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Phase I Study of Vorinostat and Temsirolimus in Newly Diagnosed or Progressive Diffuse Intrinsic Pontine Glioma

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Abstract

Background: Diffuse intrinsic pontine glioma (DIPG) carries a poor prognosis with a median survival of less than 12 months. Key molecular features include histone H3 mutation (K27M) and AKT pathway dysregulation. There is currently no curative treatment.

Methods: This is a Phase I study of vorinostat and temsirolimus in newly diagnosed (Stratum 1) and progressive (Stratum 2) DIPG (NCT02420613). The primary aims are to determine the safety, maximum tolerated dose (MTD), and toxicities. A modified 3 + 3 design was used to establish the MTD, where the first three patients were assigned the first dose level regardless of stratum. Stratum 1 received radiotherapy with vorinostat, followed by up to 10 cycles of vorinostat and temsirolimus. Stratum 2 received up to 12 cycles of vorinostat and temsirolimus. Vorinostat was administered at a fixed dose of 230 mg/m^2 daily on Days 1-8, and temsirolimus was administered on Days 1 and 8 at 25 mg/m^2 (Dose level 1) or 35 mg/m^2 (Dose level 2).

Results: Six patients were enrolled, three in each stratum. No dose-limiting toxicity was observed, and most adverse effects were limited to Grades 1 or 2, including fatigue, myelosuppression, hyperlipidemia, hyperglycemia, elevated creatinine, nausea, vomiting, and headache. One patient experienced Grade 3 leukopenia. In the study, the MTD with acceptable toxicity was vorinostat 230 mg/m^2 and temsirolimus 35 mg/m^2.

Conclusions: Overall, the combination of temsirolimus and vorinostat is well-tolerated and safe, prompting the need for larger studies to investigate its efficacy.

Keywords: diffuse intrinsic pontine glioma (DIPG) | H3 K27M-mutant glioma | Phase I clinical trial | targeted therapy.