PRELIMINARY SAFETY AND EFFICACY DATA OF BGB-A333, AN ANTI-PD-L1 MONOCLONAL ANTIBODY, ALONE AND IN COMBINATION WITH TISLELIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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BACKGROUND

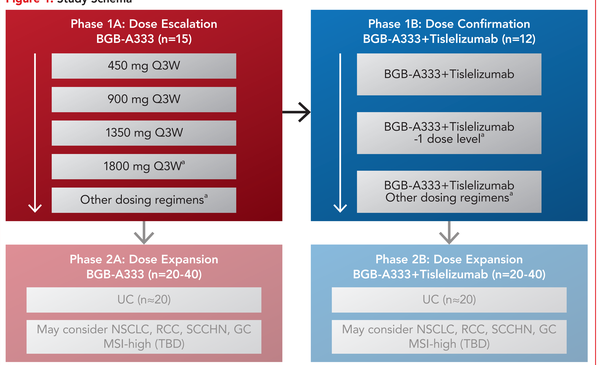
- Programmed cell death protein-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), play critical roles in the immune modulation of tumor progression[1,2]
  - Although both pathways have overlapping elements, each has a distinct mechanism of action
- Clinical trials are currently exploring if simultaneous blockade of both the PD-1 and PD-L1 pathway will result in synergistic antitumor effects[3]
- BGB-A333 is an investigational humanized IgG1 monoclonal antibody against PD-L1 that has antitumor activity in xenograft models[4]
  - 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
- Tislelizumab is a clinical-stage humanized monoclonal antibody with high affinity and specificity for PD-1 that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[5,6]
- Tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and has demonstrated evidence of antitumor activity in previous reports of patients with solid tumors[7-10]
  - The recommended dose of tislelizumab has been established as 200 mg administered intravenously (IV) every 3 weeks (Q3W)
- Here we report preliminary results from phase 1 of an open-label phase 1/2 study (NCT03379259) of BGB-A333 alone and in combination with tislelizumab in patients with advanced solid tumors

METHODS

Overall Design and Study Objectives

- The overall design of this open-label, nonrandomized phase 1/2 study (NCT03379259) is detailed in Figure 1
- Phase 1 of this study consisted of two parts:
  - In *Part A* (dose escalation), patients received single-agent BGB-A333 IV Q3W at increasing doses (450, 900, 1350, and 1800 mg)
  - In *Part B* (dose confirmation), patients received BGB-A333 1350 mg IV in combination with tislelizumab 200 mg IV Q3W

Figure 1: Study Schema



[a]If needed.
Abbreviations: GC, gastric cancer; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TBD, to be determined; UC, urothelial carcinoma.

Key Eligibility Criteria for Phase 1

- The study population consisted of adult patients (per local regulations) with histologically or cytologically confirmed advanced or metastatic cancer who progressed during or after standard therapy or for which treatment was not available, not tolerated, or refused
- All patients had at least one measurable lesion as defined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1
- Key exclusion criteria included active leptomeningeal disease or uncontrolled brain metastases; active autoimmune diseases or history of autoimmune diseases that may relapse; and severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy

Study Endpoints and Assessments

- The primary endpoint of phase 1 was to establish the safety/tolerability profile of BGB-A333 alone and in combination with tislelizumab, including determining the maximum tolerated dose (MTD), if any, and the recommended phase 2 dose (RP2D)
  - Adverse events (AEs) and serious AEs were monitored throughout the study per the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.03
  - The MTD and RP2D were determined by a safety monitoring committee (SMC) after an assessment of dose-limiting toxicities (DLTs) and any clinically significant toxicities
- Secondary endpoints included investigator-assessed antitumor activity per RECIST v1.1 and the pharmacokinetic (PK) parameters of each antibody by dose cohort

