TITLE: A Phase 1b Study of the anti-PD-1 Monoclonal Antibody BGB-A317 (A317) in combination with the PARP inhibitor BGB-290 (290) in Advanced Solid Tumors.

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Background: The release of tumor-associated antigens may enhance the response to immunotherapy. BGB-A317, a humanized IgG4 variant monoclonal antibody engineered to have no Fc gamma receptor binding, targets the programmed cell death-1 (PD-1) receptor. It is being developed in solid and hematologic malignancies at a dose of 200 mg IV Q3W. BGB-290, a potent inhibitor of PARP 1/2, is hypothesized to promote neoantigen release that will potentially increase the efficacy of BGB-A317. A phase 1 study identified 60mg BID as the recommended Phase 2 dose (RP2D) for BGB-290. This study consists of initial dose escalation to determine the maximum-tolerated dose (MTD), safety, PK profile, and preliminary anti-tumor activity of the combination, followed by expansion into ovarian, breast, prostate, gastric, bladder, pancreatic and small cell lung cancers. **Methods:** Cohorts of 6 -12 pts with advanced solid tumors were treated in each of 5 planned dose levels (DLs). In DLs 1-3, BGB-290 doses ranged between 20-60mg PO BID with BGB-A317 2mg/kg IV Q3W. In DLs 4 - 5, BGB-290 doses were 40 or 60 mg BID; A317 was given at 200 mg IV Q3W based on PK data from a single agent Phase 1 study. **Results:** As of 16 Jan 2017, 38 pts [median age 59 years (34-75)] were treated in DLs 1-4; enrollment to DL5 is ongoing. One DLT of persistent Gr 2 nausea was reported in DL 4. The most common adverse event (AE) considered related to both study drugs was fatigue (10.5%). Immune-related AEs were Gr 3 hypophysitis (n=1), Gr 3 or 4 autoimmune hepatitis(n=2), and Gr 2 elevated AST/ALT (n=1). Decreases in tumor burden have been observed in 16 pts; 7 achieved a PR (5 with ovarian and one each with uterine and pancreatic cancer) and one CR was observed in ovarian cancer. Six pts had SD for > 6 months including 2 pts with pancreatic cancer who received BGB-A317+BGB-290 for 189 and 281 days. Plasma/serum exposure of BGB-290 and BGB-A317 were consistent with those in single-agent trials. **Conclusions:** BGB290 and BGB-A317 can be combined. Dose expansion in multiple tumor types is planned to commence in 2017 once the RP2D is determined. NCT02660034