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

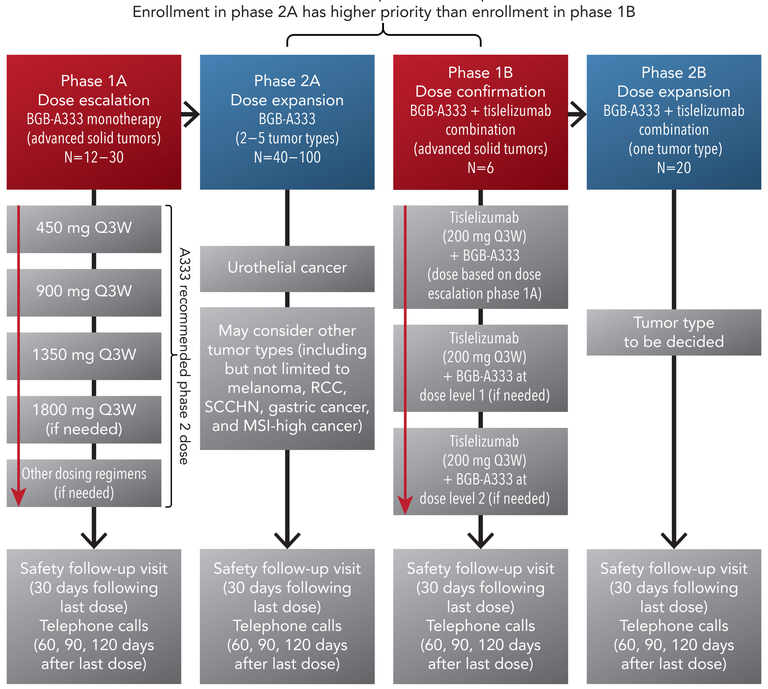
- Programmed cell death receptor-1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), play critical roles in the immune modulation of tumor progression[1,2]
  - PD-L1 induces key inhibitory signaling in the T cells and other immune cells when it engages with its receptor, PD-1. The PD-L1/PD-1 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 energy 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 3+3 design to establish the recommended phase 2 dose of BGB-A333 (primary objective)
  - Phase 1B (combination dose confirmation) will explore the safety and tolerability of intravenous (IV) BGB-A333 in combination with IV tislelizumab (primary objective) in approximately six patients with solid tumors
  - Secondary objectives will be to assess the preliminary antitumor activity, characterize the pharmacokinetics, and assess 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 three more cohorts of patients with other tumor types
  - Phase 2B (combination dose expansion) will enroll approximately 20 patients with specific tumor types; patients will be chosen based on data from phase 2A and other studies
  - 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
  - Approximately 156 patients will be enrolled globally

Figure 1: Study Design



Abbreviations: MSI, microsatellite instability-high; Q3W, once every 3 week; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head.

Patients

- Adult patients, aged ≥18 years, will be eligible for the study if:
  - Histologically or cytologically confirmed unresectable advanced or metastatic disease that is resistant to standard therapy, or for which treatment is not available, not tolerated, or refused
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Additional inclusion criteria for phase 2 are as follows:
  - Patients with urothelial cancer must have progressed after platinum-based chemotherapy
  - All patients must have at least one measurable lesion as defined per RECIST v1.1
- Patients will be excluded if:
  - 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)
  - Cardiac chest pain 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 3+3 design for dose escalation. At least six evaluable patients will be enrolled in the maximum tolerated dose (MTD) or highest dose level if MTD is not reached
- 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 recommended phase 2 dose (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, unacceptable toxicity, or withdrawal of consent
- In phase 1A, patients with progressive disease and no safety concerns may be treated with a higher dose of BGB-A333; in phase 1A and 2A, patients with progressive disease while on BGB-A333 monotherapy may receive combination therapy with BGB-A333 and tislelizumab
- No other dose modifications for BGB-A333, and no dose modifications for tislelizumab, will be permitted during the study. Two treatment delays because of treatment-related adverse events (AEs) will be allowed

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Phase 1
  - The primary endpoints in phase 1 will be 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 recommended phase 2 dose for BGB-A333 alone and in combination with tislelizumab is also a co-primary endpoint
    - Dose-limiting toxicities will be assessed among evaluable patients within 21 days after the first dose of BGB-A333, and these will be used in dose-escalation decisions; dose-limiting toxicities within 21 days and clinically significant toxicities will be considered when determining the MTD and the recommended phase 2 dose
  - 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)
- 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

REFERENCES

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