845 ABL503 (TJ-L14B), PD-L1×4–1BB BISPECIFIC ANTIBODY, REINVIGORATES EXHAUSTED TUMOR-INFILTRATING CD8+ T CELLS AND SYNERGIZES WITH PD-1 BLOCKADE

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Background ABL503 (also known as TJ-L14B) is a bispecific antibody designed to simultaneously target PD-L1 and 4–1BB, and functions as both 'PD-(L)1 inhibitor' and 'PD-L1-dependent 4–1BB agonist', overcoming the known 4–1BB agonist-related hepatotoxicity in clinical studies. Previously, we showed that ABL503 (TJ-L14B) was able to activate 4–1BB signaling in PD-L1 engagement-dependent manner and successfully exerted its function without considerable toxicities. The phase I clinical trial is currently ongoing in the U.S., in patients with locally advanced/metastatic solid tumors (NCT04762641). Published data on PD-L1×4–1BB bispecific antibodies suggest therapeutic synergy could be provided by the combination of anti-PD-1 and ABL503 (TJ-L14B) to broader patient populations, so we performed combination studies with additional PD-1-blocking immunotherapy. Given that the tumor-infiltrating $CD8^+$ T cells reportedly play a pivotal role in PD-1 blockade-mediated tumor regression and synergistic anti-tumor effects were observed in combinations of anti-4–1BB with anti-PD-1, we have investigated whether ABL503 (TJ-L14B) synergistically activates tumor-infiltrating lymphocytes (TILs) and inhibits tumor growth when combined with the PD-1 inhibitor, Pembrolizumab, *in vitro* and *in vivo*.

Methods To assess the activity of ABL503 (TJ-L14B) and Pembrolizumab *in vitro*, $CD8^+$ TILs were isolated from patient-derived tumor tissue (hepatocellular carcinoma and ovarian cancer) followed by co-culture with ABL503 (TJ-L14B) and/or Pembrolizumab, along with anti-CD3 stimulation. Following co-culture, the effector function of $CD8^+$ TILs was analyzed by measuring cytokine secretion and proliferation using flow cytometry. The *in vivo* synergistic anti-tumor efficacy of ABL503 (TJ-L14B) and Pembrolizumab was evaluated in human PD-L1-overexpressing MC38 tumor-bearing human 4–1BB/PD-1/PD-L1 triple knock-in mouse model.

Results We found that ABL503 (TJ-L14B) restored the effector function of $4–1BB^+$ exhausted $CD8^+$ TILs that were enriched for tumor-specific T cells but unresponsive to the Pembrolizumab. More importantly, the combination of ABL503 (TJ-L14B) and Pembrolizumab significantly further enhanced the functional restoration of human $CD8^+$ TILs compared to Pembrolizumab alone. Consistently, the combination of ABL503 (TJ-L14B) with Pembrolizumab synergistically alleviated tumor growth in the mouse model, with enhanced infiltration and activation of $CD8^+$ TILs in the tumor microenvironment. Moreover, transcriptomic analysis of $CD8^+$ TILs from the mouse model verified that the combination treatment significantly enhanced the activation status of $CD8^+$ TILs.

Conclusions In conclusion, ABL503 (TJ-L14B), PD-L1 and 4–1BB dual-targeting bispecific antibody, elicits a pronounced synergetic tumor growth inhibition with increased infiltration and functionality of exhausted $CD8^+$ T cells which in turn enhance the anti-cancer effects of Pembrolizumab, expecting the therapeutic benefit of ABL503 (TJ-L14B) in combination with PD-1 inhibitors in clinical trials.

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