ONCT-808 ROR1 CAR T CELLS INDUCE SIGNIFICANT CANCER CELL DEATH IN MANTLE CELL LYMPHOMA CELL LINE-DERIVED CDX MODELS AND IN VITRO KILLING ASSAYS

Shuguang Bi*, Gunnar Kaufmann, James Breitmeyer, Rajesh Krishnan. Oncternal Therapeutics Inc, San Diego, CA, USA

Background Type 1 transmembrane protein receptor tyrosine kinase-like orphan receptor 1 (ROR1) is expressed at high levels on many hematologic and solid malignancies, but minimally in healthy adult tissues. ROR1 expression increases on tumor cells post-chemotherapy or cell therapy, making it an attractive target for immunotherapy. Oncternal’s ONCT-808 autologous CAR T cells are genetically modified via ex vivo transduction with a self-inactivating lentivirus vector to express a ROR1-directed CAR containing single chain variable fragment derived from Oncternal’s clinical stage anti-ROR1 zilvertamab.

Mantle cell lymphoma (MCL) is an aggressive non-Hodgkin lymphoma with a short remission from standard therapies. In this study, ONCT-808 treatment on MCL was investigated as a representative preclinical model of ONCT-808 treatment on various types of cancers.

Methods ONCT-808 ROR1 CAR T cells, currently in Phase I clinical trials, are manufactured with CliniMACS Prodigy. ONCT-808 manufactured with apheresis from healthy donors were used in the study. At completion of the manufacturing, T cell transduction rate, purity and T cell differentiation were analyzed with flow cytometry. For in vitro killing assays, ONCT-808 cells were incubated overnight with Jeko-1 (ROR1 expression high MCL cell line), Raji (ROR1 dim) and K562 (ROR1 negative) cells. Cancer cell death was analyzed with flow cytometry. Killing assay cell culture supernatant was analyzed for ONCT-808 cytokine release upon interaction with target cells using multiplex Luminex assays.

To explore the in vivo cancer treatment efficacy, cell line-derived xenograft (CDX) NSG models were established with Jeko-1 and Raji cells via subcutaneous inoculation. When average tumor volume reached 150 mm³, ONCT-808 and untransduced T cells were intravenously injected into the mice. Tumor growth was monitored via measuring tumor volume with clippers.

Results Majority of ONCT-808 cells expressed central memory and stem central memory phenotypes. ONCT-808 induced significant ROR1 specific cell death in vitro in ROR1 positive (high expression) Jeko-1 cells, but not in ROR1 dim Raji or ROR1 negative K562 cells. ONCT-808 secreted type 1 cytokines, such as IFN-γ and TNF-α, upon interaction with Jeko-1 cells. In cancer therapy efficacy studies using CDX models, treatment with ONCT-808 cells resulted in complete tumor remission in ROR1 Jeko-1 cell-derived CDX mice, and controlled tumor growth in Raji cell-derived CDX mice, reflecting the specificity of the ONCT-808 cells to the ROR1 target.

Conclusions ONCT-808 demonstrated high efficacy in inducing ROR1 specific cancer cell death in both in vivo and in vitro studies, suggesting its potential in treating human cancer patients.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0230