First-in-human, phase 1a, dose escalation study of BGB-B167, a CEA x 4-1BB bispecific antibody, as monotherapy or combined with tislelizumab (anti-PD-1), in patients with selected advanced or metastatic solid tumors

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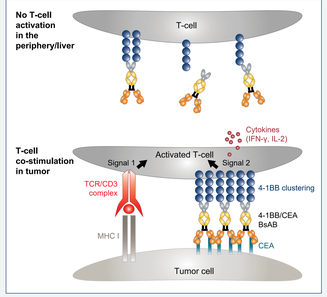
Introduction

- Despite the approval of immune checkpoint inhibitors for the treatment of cancer, these are ineffective in a significant number of patients, and some responders may develop resistance
- 4-1BB is a key T-cell co-stimulatory receptor expressed on activated CD4+/CD8+ T lymphocytes that induces an antitumoral immune response.[1] Carcinoembryonic antigen (CEA) is a tumor-associated antigen overexpressed in many cancers, including colorectal cancer (CRC), gastric cancer (GC), non-small cell lung cancer (NSCLC), pancreatic cancer, hepatocellular carcinoma, breast cancer and thyroid cancer
- BGB-B167 is an immunoglobulin G based bispecific antibody that targets 4-1BB and CEA (**Figure 1**)
  - Preclinical data suggest that BGB-B167 binds to CEA and 4-1BB with high specificity and affinity, enhancing T-cell activation and antitumor activity,[2] with potential for mitigating strong adverse events (AEs) such as cytokine release syndrome and hepatoxicity

Figure 1. Mechanism of action



BsAb, bispecific antibody; IFN-γ, interferon gamma; IL-2, interleukin 2; MHC, major histocompatibility complex; TCR, T-cell receptor

Objective

- Here, we present results from the dose-escalation portion of a first-in-human, phase 1, dose-escalation/expansion, open-label, multicenter trial of BGB-B167 given as monotherapy (Part A) or in combination with tislelizumab (Part B) in patients with selected solid tumors (NCT05494762)

Methods

Trial design

- This first-in-human, phase 1, dose-escalation/expansion, open-label, multicenter trial was conducted in Australia and the United States and consisted of two parts (**Figure 2**)
  - In the dose-escalation portion, increasing doses of intravenous BGB-B167 as monotherapy or combined with tislelizumab were administered to patients with selected advanced or metastatic solid tumors

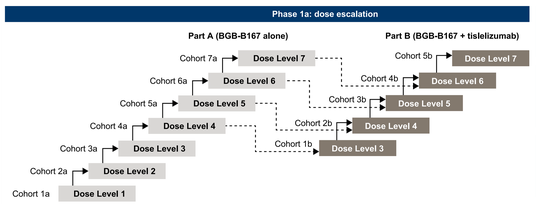
Key eligibility criteria for phase 1a

- Adults ≥18 years of age
- Histologically/cytologically confirmed unresectable locally advanced or metastatic CRC, GC or NSCLC previously treated with standard systemic therapy or for whom treatment is not available, not tolerated, refused or not expected to provide significant clinical benefit or be tolerated per investigator
  - CRC and known microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) status: must have received prior immune checkpoint inhibitors, if available
  - GC or NSCLC: serum CEA ≥5 ng/mL or tumor tissue CEA positive by immunohistochemistry testing
  - Prior therapy targeting immune checkpoints permitted; however, patients must not have received therapies targeting CEA or 4-1BB
- ECOG PS ≤1
- Adequate organ function as assessed during screening or ≤7 days before the first dose of study drug

Analysis and statistical methods

- Dose escalation was guided using the modified toxicity probability interval-2 (mTPI-2) method

Figure 2. Study design



Primary endpoints
- Safety and tolerability
- MTD/MAD and RP2D/RDFE

Secondary endpoints
- Preliminary antitumor activity
- PK/PD
- Host immunogenicity

Exploratory endpoints
- Additional preliminary antitumor activity
- Predictive, prognostic and/or PD biomarkers

All antitumor endpoints were assessed per RECIST v1.1 by investigator.
MAD, maximum administered dose; MTD, maximum tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; RDFE, recommended dose for expansion; RP2D, recommended phase 2 dose; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

