BGB-A425, AN INVESTIGATIONAL ANTI-TIM-3 MONOCLONAL ANTIBODY, IN COMBINATION WITH TISLELIZUMAB, AN ANTI-PD-1 MONOCLONAL ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS: A PHASE 1/2 TRIAL IN PROGRESS

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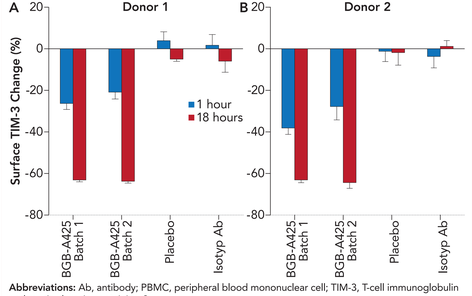
BACKGROUND

- While immune surveillance plays a critical role in preventing tumor proliferation and metastasis, tumors are still able to develop resistance mechanisms to suppress and/or escape the immune system[1,2]
- T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and programmed cell death protein-1 (PD-1) function as immune checkpoint receptors on tumor-infiltrating lymphocytes[2,3]
  - TIM-3, a type I transmembrane glycoprotein receptor, plays an important role in promoting T-cell exhaustion and tumor escape from immune surveillance[4-6]
- Overlap in both expression and function suggests TIM-3 and PD-1 cooperate to maximize effector T-cell exhaustion, leading to a decreased antitumor immune response[7]
- Blocking antibodies targeting the PD-1/programmed death-ligand 1 pathway have achieved remarkable results in the treatment of many different tumor types; however, based upon the rates of resistance, it is apparent that additional immunoregulatory mechanisms underlie tumor immune escape[8]
- BGB-A425, an investigational IgG1-variant monoclonal antibody against TIM-3, binds TIM-3 with high specificity and affinity, competitively blocking the binding of the TIM-3 ligand, phosphatidylserine (PtdSer) while concomitantly inducing TIM-3 internalization (**Figure 1**)
  - Antibody-induced receptor endocytosis leads to down-modulation of receptors on the cell surface and inhibition of receptor-dependent signaling
  - By inducing TIM-3 internalization, BGB-A425 potentially reduces multiple TIM-3:ligand interactions

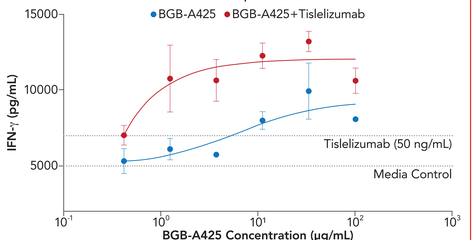
Figure 1: BGB-A425–Induced Internalization of TIM-3 Receptor in IL-2–Stimulated PBMCs From Two Healthy Donors



Abbreviations: Ab, antibody; PBMC, peripheral blood mononuclear cell; TIM-3, T-cell immunoglobulin and mucin-domain containing-3.

- While TIM-3 blockade by itself is unlikely to result in an efficacious antitumor immune response, a combined TIM-3/PD-1 blockade may enhance the antitumor properties of anti-PD-1 therapies
- Tislelizumab is a clinical stage monoclonal antibody with high affinity and specificity for PD-1[9]
  - Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[9]
- In vitro evidence demonstrated that combining BGB-A425 with tislelizumab significantly increased IFN-γ production compared with BGB-A425 or tislelizumab alone (**Figure 2**), suggesting the combined blockade of TIM-3 and PD-1 can mitigate effector cell exhaustion following activation and chronic antigen stimulation

Figure 2: Combined Blockade of TIM-3 and PD-1 With BGB-A425 and Tislelizumab Enhances IFN-γ Secretion



Abbreviations: PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3.

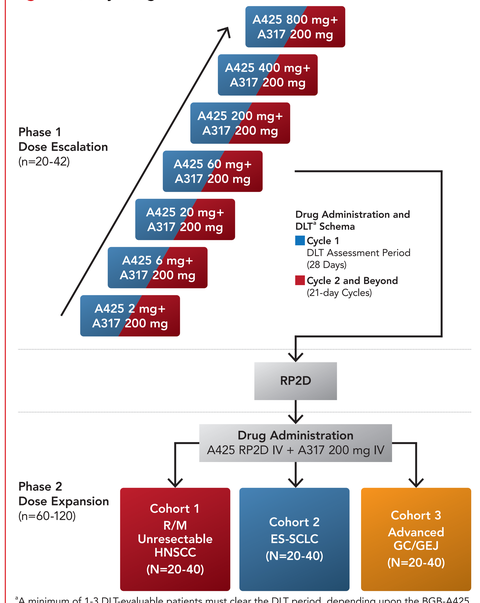
- As such, there is a strong scientific rationale for clinically evaluating BGB-A425 with tislelizumab, as this combination may enhance the antitumor properties of tislelizumab

