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Preclinical Studies

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Abstract 2

Development of CAR-NK Cell Therapy for Hematologic Malignancies

Carrie Stoltzman[1,2], Devikha Chandrasekaran[1], Erika von Euw[1], Cyd McKay[2], Christina Root[2], Colleen Delaney[1,2]

[1]Deverra Therapeutics, Inc., Seattle, WA, USA
[2]Fred Hutchinson Cancer Center, Seattle, WA, USA

Introduction: Natural killer (NK) cells can kill tumor cells without priming or prior activation through their complement of activating and inhibitory surface molecules. Chimeric antigen receptor (CAR) expression by engineered NK cells can improve both specificity and potency of the NK cells' anti-tumor efficacy. CAR-NK cell therapy may be a safer, more clinically accessible, and cost effective allogeneic cellular therapy in comparison to autologous CAR-T cell therapy, as NK cells do not cause graft versus host disease (GvHD) or cytokine release syndrome (CRS).

Objective: We aimed to develop an allogeneic, cryopreserved, off-the-shelf CAR-NK cell product for the treatment of hematologic malignancies.

Methods: Our CD56+ NK cells are generated from cord blood-derived CD34+ cells, which undergo expansion and priming on a proprietary Notch ligand cell culture platform followed by a second culture phase of NK cell differentiation. These cells were transduced using a viral vector to express a CAR specific for an antigen expressed on the cell surface of acute lymphoblastic leukemia (ALL) cells. The CAR-NK cells were assessed for CAR expression, NK cell phenotype, and in vitro cytotoxicity both pre- and post-cryopreservation. An ALL xenograft mouse model was treated using repeat doses of cryopreserved CAR-NK cell product, with readouts of body weight, tumor growth, and survival.

Results: The transduced CAR-NK cell product displayed viability and phenotyping comparable to the untransduced control NK cell product but possessed significantly enhanced cytotoxicity against ALL target cells in vitro. Following cryopreservation and thaw, the CAR-NK cell product retained CAR expression and maintained enhanced anti-tumor function in vitro. Cryopreserved CAR-NK cell product was safely given in up to 8 repeat doses to ALL xenograft mice and significantly inhibited tumor growth as well as increased survival compared with control NK cell product.

Discussion: We have demonstrated in this proof-of-concept study that our cord blood CD34+ cell-derived CAR-NK cell product can maintain CAR expression, with specific and enhanced potency both in vitro and in vivo, following cryopreservation and thaw. Additional preclinical studies are planned to develop CAR-NK off-the-shelf cell therapy for AML and other hematologic malignancies.