PHASE 1/2 STUDY INVESTIGATING THE 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

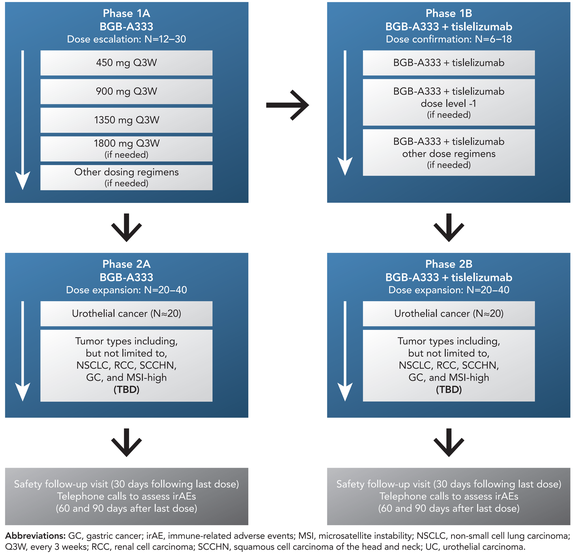
- Programmed cell death receptor-1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), play critical roles in the immune modulation of tumor progression[1,2]
  - PD-L1 induces key inhibitory signaling in the T cells and other immune cells when it engages with its receptor, PD-1. The PD-L1/PD-1 signaling cascade negatively regulates T-cell receptor activation and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion[1,2]
  - PD-1 is markedly increased on tumor-infiltrating lymphocytes and PD-L1 is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines[1,2]
- 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 dose of 200 mg administered every 3 weeks (Q3W)[3]
- 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 the inhibitory signals to T cells, enhances T-cell expansion, and prevents T-cell anergy induction
- A combination of anti-PD-1 and anti-PD-L1 can therefore potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments

METHODS

Overall Design and Study Objectives

- This open-label study (NCT03379259) will consist of two phases, each phase having two parts (Figure 1)
- Phase 1
  - Phase 1A (BGB-A333 dose escalation) will enroll patients with solid tumors and will follow a modified 3+3 design to evaluate approximately 3–5 dose levels of BGB-A333
  - Phase 1B (combination dose confirmation) will enroll a cohort of approximately 6 patients with solid tumors who will be treated with BGB-A333 and tislelizumab (200 mg, Q3W, IV)
  - The primary objectives will be to assess the safety and tolerability, and to determine the MTD, if any, and RP2D of BGB-A333 alone and in combination with tislelizumab, in patients with advanced solid tumors
  - Secondary objectives will be to assess the preliminary antitumor activity, characterize the pharmacokinetics, and assess the immunogenicity of BGB-A333 alone and in combination with tislelizumab
- Phase 2
  - Phase 2A (BGB-A333 dose expansion) will enroll approximately 20 patients with urothelial carcinoma, with the potential to add more cohorts of patients with other tumor types
  - Phase 2B (combination dose expansion) will enroll approximately 20 patients with urothelial carcinoma, with the potential to add more cohorts of patients with other tumor types
  - The primary objective of phase 2 will be to assess the objective response rate (ORR), per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, of BGB-A333 alone and in combination with tislelizumab
  - Secondary objectives will be to assess other tumor assessment outcomes, such as duration of response (DoR), progression-free survival (PFS), and disease control rate (DCR), per RECIST V1.1, along with the safety, tolerability, and pharmacokinetics of BGB-A333 alone and in combination with tislelizumab; the immunogenicity to BGB-A333 and tislelizumab will also be assessed

Figure 1: Study Design



Abbreviations: GC, gastric cancer; irAE, immune-related adverse events; MSI, microsatellite instability; NSCLC, non-small cell lung carcinoma; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

Patients

- Adult patients, aged ≥18 years, will be eligible for the study if they have:
  - For phase 1 only: patients with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors who have progressed during or after standard therapy or for which treatment is not available, not tolerated, or refused
  - For phase 2 only:
    - Arm 1: Patients with locally advanced and metastatic urothelial carcinoma who have progressed during or after treatment with platinum-based chemotherapy or who could not tolerate platinum-based chemotherapy
    - Other tumor types, including but not limited to, non-small cell lung carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, gastric cancer, and microsatellite-high cancer may be considered. The eligibility criteria for patients with these tumor types will be defined in future protocol amendments
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- All patients must have at least one measurable lesion as defined per RECIST v1.1
- Patients will be excluded if they have:
  - Active brain or leptomeningeal metastasis
  - Any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 14 days before study treatment
  - Known history of HIV infection, hepatitis B virus or hepatitis C virus infection (except for patients with hepatocellular carcinoma who must also meet Child-Pugh A classification)
  - Cardiac chest pain episode of syncope, uncontrolled hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg despite anti-hypertension medications), or symptomatic pulmonary embolism within 28 days before study drug administration; or history of acute myocardial infarction, heart failure meeting New York Heart Association Classification III or IV, ventricular arrhythmia event grade 2 or higher, or history of cerebrovascular accident, all within 6 months before administration of the study drug

TREATMENT

- Phase 1A (BGB-A333 dose escalation): BGB-A333 monotherapy at approximately 3–5 dose levels (450 mg Q3W to 1350 mg Q3W or higher if needed) will be evaluated in patients with solid tumors using a modified 3+3 design for dose escalation
- Phase 1B (combination dose confirmation): IV BGB-A333 (dose determined based on dose escalation from phase 1A) will be administered in combination with IV tislelizumab 200 mg Q3W. If the initial dose of BGB-A333 is not tolerated, additional cohorts may be enrolled to evaluate lower doses or alternative dosing regimens
- Phase 2A (BGB-A333 dose expansion): IV BGB-A333 monotherapy at RP2D determined in phase 1A
- Phase 2B (combination dose expansion): IV BGB-A333 (dose determined in phase 1B) will be administered in combination with IV tislelizumab 200 mg Q3W
- Patients will receive treatment until they are no longer achieving clinical benefit, or until unacceptable toxicity or withdrawal of consent

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Phase 1
  - The primary endpoints in phase 1 will be the safety and tolerability of BGB-A333 alone and in combination with tislelizumab assessed through AE monitoring throughout the study, and through physical examination, electrocardiograms, and laboratory assessments as needed. Establishing the MTD (defined as the highest dose at which less than 33% of the patients experience a dose-limiting toxicity) and the RP2D for BGB-A333 alone, and in combination with tislelizumab, is also a co-primary endpoint
  - Secondary endpoints will be ORR, DoR, and DCR as determined by the investigators based on RECIST v1.1; pharmacokinetics for individual BGB-A333 and tislelizumab concentrations tabulated by dose cohort; and immunogenic responses to each treatment summarizing the number and percentage of patients by dose cohort who develop detectable antidrug antibodies
- Phase 2
  - The primary endpoint in phase 2 will be ORR as assessed by investigators based on RECIST v1.1
  - Secondary endpoints will be DoR, PFS, and DCR as determined by investigators based on RECIST v1.1; safety and tolerability of BGB-A333 alone and in combination with tislelizumab assessed using AE monitoring, physical examination, electrocardiograms, and laboratory assessments; pharmacokinetics for individual BGB-A333 and tislelizumab concentrations; and immunogenic responses (as assessed in phase 1)
- Tumor response will be assessed by the investigators using RECIST v1.1
- Radiological assessment of tumor response status will be performed approximately every 9 weeks in the first year, and every 12 weeks thereafter
- Descriptive statistics will be used to summarize efficacy and safety data, with no testing of statistical hypotheses

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