A First-in-Human Phase 1a Dose-Escalation Study of BGB-15025 (HPK1 Inhibitor) as Monotherapy and in Combination with Tislelizumab (TIS; Anti-PD-1 Antibody) in Patients with Advanced Solid Tumors

Sanjeev Deva,[1] Wei Li,[2] Sarwan Bishnoi,[3] Peter Lau,[4,5] Ben Tran,[6] Yi Ba,[7] Matthew Galsky,[8] Yongsheng Wang,[9] Yangiao Zhang,[10] Suxia Luo,[11] Victoria Chang,[12] Cunjing Yu,[13] Teresa Zhang,[12] Heather Zhang,[12] Yue Tian,[13] Kirsha Naicker,[14] Timothy A. Yap[15]

[1]Auckland City Hospital, Auckland, New Zealand; [2]Shanghai Pulmonary Hospital, Shanghai, China; [3]Ashford Cancer Centre Research, ICON Cancer Centre, Kurralta Park, SA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Harry Perkins Institute of Medical Research, Nedlands, WA, Australia; [6]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [7]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [8]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [9]West China Hospital, Sichuan University, Chengdu, China; [10]Harbin Medical University Cancer Hospital, Harbin, China; [11]Henan Cancer Hospital, Zhengzhou, China; [12]BeiGene USA, Inc., San Mateo, CA, USA; [13]BeiGene (Beijing) Co., Ltd., Beijing, China; [14]BeiGene UK, Ltd., London, UK; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract: 2585 presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Conclusions

In this first-in-human phase 1a study, BGB-15025 monotherapy and BGB-15025 + tislelizumab were generally tolerable

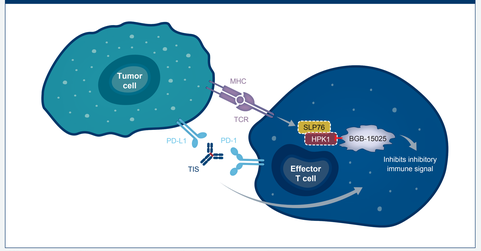
The antitumor activity of BGB-15025 was improved when given in combination with tislelizumab

Further investigation of BGB-15025 + tislelizumab with and without chemotherapy is ongoing in the phase 1b expansion part of this trial, and also in a phase 2 international umbrella study in patients with non-small cell lung cancer (NCT05635708)

Background

- Hematopoietic progenitor kinase 1 (HPK1), a hematopoietic cell-restricted serine/threonine protein kinase, is a critical negative feedback regulator of T cells through phosphorylation of the adaptor protein SH2-domain-containing leukocyte protein of 76 kDa (SLP76) in the T-cell receptor complex[1,2] (**Figure 1**)
- The kinase activity of HPK1 is essential for antitumor immune surveillance; preclinical studies have shown that HPK1 blockade can potentially be combined with immune checkpoint inhibitor (CPI) therapy for effective cancer treatment[3,4]
- BGB-15025 is a novel, selective small-molecule HPK1 inhibitor that has demonstrated potent SLP76 inhibition *in vitro*
- Tislelizumab is a humanized IgG4 anti-programmed cell death protein-1 (PD-1) monoclonal antibody that blocks the PD-1/programmed death-ligand 1 immune checkpoint, resulting in T-cell activation[5] (**Figure 1**)
- Preclinical studies demonstrated preliminary anti-tumor effects of BGB-15025 monotherapy; the anti-tumor activity of BGB-15025 was enhanced when administered in combination with an anti-PD-1 antibody[6]
- We present data from the dose-escalation part of a first-in-human phase 1 trial of BGB-15025 monotherapy and BGB-15025 + tislelizumab in patients with advanced solid tumors

Figure 1. BGB-15025 Proposed Mechanism of Action in Combination with Tislelizumab



BGB-15025, HPK1 inhibitor; HPK1, hematopoietic progenitor kinase 1; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; SLP76, SH2-domain-containing leukocyte protein of 76 kDa; TCR, T-cell receptor; TIS, tislelizumab.

