A Phase 1 Study of BGB-B2033 (GPC3x4-1BB Bispecific Antibody) Monotherapy in Patients With Selected Advanced or Metastatic Solid Tumors: First Disclosure of Clinical Data

Hong Jae Chon,[1] Jung Yong Hong,[2] Xueli Bai,[3] Tao Zhang,[4] Ed Gane,[5] Yabing Guo,[6] Tongsen Zheng,[7] Jianbing Wu,[8] Yao Huang,[9] Vivek Subbiah,[10] Ghassan K. Abou-Alfa,[11,12,13] Xiyan Mu,[14] Zhaoyin Zhu,[15] Jiadong Zhou,[15] Hugh Giovinazzo,[15] Rose Huang,[16] Tingbo Liang[3]

[1]CHA Bundang Medical Center, Bundang, Republic of Korea; [2]Samsung Medical Center, Seoul, Republic of Korea; [3]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [4]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [5]Auckland City Hospital, Auckland, New Zealand; [6]Nanfang Hospital of Southern Medical University, Guangzhou, China; [7]Harbin Medical University Cancer Hospital, Harbin, China; [8]The Second Affiliated Hospital of Nanchang University, Nanchang, China; [9]Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China; [10]SCRI Oncology Partners, Nashville, TN, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, United States; [12]Weill Cornell College at Cornell University, New York, NY, United States; [13]Trinity College Dublin, Dublin, Ireland; [14]BeOne Medicines, Ltd, Sydney, NSW, Australia; [15]BeOne Medicines, Ltd, Cambridge, MA, United States; [16]BeOne Medicines, Ltd, Beijing, China

Key Takeaway Points

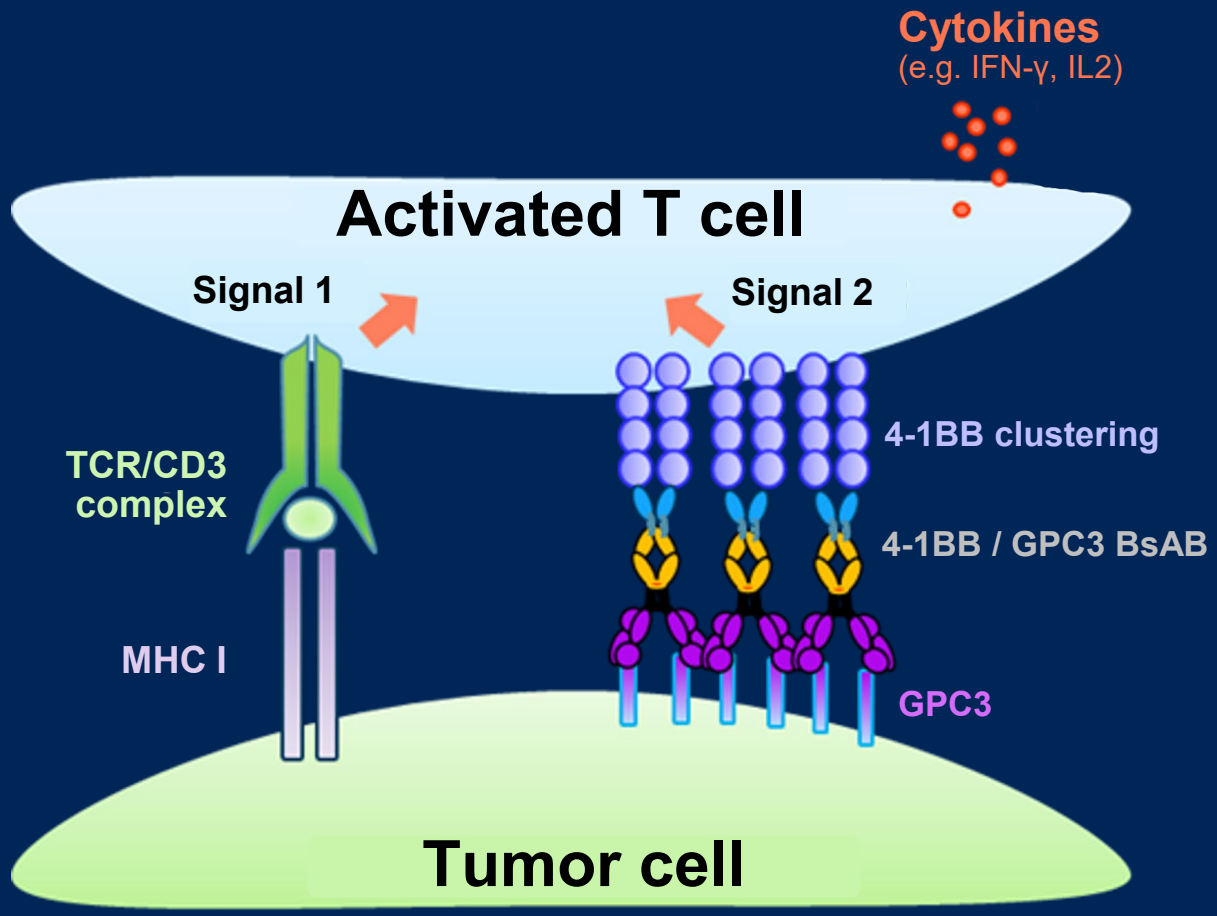
1. BGB-B2033, a first-in-class bispecific antibody targeting GPC3 and 4-1BB, was rationally designed to induce intra-tumoral T cell activation