Baseline characteristics and patient disposition

- As of the final database lock on September 23, 2024, 54 patients were enrolled (31 in Part A and 23 in Part B), with BGB-B167 dose ranges of 5–1200 mg IV QW assessed in Part A and 50–600 mg IV QW in Part B
  - Median (range) follow-up time was 5.6 (0.7–15.4) months for Part A and 4.3 (1.2–15.2) months for Part B
  - In Part A, 24 (77.4%) patients discontinued treatment and 31 (100%) discontinued from the trial
    - 20 (64.5%) discontinued treatment due to progressive disease and 4 (12.9%) for other reasons
    - 14 (45.2%) discontinued the trial due to death,13 (41.9%) due to study completion per protocol, 3 (9.7%) withdrew themselves and 1 (3.2%) was lost to follow-up
  - In Part B, 23 (100%) patients discontinued treatment and the trial
    - 18 (78.3%) discontinued treatment due to progressive disease, 2 (8.7%) due to physician decision, 1 (4.3%) due to AE, 1 (4.3%) due to drug withdrawal by patient and 1 (4.3%) for other reasons
    - 10 (43.5%) discontinued the trial due to study completion per protocol, 6 (26.1%) due to death, 4 (17.4%) withdrew themselves, 2 (8.7%) were lost to follow-up and 1 (4.3%) for other reasons
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline characteristics (safety analysis set)

	Part A BGB-B167 monotherapy (N=31)	Part B BGB-B167 + tislelizumab (N=23)
Median (range) age, years	59.0 (36–79)	55.0 (37–72)
Sex, n (%)		
Female	10 (32.3)	10 (43.5)
Race, n (%)		
Asian	2 (6.5)	1 (4.3)
Black or African American	0 (0.0)	1 (4.3)
White	25 (80.6)	16 (69.6)
Multiple	1 (3.2)	2 (8.7)
Not reported/unknown	2 (6.5)	2 (8.7)
Other*	1 (3.2)	1 (4.3)
ECOG PS, n (%)		
0	12 (38.7)	9 (39.1)
1	19 (61.3)	14 (60.9)
Cancer type, n (%)		
CRC	29 (93.5)	18 (78.3)
GC	2 (6.5)	3 (13.0)
NSCLC	0 (0)	2 (8.7)
MSI status, n (%)†		
MSS/MSI-L	17 (58.6)	12 (66.7)
MSI-H	1 (3.4)	1 (5.6)
Unknown	11 (37.9)	5 (27.8)
MMR status, n (%)†		
dMMR	1 (3.4)	2 (11.1)
pMMR	23 (79.3)	15 (83.3)
Unknown	5 (17.2)	1 (5.6)
Metastatic disease at study entry, n (%)	31 (100.0)	23 (100.0)
Location of metastases at initial diagnosis of metastatic disease, n (%)		
Adrenal gland	1 (3.2)	1 (4.3)
Bone	2 (6.5)	2 (8.7)
Brain	1 (3.2)	0 (0)
Kidney	2 (6.5)	3 (13.0)
Liver	19 (61.3)	18 (78.3)
Lung	20 (64.5)	14 (60.9)
Lymph nodes	13 (41.9)	12 (52.2)
Peritoneal	6 (19.4)	7 (30.4)
Soft tissue	2 (6.5)	1 (4.3)
Other	9 (29.0)	5 (21.7)
Median (range) time from initial diagnosis of metastatic disease, months	32.3 (5.0–83.5)	36.6 (3.2–129.5)
Patients with any prior systemic therapy, n (%)	30 (96.8)	23 (100.0)
Number of prior lines of therapy, n (%)		
1	5 (16.1)	3 (13.0)
2	5 (16.1)	6 (26.1)
≥3	20 (64.5)	14 (60.9)
Patients with prior anti-PD-1/PD-L1 inhibitors, n (%)	6 (19.4)	8 (34.8)

*'Other' includes races beyond the prespecified options. †For patients with CRC; denominator of 29 for Part A and 18 for Part B.
CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stability; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; pMMR, proficient mismatch repair; PS, performance status.

