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# Phase I/II and Window-of-Opportunity Study of Pamiparib and Metronomic Temozolomide for Recurrent IDH Mutant Gliomas

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## Abstract

**Background:** Preclinical studies demonstrate activity of PARP inhibitors in IDH mutant gliomas. We investigated safety, tolerability, pharmacokinetics, and efficacy of the PARP inhibitor pamiparib in conjunction with metronomic low-dose temozolomide in patients with recurrent IDH mutant (IDHmt) gliomas in a multicenter Phase I/II/window of opportunity study.

**Methods:** Patients received pamiparib in conjunction with daily temozolomide. Following Phase I determination of MTD, we enrolled two patient cohorts (Arm A, multiple prior chemotherapy regimens; Arm B, single prior regimen) in a two-stage design. Exploratory cohorts examined grade 4 IDHmt patients and intratumoral pharmacokinetics of pamiparib. The primary endpoint was objective radiographic response (ORR) by RANO criteria.

**Results:** 66 subjects were enrolled. We established pamiparib 60 mg twice daily with temozolomide 20 mg daily as the phase II dose. In non-enhancing and enhancing tumor, pamiparib exhibited an unbound tumor/plasma ratio of 0.92 and 0.98 respectively. 0/15 Arm A and 1/24 Arm B patients achieved a centrally confirmed partial response. Median progression-free survival for Arm A was 5.9 months (95% CI, 1.2-14.8 months), and for Arm B 9.7 months (95% CI, 5.7-21.7 months). Grade 3+ anemia and neutropenia affected 24% and 33% of patients respectively. Twenty-two of 66 patients (33.3%) discontinued study treatment for reasons other than tumor progression.

**Conclusion:** Pamiparib appeared to achieve sufficient pharmacologically active concentrations in both enhancing and non-enhancing tumors. While some patients achieved prolonged progression-free survival, combination with temozolomide did not produce a meaningful ORR in IDHmt recurrent gliomas. Cumulative hematologic toxicity was substantial and impacted long-term tolerability.

**Keywords:** IDH mutation; PARP inhibitors; clinical trial; glioma; temozolomide.