2. BGB-B2033 demonstrates unprecedented antitumor activity in a heavily pretreated HCC population

3. BGB-B2033 exhibited a highly favorable safety profile with excellent tolerability, particularly in late-line HCC; MTD has not been determined

Background

- **Glypican-3 (GPC3)**: tumor-associated antigen highly expressed in multiple tumors, including in ~90% of HCC with any staining[1]
- **4-1BB (CD137):** key costimulatory receptor of T cells and a promising therapeutic target in cancer
- **BGB-B2033** is a novel, rationally designed IgG-based GPC3 x 4-1BB bispecific antibody
  - Activates 4-1BB on CD8+ T-cells only in the presence of GPC3-expressing tumor cells, enabling targeted tumor activity
  - Engineered Fc region designed to extend PK exposure while maintaining localized immune activation[2]



1. Ishiguro et al, *Sci. Transl. Med*. 9, eaal4291 (2017) 2. Li et al. Poster #6009 AACR 2025

Study Design (NCT06427941)

Phase 1 study of BGB-B2033 alone or in combination with tislelizumab with or without bevacizumab in patients with advanced solid tumors

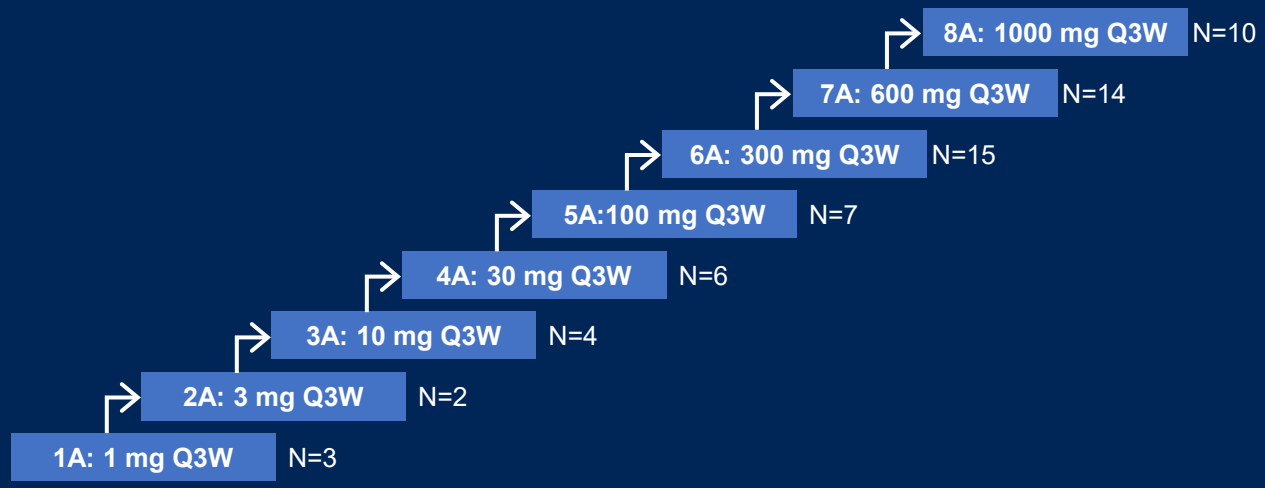
KEY ELIGIBILITY CRITERIA

- Pretreated advanced HCC
  - Child Pugh A
- GPC3 expressing tumors having received at least 1 prior therapy including:
  - Squamous NSCLC
  - AFP+ GC
- ECOG 0-1
- At least 1 measurable lesion by RECIST 1.1
- Archival tissue or fresh biopsy for GPC3 testing

MONOTHERAPY DOSE ESCALATION

BGB-B2033 Q3W

Total Enrollment = 61



DCO: April 15, 2026; median study follow-up was 4.8 (range, 0.3-15.5) months

ENDPOINTS

Primary

- Safety
- Recommended dose for expansion
- MTD

Secondary

- Objective response rate by investigator per RECISTv1.1
- Pharmacokinetics/ pharmacodynamics
- Immunogenicity

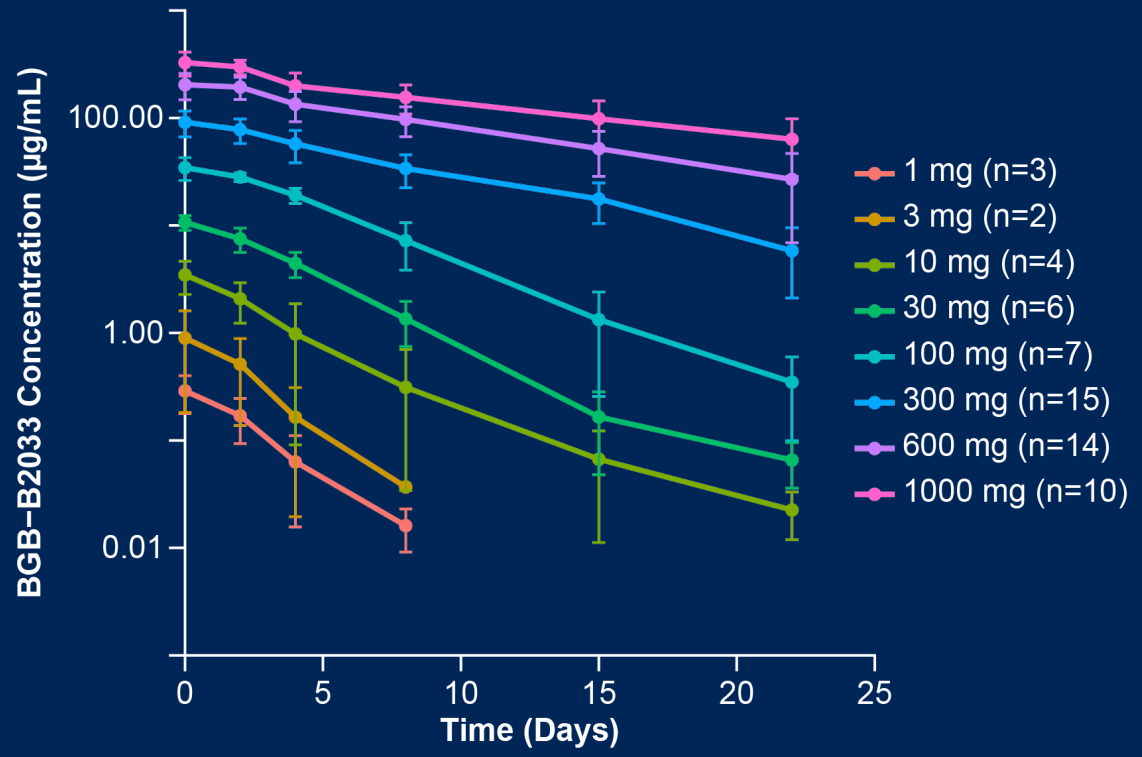
AFP, alpha-fetoprotein; CPI, checkpoint inhibitors; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GPC3, Glypican-3; HCC, hepatocellular carcinoma; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors

