Pamiparib in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with newly diagnosed (ND) or recurrent/refractory (R/R) glioblastoma (GBM); phase 1b/2 study update

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Pamiparib, an investigational, oral PARP 1/2 inhibitor, demonstrated preclinical brain penetration and synergistic cytotoxicity with TMZ. We report updated safety and antitumor data for pamiparib plus RT and/or TMZ in ND-GBM or R/R-GBM (SNO 2019, ACTR-39). This dose-escalation/expansion study includes three arms: *A*, pamiparib (2, 4, or 6 weeks) plus RT (6-7 weeks) in ND-GBM with unmethylated *MGMT* promoter (unmethylated-GBM); *B,* pamiparib (6 weeks) plus RT and increasing TMZ doses in Weeks 1 and 5 of RT in unmethylated ND-GBM; and *C*, pamiparib plus increasing TMZ doses in methylated/unmethylated R/R-GBM. Most patients in *Arms A* (expansion) and *B* received maintenance pamiparib plus TMZ after post-RT rest period at *Arm* C expansion. As of April 10, 2020, enrollment was complete (N=116; *A,* n=60; *B*, n=9; *C*, n=47). Median study follow-up was 11.3 mo (*A*/*B*) and 7.1 mo *(C)*. Common grade ≥3 AEs were anemia (10%) in *Arm A;* decreased neutrophil and white blood cell count (each 22%) in *B;* anemia, fatigue, and decreased lymphocyte count (each 11%) in *C.* Brain edema (*A*) and pneumonia (*C*) (n=1 each) were fatal treatment-unrelated AEs. In ND-GBM, modified disease control rate (DCR following post-RT rest period) was 69.8% (95% CI, 55.7-81.7) overall, 68.8% (50.0-83.9) in *A*, and 80.0% (28.4-99.5) in *B*. Median duration of response was 5.1 mo (overall), 3.8 mo (*A*), and NE (*B*). In *Arms A*/*B*, median progression-free survival (PFS) and median overall survival (OS) were 4.4 mo and 12.7 mo, respectively; 12-mo OS rate, 54% (95% CI, 40-66). In R/R-GBM (*Arm C*), confirmed ORR was 9.1% (95% CI, 2.5-21.7); median PFS and OS were 1.9 mo and 7.3 mo, respectively; 6-mo PFS rate, 19% (95% CI, 9-32). These results

showed a manageable safety profile for pamiparib +/- RT +/-TMZ; response and survival results support further evaluation of these combinations in GBM.