RESULTS

- As of March 10, 2020, 15 patients were enrolled in phase 1A (450 mg, n=3; 900 mg, n=3; 1350 mg, n=6; 1800 mg, n=3) and 12 in phase 1B; 10 patients in phase 1A and eight in phase 1B discontinued from the study
  - Five patients in phase 1A and four patients in phase 1B remained on study
  - Median treatment follow-up was 3.5 months (range: 1.5, 20.8) in phase 1A and 3.6 months (range: 0.3, 17.5) in phase 1B
- Demographics, baseline characteristics, and study drug exposure are shown in Table 1
- Thirteen patients (48%) had ≥2 lines of prior systemic therapy

Table 1: Demographics, Baseline Characteristics, and Study Drug Exposure

		Single Agent BGB-A333					Combination Therapy
		Phase 1A BGB-A333 450 mg (n=3)	Phase 1A BGB-A333 900 mg (n=3)	Phase 1A BGB-A333 1350 mg (n=6)	Phase 1A BGB-A333 1800 mg (n=3)	Phase 1A All Doses (n=15)	Phase 1B BGB-A333 1350 mg + Tislelizumab 200 mg (n=12)
Median age, years (range)		58 (48, 62)	63 (48, 70)	66 (30, 67)	66 (39, 69)	63 (30, 70)	72 (48, 76)
Sex, n (%)	Male	1 (33.3)	1 (33.3)	2 (33.3)	1 (33.3)	5 (33.3)	5 (41.7)
	Female	2 (66.7)	2 (66.7)	4 (66.7)	2 (66.7)	10 (66.7)	7 (58.3)
ECOG status, n (%)	0	3 (100.0)	1 (33.3)	2 (33.3)	3 (100.0)	9 (60.0)	6 (50.0)
	1	0	2 (66.7)	4 (66.7)	0	6 (40.0)	6 (50.0)
Type of solid tumor	Squamous cell carcinoma	1 (33.3)	1 (33.3)	1 (16.7)	0	3 (20.0)	2 (16.7)
	Ovarian cancer	1 (33.3)	1 (33.3)	1 (16.7)	0	3 (20.0)	1 (8.3)
	Cervical cancer	1 (33.3)	0	1 (16.7)	0	2 (13.3)	1 (8.3)
	Breast cancer	0	0	0	1 (33.3)	1 (6.7)	2 (16.7)
	Sarcoma	0	1 (33.3)	1 (16.7)	0	2 (13.3)	0
	Gastric cancer	0	0	0	1 (33.3)	1 (6.7)	0
	Esophageal cancer	0	0	0	1 (33.3)	1 (6.7)	0
	Bladder cancer	0	0	1 (16.7)	0	1 (6.7)	0
	Gall bladder cancer	0	0	1 (16.7)	0	1 (6.7)	0
	Prostate cancer	0	0	0	0	0	1 (8.3)
	Small cell lung cancer	0	0	0	0	0	1 (8.3)
	Pancreatic cancer	0	0	0	0	0	1 (8.3)
	Colorectal cancer	0	0	0	0	0	1 (8.3)
	Neuro-endocrine cancer	0	0	0	0	0	1 (8.3)
	Thymoma	0	0	0	0	0	1 (8.3)
Number of prior systemic therapies, n (%)	1	0	1 (33.3)	3 (50.0)	2 (66.7)	6 (40.0)	4 (33.3)
	2	2 (66.7)	1 (33.3)	1 (16.7)	0	4 (26.7)	4 (33.3)
	≥3	1 (33.3)	0	2 (33.3)	1 (33.3)	4 (26.7)	1 (8.3)
Median duration of treatment, months (range)		2.83 (2.8, 5.5)	3.45 (2.1, 12.8)	5.08 (1.7, 18.6)	2.86 (1.4, 20.8)	3.45 (1.4, 20.8)	3.84 (0.7, 17.5)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Safety and Tolerability

- A review of clinically relevant safety data from phase 1A by the SMC established 1350 mg as the RP2D for BGB-A333
- One patient in phase 1B experienced multiple DLT events of acute kidney injury
  - The first event began as a moderate (grade 2) AE that recovered and resolved with sequelae and was considered at least possibly related to treatment
  - A second event (grade 3) occurred the following day; study drug was withdrawn and the event resolved with sequelae
  - Two additional events occurred after treatment withdrawal, ultimately resulting in a fatal event 2 months after treatment discontinuation
- Across the 27 patients enrolled in phase 1, 24 experienced ≥1 AE (Table 2)

