First-in-Human, Phase 1 Study of BGB-26808 (Hematopoietic Progenitor Kinase 1 Inhibitor) ± Tislelizumab in Advanced Solid Tumors

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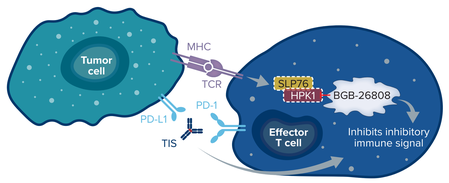
CONCLUSIONS

- BGB-26808 alone or in combination with tislelizumab was generally tolerable and manageable in patients with advanced solid tumors
- BGB-26808 in combination with tislelizumab showed potential antitumor activity in advanced solid tumors
- Further investigation of BGB-26808 in combination with tislelizumab with or without chemotherapy is ongoing in the dose expansion phase

INTRODUCTION

- Hematopoietic progenitor kinase 1 (HPK1) is a hematopoietic cell-restricted serine/threonine protein kinase that acts as a negative feedback regulator of T lymphocyte and dendritic cell activation[1-3]
  - The kinase activity of HPK1 is essential for antitumor immune surveillance[4]
- Preclinical studies have shown that HPK1 blockade can potentially be combined with immune checkpoint inhibitor (CPI) therapy for effective cancer treatment[4,5]
- BGB-26808 has been designed with a different scaffold to BGB-15025, a previously developed HPK1 inhibitor, and other clinical-stage HPK1 inhibitors, allowing high kinome specificity
  - BGB-26808 is a potent and selective HPK1 inhibitor that has demonstrated antitumor effects when used as monotherapy and combined with an anti-programmed cell death protein 1 (PD-1) antibody in preclinical studies[6]
- Tislelizumab is an anti-PD-1 monoclonal antibody that blocks the PD-1/programmed cell death-ligand 1 (PD-L1) immune checkpoint, resulting in T-cell activation
- Here, we present results from the dose-escalation part of a phase 1, open-label, multicenter trial of BGB-26808 with or without tislelizumab in patients with advanced solid tumors (NCT05981703)

Figure 1. Proposed Mechanism of Action of BGB-26808 Plus Tislelizumab



Abbreviations: MHC, major histocompatibility complex; TCR, T-cell receptor; TIS, tislelizumab.

METHODS

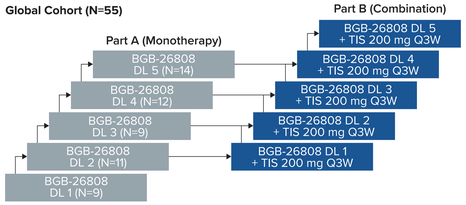
Trial Design

- BGB-A317-26808-101 is a phase 1a/b, open-label, multicenter trial, in which the dose-escalation part is investigating the safety, tolerability, pharmacokinetics (PKs) and preliminary antitumor activity of BGB-26808 monotherapy (Part A) or BGB-26808 + tislelizumab (Part B) in patients with advanced solid tumors (**Figure 2**)

Figure 2. BGB-A317-26808-101 Phase 1a Study Design

Key Eligibility Criteria

- Key eligibility criteria for phase 1a
  - Adults ≥18 years
  - ECOG PS ≤1
  - Histologically/cytologically confirmed advanced, metastatic, and unresectable solid tumors
  - Previously received standard systemic therapy or for whom treatment is not available, not tolerated, or not appropriate based on investigator's judgement
    - Prior HPK1-targeting therapies not permitted
    - Prior CPIs permitted
  - ≥1 measurable lesion per RECIST v1.1



Endpoints

- **Primary:** Safety and tolerability; MTD, MAD, and RDFE
- **Secondary:** ORR, DoR, DCR, and CBR; PKs for BGB-26808
- **Exploratory:** PFS; predictive, prognostic, and/or pharmacodynamic biomarkers; PKs (serum concentration of TIS); host immunogenicity to TIS

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; DL, dose level; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; Q3W, once every 3 weeks; QD, once daily; RDFE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors.

