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Microbubble-enhanced transcranial focused ultrasound with temozolomide for patients with high-grade glioma (BT008NA): a multicentre, open-label, phase 1/2 trial

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Abstract

Background: Brain-infiltrating tumour cells from high-grade glioma remain shielded from drug treatments by the blood-brain barrier, leading to inevitable recurrence. Microbubble-enhanced transcranial focused ultrasound (MB-FUS) enables controlled blood-brain barrier opening (BBBO), permitting localised drug delivery. We aimed to assess safety and feasibility of MB-FUS plus standard-of-care chemotherapy for individuals with high-grade glioma.

Methods: BT008NA was an open-label, single-arm, phase 1/2 trial conducted at five sites in the USA and Canada (part of the ReFOCUSED Consortium). Key eligibility criteria were participants with newly diagnosed high-grade glioma (glioblastoma as per WHO 2016 classification), aged 18-80 years, with normal organ function, a baseline Karnofsky Performance Status score of 70 or higher, who had received maximal safe resection and 6-week chemoradiotherapy and were to start standard-of-care monthly adjuvant temozolomide chemotherapy (150 mg/m^2 of body surface area). MRI-guided, 220 kHz transcranial MB-FUS treatments were delivered in periresectional (tumour-infiltrative) regions, on any of the first 3 days of a 28-day temozolomide cycle, for up to six cycles. Primary outcomes were safety (adverse events) and feasibility (BBBO: new contrast enhancement on post-procedure T1-weighted MRI). Protocol-prespecified secondary outcomes were overall survival and progression-free survival. Analyses were done in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT03551249 (USA) and NCT03616860 (Canada), and is closed to enrolment.

Findings: Between Oct 16, 2018, and March 9, 2022, we enrolled 34 participants, all evaluable for prespecified primary and secondary endpoints, with a mean age of 51·5 years (SD 13·0) and median follow-up 44·5 months (95% CI 34·9-57·3). By self-reporting, 18 (53%) participants were female and 16 (47%) male, 28 (82%) were White, and 34 (100%) were non-Hispanic. 176 adverse events were

captured: 54 (31%) chemotherapy-related, 10 (6%) disease-related, 87 (49%) related to undergoing MB-FUS (40 [46%] grade 1, 46 [53%] grade 2, and one [1%] grade 3), and 25 (14%) unrelated. Two (1%) of the adverse events were grade 5 (disease-related deaths), three (2%) grade 4 (temozolomide-related haematological abnormalities), and eight (5%) grade 3 (three [2%] temozolomide-related, one [1%] MB-FUS-related, three [2%] disease-related, and one [1%] unrelated); these occurred across seven (21%) of 34 participants. No treatment-related deaths occurred during the trial. BBBO was visualised in all treatments. Median overall survival was 31·3 months (95% CI 21·1-not reached) and median progression-free survival was 13·5 months (9·9-26·9) with patient-specific disease courses found concordant with trajectories of MB-FUS-enriched plasma cell-free DNA.

Interpretation: MB-FUS plus temozolomide is a safe combinatorial therapeutic approach for individuals with high-grade glioma, with the potential to improve survival and enable non-invasive plasma biomarker-based disease surveillance (sono-liquid biopsy), warranting randomised controlled trials.

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