Methods

- BGB-A317-15025-101 (NCT04649385) is a phase 1, non-randomized, open label, multicenter trial investigating the safety, tolerability, PK and preliminary antitumor activity of BGB-15025 monotherapy and BGB-15025 + tislelizumab in patients with advanced solid tumors
- The trial is comprised of phase 1a (dose-escalation) and phase 1b (dose-expansion)
- **Phase 1a** eligibility criteria, treatments, and objectives are summarized in **Figure 2**

Statistical Analyses

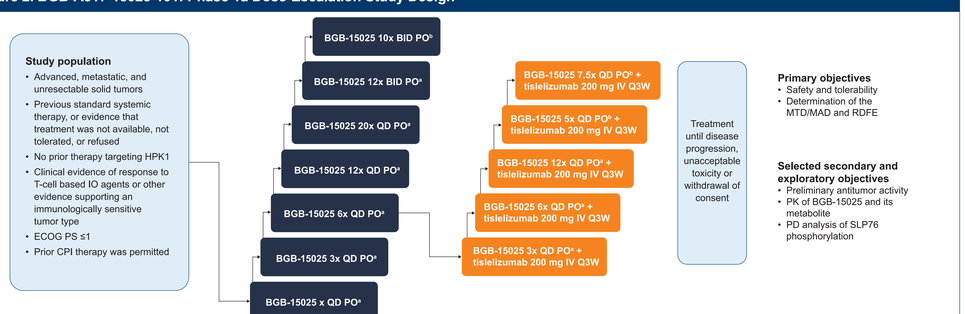
- Safety and efficacy were analyzed in all dosed patients
- Safety was assessed by the frequency and severity of AEs per NCI CTCAE v5.0
- Efficacy was assessed by the investigators using RECIST v1.1
- PK parameters were determined using a non-compartmental analysis method
- Pharmacodynamic modification of SLP76 phosphorylation was evaluated directly in whole blood using flow cytometry

Results

Patients and Treatment

- As of November 21, 2023, 60 patients received BGB-15025 monotherapy and 49 received BGB-15025 + tislelizumab
- Median follow-up was 2.3 months for BGB-15025 monotherapy and 4.8 months for BGB-15025 + tislelizumab
- Patient demographics and baseline characteristics are presented in **Table 1**
- Prior checkpoint inhibitor therapy was recorded for 46.7% of patients who received BGB-15025 monotherapy and for 40.8% of patients who received BGB-15025 + tislelizumab
- The most common tumors were kidney cancer, non-small cell lung cancer, cervical cancer, colorectal cancer, gastric or gastroesophageal junction cancer, and head and neck cancer

Figure 2. BGB-A317-15025-101: Phase 1a Dose-Escalation Study Design



[a]Free base capsule. [b]Citrate salt tablet.
x denotes the starting dose of BGB-15025 used for escalation.
BID, twice a day; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HPK1, hematopoietic progenitor kinase 1; IO, immuno-oncology; IV, intravenously; MAD; maximum administered dose; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PO, orally; Q3W, every 3 weeks; QD, daily; RDFE, recommended dose(s) for expansion; SLP76, SH2-domain-containing leukocyte protein of 76 kDa.

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	BGB-15025 Monotherapy (N=60)	BGB-15025 + Tislelizumab (N=49)
Age, median (range), years	59.0 (29, 80)	62.0 (30, 79)
Male, n (%)	34 (56.7)	33 (67.3)
ECOG Performance Status, n (%)		
0	25 (41.7)	27 (55.1)
1	35 (58.3)	22 (44.9)
Ethnicity, n (%)		
Hispanic or Latino	1 (1.7)	2 (4.1)
Not Hispanic or Latino	59 (98.3)	44 (89.8)
Not reported	0	2 (4.1)
Unknown	0	1 (2.0)
Lines of Prior Systemic Therapy in the Metastatic and Locally Advanced Setting, Median (range)	2 (0, 7)	2 (0, 5)
CPI Treated at Initial Diagnosis, n (%)	28 (46.7)	20 (40.8)

CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group.