Analysis and Statistical Methods

- The safety analysis set included all patients who received ≥1 dose of study drug(s) and was the analysis set for safety and efficacy analyses
- Safety was assessed by the type, frequency, and severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0) of adverse events (AEs)
- Efficacy was assessed by the investigator per RECIST v1.1
- PK parameters were determined using non-compartmental analysis
- Data from phase 1a were summarized by dose level/schedule and total

RESULTS

Baseline Characteristics and Patient Disposition

- As of the data cutoff date of August 17, 2025, 107 patients were enrolled (55 in Part A and 52 in Part B)
- Median (range) study follow-up time was 4.2 (0.3-17.9) months for Part A and 4.3 (0.5-16.3) months for Part B
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline Characteristics (Safety Analysis Set)

	Part A BGB-26808 monotherapy (N=55)	Part B BGB-26808 + TIS (N=52)
Median (range) age, years	66.0 (30.0-84.0)	62.5 (28.0-80.0)
Sex, n (%)		
Male	35 (63.6)	33 (63.5)
Female	20 (36.4)	19 (36.5)
Race		
Asian	31 (56.4)	16 (30.8)
Black or African American	1 (1.8)	3 (5.8)
Native Hawaiian or Other Pacific Island	1 (1.8)	0 (0)
White	17 (30.9)	29 (55.8)
Other	5 (9.1)	3 (5.8)
Multiple	0 (0)	1 (1.9)
ECOG PS, n (%)		
0	17 (30.9)	18 (34.6)
1	38 (69.1)	34 (65.4)
Patients with prior CPI therapies, n (%)	33 (60.0)	30 (57.7)
Number of prior lines of systemic therapies, n (%)		
1	11 (20.0)	9 (17.3)
2	10 (18.2)	5 (9.6)
3	14 (25.5)	13 (25.0)
4	5 (9.1)	11 (21.2)
5	6 (10.9)	5 (9.6)
≥6	6 (10.9)	6 (11.5)

Safety and Tolerability

- BGB-26808 with or without tislelizumab was generally tolerated (**Table 2**)
  - The most common BGB-26808-related treatment-emergent AEs (TEAEs) are presented in **Table 3**
  - Grade ≥3 treatment-related TEAEs occurred in 21.8% (12/55) of patients in Part A and 21.2% (11/52) of patients in Part B
    - In Part B, 19.2% (10/52) of Grade ≥3 treatment-related TEAEs were BGB-26808 related
  - Treatment-related serious TEAEs occurred in 14.5% (8/55) of patients in Part A and 13.5% (7/52) of patients in Part B
    - In Part B, 11.5% (6/52) of treatment-related serious TEAEs were BGB-26808 related
  - Treatment-related TEAEs leading to treatment discontinuation or death occurred in 11.5% (6/52) and 1.9% (1/52) of patients in Part B, respectively
    - In Part A there were no treatment-related TEAEs leading to treatment discontinuation or death
  - Immune-mediated AEs (imAEs) occurred in 10.9% (6/55) of patients in Part A and 11.5% (6/52) of patients in Part B
    - The most common imAEs were rash and hypothyroidism (3.6%; 2/55 each) in Part A and hypothyroidism (5.8%; 3/52) in Part B
  - Dose-limiting toxicities occurred in two patients in Part A (gastritis in a patient who received BGB-26808 at DL 4 and diarrhea in a patient who received BGB-26808 at DL 5) and two patients in Part B (hepatitis and upper gastrointestinal hemorrhage in a single patient each who received BGB-26808 at DL 4 plus tislelizumab)
  - The MTD for BGB-26808 was DL 4 for Parts A and B

Table 2. Overall Safety Summary (Safety Analysis Set)

	Part A BGB-26808 monotherapy (N=55)	Part B BGB-26808 + TIS (N=52)
Any TEAE, n (%)	53 (96.4)	52 (100.0)
Grade ≥3	22 (40.0)	20 (38.5)
Serious	20 (36.4)	17 (32.7)
Leading to death	1 (1.8)	2 (3.8)
Leading to treatment discontinuation	1 (1.8)	6 (11.5)
Any treatment-related TEAE, n (%)	38 (69.1)	37 (71.2)
Grade ≥3	12 (21.8)	11 (21.2)
Serious	8 (14.5)	7 (13.5)
Leading to death	0 (0)	1 (1.9)[a]
Leading to treatment discontinuation	0 (0)	6 (11.5)
Any imAE, n (%)	6 (10.9)	6 (11.5)
Grade ≥3	0 (0)	2 (3.8)

AEs were graded for severity using NCI-CTCAE v5.0. Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.
[a]The treatment-related TEAE that led to death was upper gastrointestinal hemorrhage; disease progression of advanced intrahepatic cholangiocarcinoma with distant metastasis may have contributed to gastrointestinal bleeding.

Table 3. BGB-26808-related TEAEs in ≥10% of Patients in Part A or Part B (Safety Analysis Set)

	Part A BGB-26808 monotherapy (N=55)	Part B BGB-26808 + TIS (N=52)
Any BGB-26808-related TEAE, n (%)	38 (69.1)	35 (67.3)
Diarrhea	16 (29.1)	9 (17.3)
Platelet count decreased	12 (21.8)	5 (9.6)
Anaemia	12 (21.8)	8 (15.4)
AST increased	11 (20.0)	5 (9.6)
Fatigue	7 (12.7)	9 (17.3)
Nausea	7 (12.7)	6 (11.5)
Vomiting	6 (10.9)	3 (5.8)
Decreased appetite	6 (10.9)	4 (7.7)
Lymphocyte count decreased	4 (7.3)	5 (9.6)
Hypoalbuminemia	6 (10.9)	0 (0)

AEs were classified based on MedDRA v28.0. Patients with multiple events for a given preferred term were counted once at the preferred term level. Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.
Abbreviations: AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.

Antitumor Activity

- There were no responders in Part A; in Part B, unconfirmed ORR (uORR) was 15.4% (95% confidence interval [CI]: 6.9-28.1) (**Table 4**)
  - In Part B, there was 1 complete response (CR) and 7 partial responses (PRs); the CR and 4 of the PRs were confirmed with subsequent tumor assessments
- Best percent change from baseline in target lesion sum of diameters and duration of treatment and overall response are presented in **Figure 3** and **Figure 4**, respectively

Table 4. Efficacy Data (Safety Analysis Set)[a]

	Part A BGB-26808 monotherapy (N=55)	Part B BGB-26808 + TIS (N=52)
uORR, n (% [95% CI[b]])	0 (0.0 [0-6.5])	8 (15.4 [6.9-28.1])
BOR, n (%)		
CR	0 (0)	1 (1.9)
PR	0 (0)	7 (13.5)
SD	21 (38.2)	23 (44.2)
PD	20 (36.4)	17 (32.7)
Not evaluable	14 (25.5)	4 (7.7)
DCR, n (% [95% CI[b]])	21 (38.2 [25.4-52.3])	31 (59.6 [45.1-73.0])
CBR, n (% [95% CI[b]])	3 (5.5 [1.1-15.1])	11 (21.2 [11.1-34.7])
Median DoR, days (95% CI)	-	175.0 (127.0-NE)

[a]All efficacy endpoints are unconfirmed. [b]95% CI was estimated using the Clopper–Pearson method.
Abbreviations: BOR, best overall response; NE, not estimable; PD, progressive disease; SD, stable disease.

Figure 3. Best Percent Change From Baseline in Target Lesion Sum of Diameter for Parts A and B (Safety Analysis Set)

