892 **ABL503 (TJ-L14B), PD-L1X4–1BB BISPECIFIC ANTIBODY INDUCES SUPERIOR ANTI-TUMOR ACTIVITY BY PD-L1-DEPENDENT 4–1BB ACTIVATION WITH THE INCREASE OF 4–1BB+CD8+ T CELLS IN TUMOR MICROENVIRONMENT**

[1]Uijung Jung, [1]Jaehyoung Jeon, [1]Shinai Lee, [2]Hyung-Seung Jin, [1]Youngkwang Kim, [1]Eunsil Sung, [1]Hyunjoo Kim, [1]Yangmi Lim, [1]Jonghwa Won, [3]Zhengyi Wang, [3]Wenqing Jiang, [1]Jaeho Jung, [1]Gihoon You*. *[1]ABL Bio Inc., Seongnam, Korea, Republic of; [2]Asan Medical Center, Seoul, Korea, Republic of; [3]I-Mab Biopharma, Shanghai, China*

Background PD-(L)1 inhibitor has revolutionized cancer treatment, but there are unmet clinical needs for PD-(L)1 inhibitor-resistant/refractory patients. Activation of T cells in tumor microenvironment by 4-1BB agonist antibodies is one of the promising approaches to complement the current limitation of PD-(L)1 inhibitors. Although 4-1BB is a promising target for immunotherapy, clinical studies using 4-1BB agonist antibodies showed systemic immune cell activation resulting in dose-limiting hepatotoxicity. We generated ABL503 (TJ-L14B), a bispecific antibody that combines PD-(L)1 blockade and PD-L1-dependent 4-1BB agonistic activity by binding both PD-L1 and 4-1BB to limit unwanted toxicities while exerting a potent anti-tumor efficacy. Here, we reported the pre-clinical properties of ABL503 (TJ-L14B) in various studies.

Methods The activity of ABL503 (TJ-L14B) was characterized and evaluated in 1) PD-1 and 4-1BB signaling reporter cells cocultured with various tumor cells and PBMCs, 2) hPD-L1/h4-1BB knock-in mice implanted with MC38 tumor expressing different level of hPD-L1, 3) patient-derived lung cancer organoids cocultured with autologous PBMCs, and 4) PBMCs from healthy donors to measure cytokine release.

Results Functional evaluation of ABL503 (TJ-L14B) indicates the activation of 4-1BB signaling was solely dependent on engagement of hPD-L1 expressed on immune cells as well as on tumor cells, pointing to pivotal roles of PD-L1 on both immune cells and tumor cells for the activity of ABL503 (TJ-L14B). In vivo anti-tumor activity of ABL503 (TJ-L14B) across different hPD-L1 levels showed prominent anti-tumor effect with significantly increased number of CD8+ cells and 4-1BB + cells in the tumor. This anti-tumor activity was correlated with the proliferation (Ki-67+) of CD8+ T cells in the tumor microenvironment. Ex vivo assays utilizing patient-derived lung cancer organoids revealed that ABL503 (TJ-L14B) exhibits superior tumor-killing activity than that by benchmark PD-L1 antibody, Atezolizumab. In addition, cytokine release assay demonstrated that ABL503 (TJ-L14B) did not induce non-specific pro-inflammatory cytokine release by human PBMCs.

Conclusions Our data indicate that PD-L1 and 4-1BB dual targeting bispecific antibody, ABL503 (TJ-L14B), shows potent 4-1BB agonistic activity and anti-tumor effect in a PD-L1-dependent fashion concomitant with 4-1BB+/CD8+ T cell activation and proliferation to overcome limitations of PD-(L)1-targeted therapy while minimizing the risk of peripheral toxicity. The phase 1 clinical trial in the U.S. is currently ongoing in patients with locally advanced or metastatic solid tumors (NCT04762641).

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