PD-L1-TARGETED ISAC COMBINES MYELOID CELL ACTIVATION, IMMUNE-CHECKPOINT INHIBITION AND ADCP TO IMPROVE ANTI-TUMOR EFFICACY OVER ANTI-PD-L1 ANTIBODIES IN PRECLINICAL MODELS

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Background PD-L1 is an immune checkpoint that regulates anti-tumor T cell responses and is expressed on tumor cells as well as tumor-infiltrating immune cells across many tumor types. Immune-stimulating antibody conjugates (ISACs) consist of tumor-targeting antibodies conjugated to immune stimulants and are designed to activate the innate and adaptive immune systems against tumor cells following systemic administration. Here we show that PD-L1-targeted TLR7/8 ISACs elicit robust myeloid cell activation which leads to improved anti-tumor responses compared to anti-PD-L1 treatment in pre-clinical tumor models.

Methods A panel of proprietary anti-PD-L1 antibodies was identified through a phage display screen and subsequently tested for PD-L1 binding affinity and specificity, PD-L1/PD-1 blocking, antibody-dependent cellular phagocytosis (ADCP) by myeloid cells, and anti-tumor efficacy. Lead antibodies were conjugated to proprietary TLR7/8 agonists, and the resulting PD-L1 ISACs were evaluated for in vitro myeloid cell activation and in vivo efficacy against syngeneic and xenograft tumors.

Results Anti-PD-L1 antibodies induced robust ADCP by myeloid effector cells and medium to strong PD-L1/PD-1 blockade in vitro. Selected antibodies inhibited the growth of syngeneic MC38-hPD-L1 tumors in vivo, confirming efficient immune-checkpoint blockade. The conjugated PD-L1 ISACs induced robust, target-dependent activation of myeloid cells when co-cultured with PD-L1-expressing tumor cells, as measured by increased secretion of such cytokines as IL-12p70, IFN-alpha, and TNF-alpha. Importantly, myeloid activation was observed following co-culture with tumor cells having various levels of endogenous PD-L1 expression that was within the range of PD-L1 expression observed in human tumors. Systemically administered surrogate PD-L1 ISACs were well tolerated in mice and showed improved anti-tumor efficacy over anti-PD-L1 antibodies, with significant tumor growth delay or complete responses frequently observed in syngeneic (e.g. MB49, MC38-hPD-L1) as well as xenograft (e.g. HCC1954-hPD-L1) tumor models.

Conclusions These data demonstrate the potential of a PD-L1-targeted ISAC as a multifunctional therapeutic that may improve efficacy of PD-L1/PD-1 inhibition by combining three mechanisms of action into a single molecule: TLR-mediated myeloid cell activation, T cell activation through immune-checkpoint inhibition as well as ADCP.

Ethics Approval All animal studies were performed in accordance with Institutional Animal Care and Use Committee (IACUC)-approved protocols.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.782>