A First-in-Human, Phase 1a, Dose-Escalation Study of BGB-10188, a Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor, + Tislelizumab (Anti–PD-1) in Patients With Solid Tumors

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Conclusions

In this first-in-human phase 1a study, BGB-10188 + tislelizumab showed preliminary antitumor activity and was generally tolerable across all doses in heavily pretreated patients with solid tumors.

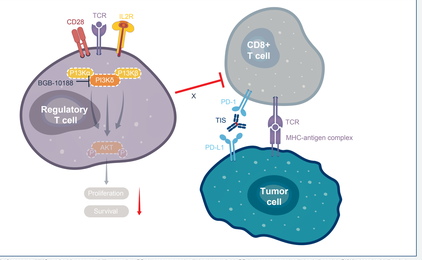
Pharmacokinetic (PK) and pharmacodynamic (PD) data indicate valid target engagement. The PK half-life indicates that BGB-10188 is suitable for once-daily dosing.

BGB-10188 + tislelizumab will be further evaluated in patients with ovarian cancer in dose expansion (Part E).

Background

- The phosphatidylinositol 3-kinase (PI3K) signaling pathway is often hyperactivated in many tumor types; recent studies have suggested that inhibition of the p110δ catalytic subunit of PI3K (PI3Kδ) hampers regulatory T-cell proliferation and function, thereby potentially optimizing CD8+ T-cell activation for antitumor immunity in solid tumors (**Figure 1**)[1,2]
- BGB-10188, a novel PI3Kδ inhibitor, showed high selectivity and potency, and was associated with lower rates of hepatotoxicity compared with the PI3Kδ inhibitor idelalisib in preclinical studies[3]
- In a preclinical colorectal tumor model, antitumor activity and prolonged survival were significantly improved with the combination of BGB-10188 and mouse anti–PD-1 antibody[3]
- Tislelizumab (TIS) is an anti–PD-1 monoclonal antibody (mAb) that blocks the PD-1/PD-L1 immune checkpoint, resulting in T-cell activation.[4]
- Here, we present the results from the dose-escalation portion (Part D) of the first-in-human, phase 1a, open-label, multicenter, 5-part, phase 1/2 study (NCT04282018), assessing BGB-10188 + TIS in patients with solid tumors

Figure 1. Proposed Mechanism of Action of BGB-10188 + TIS[2,5]



IL2R, interleukin-2 receptor; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; PI3K, phosphatidylinositol 3-kinase; TCR, T-cell receptor; TIS, tislelizumab.

Methods

Trial Design

- BGB-A317-3111-10188-101 is an open-label, multicenter, 5-part, phase 1/2, dose escalation and expansion study
  - Part D assessed the safety and antitumor activity of BGB-10188 + TIS in patients with solid tumors (**Figure 2**)

Analysis and Statistical Methods

- The safety and efficacy analysis sets were defined as all patients who received ≥1 medication of BGB-10188 and/or TIS
- Efficacy was assessed by the investigators using RECIST v1.1
- Assessments of safety and tolerability included adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs
  - Adverse events were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 based on Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0
- A Bayesian model-based dose-escalation approach was used for patients enrolled in Australia; patients enrolled in China were then treated with the dose most recently identified as safe by the safety monitoring committee
- PK parameters were determined using a noncompartmental analysis (NCA) method
- Phosphorylated AKT (pAKT) level in B cells from peripheral blood samples were determined and used as a direct PD biomarker for PI3Kδ inhibition

Results

Baseline Characteristics and Patient Disposition

- At the data cutoff date of August 30, 2023 (median [range] follow-up: 4.65 [0.3–17.5] months), 44 patients were treated
  - 43 patients were treated with BGB-10188 + TIS (1 patient received BGB-10188 only and discontinued before receiving TIS)
- Baseline characteristics are shown in **Table 1**
  - The most common tumors enrolled were melanoma, endometrial cancer, esophageal cancer, and gastric or gastroesophageal junction carcinoma
  - 41 (93.2%) patients had discontinued study drug treatment, mainly due to disease progression (32 patients [72.7%]); 3 (6.8%) patients remain on treatment

Table 1. Baseline Characteristics

	BGB-10188 (all doses) + TIS (N=44)[a]
Median (range) age, years	61 (29–82)
Sex, n (%)	
Female	29 (65.9)
Race, n (%)	
Asian	19 (43.2)
White	25 (56.8)
ECOG performance status, n (%)	
0	19 (43.2)
1	25 (56.8)
Metastatic disease at study entry, n (%)	43 (97.7)
Median (range) number of prior lines of therapy	2 (1–11)
Number of prior lines of therapy, n (%)	
1	10 (23.8)
2	13 (31.0)
3	8 (19.0)
4	4 (9.5)
5	2 (4.8)
≥6	5 (11.9)
Reason for discontinuing prior line of therapy, n (%)[b]	
Completion of therapy	5 (11.9)
Progressive disease	30 (71.4)
Toxicity	1 (2.4)
Other	6 (14.3)

