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

Jayesh Desai FRACP,[1]* Diwakar Davar MD,[2] Sanjeev Deva FRACP,[3] Bo Gao FRACP,[4] Tianshu Liu MD,[5] Marco Matos FRACP,[6] Tarek Meniawy FRACP,[7] Kenneth J O'Byrne FRACP,[8] Meili Sun MD,[9] Mark Voskoboynik FRACP,[10] Kunyu Yang MD,[11] Xinmin Yu MD,[12] Xin Chen PhD,[13] Yan Dong PhD,[14] Hugh Giovinazzo PharmD, PhD,[15] Shiangjiin Leaw MD,[16] Deepa Patel MD,[13] Tahmina Rahman MD,[15] Yanjie Wu MD,[16] Daphne Day FRACP,[17] on behalf of the BGB-A317-A445-101 Clinical Study Team

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [3]Auckland City Hospital, Auckland Cancer Trials Centre Governance Group, and Harbour Cancer & Wellness, Auckland, New Zealand; [4]Blacktown Cancer and Haematology Centre, Blacktown Hospital, Blacktown, NSW, Australia; [5]Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; [6]Pindara Private Hospital, Benowa, QLD; Medical Oncology Group of Australia, Sydney, NSW; Australian Medical Council, Canberra, ACT; Medical Board of Queensland, Brisbane, QLD; Australia; [7]Linear Cancer Research and University of Western Australia, Nedlands, WA, Australia; [8]Princess Alexandra Hospital and Queensland University of Technology, Brisbane, QLD, Australia; [9]Jinan Central Hospital, Shandong University; Central Hospital Affiliated to Shandong First Medical University; Shandong, China; [10]Nucleus Network and Monash University, Melbourne, VIC, Australia; [11]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [12]Zhejiang Cancer Hospital, Hangzhou, China; [13]BeiGene USA, Inc., Ridgefield Park, NJ, USA; [14]BeiGene USA, Inc., Cambridge, MA, USA; [15]BeiGene USA, Inc., San Mateo, CA, USA; [16]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]Department of Medical Oncology, Monash Health, Melbourne, VIC; and Faculty of Medicine, Monash University, Melbourne, VIC, Australia.
*Corresponding author

Poster No: 2574 presented at ASCO, Chicago, IL, June 2023

Conclusions

This ongoing dose-escalation part of a multicenter, phase 1 study (NCT04215978) is investigating BGB-A445 alone or in combination with tislelizumab in patients with advanced solid tumors

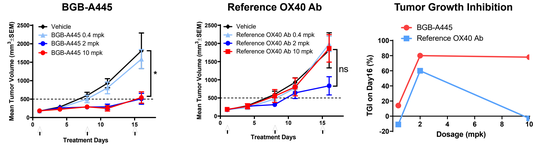
There were no dose limiting toxicities with a favorable safety and tolerability profile and promising antitumor activity at up to 2400 mg as monotherapy and combination therapy

The dose expansion part of this study is ongoing in non-small cell lung cancer and head and neck squamous cell carcinoma; BGB-A445 is also being further evaluated in melanoma, renal cell carcinoma, and urothelial carcinoma

Background

- OX40 is an immune costimulatory receptor, expressed on activated CD4$^+$ and CD8$^+$ T cells, that promotes T-cell proliferation and survival in the tumor microenvironment[1]
- BGB-A445 is a novel monoclonal antibody (mAb) OX40 agonist that does not compete with endogenous OX40 ligand binding[2]
- In preclinical rodent studies, BGB-A445 has demonstrated antitumor activity as a single agent and in combination with an anti–PD-1 mAb[2]
  - In preclinical models, BGB-A445 had dose-dependent antitumor effects, without the hook effects that have been observed at high antibody concentrations with ligand-competitive OX40 antibodies (**Figure 1**)
- This ongoing dose-escalation part of a multicenter, phase 1 study (NCT04215978) is investigating BGB-A445 alone or in combination with tislelizumab in patients with advanced solid tumors