Safety of BGB-15025 Monotherapy and BGB-15025 + Tislelizumab

- Safety data are summarized in **Table 2**
- No dose limiting toxicities (DLTs) were observed with BGB-15025 monotherapy
- Five DLTs were observed with BGB-15025 + tislelizumab (1 grade 3 and 1 grade 4 ALT/AST increased, 1 grade 3 colitis, 1 grade 3 immune-related hepatitis, 1 grade 3 gamma-glutamyltransferase increased)
- The maximum administered dose was 200 mg BID for BGB-15025 monotherapy; maximum tolerated dose was 150 mg QD for BGB-15025 + tislelizumab

Table 2. Safety Analyses

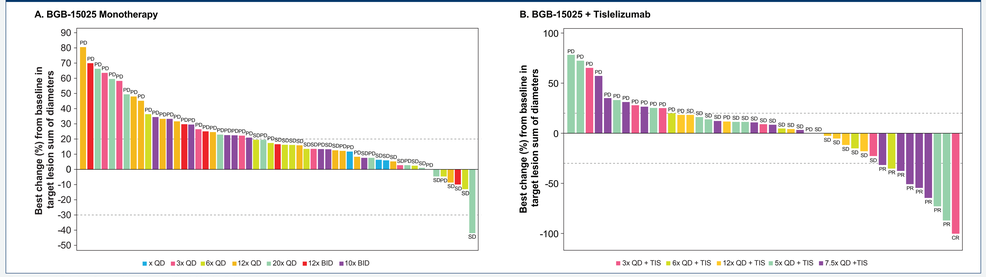
Patients, n (%)	BGB-15025 Monotherapy (N=60)	BGB-15025 + Tislelizumab (N=49)
Any TEAEs[a]	57 (95.0)	48 (98.0)
Treatment related	42 (70.0)	35 (71.4)
TRAEs occurring in ≥15% of patients[b]		
Diarrhea	11 (18.3)	14 (28.6)
Vomiting	9 (15.0)	6 (12.2)
Blood creatinine increased	9 (15.0)	3 (6.1)
Fatigue	7 (11.7)	10 (20.4)
Nausea	5 (8.3)	15 (30.6)
Grade ≥3	27 (45.0)	22 (44.9)
Treatment related	7 (11.7)	10 (20.4)
Serious	26 (43.3)	21 (42.9)
Treatment related	4 (6.7)	10 (20.4)
Leading to Death	4 (6.7)	3 (6.1)
Treatment related	0 (0)	0 (0)
Leading to Treatment Discontinuation	0 (0)	11 (22.4)
Treatment related	0 (0)	6 (12.2)
Treatment-Emergent Immune-Related AEs	7 (11.7)	13 (26.5)
Grade ≥3	1 (1.7)	6 (12.2)
Dose Limiting Toxicity Event	0 (0)	5 (10.2)

[a]Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0. [b]In either treatment group.
AEs, adverse events; TEAEs, treatment-emergent adverse events; TRAEs, treatment related AEs.

Efficacy of BGB-15025 Monotherapy and BGB-15025 + Tislelizumab

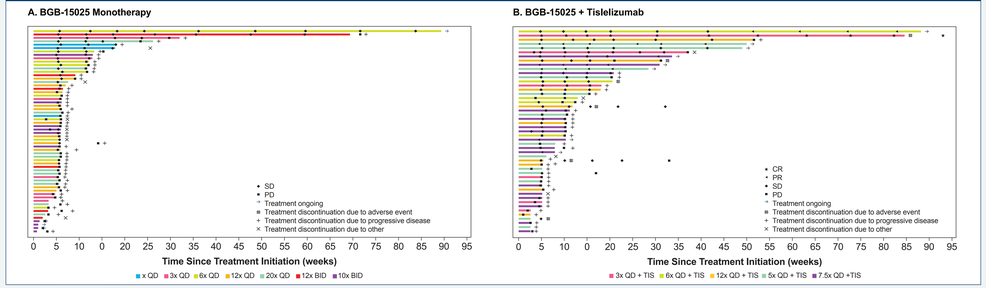
- Efficacy data are summarized in **Table 3**, **Figure 3**, and **Figure 4**
- There were no responders for BGB-15025 monotherapy; both confirmed and unconfirmed disease control rate (DCR) was 35.0% and clinical benefit rate (CBR) was 6.7%
- Three patients remained on BGB-15025 monotherapy for >6 months (2 patients are still on treatment for >60 and 84 weeks, respectively)
- The objective response rate (ORR), DCR, and CBR for all doses of BGB-15025 + tislelizumab combined were 18.4% (including 1 complete response), 57.1%, and 30.6%, respectively (all unconfirmed)
- The ORR, DCR, and CBR for BGB-15025 + tislelizumab for RDFE were 31.3%, 56.3%, and 31.3%, respectively (all unconfirmed)

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



Response category is the best overall response determined based on RECIST v1.1 per investigator assessment.
BID, twice a day; CR, complete response; PD, progressive disease; PR, partial response; QD, daily; SD, stable disease; TIS, tislelizumab.