Safety and tolerability

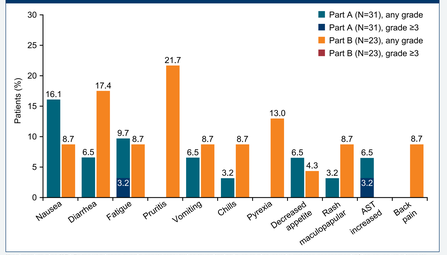
- Overall, BGB-B167 as monotherapy or in combination with tislelizumab was well tolerated, with minor differences observed between dose levels (**Table 2**)
  - The most common treatment-related TEAEs can be seen in **Figure 3**
  - The majority of treatment-related TEAEs were Grade 1 or 2; Grade ≥3 treatment-related TEAEs included anemia, fatigue, increased AST and decreased neutrophil count (each in a single patient in Arm A) and eye swelling and Stevens–Johnson Syndrome (in a single patient in Arm B)
    - Grade ≥3 treatment-related TEAEs resolved without any intervention, or with treatment modification or discontinuation
  - No treatment-related TEAEs were indicative of hepatotoxicity or CRS
- A single DLT of Grade 3 Stevens–Johnson Syndrome occurred in a patient who received BGB-B167 600 mg QW combined with tislelizumab; this patient recovered after treatment discontinuation
- MTD was not reached in either Part A or Part B, and the MAD was 1200 mg QW as monotherapy and 600 mg QW in combination with tislelizumab

Table 2. Overall safety summary (safety analysis set)

	Part A BGB-B167 monotherapy (N=31)	Part B BGB-B167 + tislelizumab (N=23)
Patients with any TEAE, n (%)	31 (100.0)	23 (100.0)
Grade ≥3	12 (38.7)	5 (21.7)
Serious	12 (38.7)	7 (30.4)
Leading to death	4 (12.9)	1 (4.3)
Leading to treatment discontinuation	2 (6.5)	3 (13.0)
Patients with any treatment-related TEAE, n (%)	17 (54.8)	15 (65.2)
Grade ≥3	4 (12.9)	1 (4.3)
Serious	0 (0)	2 (8.7)
Leading to death	0 (0)	0 (0)
Leading to treatment discontinuation	0 (0)	1 (4.3)
Patients with any immune-mediated AEs*	2 (6.5)	6 (26.1)
Patients with IRR	4 (12.9)	6 (26.1)

A TEAE is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug and up to 30 days after the last dose of study drug(s) or the initiation of new anticancer therapy, whichever is earlier. Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.
AEs were classified based on MedDRA v27.0 and were graded for severity using CTCAE v5.0.
*Immune-mediated AEs occurring in more than one patient included rash and rash maculopapular.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Figure 3. Treatment-related TEAEs in ≥5% of patients (safety analysis set)*



Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. AEs were classified based on MedDRA v27.0 and graded for severity using CTCAE v5.0. Patients with multiple events for a given preferred term and multiple preferred terms within a system organ class were counted once at the preferred term and system organ class levels, respectively.
*Occurring in ≥5% of patients in Part A or B.
AE, adverse event; AST, aspartate aminotransferase ;TEAE, treatment-emergent adverse event.

Anti-drug antibodies (ADAs) to BGB-B167

- A total of 43.3% (13/30) of patients in Arm A and 34.8% (8/23) of patients in Arm B had treatment-induced ADAs
  - ADAs were not analyzed for neutralization

Antitumor activity

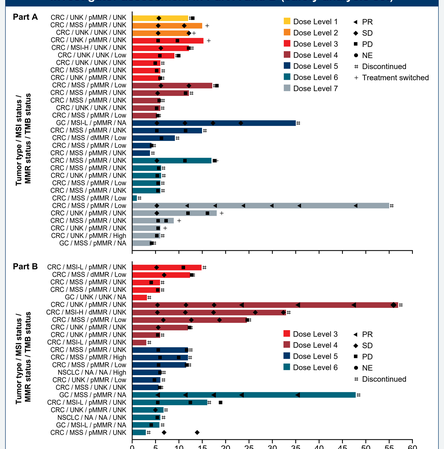
- Confirmed ORR (95% CI) was 3.3% (0.1–17.2%) in Part A and 9.1% (1.1–29.2%) in Part B
  - Three patients (one with CRC in Part A; one with CRC and one with GC in Part B) had confirmed PRs (**Table 3**)
    - The responder in Part A had low tumor mutational burden, metastases in the lung and lymph node, and received prior anti-PD-1/PD-L1 inhibitors
    - MMR status was pMMR for all three responders
    - DoR was 8.3 months for the patient in Part A and 7.5 and 6.9 months for the patients in Part B
      - Treatment duration and overall response by patient can be seen in **Figure 4**

