic therapy. Co-targeting tumor angiogenesis and tumor hypoxia, a key driver of treatment resistance, is one approach to potentially prevent or reverse this mechanism of resistance. An ongoing Phase 1/2 study investigates TH-302 with bev in patients (pts) with recurrent GBM following bev failure. Median PFS and 3-mo PFS (PFS-3) in this pt population has been reported as 37.5 days and ~16% (Quant et al. Neuro-Oncol 2009).

METHODS: Single center, dose-escalation, prospective study (NCT01403610) with 2:1 randomization to TH-302 single dose of 575 mg/m^2 or placebo administered pre-surgery (cohorts 1-3 only), followed by post-surgery combination therapy of bev at 10 mg/kg and TH-302 dose escalated 240-670 mg/m^2 every 2 weeks (4 week cycle) until disease progression. Following the first 5 pts in cohort 3, pts were allowed to proceed directly to TH-302/bev combination therapy without surgery. Resected tumor tissue was evaluated for hypoxia induced pimonidazole (PIMO) adducts, endogenous CA-IX staining, ɣH2AX and TUNEL DNA damage biomarkers, and by metabolomic profiling.

RESULTS: 21 pts have been enrolled: 14 randomized in presurgery cohorts 1-3 with 9 proceeding to TH-302/bev after surgery and 7 pts proceeding directly to TH-302/bev. No Gr 4 AEs were observed. Two Gr 3 AEs were observed at 340 mg/m^2 (skin ulceration) and 670 mg/m^2 (thrombocytopenia). Primary TH-302 related toxicities were mucosal but not dose limiting: rectal mucositis in 2/4 pts at 480 mg/m^2 and 4/4 pts at 670 mg/m^2. Oral mucositis was limited. Co-localized PIMO and CA-IX staining showed extensive tumor hypoxia. MR-spectra showed significant differences in metabolites before treatment compared to at progression. Best tumor responses in 16 evaluable pts: 1 CR, 2 PRs, and 9 SDs. Median PFS is 3.1 mos (95% CI: 2.1 to 4.0 mos) and PFS-3 is 52% (95% CI: 27% to 78%).

CONCLUSIONS: Extensive tumor hypoxia was observed in GBM pts previously treated with bev. The recommended Phase 2 dose of TH-302 is 670 mg/m^2 when combined with bev. These preliminary data suggest potential activity of TH-302/bev in GBM pts with poor prognosis. Dose expansion at 670 mg/m^2 is ongoing.