Figure 4. Duration of Treatment and Overall Response



Investigator timepoint assessments per RECIST v1.1.
BID, twice a day; CR, complete response; PD, progressive disease; PR, partial response; QD, daily; SD, stable disease; TIS, tislelizumab.

Table 3. Efficacy[a] Analyses

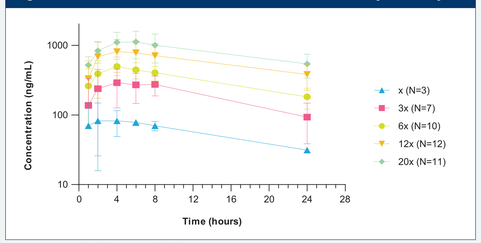
Patients, n (%)	BGB-15025 Monotherapy (N=60)	BGB-15025 + Tislelizumab (N=49)
Objective Response Rate[b]	0	9 (18.4)
Best Overall Response[b]		
Complete response	0	1 (2.0)
Partial response	0	8 (16.3)
Stable disease	21 (35.0)	19 (38.8)
Progressive disease	36 (60.0)	17 (34.7)
Not evaluable or not assessed	3 (5.0)	4 (8.2)
Disease Control Rate[b]	21 (35.0)	28 (57.1)
Clinical Benefit Rate[c]	4 (6.7)	15 (30.6)

[a]All efficacy endpoints are unconfirmed. [b]By the investigator per Response Evaluation Criteria in Solid Tumors version 1.1. [c]Defined as complete response, partial response, or durable stable disease.

Pharmacokinetic Analyses

- Plasma exposure to BGB-15025 increased in a dose-dependent manner (**Figure 5**)
- Peak concentration was reached at approximately 4 hours with a median half life ($t_{1/2}$) of approximately 13 hours across doses
- Consistent with its $t_{1/2}$, minimal accumulation of plasma exposure was observed after repeated BGB-15025 dosing once daily, compared with that after a single dose
- The active metabolite, BGB-21958, demonstrated a comparable $t_{1/2}$ to BGB-15025, with mean exposure varying between 18%–40% of BGB-15025 across doses
- BGB-15025 PK profiles were similar as monotherapy and with tislelizumab

Figure 5. BGB-15025 Concentration Time Profiles on Cycle 1 Day 1



x denotes the starting dose of BGB-15025 used for escalation. BGB-15025 was evaluated in the form of capsules containing free base drug substance.

Pharmacodynamics of SLP76 Phosphorylation

- BGB-15025 dosage showed a trend of correlation with pSLP76 inhibition in CD8+CD45RA- T cells (**Supplementary Figure 1**, available for download by scanning the quick response (QR) code at the bottom right of the poster)
- A stronger trend of pSLP76 inhibition was observed at BGB-15025 doses ≥12x
- A similar trend was observed in other T-cell populations (data not shown)

References

1. Shui JW, et al. *Nat Immunol.* 2007;8(1):84-91.
2. Wang X, et al. *J Biol Chem.* 2012;287(41):34091-34100.
3. Hernandez S, et al. *Cell Rep.* 2018;25(1):80-94.
4. Liu J, et al. *PLoS One.* 2019;14(3):e0212670.
5. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079-90.
6. Liu Y, et al. *Cancer Res.* 2022;82(12_Supplement):5541.

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. Caicun Zhou, Shanghai Pulmonary Hospital, Shanghai, China, and Jiafang Ma, BeiGene (Beijing) Co., Ltd., Beijing, China, contributed to the drafting and reviewing of the submitted abstract. This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Steven Moore, PhD, and Smitha Reddy, PhD, of Envision Pharma Inc., and was funded by BeiGene.

Presenter disclosures

The presenting author Sanjeev Deva received travel, accommodation, or expenses from Roche.

Contact: sanjeevd@adhb.govt.nz (Sanjeev Deva)