Phase 1/2 Study Investigating Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination With Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients With Advanced Solid Tumors

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Background: PD-1 and its ligand, PD-L1, play critical roles in immune modulation of tumor progression. Tislelizumab is a humanized IgG4 monoclonal antibody against PD-1. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors at the recommended phase 2 dose (RP2D) of 200 mg administered every 3 weeks (Q3W). BGB-A333 is a humanized IgG1 monoclonal antibody against PD-L1 that increased functional activities of human T cells in *in vitro* studies, and showed antitumor activity in various cancer xenograft models. BGB-A333 blocks the interaction between PD-L1 and CD80 (B7-1), which in turn releases inhibitory signals to T cells, enhances T-cell expansion, and prevents T-cell anergy induction. Therefore, the combination of anti-PD-1 and anti-PD-L1 can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments.

Trial design: This open-label study (NCT03379259) consists of two phases, each phase consisting of two parts. Phase 1 will investigate the safety and tolerability of the BGB-A333 alone and in combination with tislelizumab. Phase 1A (BGB-A333 dose escalation) will follow a 3+3 design to establish the RP2D of BGB-A333. Phase 1B (combination dose confirmation) explores the safety and tolerability of IV BGB-A333 (dose determined from dose escalation) in combination with IV tislelizumab (200 mg Q3W). Phase 2 will evaluate the antitumor activity of BGB-A333 alone and in combination with tislelizumab. Phase 2A (BGB-A333 dose expansion) has two cohorts: non-small cell lung cancer and urothelial carcinoma. Phase 2B (combination dose expansion) will enroll patients with specific tumor types, which will be chosen based on data from phase 2A and other studies. The primary endpoint of the phase 2 study is overall response rate. A total of 156 patients are estimated to be enrolled; as of 11 April 2018, 9 patients have been enrolled.