A Phase 1 Study of the OX40 Agonist, BGB-A445, With or Without Tislelizumab, an Anti-PD-1 Monoclonal Antibody, in Patients with Advanced NSCLC, HNSCC or NPC

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CONCLUSIONS

- BGB-A445 alone or in combination with tislelizumab and chemotherapy was generally well tolerated in patients with advanced non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and nasopharyngeal carcinoma (NPC), and showed preliminary antitumor activity in patients with NPC

INTRODUCTION

- OX40 is an immune co-stimulatory receptor that is primarily expressed on activated T cells and intratumor regulatory T cells, and to a lesser extent on neutrophils, natural killer cells and natural killer T cells, that plays a role in promoting T-cell survival, proliferation, and proinflammatory cytokine expression in the tumor microenvironment[1-3]
- BGB-A445 is a humanized Immunoglobulin G1 (IgG1), FC-competent monoclonal antibody OX40 agonist that binds at a unique, non-blocking membrane proximal site of OX40 that allows endogenous OX40 receptor and ligand interactions
  - Based on in vitro and in vivo preclinical data, BGB-A445 activates T cells, and depletes intratumor regulatory T cells, which highly express OX40, thereby stimulating antitumor responses[4]
  - Due to the differentiated mechanism of binding and action, BGB-A445 has shown dose-dependent antitumor effects in preclinical models, without the hook effect that has been observed at high antibody concentrations with ligand-competitive anti-OX40 antibodies[4]
- Results from the dose-escalation part of the phase 1, open-label, multicenter, non-randomized, dose-escalation/expansion trial of BGB-A445 in patients with advanced solid tumors have been previously reported (NCT04215978)[5]
  - BGB-A445 alone or in combination with tislelizumab had a favorable safety/tolerability profile with no dose-limiting toxicities and showed promising antitumor activity across the dose range assessed in the dose-escalation phase[5]
- Here, we present results from the dose-expansion phase investigating the effects of BGB-A445 monotherapy or in combination with tislelizumab and chemotherapy in previously treated patients with advanced solid tumors

METHODS

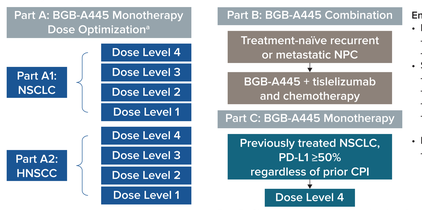
Trial Design

- This dose-expansion part of the phase 1, open-label, multicenter, dose-escalation/expansion trial consisted of multiple parts (**Figure 1**)

Analysis and Statistical Methods

- Data from phase 1b were summarized by each tumor type, unless otherwise specified

Figure 1. Study Design



Part B: Chemotherapy for 4-6 cycles (cisplatin on day 1; gemcitabine on days 1 and 8)

Part C: Local PD-L1 testing is acceptable for enrollment

Key eligibility criteria for phase 1b
- Adults ≥18 years
- Histologically/cytologically confirmed advanced solid tumors
- Prior permitted systemic therapies
  - Parts A1 and C: 1-3 lines prior systemic therapy for advanced/metastatic disease and a platinum-based agent for patients who progressed <6 months following completion of systemic therapy for local disease
  - Part A2: 1-3 lines prior systemic therapy for recurrent/metastatic disease or progressed <6 months following completion of systemic therapy for local disease
  - Part B: Prior neoadjuvant (not exceeding ≤3 cycles) or adjuvant chemotherapy, radiotherapy or chemoradiotherapy for non-metastatic disease must be associated with a treatment-free interval of ≥6 months from the last dose of chemotherapy and/or radiotherapy
- Prior permitted targeted therapy
  - Parts A1, A2, and C: Targeted therapy with locally approved therapy if actionable oncogenic driver mutations identified and prior CPI therapy permitted; prior therapy targeting OX40 or any other T-cell agonist not permitted

[a]Enrollment completed

Abbreviations: CPI, checkpoint inhibitor; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; PD-L1, programmed cell death protein-1; PFS, progression-free survival; RP2D, recommended phase 2 dose.

RESULTS

Baseline Characteristics and Patient Disposition

- As of the data cutoff date of February 26, 2025, 92 patients were enrolled (54 in Part A1, 19 in Part A2, 12 in Part B, and 7 in Part C)
- Median (range) follow-up time was 4.7 (0.2-28.6) months for Part A1, 4.2 (0.7-15.7) months for Part A2, 12.3 (0.9-14.5) months for Part B, and 6.2 (2.9-13.2) months for Part C
- Baseline characteristics are shown in **Table 1**

Antitumor Activity

- No confirmed responses were observed in Parts A1, A2, and C; confirmed overall response rate (ORR) (95% confidence interval [CI]) was 70% (34.8-93.3) in Part B (**Table 2**)
  - In Part B, one out of 10 patients achieved a complete response (CR), and six out of 10 patients achieved partial responses (PR)
- Confirmed disease control rate (DCR) (95% CI) was 49.0% (34.4-63.7), 33.3% (13.3-59.0), 100.0% (69.2-100.0), and 57.1% (18.4-90.1) in Parts A1, A2, B, and C, respectively (**Table 2**)
- Confirmed median duration of response (DoR) (95% CI) for Part B was 11.5 (7.1-not evaluable [NE]) months
- Median progression-free survival (PFS) (95% CI) for Part B was 12.6 (8.2-NE) months

