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A Phase 0/1 Pharmacokinetic and Pharmacodynamics and Safety and Tolerability Study of Letrozole in Combination with Standard Therapy in Recurrent High-Grade Gliomas

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Abstract

Purpose: High grade gliomas (HGGs) carry a poor prognosis, with glioblastoma accounting for almost 50% of primary brain malignancies in the elderly. Unfortunately, despite the use of multiple treatment modalities, the prognosis remains poor in this population. Our pre-clinical studies suggest that the presence of aromatase expression, encoded by CYP19A1, is significantly upregulated in HGGs. Remarkably, we find that letrozole (LTZ), an FDA approved aromatase inhibitor, has marked activity against HGGs.

Methods: We conducted a phase 0/I single center clinical trial (NCT03122197) to assess the tumoral availability, pharmacokinetics (PK), safety and tolerability of LTZ in recurrent HGG patients. Planned dose cohorts included 2.5, 5, 10, 12.5, 15, 17.5 and 20 mg of LTZ administered daily pre- and post-surgery or biopsy. Tumor samples were assayed for LTZ content and relevant biomarkers. The Recommended Phase 2 Dose (R2PD) was determined as the dose that resulted in predicted steady state tumoral extracellular fluid (ECF) (Css,ecf) > 2 μM and did not result in ≥ 33% dose limiting adverse events (AEs) assessed using CTCAE v5.0.

Results: Twenty-one patients were enrolled. Common LTZ related AEs included fatigue, nausea, musculoskeletal, anxiety and dysphoric mood. No DLTs were observed. The 15 mg dose achieved a Css,ecf of 3.6 +/- 0.59 μM. LTZ caused dose-dependent inhibition of estradiol synthesis and modulated DNA damage pathways in tumor tissues as evident using RNA-seq analysis.

Conclusion: Based on safety, brain tumoral PK, and mechanistic data, 15 mg daily is identified as the RP2D for future trials.