Data cutoff: August 30, 2023.
[a]One patient received BGB-10188 only and discontinued before receiving TIS. [b]Percentages are based on the number of patients with any prior therapies (n=42).
ECOG, Eastern Cooperative Oncology Group; TIS, tislelizumab.

Safety and Tolerability

- Overall, BGB-10188 + TIS was generally well tolerated in patients with solid tumors (**Table 2**)
- 36 patients (81.8%) had ≥1 BGB-10188–related TEAE (**Table 3**)
- The proportion of patients who experienced common toxicities associated with PI3Kδ inhibitors, including rash, colitis, and increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST), remains acceptable (**Table 4**); among these, colitis was considered the late-onset toxicity, with median time to onset of 80 days
- Three dose-limiting toxicities for BGB-10188 + TIS were observed: grade 5 pneumonia and intracranial hemorrhage (160 mg), grade 3 ALT/AST increase (320 mg), and grade 3 rash (540 mg)
- Maximum tolerated dose was not reached

Table 2. Overall Safety Summary

	BGB-10188 (all doses) + TIS (N=44)[a]
Patients with any TEAE, n (%)	43 (97.7)
≥Grade 3	24 (54.5)
Serious	19 (43.2)
Leading to death	1 (2.3)
Leading to dose modification	22 (50.0)
Leading to treatment discontinuation	6 (13.6)
Patients with any TRAE (related to either BGB-10188 or TIS), n (%)	37 (84.1)
≥Grade 3	9 (20.5)
Serious	6 (13.6)
Leading to death[b]	1 (2.3)
Leading to dose modification	11 (25.0)
Leading to treatment discontinuation	6 (13.6)
Immune-mediated AE[c]	20 (45.5)[d]

AEs were graded using NCI-CTCAE v5.0 based on MedDRA Version 26.0.
[a]One patient received BGB-10188 only and discontinued before receiving TIS. [b]The patient experienced grade 5 intracranial hemorrhage on Day 20. Insufficient differential diagnosis was conducted for causality assessment, due to the acute onset of the event. [c]Per investigators' discretion. [d]Represents any-grade irAEs. Grade ≥3 irAEs were reported in 8 patients (18.2%).
AE, adverse event; irAE, immune-mediated AE; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

Table 3. Most Common[a] BGB-10188–Related TEAEs

	BGB-10188 (all doses) + TIS (N=44)[b]
	Any grade
Patients with any BGB-10188–related TEAEs, n (%)[c]	36 (81.8)
Nausea	10 (22.7)
Decreased appetite	8 (18.2)
Fatigue	8 (18.2)
ALT increased	6 (13.6)
AST increased	5 (11.4)
Rash	5 (11.4)
Diarrhea	4 (9.1)
Malaise	4 (9.1)
Pruritus	3 (6.8)
Pyrexia	3 (6.8)
Stomatitis	3 (6.8)
Vomiting	3 (6.8)

Safety analysis set. Data cutoff: August 30, 2023. Patients with multiple events for a given preferred term are counted only once for each preferred term.
[a]Occurring in ≥5% of patients. [b]One patient received BGB-10188 only and discontinued before receiving TIS. [c]Six (13.6%) patients experienced grade 3 BGB-10188–related TEAEs: ALT increase (n=2, 4.5%), AST increase (n=2, 4.5%), rash (n=2, 4.5%), abnormal hepatic function (n=1, 2.3%), anemia (n=1, 2.3%), hypoproteinemia (n=1, 2.3%), immune-mediated enterocolitis (n=1, 2.3%), intracranial hemorrhage (n=1, 2.3%), nausea (n=1, 2.3%), pneumonia (n=1, 2.3%). There were no instances of grade 4 BGB-10188–related TEAEs.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TIS, tislelizumab.