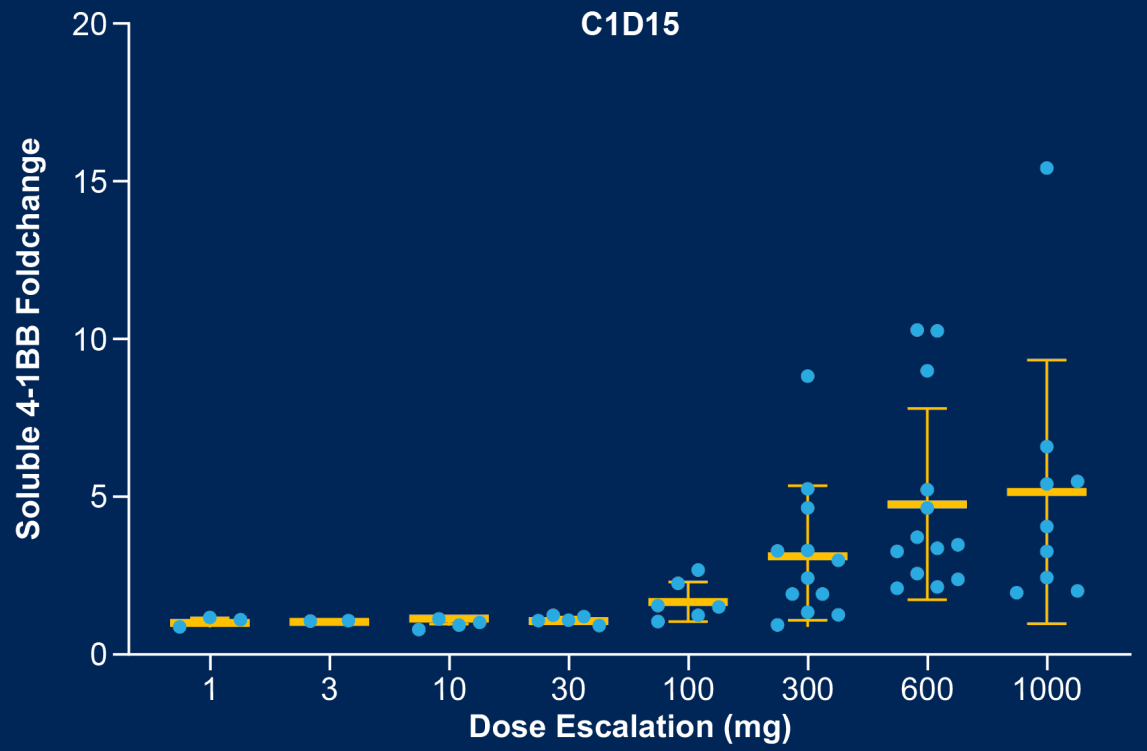
Baseline Demographics and Disease Characteristics

		Total (N=61)
Male , n (%)		54 (88.5)
Race, n (%)	Asian	56 (91.8)
	Black or African American	1 (1.6)
	Native Hawaiian/Pacific Islander	3 (4.9)
	White	1 (1.6)
ECOG PS, n (%)	0	32 (52.5)
	1	29 (47.5)
Type of Cancer, n (%)	Gastric	1 (1.6)
	HCC	60 (98.4)
Etiology of Hepatitis, n (%)	HBV	53 (86.9)
	HCV	2 (3.3)
	Other	6 (9.8)
Number of Prior Lines, median (range)		2.0 (1-6)
Prior Lines of Systemic Therapy, n (%)	Prior PD(L)-1	59 (96.7)
	Prior TKI	48 (78.7)
	Prior PD(L)-1 and TKI	46 (75.4)