METHODS

Overall Design and Study Objectives

- This ongoing open-label dose-escalation/dose-expansion study (NCT03744468) was designed to assess the safety/tolerability, pharmacokinetic profile, and antitumor activity of BGB-A425 in combination with tislelizumab in patients with histologically/cytologically confirmed advanced or metastatic, unresectable solid tumors (**Figure 3**)
  - In phase 1 (dose-escalation), up to 42 patients from Australia and the United States will be enrolled into sequential cohorts of increasing doses of intravenous (IV) BGB-A425 in combination with tislelizumab 200 mg IV, based on a 3+3 study design
  - Dose escalation will proceed if no dose-limiting toxicity (DLT) is observed in ≥3 evaluable patients; if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level and the associated dose-finding decisions will proceed per 3+3 design rules (**Table 1**)
  - In phase 2 (dose-expansion), up to 120 patients from Asia, Australia, and the United States will be enrolled into separate disease cohorts based on a two-stage design for each cohort

Figure 3: Study Design



*A minimum of 1-3 DLT-evaluable patients must clear the DLT period, depending upon the BGB-A425 dose level, to dose escalate.

Abbreviations: A317, BGB-A317 (tislelizumab); A425, BGB-A425; DLT, dose-limiting toxicity; ES-SCLC, extensive-stage small-cell lung cancer; GC/GEJ, gastric or gastroesophageal junction cancer; HNSCC, head and neck squamous cell cancer; IV, intravenous; R/M, recurrent and metastatic; RP2D, recommended phase 2 dose.

Table 1: 3+3 Dose-Escalation Design Rules

Dose Escalation Continues	Dose Escalation Ceases	MTD Defined
First cycle DLT rate <33%	First cycle DLT rate ≥33%	Highest dose at which <33% of the patients experience a DLT
	A minimum of six patients will be enrolled to the dose level if the DLT rate=33% (eg, n=1/3) or the next lower dose level if the rate is >33% (n=2/3; n=3/3)	

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

- Primary objectives of phase 1 are to assess the safety and tolerability of BGB-A425 in combination with tislelizumab in patients with advanced solid tumors, and to determine the maximum tolerated dose or maximum administered dose and recommended phase 2 dose (RP2D) of BGB-A425 in combination with tislelizumab; the primary objective of phase 2 is to assess the antitumor activity of the combination of BGB-A425 and tislelizumab in patients with selected tumor types
- Secondary objectives include the further evaluation of antitumor activity, progression-free survival, characterization of the safety/tolerability and pharmacokinetic profiles of combination therapy, and assessment of BGB-A425 host immunogenicity in combination with tislelizumab

Study Population

- Adult patients (according to local regulations) with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors are eligible; all patients must also have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 and adequate organ function
  - Phase 1: patients with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors, who previously received standard systemic therapy or treatment wasn't available, not tolerated, or refused will be enrolled
  - Phase 2: patients with specific tumor types, histologically or cytologically confirmed, advanced or metastatic setting, who have progressed on the most recent line of treatment and have ≥1 measurable lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) will be enrolled
- Key exclusion criteria include:
  - Active leptomeningeal disease or uncontrolled, untreated brain metastasis
  - Active autoimmune diseases or history of autoimmune diseases that may relapse
  - Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy; and prior TIM-3 targeting therapies

Treatment

Dose-Escalation Phase

- During phase 1, BGB-A425 at fixed dose levels of 2, 6, 20, 60, 200, 400, and 800 mg, in combination with tislelizumab 200 mg, will be administered by IV every 21 days (ie, once every 3 weeks), until a discontinuation criterion (ie, disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision) is met
  - Lower, intermediate, and/or higher (eg, up to 1600 mg) dose(s), and/or alternative dosing schedule(s) of BGB-A425 may be evaluated

Dose-Expansion Phase

- During phase 2, BGB-A425 RP2D plus tislelizumab 200 mg will be administered sequentially starting on Cycle 1 Day 1 and every 21 days thereafter, until the patient experiences disease progression, unacceptable toxicity, or voluntary withdrawal

Study Assessments and Statistical Analysis

Assessment of Safety/Tolerability, Including DLTs

- Safety/tolerability will be assessed by the incidence and severity of adverse events (AEs), according to the National Cancer Institute Common Terminology Criteria for AEs v5.0 criteria, physical examinations, vital signs, electrocardiograms, ECOG scores, and laboratory test results up to 30 days after the last dose of study drug
  - Safety and tolerability will be assessed in the safety analysis set, which will consist of all subjects who receive ≥1 dose of the assigned study drug
  - The incidence of DLT events and AEs will be summarized

Assessment of Antitumor Activity

- Tumor assessments will occur at baseline, every 6 weeks for the first year, then every 12 weeks until disease progression, consent withdrawal, death, or study termination, whichever occurs first
- Antitumor activity (eg, objective response rate, disease control rate, duration of response) will be based on RECIST v1.1 criteria per investigator assessment; progression-free survival will be estimated using the Kaplan-Meier method

Pharmacokinetic Assessments

- The pharmacokinetic profile will be assessed in all patients who received at least one dose of study drug and have at least one derivable pharmacokinetic parameter
- Standard pharmacokinetic parameters (AUC, C_{max}, T_{max}) will be derived by noncompartmental analyses and summarized with descriptive statistics

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