Phase 1b/2 study to assess the clinical effects of pamiparib (BGB-290) in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with newly diagnosed or recurrent/refractory glioblastoma (GBM)

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DNA damage caused by TMZ or RT sensitizes tumors to PARP inhibitors, especially in highly replicating tumors (eg, GBM). 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. At 60mg BID, the human-equivalent dose-to-trough brain concentrations above the nonclinical efficacy threshold, pamiparib was generally well tolerated and showed antitumor activity in early clinical studies (NCT02361723; NCT03333915). This ongoing dose-escalation/expansion study (NCT03150862) will determine the safety/tolerability and antitumor effects of pamiparib (60mg BID)+RT and/or TMZ. The dose-escalation component consists of three arms. *Arm A* will establish tolerable duration of pamiparib (2, 4, 6 weeks)+RT in newly diagnosed GBM patients with unmethylated *MGMT* promoter (unmethyl-GBM). In *Arm B,* newly diagnosed patients with unmethyl-GBM will receive pamiparib+RT with increasing TMZ doses. Enrollment in *Arm B* will commence once RP2D for pamiparib+RT is established. In *Arm C*, patients with recurrent/refractory methylated- or unmethyl-GBM receive pamiparib with increasing TMZ doses. As of 28 March 2018, 15 patients were enrolled (*A:* 2-wk, n=3; 4-wk, n=6; *C:* TMZ [40mg], n=6). One DLT (grade 3 nausea) was reported in *Arm C.* Across arms, pamiparib-related AEs occurring in >3 patients were nausea (n=6) and fatigue (n=5). Two patients experienced three pamiparib-related AEs ≥grade 3 (diarrhea [*A:* 4-wk, n=1]; fatigue and nausea [*C*: n=1]). All three resolved with concomitant medication and treatment interruption (*A*) or discontinuation (*C*). Of the seven patients with ≥1 tumor assessment, one (*A:* 4-wk) achieved an unconfirmed PR; four (*A:* 2-wk, n=2; 4-wk, n=2) had SD, and two *(A:* 2-wk, n=1; *C:* n=1) had PD. Preliminary data suggests pamiparib at 60mg BID is generally well tolerated by patients when administered 4 weeks concurrently with RT for newly diagnosed unmethyl-GBM and when combined with 40 mg TMZ for recurrent/refractory GBM.