Development of targeted T-cell cancer immunotherapies based on a novel enantiomeric cationic lipid that promotes antigen cross-presentation and upregulation of type I interferons

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VERSAMUNE® TECHNOLOGY

- The enantiomeric cationic lipid R-DOTAP nanoparticle platform (Versamune®) can promote efficient cross presentation of peptides/protein antigens and upregulation of Type I interferons, leading to induction cytolitic polyfunctional CD8+ T-cells in vivo. [1]

- Versamune® based immunotherapy containing human papilloma virus (HPV) derived antigens (PDS0101) was reported to induce high levels of antigen-specific cytolitic polyfunctional CD8+ T-cells in vivo and complete regression of TC-1 tumors in preclinical models. [1]

- In a Phase II trial (NCT04287868) of patients with HPV-related cancers who failed standard of care and received combination therapy with PDS0101, NHS-IL12 and bintrafusp alfa showed tumor shrinkage and improved patient survival. [2,3]

VERSAMUNE® PLATFORM BASED IMMUNOTHERAPY FOR THE TREATMENT OF NON-VIRAL ASSOCIATED CANCERS

Versamune® based - TARP immunotherapy (PDS0102) platform contains long multi-epitope peptide antigens derived from the T-cell receptor gamma chain alternate reading frame protein (TARP), a tumor specific antigen overexpressed in prostate (~90%) and breast (~50%) cancers, as well as acute myelogenous leukemia (AML).

Figure 1. PDS0102 induces a high number of antigen-specific and polyfunctional T-cells. Antigen-specific T-cell responses in vaccinated mouse spleen were measured using mouse IFN-γ ELISPOT assay and intracellular cytokine staining assay. IFN-γ producing T-cells in response to stimulation with a mixture of long peptides covering the entire S8a TARP sequence (a) or individual peptides consisting of verified HLA-A2 epitopes (b). Data represent effector cell percentages (CD44+ CD62L-) (c,d) and polyfunctional antigen-specific effector CD8+ T-cell percentages (e,f) in sucrose or PDS0102 vaccinated mice.

Versamune® based - MUC1 immunotherapy (PDS0103) platform contains multiple agonistic CD8+ T-cell epitope antigens derived from the extracellular and intracellular domains of human Mucin 1 (MUC1) protein, a tumor-associated antigen in a variety of epithelial cancers.

Figure 2. PDS0103 induces a high number of antigen-specific CD8+ T-cells capable of killing cells presenting the human MUC1 derived peptides. AAD mice were vaccinated on day 0 and day 7 with the PDS0103 formulation. On day 14, antigen-specific T-cell responses in vaccinated mouse spleens were measured by stimulating spleen cells with validated MUC1 derived HLA-A2 binding CD8+ T-cell epitopes (V1A, V2A, C1A and C2A) and measuring IFN-γ secretion in an ELISPOT assay (a). Cytolytic activity of V1A- and V2A-specific CD8+ T-cells was measured by transferring V1A- and V2A-pulsed or control peptide-pulsed spleen cells (1:1 ratio) and enumerating change in the ratio of V1A and V2A pulsed and control cells in the spleen (b).

VERSAMUNE® MECHANISM OF ACTION

To evaluate the potential efficacy of the Versamune® platform to treat non-viral associated cancer, we developed two immunootherapy formulations:

- Versamune® based - TARP immunotherapy (PDS0102)

- Versamune® based - MUC1 immunotherapy (PDS0103)

To assess immunogenicity and biological activity, we injected human HLA-A2 expressing transgenic mice (AAD) with two doses of PDS0102 or PDS0103 formulations on day 0 and day 7 and characterized antigen-specific T cell-mediated immune responses induced by the vaccine formulations on day 14.

METHODS

- Versamune®-based nanoparticles formulated with tumor-derived antigens induced robust CD8+ and CD4+ T-cell responses. CD8+ T-cells induced by the Versamune® platform were cytotoxic and are effective in identifying and killing cells presenting human MUC1-derived antigens (Fig 2).

- These results demonstrate the Versamune®-based T-cell activating platform’s ability to generate effective anti-tumor immune responses. Further studies evaluating its potential in combination with checkpoint inhibitor therapy to promote anti-tumor immunity is ongoing.

MAJOR FINDINGS AND FUTURE DIRECTIONS

REFERENCES: