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CENTRAL NERVOUS SYSTEM TUMORS

Phase 1, multicenter, open-label, dose-escalation, study of marizomib (MRZ) and bevacizumab (BEV) in WHO grade IV malignant glioma (G4 MG).

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Abstract Disclosures

Abstract

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Background: MRZ is an irreversible, brain-penetrant, pan-proteasome inhibitor (PI). It inhibits glioma cell proliferation and invasion *in vitro*, prolongs survival in *in vivo* mg tumor models, with little effect on normal neuronal stem cells, suggesting minimal neurotoxicity (Neuro Oncol 2015 Dec 17. pii: nov299). Intravenous (IV) MRZ has been administered to ~300 patients (pts) with solid tumors and hematologic cancers. This trial is evaluating the safety, pharmacodynamics, and efficacy of MRZ and BEV in BEV-naïve pts with G4 mg who are in first or second relapse with no prior anti-angiogenic or PI therapy. **Methods:** Phase 1, dose-escalation (3+3 design) followed by dose-expansion at recommended Phase 2 Dose (RP2D); three dose cohorts - MRZ 0.55 (n = 6 pts), 0.7 (n = 3 pts), and 0.8 mg/m^2 (n = 3 pts). MRZ infused IV (10 min) on Days 1, 8, & 15; BEV IV 10 mg/kg on Days 1 & 15 (over 28-Day Cycles). Tumor response is assessed every other Cycle by RANO criteria; blood proteasome inhibition assessed every Cycle. **Results:** In dose-escalation, 12 pts enrolled: median age 53 yrs (44-61); 83% male; 83% Caucasian; Karnofsky Score > 80. As of 6 Jan 2016, duration of dosing is 5-33 weeks with treatment ongoing in 7 pts. MRZ/BEV was well tolerated; most common adverse events (AEs): headache (9), fatigue (7), hypertension (5), infusion site pain (5), and nausea (5). Grade 3 AEs related to MRZ or BEV: hypertension (2), confusional state (1), fatigue (1), hallucinations (1), and headache (1). One pt (cohort 1) had fatigue as DLT, but no DLTs at higher doses. MRZ caused > 70% inhibition of chymotrypsin-like activity on Cycle 1 Day 1 with 100% by Day 28. Transient hyperactivation of trypsin-like (T-L) and caspase-like (C-L) activities after the first 1-2 MRZ doses, followed by 40-60% inhibition of T-L and 10-30% inhibition of C-L activities in Cycle 3. RANO responses in the 3 cohorts: 4/12 partial response, 6/12 stable disease and 2/12 progressive disease. **Conclusions:** The MRZ/BEV combination was well tolerated with only one DLT at MRZ 0.5 mg/m^2. To date, rapid and pronounced pan-proteasome inhibition has been observed with 4/12 pts achieving confirmed PRs. MRZ 0.8 mg/m^2 is the RP2D in the ongoing dose-expansion stage. Clinical trial information: NCT02330562.