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.

Michael Friedlander, Tarek Meniawy, Ben Markman, Linda R. Mileshkin, Paul Harnett, Michael Millward, Joanne Lundy, Alison E. Freimund, Christie Norris, John Wu, Virginia Paton, Lai Wang, Bo Gao; The Prince of Wales Hospital, Randwick, Australia; Linear Clinical Research and Sir Charles Gairdner Hospital, University of Western Australia, Nedlands, Australia; Monash Cancer Centre, Clayton, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; Westmead Hospital, Paramatta, Australia; BeiGene Ltd, Fort Lee, NJ; BeiGene Ltd, Oakland, CA; BeiGene Ltd, Beijing, China

Abstract Text:

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 60 mg 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, pharmacokinetic (PK) profile, and preliminary antitumor activity of the combination, followed by expansion into ovarian, breast, prostate, gastric, bladder, pancreatic and small cell lung cancers. **Methods:** Cohorts of 6–12 patients with advanced solid tumors were treated in each of 5 planned dose levels (DLs). In DLs 1–3, BGB-290 doses ranged between 20–60 mg PO BID with BGB-A317 2 mg/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 31 March 2017, 43 patients [median age 63 years (34–75)] were treated in DLs 1–5. Three patients experienced four dose-limiting toxicities: grade 2 nausea (DL4), grade 2 nausea and grade 2 vomiting (DL5), and grade 4 autoimmune hepatitis (DL5). MTD was identified as BGB-A317 200 mg IV Q3W + BGB-290 40 mg PO BID. The most common adverse event (AE) considered related to both study drugs was fatigue. Immune-related AEs of Grade ≥3 were elevated alanine aminotransferase/aspartate aminotransferase (n = 3), autoimmune hepatitis (n = 3), and hepatitis (n = 1). Complete or partial response was observed in 11 patients, 4 of whom had confirmed PR or CR. Plasma/serum exposure of BGB-290 and BGB-A317 were consistent with those in single-agent trials. **Conclusions:** The combination of BGB-A317 and BGB-290 was generally well tolerated in patients with advanced solid tumors. These results support the continuation of this trial with continued enrollment into the disease-specific cohorts. NCT02660034