CDX-1402, a dendritic cell targeted fusion protein designed to elicit immunity to mesothelin and HER2 expressing tumors

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Introduction

The use of mAbs to target antigens to the endocytic receptor DEC-205 on dendritic cells (DC) is an effective means to elicit helper and cytolytic T cell responses in the presence of appropriate adjuvants to activate DC. We have translated this concept to clinical studies using a fully human DEC-205-specific mAb genetically altered to include the entire NY-ESO-1 cancer antigen (CDX-1401), which when combined with TLR agonists results in effective stimulation of both cellular and humoral NY-ESO-1-specific responses in cancer patients (Dhodapkar MV et al., J. Clin. Invest. Med. 6:239-251, 2012). Pre-treatment of patients with the DC mobilizing agent, FISL (CDX-301), was subsequently shown to significantly augment both humoral and cellular responses to CDX-1401 (Bhardwaj N et al. ASCO 2016).

Building on this concept, we developed a new fusion protein in which the DEC-205 mAb is engineered to carry two tumor-related antigens in tandem: mesothelin (MSLN) and HER2. HER2 and MSLN are broadly expressed in several tumor types, including pancreatic, ovarian and breast cancers. This expands the opportunity for this immunotherapy approach.

Mouse Surrogate Studies

Prior preclinical studies have documented the activity of DEC-205 targeted HER2 or DEC-205 targeted MSLN, including anti-tumor efficacy.


The current studies were performed to address the questions:

Can the dual-antigen construct elicit robust immune response against both HER2 and MSLN?

How does the immune response elicited by the dual-antigen construct compare to the individual targeted antigens?

Surrogate Preclinical Molecules

Dual-Antigen Construct Drives Potent HER2 and MSLN CD4 and CD8 T cell Response

Development and Analytical Characterization of CDX-1402

CDX-1402 is an antibody fusion protein that consists of the full length anti-DEC-205 IgG1 mAb, 3G9, genetically linked (at the C-terminus of the heavy chain) to MSLN (8 from, del/ing the human N-terminal sequence) and to HER2 (cysteine to serine domain).

CDX-1402 Testing in Human T cell: DC Co-culture

Conclusions

- Targeting protein antigens to DEC-205 generates robust immune responses in preclinical and clinical settings.
- Genetically linking multiple large antigens to the human anti-DEC-205 mAb 3G9 is feasible and generates a stable protein that stimulates human HER2 and MSLN-specific T cells.
- In vitro generated MSLN/HER2-peptide specific T cells produce IFNγ in response to CDX-1402 cross-presented by DCs, and can be stimulated directly by tumor cells expressing HLA and antigens.
- Through use of surrogate anti-mouse DEC-205 fusion proteins, we demonstrate the inclusion of dual antigens does not reduce the immune response from either single antigen construct.
- The data support the use of CDX-1402 as part of an immunotherapy regimen for treatment of multiple cancer types expressing MSLN and/or HER2.