Table 3. Antitumor activity (efficacy evaluable analysis set)

	Part A BGB-B167 monotherapy (N=30)	Part B BGB-B167 + tislelizumab (N=22)
ORR, n (% [95% CI*])	1 (3.3 [0.1, 17.2])	2 (9.1 [1.1, 29.2])
BOR, n (%)		
CR	0 (0)	0 (0)
PR	1 (3.3)	2 (9.1)
SD	9 (30.0)	7 (31.8)
PD	19 (63.3)	12 (54.5)
NE/NA	1 (3.3)	1 (4.5)
CBR, n (%† [95% CI*])	2 (6.7 [0.8, 22.1])	4 (18.2 [5.2, 40.3])
DCR, n (%‡ [95% CI*])	10 (33.3 [17.3, 52.8])	9 (40.9 [20.7, 63.6])

*The 95% CI was estimated using the Clopper–Pearson method. †CBR defined as the proportion of patients who have CR, PR, or durable SD of ≥24 weeks in duration. ‡DCR defined as the proportion of patients who have CR, PR, or SD.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; NA, not assessed; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4. Swimmer plot of treatment duration with overall response per investigator assessment in Part A and B (safety analysis set)

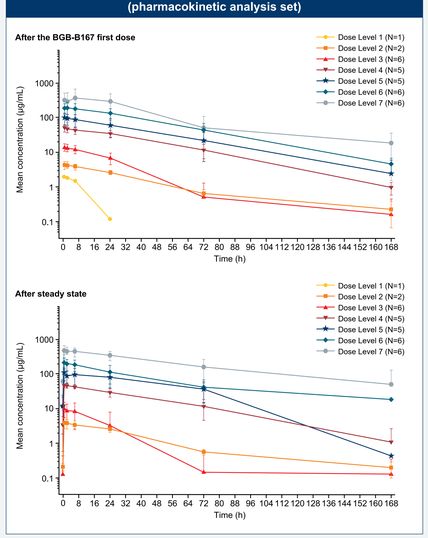


CRC, colorectal cancer; dMMR, deficient mismatch repair; GC, gastric cancer; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stability; NA, not applicable; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; pMMR, proficient mismatch repair; SD, stable disease; TMB, tumor mutation burden; UNK, unknown.

PK

- Serum exposure of BGB-B167 increased dose-dependently from 5 to 1200 mg (**Figure 5**)
- The PK of BGB-B167 exhibited non-linear kinetics with rapid clearance at low doses (likely due to target-mediated drug disposition) and in patients with ADAs
- After a single dose of BGB-B167 at cycle 1, day 1, $t_{1/2}$ was 5.18–41.59 h, CL was 60.24–253.12 mL/h, V_z was 1890.80–4706.97 mL and AUC_{0-tau} was 21.61–13399.58 h × µg/mL
- BGB-B167 PK was comparable whether used as monotherapy or in combination with tislelizumab

Figure 5. Concentration-time profile for BGB-B167 in Part A (pharmacokinetic analysis set)



Conclusions

- In the dose-escalation portion of this trial, BGB-B167 as monotherapy or combined with tislelizumab was well tolerated and demonstrated limited antitumor activity in patients with selected advanced/metastatic CEA+ solid tumors
  - Of the three patients who responded, responses were durable and ongoing at data cutoff for two patients; all responders had pMMR disease
- Serum exposure of BGB-B167 increased dose-dependently from 5 to 1200 mg with a $t_{1/2}$ of less than 2 days; treatment-induced ADAs to BGB-B167 were observed in both Arms A and B

References

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2. Li Z, *et al. Cancer Res.* 2024;84 (6 Suppl): 2371.

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Disclosures

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