Figure 1. Dose-Dependent BGB-A445 Antitumor Activity in Tumor Model

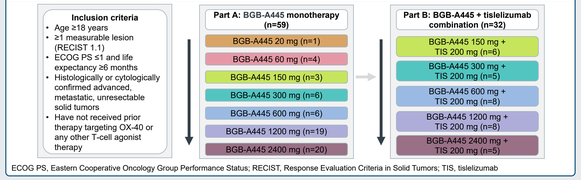


*P< .05. MC38 syngeneic tumor model.
Ab, antibody; mpk, milligrams per kilogram; ns, not significant; SEM, standard error of the mean; TGI, tumor growth inhibition

Methods

- Eligible patients were enrolled into 7 dose-escalation cohorts to receive BGB-A445 intravenous (IV) as monotherapy (Part A) or to receive 5 dose levels of BGB-A445 IV in combination with tislelizumab 200 mg IV (Part B) on day 1 of 21-day cycles (**Figure 2**)
- Dose escalation was guided by a Bayesian modified toxicity probability interval-2 approach
- The primary objective of the dose-escalation phase of the study was to assess safety and tolerability of BGB-A445 by adverse events (AEs) and to determine the maximum tolerated or administered dose
- Secondary objectives included characterizing the BGB-A445 pharmacokinetic (PK) profile and preliminary antitumor activity per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Figure 2. Study Design and Patient Enrollment



ECOG PS, Eastern Cooperative Oncology Group Performance Status; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab

Results

Patients

- As of August 31, 2022, 59 patients were enrolled in Part A and 32 patients were enrolled in Part B
- Baseline demographics were similar between Part A and Part B (**Table 1**)

Table 1. Baseline Characteristics[a]

	Part A BGB-A445 monotherapy (n=59)	Part B combination BGB-A445 + tislelizumab (n=32)
Median age (range), years	59.0 (28-80)	61.0 (37-75)
Female sex, n (%)	33 (55.9)	19 (59.4)
Race, n (%)		
Asian	16 (27.1)	4 (12.5)
White	38 (64.4)	23 (71.9)
Other	5 (8.5)	5 (15.6)[b]
ECOG PS, n (%)		
0	26 (44.1)	15 (46.9)
1	33 (55.9)	16 (50.0)
2	0	1 (3.1)
Median time from initial diagnosis to first dose (range), years	1.9 (0.3-22.2)	2.0 (0.3-5.8)
Median number of prior anti-cancer systemic therapy regimens (range)	2.0 (1.0-7.0)	2.0 (1.0-4.0)

[a] Safety population [b] Other race and unknown race
ECOG PS, Eastern Cooperative Oncology Group performance status

Safety

- Grade ≥3 treatment-emergent AEs (TEAEs) were reported in 24 patients (40.7%) in Part A and 17 patients (53.1%) in Part B, the most common of which were gastrointestinal disorders (eg, diarrhea and abdominal pain)
  - In Part A, no Grade ≥3 TEAE by preferred term occurred in ≥5% of the total group
  - In Part B, there were 4 Grade ≥3 TEAEs reported in ≥5% of the total group (diarrhea, 3 patients [9.4%]; abdominal pain, pleural effusion, and pyrexia in 2 patients [6.3%] each)
  - Grade ≥3 immune-mediated AEs (imAEs) occurred in no patients in Part A and in 1 patient (3.1%; maculopapular rash and diarrhea) in Part B
- Treatment-related AEs leading to treatment discontinuation occurred in 1 patient (1.7%) in Part A (2400 mg group) and no patients in Part B; there were no deaths due to treatment-related TEAEs (TRAEs) in either Part (**Table 2** and **3**)
- There were no dose-limiting toxicities in either part of the study

Table 2. Summary of Adverse Events: Part A BGB-A445 Monotherapy[a]