Table 4. Summary of Selected AEs[a]

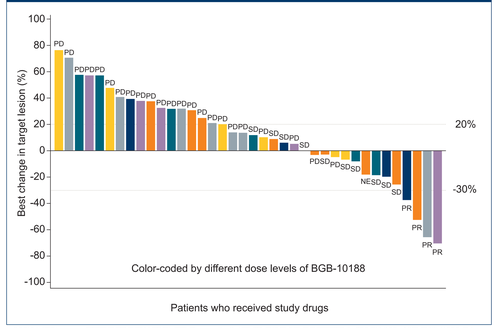
	BGB-10188 (all doses) + TIS (N=44)[b]
AE leading to dose interruption ≥7 days/EOT, n (%)	12 (27.3)
Median (range) time to first onset, days	43.0 (6–234)
Median (range) duration of event, days	31.0 (2–331)
High-grade TEAE ≥7 days, n (%)	6 (13.6)
Median (range) time to first onset, days	84.0 (47–326)
Median (range) duration of event, days	9.0 (8–32)
Rash,[c] n (%)	9 (20.5)
Median (range) time to first onset, days	24.0 (6–71)
Median (range) duration of event, days	86.0 (6–253)
Colitis-diarrhea,[c] n (%)	8 (18.2)
Median (range) time to first onset, days	80.0 (44–178)
Median (range) duration of event, days	11.5 (7–113)
ALT/AST increase,[c] n (%)	9 (20.5)
Median (range) time to first onset, days	43.0 (15–93)
Median (range) duration of event, days	26.0 (5–331)

[a]Includes events related to either BGB-10188 or TIS. [b]One patient received BGB-10188 only and discontinued before receiving TIS. [c]Rash, colitis-diarrhea, and ALT/AST increase are grouped terms based on MedDRA Version 26.0 under each system organ class.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of therapy; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TIS, tislelizumab.

Antitumor Activity

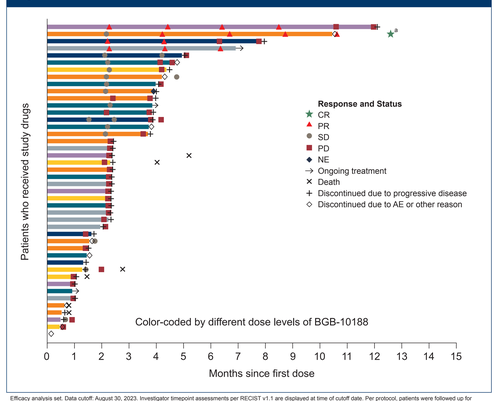
- Preliminary antitumor activity was observed with BGB-10188 + TIS in patients with solid tumors (**Figures 3** and **4**; **Table 5**)
- The duration of response ranged from 4.1 to 8.5 months

Figure 3. Best Percent Change From Baseline in Target Lesion Sum of Diameter



Data cutoff: August 30, 2023. Response categories are determined based on RECIST v1.1 with confirmation using investigator assessment at time of cutoff date. Only patients with data at both baseline and any postbaseline visits were included. Minimum duration for SD was 8 weeks.
NE, not evaluable; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 4. Duration of Treatment and Best Overall Response



Efficacy analysis set. Data cutoff: August 30, 2023. Investigator timepoint assessments per RECIST v1.1 are displayed at time of cutoff date. Per protocol, patients were followed up for disease assessments until PD even after they discontinued study drug treatment, provided that they did not discontinue due to PD.
[a]At time of analysis, 1 patient had unconfirmed CR.
AE, adverse event; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.; SD, stable disease.

Table 5. Antitumor Activity

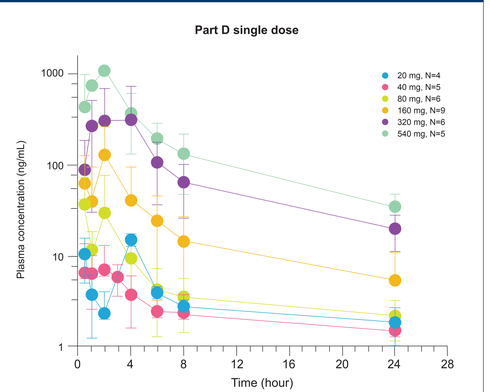
	BGB-10188 (all doses) + TIS (N=44)[a]
Objective response rate, n (%) [95% CI]	4 (9.1) [2.5–21.7]
Best overall response, n (%) [95% CI]	
Complete response	0
Partial response	4 (9.1)[b]
Stable disease	10 (22.7)
Progressive disease	23 (52.3)
Not evaluable/assessed[c]	7 (15.9)
Disease control rate,[d] n (%) [95% CI]	14 (31.8) [18.6–47.6]

Efficacy analysis set. Data cutoff: August 30, 2023. Objective response rate and best overall response per investigator assessment using RECIST v1.1
[a]One patient received BGB-10188 only and discontinued before receiving TIS. [b]Among the patients with PR, there was 1 patient who had unconfirmed CR, but was later verified as PR. [c]Six patients had a best overall response as not assessed (2 patients succumbed to death before first disease assessment and 4 patients discontinued treatment before first disease assessment). One patient had a best overall response of not evaluable due to stable disease with a duration less than 8 weeks and discontinuing treatment. [d]Minimum duration for SD was 8 weeks.
CI, confidence interval; CR, complete response; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIS, tislelizumab.

