1183 DEVELOPMENT OF CTIM-76, A HIGHLY SPECIFIC CLAUDIN 6 BISPECIFIC ANTIBODY

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Background CTIM-76 is a bispecific Claudin 6 (CLDN6) T-cell engager antibody in preclinical development for treatment of CLDN6-positive cancers, including ovarian, testicular, and non-small cell lung cancers. CLDN6 is a tight junction protein differentially expressed on cancer cells with limited, if any expression in normal healthy tissue. Discovery of therapeutic monoclonal antibodies targeting CLDN6 is difficult due to an abundance of closely related family members expressed on healthy tissues and stringent requirements for high specificity. The extracellular region of CLDN6 closely resembles other claudins including CLDN3, CLDN4, and CLDN9 that are expressed in critical organs.

Methods Starting with a panel of high specificity CLDN6 antibodies, we engineered a large set (>50) of CLDN6xCD3 bispecific antibodies using multiple bispecific formats and CD3 arms. These molecules display different geometries and binding stoichiometries which are expected to play a critical role in their *in vitro* and *in vivo* potency. *In vitro* T cell cytotoxicity, cytokine release, and developability studies were used to select the lead candidate now designated as CTIM-76. CTIM-76 is being tested *in vivo* using xenograft studies in PBMC-engrafted mice.

Results CTIM-76 demonstrated potent cytotoxic effects on cells expressing CLDN6, and results suggest a wide therapeutic window. Picomolar T cell-dependent cytotoxicity values were obtained with OV90 and OVCAR3 ovarian cancer lines, and studies in K562 cells over-expressing claudin proteins show at least a 500-fold selectivity for CLDN6 over CLDN3, CLDN4, and CLDN9. No CTIM-76 binding was observed against closely related CLDN proteins including CLDN3, CLDN4, and CLDN9, using flow cytometry at CTIM-76 concentrations up to 1 micromolar. *In vivo* studies with PBMC-engrafted animals using multiple ovarian cancer cell lines are ongoing and preliminary results suggest *in vivo* potency consistent with the *in vitro* data. CTIM-76 has entered GMP-manufacturing with productivity levels higher than standard IgG molecules and compatibility with standard purification and formulation. CTIM-76 has also begun PK and GLP-tox studies in cynomolgus monkeys.

Conclusions The exquisite specificity of CTIM-76 and potent cell-killing effects suggests it has significant potential as a potent and safe therapeutic against CLDN6-positive cancers. Context Therapeutics will be responsible for the clinical development of CTIM-76, and IND filing for this molecule is anticipated to occur in Q1 2024.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1183