	BGB-A445 20 mg (n=1)	BGB-A445 60 mg (n=4)	BGB-A445 150 mg (n=3)	BGB-A445 300 mg (n=6)	BGB-A445 600 mg (n=6)	BGB-A445 1200 mg (n=19)	BGB-A445 2400 mg (n=20)	Total (N=59)
No. of patients with ≥1 TEAE	1 (100.0)	4 (100.0)	3 (100.0)	5 (83.3)	5 (83.3)	16 (84.2)	20 (100.0)	54 (91.5)
No. of patients with ≥1 TRAE	0 (0.0)	1 (25.0)	2 (66.7)	3 (50.0)	5 (83.3)	9 (47.4)	14 (70.0)	34 (57.6)
Grade ≥3 TRAEs	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	2 (10.0)	4 (6.8)
Serious TRAEs	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	2 (10.0)	4 (6.8)
TRAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRAEs leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.7)
TRAEs leading to dose modification	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (16.7)	1 (5.3)	5 (25.0)	8 (13.6)
Immune-related TRAEs	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	3 (50.0)	1 (5.3)	6 (30.0)	11 (18.6)
Most common TRAE by PT (≥10% in total group)								
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	2 (10.5)	2 (10.0)	7 (11.9)
Arthralgia	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	4 (20.0)	6 (10.2)

[a] Safety population
PT, preferred term; TEAE, treatment-emergent adverse event; TRAE, treatment-related treatment-emergent adverse event

Table 3. Summary of Adverse Events: Part B Combination BGB-A445 + Tislelizumab[a]

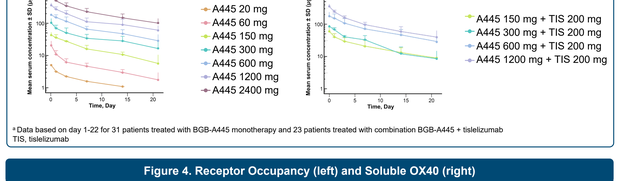
	A445 150 mg + TIS 200 mg (n=6)	A445 300 mg + TIS 200 mg (n=5)	A445 600 mg + TIS 200 mg (n=8)	A445 1200 mg + TIS 200 mg (n=8)	A445 2400 mg + TIS 200 mg (n=5)	Total (N=32)
No. of patients with ≥1 TEAE	6 (100.0)	5 (100.0)	8 (100.0)	8 (100.0)	4 (80.0)	31 (96.9)
No. of patients with ≥1 TRAE	5 (83.3)	3 (60.0)	8 (100.0)	4 (50.0)	2 (40.0)	22 (68.8)
Grade ≥3 TRAEs	1 (16.7)	0 (0.0)	1 (12.5)	1(12.5)	0 (0.0)	3 (9.4)
Serious TRAEs	1 (16.7)	0 (0.0)	1 (12.5)	1(12.5)	1 (20.0)	4 (12.5)
TRAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRAEs leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRAEs leading to dose modification	2 (33.3)	1 (20.0)	2 (25.0)	3 (37.5)	0 (0.0)	8 (25.0)
Immune-related TRAEs	3 (50.0)	3 (60.0)	4 (50.0)	3 (37.5)	1 (20.0)	14 (43.8)
Most common TRAE by PT (≥10% in total group)						
Fatigue	0 (0.0)	2 (40.0)	4 (50.0)	1 (12.5)	0 (0.0)	7 (21.9)
Nausea	1 (16.7)	1 (20.0)	2 (25.0)	2 (25.0)	1 (20.0)	7 (21.9)
Pruritus	0 (0.0)	1 (20.0)	3 (37.5)	1 (12.5)	1 (20.0)	6 (18.8)
Rash macropapular	1 (16.7)	2 (40.0)	2 (25.0)	1 (12.5)	0 (0.0)	6 (18.8)
Hypothyroidism	2 (33.3)	1 (20.0)	1 (12.5)	1 (12.5)	0 (0.0)	5 (15.6)
Pyrexia	2 (33.3)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	4 (12.5)
Diarrhea	2 (33.3)	1 (20.0)	0 (0.0)	1 (12.5)	0 (0.0)	4 (12.5)

[a] Safety population
PT, preferred term; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related treatment-emergent adverse event