Pharmacokinetics

- The plasma exposure to BGB-10188 exhibited a dose-dependent increase across a range of 20 to 540 mg (**Figure 5**)
  - The peak concentration (C_{max}) of BGB-10188 typically occurred approximately 2 hours post dose
  - The PK was characterized by two-compartment model with a fast distribution phase followed by an elimination phase, with the mean half-life ($t_{1/2}$) ranging from 8 to 13 hours across all dose levels
  - After repeated dosing, low accumulation of BGB-10188, as indicated by the area under the curve from 0 to 24 hours ($AUC_{0\text{-}24}$), was observed compared to that on Day 1

Figure 5. Single-Dose Pharmacokinetics of BGB-10188

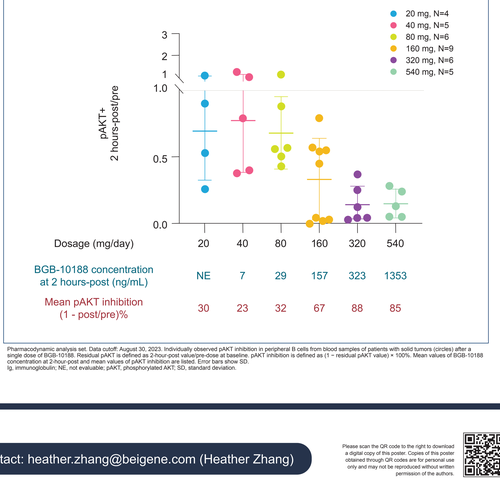


Pharmacokinetic analysis set. Data cutoff: August 30, 2023. Mean plasma BGB-10188 concentration versus time following single-dose administration (Cycle 1 Day 1). Error bars show standard deviation.

Pharmacodynamics

- Peripheral pAKT inhibition exhibited a dose-dependent increase, suggesting valid target engagement of BGB-10188 (**Figure 6**)
- Moderate correlation was observed between PK and pAKT inhibition at single- and repeated dosing
- Single-dose pAKT inhibition indicated a plateau at ~84% (data not shown)

Figure 6. Single-Dose Pharmacodynamics of BGB-10188: Dose-Dependent pAKT Inhibition in Peripheral B Cells



Pharmacodynamic analysis set. Data cutoff: August 30, 2023. Individually observed pAKT inhibition in peripheral B cells from blood samples of patients with solid tumors (circles) after a single dose of BGB-10188. Residual pAKT is defined as 2-hour-post value/pre-dose at baseline. pAKT inhibition is defined as (1 − residual pAKT value) × 100%. Mean values of BGB-10188 concentration at 2-hour post and mean values of pAKT inhibition are listed. Error bars show SD.
Ig, immunoglobulin; NE, not evaluable; pAKT, phosphorylated AKT; SD, standard deviation.

Figure 2. Study Design (Part D)

Key inclusion criteria:
- Age ≥18 years
- ECOG PS 0 or 1
- Histologically confirmed locally advanced or metastatic solid tumors
- ≥1 measurable lesion per RECIST v1.1
- Previously treated with standard systemic therapy or for which effective standard treatment is not available or not tolerated
- No prior exposure to PI3K inhibitors

BGB-10188 20, 40, 80, 160, 320, or 540 mg PO QD + TIS 200 mg IV Q3W[a]

Treatment until disease progression, unacceptable toxicity, death, or withdrawal of consent

Primary objective:
- Safety and tolerability of BGB-10188 + TIS

Secondary endpoints included:
- Investigator-assessed ORR, DoR, and DCR per RECIST v1.1
- PK characteristics of BGB-10188 in combination with TIS

Exploratory endpoint included:
- PD biomarkers (single- and repeated dosing)

[a]Tislelizumab was administered intravenously on Day 8 of the first 28-day cycle and Day 1 of all subsequent 21-day cycles.
DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; ORR, objective response rate; PD, pharmacodynamics; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetics; PO, orally; PS, performance status; QD, once daily; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIS, tislelizumab.

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Presenter disclosure

HZ: Employed by BeiGene and may hold stock or other ownership.

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