ECOG PS, European Cooperative Oncology Group Performance Score; HBV, Hepatitis B; HCV, Hepatitis C; HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1;PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor

Doses of >300 mg Exhibit Linear PK and Increased Soluble 4-1BB



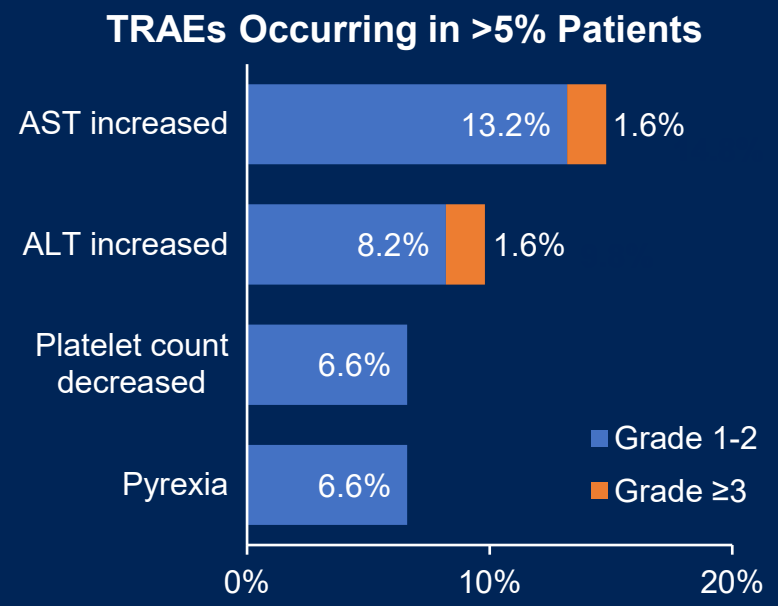


- Mean $t_{1/2}$ range of 5-11 days at doses >300 mg

Data cut-off: 15 April 2026

BGB-B2033 Was Well Tolerated, With Limited AEs

n, (%)	1-100 mg N=22	300 mg N=15	600 mg N=14	1000 mg N=10	Total N=61
Any TEAE	15 (68.2)	9 (60.0)	9 (64.3)	9 (90.0)	42 (68.9)
Grade ≥3 TEAEs	5 (22.7)	4 (26.7)	0	5 (50.0)	14 (23.0)
Any TRAEs	8 (36.4)	9 (60.0)	7 (50.0)	5 (50.0)	29 (47.5)
Grade ≥3 TRAEs	2 (9.1)	2 (13.3)	0	1 (10.0)	5 (8.2)
Any Serious TEAEs	1 (4.5)	0	2 (14.3)	4 (40.0)	7 (11.5)
TEAEs Leading to Discontinuation	0	0	0	2 (20.0)	2 (3.3)
DLT, n	0	1	0	0	1