Pharmacokinetics and Pharmacodynamics

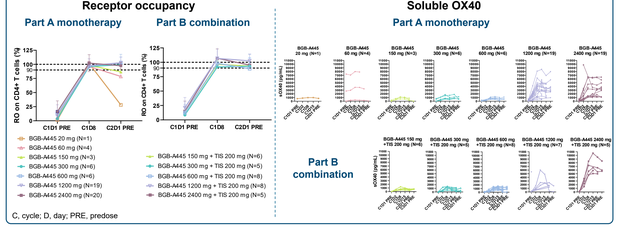
- BGB-A445 exposure was similar as monotherapy and in combination with tislelizumab
- BGB-A445 PK (maximum concentration and area under the curve from days 0 to 21) were linear and dose proportional in all tested dose ranges (**Figure 3**)
- OX40 receptor occupancy was saturated at BGB-A445 ≥300-mg dose levels as monotherapy and in combination with tislelizumab; higher soluble OX40 levels were observed at BGB-A445 ≥1200-mg dose levels as monotherapy and in combination with tislelizumab (**Figure 4**)

Figure 3. Preliminary Cycle 1 Serum PK Profile of BGB-A445 Monotherapy (left) or Combination Therapy (right)[a]



[a] Data based on day 1-22 for 31 patients treated with BGB-A445 monotherapy and 23 patients treated with combination BGB-A445 + tislelizumab
TIS, tislelizumab

Figure 4. Receptor Occupancy (left) and Soluble OX40 (right)

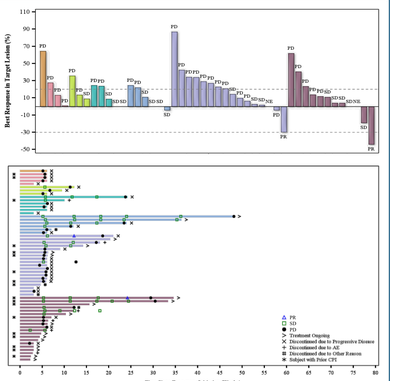


C, cycle; D, day; PRE, predose

Efficacy

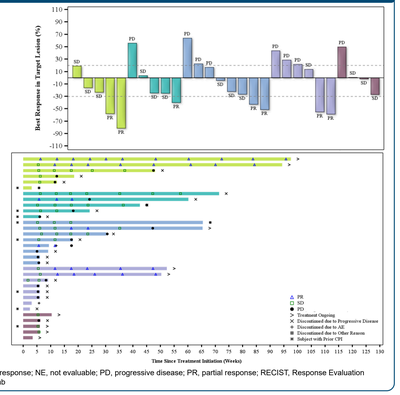
- Of 50 patients in the efficacy-evaluable population of Part A, 2 patients (4.0%) achieved unconfirmed partial response (uterine carcinosarcoma [1200 mg], metastatic lung adenocarcinoma [2400 mg]), 18 patients (36.0%) had stable disease, 26 patients (52.0%) had progressive disease, and 6 patients were not evaluable/assessed (**Figure 5**)
- Of 30 patients in the efficacy-evaluable population of Part B, 7 patients (23.3%) achieved confirmed partial response (colorectal cancer [150 mg], anal cancer [150 mg], cervical cancer [300 mg], bladder cancer [600 mg], urothelial carcinoma of the upper tract [600 mg], NSCLC-nonsquamous [1200 mg], colorectal cancer [1200 mg]), 13 patients (43.3%) had stable disease, 8 patients (26.7%) had progressive disease, and 2 patients were not evaluable/assessed (**Figure 6**)

Figure 5. Response: Part A BGB-A445 Monotherapy



[a] Efficacy-evaluable population [b] Safety population
AE, adverse event; CPI, checkpoint inhibitor; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Figure 6. Response: Part B Combination BGB-A445 Plus Tislelizumab



[a] Efficacy-evaluable population [b] Safety population
AE, adverse event; CPI, checkpoint inhibitor; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TIS, tislelizumab

References

1. Croft M, et al. *Immunol Rev.* 2009;229(1):173-191.
2. Jiang B, et al. *J ImmunoTher of Cancer.* 2020;8;699.

Acknowledgments

The authors wish to thank all BGB-A317-A445-101 study investigators, research staff, and patients. This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Sarah Engelberth, PhD, of Medical Expressions (Chicago), an Inizio company, and was funded by BeiGene, Ltd.

Disclosures

Dr. Desai reports grants, personal fees, and nonfinancial support from BeiGene; grants from Roche/Genentech, Bristol-Myers Squibb, Novartis, and AstraZeneca; grants and personal fees from Amgen; and personal fees and other from Pierre Fabre, outside the submitted work.