Table 2: Summary of Treatment-Emergent Adverse Events

	Single Agent BGB-A333					Combination Therapy
	Phase 1A BGB-A333 450 mg (n=3)	Phase 1A BGB-A333 900 mg (n=3)	Phase 1A BGB-A333 1350 mg (n=6)	Phase 1A BGB-A333 1800 mg (n=3)	Phase 1A All Doses (n=15)	Phase 1B BGB-A333 1350 mg + Tislelizumab 200 mg (n=12)
Any TEAE	1 (33.3)	2 (66.7)	6 (100.0)	3 (100.0)	12 (80.0)	12 (100.0)
TEAE of grade ≥3	0	1 (33.3)	3 (50.0)	1 (33.3)	5 (33.3)	7 (58.3)
Serious TEAE	0	1 (33.3)	3 (50.0)	1 (33.3)	5 (33.3)	5 (41.7)
TEAE leading to death	0	0	0	0	0	1 (8.3)
TEAE leading to permanent discontinuation	0	0	0	0	0	3 (25.0)
TEAE leading to dose modification[a]	0	1 (33.3)	3 (50.0)	2 (66.7)	6 (40.0)	1 (8.3)
Any TRAE	1 (33.3)	1 (33.3)	4 (66.7)	2 (66.7)	8 (53.3)	7 (58.3)[b]
TRAE of grade ≥3	0	1 (33.3)	1 (16.7)	0	2 (13.3)	3 (25.0)[b]
Serious TRAE	0	0	0	0	0	2 (16.7)[c]
TRAE leading to death	0	0	0	0	0	1 (8.3)[b]
Immune-related AE	0	1 (33.3)	2 (33.3)	0	3 (20.0)	3 (25.0)
Immune-related AE of grade ≥3	0	1 (33.3)	1 (16.7)	0	2 (13.3)	2 (16.7)
DLT	0	0	0	0	0	1 (8.3)

[a]All dose modifications were dose holds/interruptions; no dose reductions were needed.
[b]Six patients in phase 1B had AEs considered related to BGB-A333 and seven patients had AEs related to tislelizumab; all TRAEs of grade ≥3, serious TRAEs, and TRAEs leading to death were attributed to both BGB-A333 and tislelizumab in phase 1B.
Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- The most common TEAEs in phase 1A and 1B are shown in Table 3
  - The majority of AEs were mild to moderate in severity
- Serious TEAEs occurred in 10 patients (phase 1A, n=5; phase 1B, n=5) regardless of attribution; no serious AE occurred in more than one patient in either arm
- In phase 1A, three patients experienced four immune-related TEAEs (irAEs; grade 3 lichenification, grade 3 maculo-papular rash, grade 2 pneumonitis, grade 1 generalized rash)
- In phase 1B, three patients experienced five irAEs (grade 5 acute kidney injury, grade 4 immune-mediated hepatitis, grade 3 maculo-papular rash, grade 1 diarrhea, and grade 1 fatigue)

Table 3: Treatment-Emergent Adverse Events Occurring in ≥2 Patients Across Any Dose Cohort

	Single Agent BGB-A333								Combination Therapy	
	Phase 1A BGB-A333 450 mg (n=3)		Phase 1A BGB-A333 900 mg (n=3)		Phase 1A BGB-A333 1350 mg (n=6)		Phase 1A BGB-A333 1800 mg (n=3)		Phase 1B BGB-A333 1350 mg + Tislelizumab 200 mg (n=12)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	1 (33.3)	0	0	0	3(50.0)	0	0	0	4(33.3)	0
Diarrhea	0	0	0	0	1 (16.7)	0	1 (33.3)	0	4(33.3)	0
Fatigue	0	0	1 (33.3)	0	1 (16.7)	0	2 (66.7)	0	2(16.7)	1 (8.3)
Anemia	0	0	1 (33.3)	1 (33.3)	0	0	1 (33.3)	0	3(25.0)	1 (8.3)
Vomiting	0	0	1 (33.3)	0	3 (50.0)	0	0	0	1(8.3)	0
Cough	0	0	1 (33.3)	0	0	0	1 (33.3)	0	3(25.0)	0
Myalgia	0	0	1 (33.3)	0	0	0	2 (66.7)	0	1(8.3)	0
Musculoskeletal chest pain	0	0	0	0	0	0	1 (33.3)	0	2(16.7)	0
Pruritus	0	0	0	0	0	0	1 (33.3)	0	2(16.7)	0
Maculo-papular rash	0	0	1 (33.3)	1 (33.3)	0	0	1 (33.3)	0	2(16.7)	1 (8.3)
Lower respiratory tract infection	0	0	0	0	2 (33.3)	0	0	0	0	0
Pain in extremity	0	0	0	0	0	0	0	0	2(16.7)	0
Perineal pain	0	0	0	0	0	0	0	0	2(16.7)	0

