 TIM1 BACKGROUND

- TIM1 (T cell Ig and mucin domain-containing protein-1) is a type I transmembrane protein with an Ig V-V′ (IgV) domain and a mucin domain with O-linked glycosylation.
- TIM1 is also known as kidney injury molecule-1 (KIM-1) and hepatitis B virus surface antigen.
- TIM1 is expressed on activated T cells and B cells and thought to function as a co-stimulatory molecule.
- TIM1 deficient mice do not exhibit significant phenotypes or defects in immune system development.
- TIM1 is overexpressed in renal cell carcinoma and ovarian clear cell carcinoma and the shed ectodomain is a predictive biomarker of tumor progression.

ANTI-TIM1 mAb, CR014, ADC

- Fully human mAb CR014 was produced by immunization of human Ig expressing mice (Xenomouse) with the extracellular domain of human TIM1.
- Kd of CR014 for human TIM1 is 2.71 x 10^-11 M.
- CR014 binds to human domain of TIM-1 and cross reacts with non-human primate TIM-1.
- CR014 was expressed as human IgG4 and IgG1 isotypes.
- CR014 was conjugated to monomethylauristatin-E (MMAE) using Seattle Genetics Antibody Drug Conjugate technology.

CHARACTERIZATION OF IgG1 AND IgG4 VERSIONS OF ANTI-TIM1

- Cell viability, cell cycling and proliferation were assessed with CellTiter-Glo, CellTiter-Blue and MTS assays.
- ADCs were tested in a T-cell proliferation assay using E.G7 cells coated with recombinant human TIM.

CHARACTERIZATION OF IgG1 AND IgG4 VERSIONS OF ANTI-TIM1

- Characterization of ADCs was performed with different methods, including cell viability, cell cycling, and proliferation assessments.
- CR014 was shown to induce significant cytotoxicity against ovarian and renal carcinoma cell lines.

SUMMARY AND FUTURE DIRECTIONS

- TIM-1 expression is upregulated in several human cancers, most notably in renal cell and ovarian carcinomas, but has very restricted expression in healthy tissues thus representing a promising target for antibody mediated therapy.
- We have developed CR014, a fully human monoclonal IgG4 and IgG1 antibody specific for extracellular domain of TIM-1.
- This antibody was shown to bind purified recombinant TIM-Fc protein and TIM-1 expressed on a variety of transformed cell lines, including Caki-1 (human renal clear cell carcinoma) and IGROV-1 (human ovarian adenocarcinoma) and A498 (lung carcinoma).
- Internalization studies using confocal microscopy revealed the antibody was rapidly internalized by cells in vitro.
- Antibody-drug conjugates (ADCs) were produced with CR014 covalently linked to a potent cytotoxin, monomethylauristatin E (MMAE).
- The ADCs were shown to exhibit in vitro cytotoxicity or cytostatic activity against a variety of TIM-1 expressing cell lines, but not on negative cell lines.
- CR014 IgG1 vcmMMAE and CR014 IgG4 vcmMMAE showed significant anti-tumor activity in Caki-1, IGROV-1 and A498 xenograft models, with both ADCs exhibiting robust activity.
- Similar ADC activity was observed with CR014 IgG1 vcmMMAE.
- We have selected the CR014 IgG1 for manufacturing and IND-enabling studies in order to advance CR014 IgG1 vcmMMAE (CDX-014) towards clinical studies in renal cell carcinomas and potentially other TIM-1 expressing tumors.

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Development of an Antibody-drug Conjugate Targeting TIM-1 for the Treatment of Ovarian and Renal Cell Carcinoma


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