Table 1. Baseline Characteristics (Safety Analysis Set)

	Part A1 NSCLC (N=54)	Part A2 HNSCC (N=19)	Part B NPC (N=12)	Part C NSCLC and PD-L1 ≥50% (N=7)
Median (range) age, years	64.5 (33-87)	56.0 (44-73)	54.5 (26-73)	65.0 (47-70)
Sex, n (%)				
Male	34 (63.0)	15 (78.9)	10 (83.3)	2 (28.6)
Female	20 (37.0)	4 (21.1)	2 (16.7)	5 (71.4)
Race, n (%)				
Asian	44 (81.5)	13 (68.4)	12 (100.0)	6 (85.7)
White	5 (9.3)	4 (21.1)	0 (0)	1 (14.3)
Other	5 (9.3)	2 (10.5)	0 (0)	0 (0.0)
ECOG PS, n (%)				
0	6 (11.1)	3 (15.8)	6 (50.0)	1 (14.3)
1	48 (88.9)	16 (84.2)	6 (50.0)	6 (85.7)
Patients with any prior anti-cancer therapy, n (%)	54 (100.0)	19 (100.0)	8 (66.7)	7 (100.0)
Patients with any prior radiotherapies, n (%)	33 (61.1)	15 (78.9)	8 (66.7)	4 (57.1)
Patients with any prior CPI therapies, n (%)	42 (77.8)	14 (73.7)	1 (8.3)	5 (71.4)
Median (range) number of prior lines of therapy	1 (1-3)	2 (1-3)	1 (1-1)	1 (1-2)
Number of prior lines of therapies, n (%)				
1	32 (59.3)	5 (26.3)	4 (50.0)[a]	5 (71.4)
2	17 (31.5)	12 (63.2)	0 (0)	2 (28.6)
3	5 (9.3)	2 (10.5)	0 (0)	0 (0.0)
Unknown	0 (0)	0 (0)	4 (50.0)[a]	0 (0)

[a]For Part B, the denominator is 8 as this is the number of patients who received any prior anti-cancer therapy.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Efficacy Data (Efficacy Evaluable Analysis Set)

	Part A1 NSCLC (N=49)	Part A2 HNSCC (N=18)	Part B NPC (N=10)	Part C NSCLC and PD-L1 ≥50% (N=7)
ORR, n (% [95% CI[a]])	0 (0.0 [-])	0 (0.0 [-])	7 (70.0 [34.8-93.3])	0 (0.0 [-])
BOR, n (%)				
CR	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
PR	0 (0.0)	0 (0.0)	6 (60.0)	0 (0.0)
SD	24 (49.0)	6 (33.3)	3 (30.0)	4 (57.1)
PD	23 (46.9)	10 (55.6)	0 (0.0)	3 (42.9)
NE/NA	2 (4.1)	2 (11.1)	0 (0.0)	0 (0.0)
DCR, n (% [95% CI[a]])[b]	24 (49.0 [34.4-63.7])	6 (33.3 [13.3-59.0])	10 (100.0 [69.2-100.0])	4 (57.1 [18.4-90.1])

All antitumor endpoints were assessed per RECIST v1.1 by investigator.

[a]95% CI was estimated using the Clopper-Pearson method. [b]DCR defined as the proportion of patients who have CR, PR, or SD.

Abbreviations: BOR, best overall response; NA, not assessable; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Safety and Tolerability

- Overall, BGB-A445 as monotherapy in Parts A1, A2, or C, or combined with tislelizumab and chemotherapy in Part B, was generally well tolerated and toxicities were manageable (**Table 3**)
  - Grade ≥3 treatment-related treatment-emergent adverse events (TEAEs) occurred in 1.9% (1/54) patients in Part A1 and 91.7% (11/12) patients in Part B; most Grade ≥3 treatment-related TEAEs in Part B were related to chemotherapy
  - The most common BGB-A445-related TEAEs are presented in **Tables 4 and 5**
    - Grade ≥3 BGB-A445-related TEAEs were asthenia in Part A1 and neutrophil count decreased and white blood cell count decreased in a single patient in Part B
  - Treatment-related serious TEAEs occurred in 3.7% (2/54) of patients in Part A1 (pyrexia and asthenia in a single patient each) and 8.3% (1/12) of patients in Part B (febrile neutropenia)
  - Treatment-related TEAEs leading to treatment discontinuation occurred in 16.7% (2/12) of patients in Part B; these were related to chemotherapy
  - There were no treatment-related TEAEs leading to death
- Overall, the most common immune-mediated adverse event (imAE) was rash, which occurred in 1.9% (1/54) of patients in Part A1 and 33.3% (4/12) of patients in Part B
  - No grade ≥3 imAEs were reported
- No grade ≥3 infusion-related reactions (IRRs) were reported

