CDX-585, A BISPECIFIC ANTIBODY WITH DUAL TARGETING OF ILT4 AND PD-1 CHECKPOINT PATHWAYS

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Background Activation of the ITIM-bearing ILT4/LILRB2 receptor by its cognate ligands (HLA-G and HLA Class I) has been postulated as a resistance mechanism for checkpoint blockade of PD-1 and CTLA-4. Dual inhibition of receptors that suppress myeloid and T cell compartments through the generation of bispecific antibodies (bsAbs) is a promising strategy to improve outcomes for patients whose tumors are resistant to checkpoint inhibition.

Methods We describe the discovery and characterization of CDX-585 a bsAb developed from novel ILT4 and PD-1 antagonist mAbs that revert myeloid cell suppression by antagonizing ILT4 and activating T-cell responses through PD-1 inhibition. The bsAb was engineered as a tetravalent molecule using the PD-1 IgG1 mAb linked to scFv of the ILT4 mAb at the C-terminus of the heavy chain. A series of mutations were introduced in the Fc domain to eliminate Fcγ receptor binding and increase affinity to the neonatal Fc receptor. CDX-585 has good biophysical characteristics and retains functional properties similar to, or better, than the parental mAbs.

Results CDX-585 has sub-nanomolar affinity binding to ILT4 and PD-1 and is a potent competitor of their respective ligands. Primary cultures of human macrophages and dendritic cells treated with CDX-585 enhanced production of inflammatory cytokines/chemokines, which was further potentiated in the presence of toll like receptor activation with lipopolysaccharide (LPS). CDX-585 was particularly effective in promoting T cell activation as measured by mixed lymphocyte reactions, and in polarizing macrophages towards M1 based on their cytokine profile. Pilot studies in mice and cynomolgus macaques confirmed a favorable pharmacokinetic profile without adverse effects of treatment noted in clinical observations or clinical chemistry.

Conclusions CDX-585 effectively combines ILT4 and PD-1 blockade into one molecule with favorable biophysical and functional characteristics supporting the initiation of development activities including manufacturing and IND-enabling studies.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.798>