Antitumor Activity

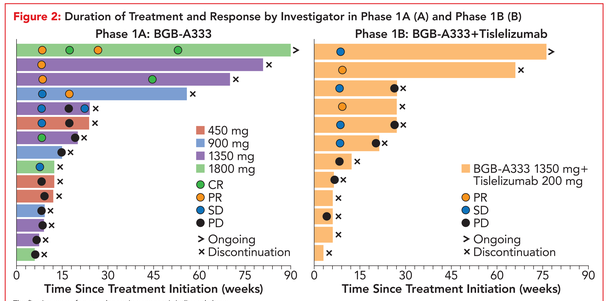
- Clinical response was observed with BGB-A333 both as a single agent and in combination with tislelizumab (Table 4; Figure 2)
- Of the 15 patients receiving BGB-A333 monotherapy in *Part A*, three (20%) achieved a confirmed complete response and two (13.3%) achieved a confirmed partial response
  - Across the escalating doses, objective response rate (ORR) was 33.3% (95% CI: 11.8, 61.6)
- Two of the 12 (16.7%) patients receiving combination therapy in *Part B* achieved a partial response; preliminary ORR with combination therapy was 16.7% (95% CI: 2.1, 48.4)
- Patients receiving BGB-A333 monotherapy had a disease control rate (DCR) of 53.3% and a durable clinical benefit rate (CBR) of 33%; patients receiving combination therapy had similar DCR and durable CBR of 58.3% and 41.7%, respectively

Table 4: Confirmed Best Overall Response

		Single Agent BGB-A333					Combination Therapy
		Phase 1A BGB-A333 450 mg (n=3)	Phase 1A BGB-A333 900 mg (n= 3)	Phase 1A BGB-A333 1350 mg (n=6)	Phase 1A BGB-A333 1800 mg (n=3)	Phase 1A All Doses (n=15)	Phase 1B BGB-A333 1350 mg + Tislelizumab 200 mg (n=12)
Best overall response, n (%)	CR	0	0	2 (33.3)	1 (33.3)	3 (20.0)	0
	PR	0	1 (33.3)	1 (16.7)	0	2 (13.3)	2 (16.7)
	SD	1 (33.3)	0	1 (16.7)	1 (33.3)	3 (20.0)	5 (41.7)
	PD	2 (66.7)	2 (66.7)	2 (33.3)	1 (33.3)	7 (46.7)	3 (25.0)
	NE	0	0	0	0	0	2 (16.7)
ORR, % (95% CI)		0 (0, 70.8)	33.3 (0.84, 90.6)	50.0 (11.8, 88.2)	33.3 (0.84, 90.6)	33.3 (11.8, 61.6)	16.7 (2.1, 48.4)
DCR, % (95% CI)		33.3 (0.84, 90.6)	33.3 (0.84, 90.6)	66.7 (22.3, 95.7)	66.7 (9.4, 99.2)	53.3 (26.6, 78.7)	58.3 (27.7, 84.8)
CBR, % (95% CI)		0 (0, 70.8)	33.3 (0.84, 90.6)	50.0 (11.8, 88.2)	33.3 (0.84, 90.6)	33.3 (11.8, 61.6)	41.7 (15.2, 72.3)

ORR was defined as CR+PR. DCR was defined as CR+PR+SD. CBR was defined as CR+PR+SD >6 months.
Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease.