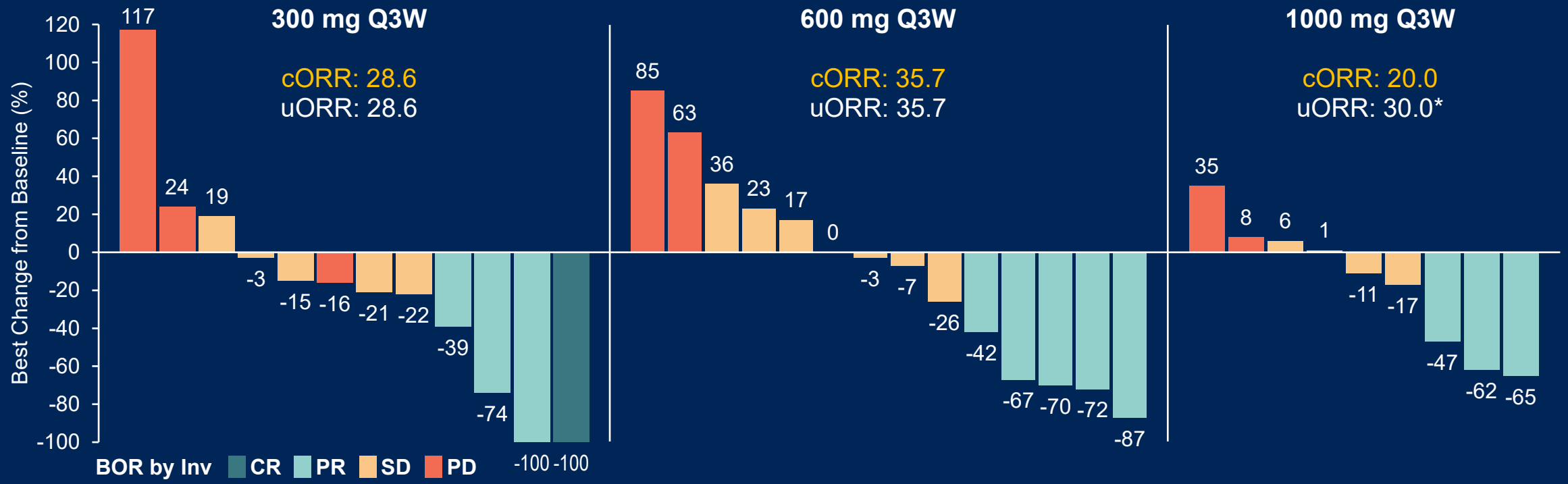
- IMAEs occurred in 4 (6.6%)[a] patients, none of which were Grade ≥3
- Two patients discontinued treatment due to AEs, only 1 due to TRAE (Grade 3 drug eruption)
- One DLT (Grade 3 ALT increased) occurred and resolved after dose interruption

Data cut-off: 15 April 2026

[a]Two hypothyroidism and two rash.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; IMAE, immune-mediated adverse events; TEAE, treatment emergent adverse event; TRAE, treatment-related treatment emergent adverse event

Promising Antitumor Activity in Heavily Pretreated HCC



- At doses ≥300 mg, confirmed ORR was 28.9% and unconfirmed ORR was 31.6%

Data cut-off: 15 April 2026

*A PR at week 36 was reported at 1000 mg, with patient on treatment, pending for confirmation in the next tumor assessment.

BOR, best overall response; c, confirmed; CR, complete response; HCC, hepatocellular carcinoma; Inv, investigator; ORR, objective response; PD, progressive disease; PR, partial response; SD, stable disease; u, unconfirmed

Conclusions

- The first-in-class GPC3x4-1BB bispecific antibody, BGB-B2033, demonstrated a favorable safety and tolerability profile in heavily pretreated patients with HCC
  - Frequency and severity of AEs were low (8% Grade ≥3 TRAEs; no Grade ≥3 IMAEs)
- BGB-B2033 demonstrated approximately linear PK and a prominent PD effect, with an increase in soluble 4-1BB at dose levels ≥300 mg
- Unprecedented antitumor activity was observed in heavily pretreated advanced HCC
  - Confirmed ORR of 28.6, 35.7, and 20% at 300, 600 and 1000 mg, respectively
  - At doses ≥300 mg, confirmed ORR was 28.9% and unconfirmed ORR was 31.6%
- Given the compelling antitumor activity and favorable safety profile, registration-enabling studies are in active development

Acknowledgements

We want to thank the patients, their families and caretakers, the co-investigators and staff of the study sites

This study was sponsored by BeOne Medicines, Ltd. Medical writing support under the direction of the authors was provided by Jose Casasnovas Nieves, an employee of BeOne Medicines, Ltd

For questions, please reach out to
Professor Hong Jae Chon, minidoctor@cha.ac.kr