Interim analysis of first-in-human phase 1 study to assess safety and efficacy of YBL-006, an anti-PD-1 antibody in advanced solid tumor with exploratory biomarker analysis of tumor mutational burden and artificial intelligence (AI)-powered spatial analysis of tumor-infiltrating lymphocytes.

John J. Park, Keun Wook Lee, Do-Youn Oh, Dhanusha Sabanathan, Se Hyun Kim, Tae Min Kim, Myungsuk Kim, Jaebong Yoon, Hyunmi Lee, Boram Kim, Yunjung Ko, Eunyoung Jeon, Seonghye Cheon, Eunyoung Shim, Bum-Chan Park, Han Seung Lee, Seongyeol Park, Kyunghyun Paeng, Chan-Young Ock; Department of Clinical Medicine, Macquarie University, Sydney, Australia; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea, Republic of (South); Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea, Republic of (South); Y-Biologics Inc., Daejeon, Korea, Republic of (South); Genome Insight Inc., Daejeon, Korea, Republic of (South); Lunit Inc., Seoul, Korea, Republic of (South)

Background: YBL-006 is an anti-programmed death-1 (PD-1) antibody with a higher affinity compared to that of other PD-1 antibodies, which showed a favorable safety profile in animal models. We designed the first-in-human phase I trial of YBL-006 to assess its safety and efficacy with exploratory biomarker analysis in patients with advanced solid tumors refractory to standard of treatment.

Methods: A modified "3+3" design, with the first patient dosed at 0.5 mpk, was followed by conventional dose escalation of 2, 5, and 10 mpk IV. Pharmacokinetics (PK) and pharmacodynamics, including PD-1 receptor occupancy (RO) and serum levels of interferon-gamma (IFN-γ), were assessed. Adverse events (AEs) were graded using the CTCAE v4.03. Tumor response was assessed using the RECIST v1.1 every 8 weeks. For exploratory analysis, tumor mutational burden (TMB) and AI-powered spatial analysis of tumor-infiltrating lymphocyte (TIL) of tumor tissues collected before YBL-006 treatment were performed. The cut-off date for analysis was February 12th, 2021.

Results: A total of 8 patients enrolled in the 0.5, 2, and 5 mpk cohorts received at least one dose of YBL-006 and median exposure was 15 weeks (ranged 4-26). No dose limiting toxicity occurred and the maximum tolerated dose was not reached until progressing to the 5 mpk. The common treatment-related AEs were G1 fatigue (25%), and G1 hypothyroidism (12.5%). We also observed 1 case of G2 cytokine release syndrome during cycle 1 in 2 mpk which was managed with supportive care alone. No treatment-related deaths have occurred to date. YBL-006 showed a linear PK prolife and both PD-1 RO and serum IFN-γ increased by > 2 times 8 h after the first dose. Tumor evaluation data were available for 7 patients, which showed 1 confirmed complete response (CR, penile squamous cell carcinoma, 2 mpk) and 1 confirmed partial response (PR, anal squamous

cell carcinoma, 2 mpk) with durable responses lasting more than 19+ and 10+ weeks respectively, 2 stable disease (SD) and 3 progressive disease (PD). Four tumor samples were available for biomarker analysis. TMBs of patients with CR (8.3/Mb) or PR (9.3/Mb) were higher than those in 2 patients with PD (5.5 and 1.7/Mb). AI-powered spatial analysis of TIL showed that intratumoral TIL density was increased in patients who achieved CR and PR (66.1% and 95.8%, respectively) compared to those in patients who exhibited PD (25.1% and 16.5%, respectively).

Conclusions: Interim analysis of phase I study showed that YBL-006 is well tolerated and preliminary biomarker analysis showed that the TMB, and intratumoral TIL infiltration are potentially related to the response to YBL-006. Clinical trial information: NCT04450901.