Figure 2: Duration of Treatment and Response by Investigator in Phase 1A (A) and Phase 1B (B)



The first instance after any change in response is indicated above.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- BGB-A333, alone or in combination with tislelizumab, was generally well tolerated in patients with advanced solid tumors
  - The RP2D for BGB-A333 was estimated as 1350 mg
  - Adverse events reported with BGB-A333 were mostly mild to moderate in severity and consistent with other PD-L1 inhibitors
  - The incidence and frequency of observed AEs (including grade ≥3) were similar between both arms
- Preliminary antitumor activity was observed with BGB-A333 as both a single agent and in combination with tislelizumab
- Coadministration of BGB-A333 with tislelizumab did not have a significant impact on the PK profile of either compound
- Based on these data, the phase 2 expansion cohort has been initiated

- The PK profile of BGB-A333 was comparable to a typical IgG1 antibody and was similar both as a single agent and in combination with tislelizumab (Figure 3; Table 5)
  - BGB-A333 exposures increased in an approximately dose-proportional manner
  - Exposures of BGB-A333 at the 1350-mg dose were comparable between monotherapy (phase 1A) and in combination with tislelizumab (phase 1B)
  - Elimination half-life was not estimated since the 21-day sampling duration was not sufficient for its accurate characterization; however, based on the similarity to projected PK profile, a half-life of approximately 20 days is expected
- Coadministration of BGB-A333 did not impact the PK profile of tislelizumab (n=9; data not shown)

Figure 3: Serum Concentrations of BGB-A333 Over the 21-Day Dosing Period (Log Scale)

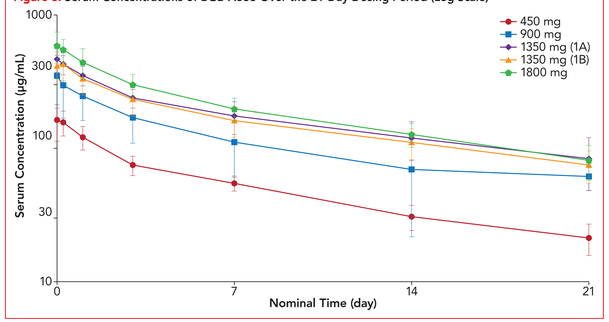


Table 5: Summary of Preliminary Pharmacokinetic Parameters of BGB-A333

	Single Agent BGB-A333					Combination Therapy
	Phase 1A BGB-A333 450 mg (n=3)	Phase 1A BGB-A333 900 mg (n=3)	Phase 1A BGB-A333 1350 mg (n=6)	Phase 1A BGB-A333 1800 mg (n=3)	Phase 1A All Doses (n=15)	Phase 1B BGB-A333 1350 mg + Tislelizumab 200 mg (n=11)[a]
Median T_{max}, day (range)	0.021 (0.021, 0.250)	0.021 (0.021, 0.021)	0.021 (0.021, 0.250)	0.021 (0.021, 0.250)	0.021 (0.021, 0.250)	0.25 (0.021, 0.250)
Mean C_{max}, μg/mL (SD)	167 (42.4)	351 (151)	466 (91.0)	594 (150)	434 (109)	
Mean C_{trough}, μg/mL (SD)	21.3 (5.7)	42.3 (34.5)	84.1 (35.9)	81.4 (23.9)	73[b] (20.7)	
Mean AUC_{0-21}, day × μg/mL	1061 (113)	2248 (1111)	3525 (873)	4064 (763)	3268[b] (878)	

[a]One patient from phase 1B was not evaluable for PK analysis due to missing Cycle 1 PK samples.
[b]Calculation of C_{max} and AUC_{0-21} from phase 1B included seven patients.
Abbreviations: AUC_{0-21}, area under the concentration-time curve from day 0 to day 21; C_{trough}, concentration at last time point; C_{max}, maximal concentration; PK, pharmacokinetic; T_{max}, time to maximal concentration.

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