Title: A phase 1 study of BGB-B2033 (GPC3 x 4-1BB bispecific antibody) monotherapy in patients with selected advanced or metastatic solid tumors: first disclosure of clinical data

Authors: 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 Abou-Alfa,[11] Xiyan Mu,[12] Zhaoyin Zhu,[13] Jiadong Zhou,[14] Hugh Giovinazzo,[15] Rose Huang,[12] Tingbo Liang[3]

Affiliations: [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]BeOne Medicines Ltd, Sydney, NSW, Australia; [13]BeOne Medicines Ltd, Cambridge, MA, United States; [14]BeOne Medicines Ltd, Beijing, China; [15]BeOne Medicines Ltd, San Carlos, CA, United States

Background: GPC3 is a tumor-specific antigen that is highly expressed in hepatocellular carcinoma (HCC) and squamous non-small cell lung cancer. 4-1BB is a co-stimulatory receptor on activated T cells that promotes proliferation, survival and cytolysis of T cells. BGB-B2033, a novel, IgG-based GPC3 x 4-1BB bispecific antibody with Fc region engineered to prevent FcγR binding and increase half-life, activates T cells while minimizing systemic toxicity. BGB-B2033 is being studied as monotherapy or in combination in patients (pts) with advanced GPC3-expressing solid tumors in a first-in-human phase 1 trial (NCT06427941). Here we report initial results from the monotherapy dose escalation and safety expansion (part A).

Methods: In part A, eligible pts with ≥1 prior systemic therapy received ascending dose levels of BGB-B2033. The primary objective was safety. Secondary objectives were preliminary antitumor activity (per investigator-assessed RECIST v1.1), pharmacokinetics and immunogenicity. Dose escalation followed the Bayesian mTPI-2 design.

Results: As of December 10, 2025, part A enrolled 61 pts; 60 (98.4%) had HCC and 56 (91.8%) were Asian. Median (range) prior lines of therapy were 2.0 (1-6). The median (range) study follow-up was 3.9 (0.3-14.9) months. Treatment-emergent adverse events

(TEAEs) were reported in 63.9% of pts across the 8 dose levels; 27 (44.3%) pts had treatment-related (TR)-TEAEs. Six grade ≥3 TR-TEAEs occurred in 5 (8.2%) pts: alanine aminotransferase (ALT) increased, aspartate aminotransferase increased, blood bilirubin increased, drug eruption, lymphopenia and neutrophil count decreased (1.6% each). One dose-limiting toxicity (ALT increased) resolved after dose reduction. Immune-mediated adverse events (imAEs) were reported in 4 (6.6%) pts; all were grades 1-2. One pt reported a grade 1 infusion-related reaction.

In the 59 efficacy-evaluable pts with HCC, confirmed ORR was 20.3% (95% CI: 11.0-32.8), with 12 partial responses; 23 pts had stable disease, 23 had progressive disease, and 1 pt was not evaluable. Ten of the 12 responders had ongoing response at data cutoff. A preliminary dose response was observed; at doses above the predicted target efficacious dose, confirmed ORR was 28.9% (11/38). Serum concentration profiles of BGB-B2033 exhibited target-mediated drug disposition at lower dose levels and decreased in a more biexponential manner at higher dose levels. Soluble 4-1BB, a pharmacodynamic marker, showed a greater increase at higher dose levels.

Conclusions: BGB-B2033 was generally well tolerated, with limited imAEs in this predominantly 2L+ HCC population. Durable responses were observed in pts with advanced HCC, including pts with prior PD-(L)1-based treatment. Triplet dose escalation with tislelizumab and bevacizumab as well as monotherapy dose expansion are ongoing.