Preliminary Results of Pamiparib (BGB-290), a PARP1/2 Inhibitor, in Combination with Temozolomide (TMZ) in Patients (pts) with Locally Advanced or Metastatic Solid Tumors

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Background DNA damage caused by TMZ can sensitize tumors to the effects of PARP inhibitors. Pamiparib is a selective PARP1/2 inhibitor with potent PARP trapping that can cross the blood-brain barrier and has shown synergistic cytotoxicity with TMZ in nonclinical experiments. In Phase 1 studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity; single-agent RP2D was defined as 60 mg PO BID.

Methods This dose-escalation/expansion study (NCT03150810) is enrolling pts using a modified 3+3 design to establish the safety and MTD of pamiparib plus TMZ. During dose escalation, pts receive pamiparib 60 mg PO BID plus escalating doses of TMZ QD on Days 1–7 (*Arm A*) or continuously (*Arm B*) for each 28-day cycle. The primary endpoint is safety/tolerability, including estimation of MTD and RP2D. Key secondary endpoints are PK profiles of TMZ and pamiparib and antitumor activity (RECIST v1.1) of combination treatment; biomarker (eg, *gBRCA*) assessment is exploratory.

Results As of 16 Feb 2018, 16 pts (*Arm A*, n=4, 40 mg TMZ; n=4, 80 mg TMZ; n=3, 120 mg TMZ; *Arm B*, n=4, 20 mg TMZ; n=1, 40 mg TMZ) with a median age of 69.5 yr (range 50–85) have enrolled; 8 remain on treatment. Prostate and small cell lung cancers (n=4 each) were the most common tumors; most pts (n=14) had received ≥3 prior treatments. Most common pamiparib-related AEs were nausea (n=6), and nausea and thrombocytopenia (n=5 each) for TMZ. In *Arm A,* 2 pts at 120 mg TMZ reported a DLT of grade 4 neutropenia >7 days. Neutropenia and thrombocytopenia (n=4 each) were the only ≥grade 3 AEs occurring in >2 pts. No AE led to treatment discontinuation or death. Plasma exposure for pamiparib and TMZ were consistent with single-agent trials. One pt with peritoneal cancer in *Arm A* had a 99.5% decrease in CA125 by wk 12. In the 7 pts with ≥1 post-baseline tumor assessment, 2 pts in *Arm A* (kidney, n=1; SCLC, n=1) achieved unconfirmed PRs.

Conclusions In pts with solid tumors, pamiparib 60 mg PO BID combined with pulsed or continuous flat dosed TMZ showed preliminary antitumor activity and was generally well tolerated with the expected toxicity of bone marrow suppression.