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LIGHT (TNFSF14) CO-STIMULATION ENHANCES MYELOID CELL ACTIVATION AND ANTI-TUMOR IMMUNITY IN THE SETTING OF PD-1 AND TIGIT CHECKPOINT BLOCKADE

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Background Co-inhibition of TIGIT and PD-1/L1 improves response rates compared to monotherapy PD-1/L1 blockade in checkpoint naïve NSCLC with PD-L1 expression >50%. TIGIT mAbs with an effector competent Fc can induce myeloid cell activation, and some have also demonstrated effector T cell depletion, which carries a clinical liability of unknown significance. TIGIT antibody blockade translates to anti-tumor activity by enabling PVR signaling through CD226 (DNAM-1), which can be directly inhibited by PD-1. Further, DNAM-1 is downregulated on TIL in advanced and CPI resistant cancers. Therefore, broadening clinical responses from TIGIT blockade into PD-L1low or CPI resistant tumors, may be enhanced by immune co-stimulation that independently operates from PD-1/L1 inhibition.

Methods Mouse and human TIGIT-Fc-LIGHT molecules were generated and assessed using Octet, MSD, and cell binding assays, and function was evaluated using in vitro/in vivo activation and anti-tumor efficacy experiments; including a pre-clinical model engineered to mimic human CPI acquired resistance.

Results TIGIT-Fc-LIGHT was nominated using in vitro and genomic screening assays designed to identify TNF costimulatory receptors widely expressed on TIL, T stem cell memory (Tscm), and NK cells; relative to DNAM-1 expression. HVEM was prioritized, and its ligand TNFSF14 (LIGHT) also directly activates myeloid cells through binding to a second receptor, LTβR. TIGIT-Fc-LIGHT simultaneously engaged TIGIT and LIGHT receptors at low nanomolar affinities (~3.5–6.5 nM), without the requirement for an effector competent Fc. HVEM signaling overlaps with DNAM-1, and TIGIT-Fc-LIGHT activated canonical and non-canonical NFκB pathways, leading to increased tumor infiltration of antigen-specific CD8+ T and NK cells. Importantly, anti-tumor efficacy induced by monotherapy TIGIT-Fc-LIGHT was maintained in aggressive anti-PD-1 acquired resistant tumors, a model where combined PD-1 and TIGIT antibody blockade was inactive. Because HVEM lacks cytoplasmic domain homology to DNAM-1, HVEM signaling is unlikely to be regulated by PD-1. Indeed, while anti-tumor activity of TIGIT-Fc-LIGHT was enhanced by PD-1/L1 blockade, it was not dependent upon combination. TIGIT-Fc-LIGHT also directly activated myeloid cells and increased the expression of CXCL10 and CXCL11, and stimulated proinflammatory cytokines, including CCL2, CCL4, and CXCL13.

Conclusions TIGIT-Fc-LIGHT was designed to overcome the limitations of TIGIT blocking antibodies through: 1) preserved costimulation in advanced tumors, 2) direct myeloid cell activation, 3) blockade of all known TIGIT ligands, and with 4) no risk of depleting effector lymphocytes since TIGIT-Fc-LIGHT activity does not require Fc function. Pre-clinical data indicate that these goals were achieved, and further development is warranted.

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