Table 3. Overall Safety Summary (Safety Analysis Set)

	Part A1 NSCLC (N=54)	Part A2 HNSCC (N=19)	Part B NPC (N=12)	Part C NSCLC and PD-L1 ≥50% (N=7)
Any TEAE, n (%)	47 (87.0)	16 (84.2)	12 (100.0)	7 (100.0)
Grade ≥3	17 (31.5)	5 (26.3)	11 (91.7)	3 (42.9)
Serious	21 (38.9)	4 (21.1)	3 (25.0)	4 (57.1)
Leading to death	4 (7.4)	2 (10.5)	2 (16.7)	0 (0)
Leading to treatment discontinuation	8 (14.8)	2 (10.5)	3 (25.0)	0 (0)
Any treatment-related TEAE, n (%)	28 (51.9)	7 (36.8)	12 (100.0)	3 (42.9)
Grade ≥3	1 (1.9)	0 (0)	11 (91.7)	0 (0)
Serious	2 (3.7)	0 (0)	1 (8.3)	0 (0)
Leading to death	0 (0)	0 (0)	0 (0)	0 (0)
Leading to treatment discontinuation	0 (0)	0 (0)	2 (16.7)	0 (0)
Any imAE, n (%)	6 (11.1)	1 (5.3)	6 (50.0)	1 (14.3)
IRR, n (%)	6 (11.1)	3 (15.8)	3 (25.0)	1 (14.3)

Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.

AEs were graded for severity using CTCAE v5.0.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. BGB-A445-Related TEAEs Occurring in ≥5% of Patients in Parts A and C (Safety Analysis Set)

	Part A1 NSCLC (N=54)			Part A2 HNSCC (N=19)		Part C NSCLC and PD-L1 ≥50% (N=7)	
	Dose Level 2 (n=11)	Dose Level 3 (n=21)	Dose Level 4 (n=22)	Dose Level 3 (n=10)	Dose Level 4 (n=9)	Dose Level 4 (n=7)	Total (N=80)
Pyrexia	1 (9.1)	4 (19.0)	2 (9.1)	0 (0.0)	1 (11.1)	0 (0.0)	8 (10.0)
Chills	0 (0.0)	1 (4.8)	1 (4.5)	0 (0.0)	2 (22.2)	0 (0.0)	4 (5.0)
Anemia	0 (0.0)	1 (4.8)	0 (0.0)	1 (10.0)	1 (11.1)	1 (14.3)	4 (5.0)

AEs were classified based on MedDRA v26.0.

Patients with multiple events for a given Preferred Term were counted once at the Preferred Term level.

Table 5. BGB-A445-Related TEAEs Occurring in ≥5% of Patients in Part B (Safety Analysis Set)

	Part B NPC (N=12)
	Dose Level 4 (N=12)
Rash	4 (33.3)
Dermatitis allergic	1 (8.3)
Pruritus	1 (8.3)
Rash macular	1 (8.3)
ALT increased	1 (8.3)
Amylase increased	1 (8.3)
AST increased	1 (8.3)
ECG QT prolonged	1 (8.3)
Neutrophil count decreased	1 (8.3)
White blood cell count decreased	1 (8.3)
Fatigue	1 (8.3)
Pyrexia	1 (8.3)
Hypothyroidism	1 (8.3)
Nausea	1 (8.3)
Otitis media	1 (8.3)
Decreased appetite	1 (8.3)

AEs were classified based on MedDRA v26.0.

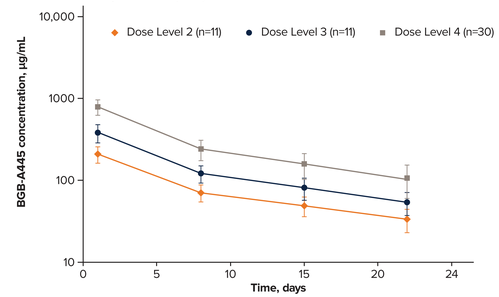
Patients with multiple events for a given Preferred Term were counted once at the Preferred Term level.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram.

Pharmacokinetics (PK)

- BGB-A445 PK (C_{max} and $AUC_{0\text{-}21d}$) were linear and dose proportional in all tested dose ranges in Parts A1 and A2 (**Figure 2**)
- Serum PK observed were within expected concentrations for BGB-A445 in Parts B and C

Figure 2. Concentration-Time Profile for BGB-A445 for Parts A1 and A2 (PK Analysis Set)



Abbreviations: SD, standard deviation.

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DISCLOSURES

MHH reports stock or other ownership in GI Cell and GI Biome; honoraria from AstraZeneca, Merck, Roche, and BeOne Medicines; consulting or advisory roles for AstraZeneca, Merck, Roche, Yuhan, BeOne Medicines, and Daiichi Sankyo/AstraZeneca; and research funding from Yuhan.

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