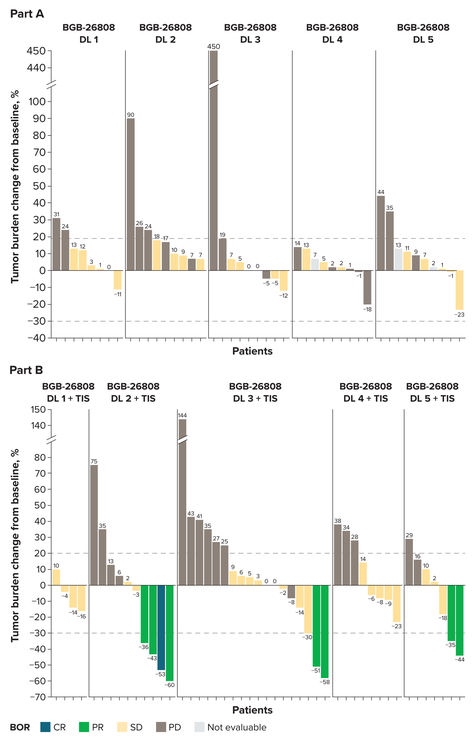
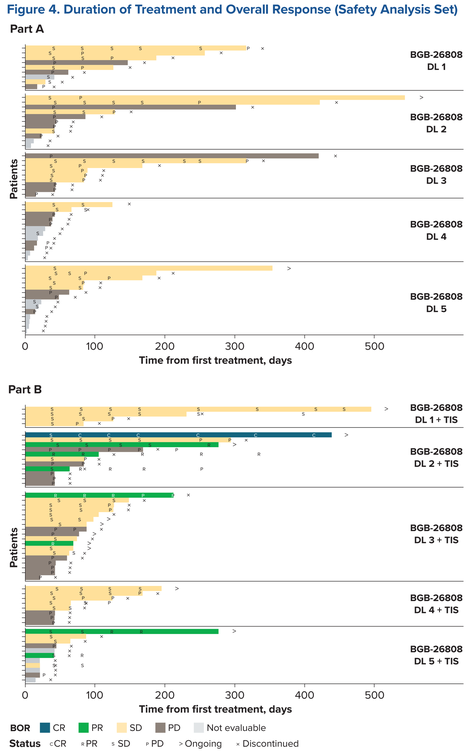


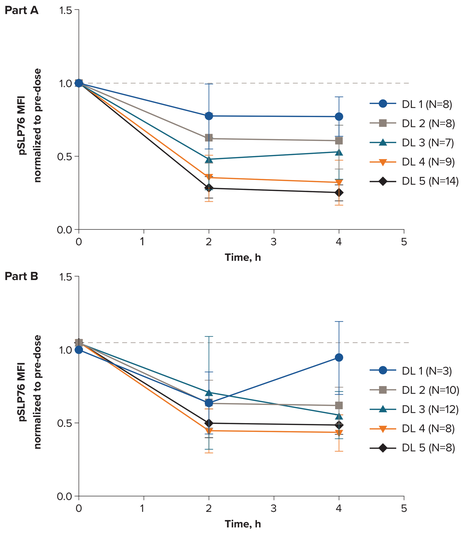
Figure 4. Duration of Treatment and Overall Response (Safety Analysis Set)



Pharmacodynamics

- A trend of dose-dependent inhibition of pSLP76 was observed in Parts A and B
  - Moderate inhibition of pSLP76 (~75%) in peripheral blood was observed with BGB-26808 monotherapy at DL 5 (**Figure 5A**) in CD8+ CD45RA− T cells. ~61% pSLP76 inhibition was observed with BGB-26808 at DL 4 combined with tislelizumab (**Figure 5B**)
    - A similar trend of pSLP76 inhibition was observed for other T-cell subpopulations
- As SLP76 is the direct substrate of HPK1 kinase activity, the decrease of SLP76 phosphorylation indicates the target engagement of HPK1 inhibitor

Figure 5. Target engagement for pSLP76 in CD8+ CD45RA− cells (Safety Analysis Set)

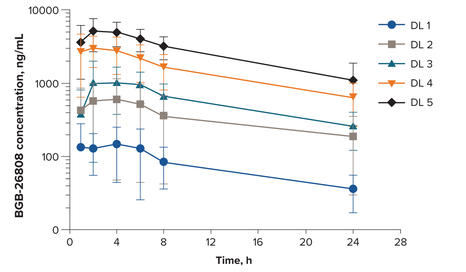


Abbreviations: MFI, mean fluorescence intensity.

PKs

- Plasma exposure to BGB-26808 increased in a dose-dependent manner (**Figure 6**)
- Time to maximum plasma concentration (T_{max}) was reached at a median of 2-4 hours with a mean half-life ($T_{½}$) of 11 hours

Figure 6. BGB-26808 Concentration–Time Profile on Cycle 1 Day 1



REFERENCES

1. Wang Y, et al. *PLoS One*. 2020;15:e0243145.
2. Alzabin S, et al. *J Immunol*. 2009;182:6187-6194.
3. Shui J, et al. *Nat Immunol*. 2007;8:84-91.
4. Liu J, et al. *PLoS One*. 2019;14:e0212670.
5. Hernandez S, et al. *Cell Rep*. 2018;25:80-94.
6. BeOne Medicines, unpublished data.

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