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Evaluating the Base Excision Repair Inhibitor TRC102 and Temozolomide for patients with Recurrent Glioblastoma in the Phase 2 Adult Brain Tumor Consortium Trial BERT

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Abstract

Purpose: Patients with glioblastoma (GBM) have a dismal prognosis. While DNA alkylating agent temozolomide (TMZ) is mainstay of chemotherapy, therapeutic resistance develops rapidly in patients. Base excision repair inhibitor TRC102 (methoxyamine) reverses TMZ resistance in preclinical glioma models. We sought to investigate efficacy and safety of oral TRC102+TMZ for recurrent GBM (rGBM).

Patients and methods: A pre-registered (NCT02395692), non-randomized, multicenter, phase 2 clinical trial (BERT) was planned and conducted through the Adult Brain Tumor Consortium (ABTC-1402). Arm 1 included bevacizumab-naïve GBM patients at first recurrence, with primary endpoint of response rates. If sufficient activity was identified, a second arm was planned in bevacizumab-refractory patients. Secondary endpoints were overall survival (OS), progression-free survival (PFS), PFS at six months (PFS-6), and toxicity.

Results: Arm 1 enrolled 19 patients with median of two treatment cycles. Objective responses were not observed, hence, arm 2 did not open. Median OS was 11.1 months (95%CI 8.2-17.9). Median PFS was 1.9 months (95%CI 1.8-3.7). PFS-6 was 10.5% (95%CI 1.3-33.1%). Most toxicities were Grade 1-2, with two Grade 3 lymphopenias and one Grade 4 thrombocytopenia. Two patients with PFS ≥17 months and OS >32 months were deemed 'extended survivors'. RNA sequencing of tumor tissue, obtained at diagnosis, demonstrated significantly enriched signatures of DNA damage response (DDR), chromosomal instability (CIN70, CIN25), and cellular proliferation (PCNA25) in 'extended survivors'.

Conclusions: These findings confirm safety and feasibility of TRC102+TMZ for rGBM patients. They also warrant further evaluation of combination therapy in biomarker-enriched trials enrolling GBM patients with baseline hyperactivated DDR pathways.