1205 SURMOUNTING CONVENTIONAL CELL THERAPY LIMITATIONS *VIA IN SITU* CAR THERAPY USING ORNA™ LIPID NANOPARTICLES

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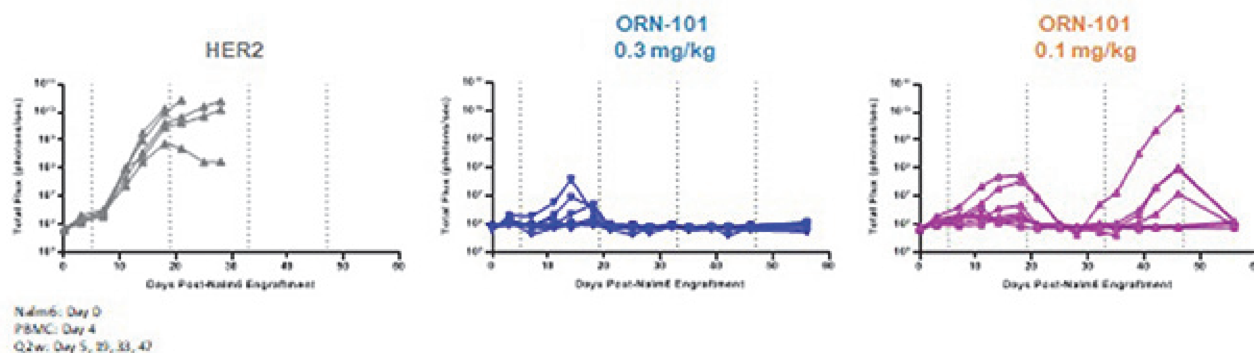
Background *Ex vivo* generated chimeric antigen receptor (CAR) T cell therapies have shown tremendous success in treating hematologic malignancies. However, this modality has significant limitations to providing treatment to a broader population: high cost of goods (COGS) and associated care, impractical redosability, requirement of cytotoxic lymphodepletion protocols, and insufficient accessibility to cell therapy centers for a large number of cancer patients who qualify for this treatment. LNP-mediated delivery of long coding RNA has been clinically validated for protein replacement, vaccines and gene editing.

Methods We have been developing a novel, synthetic, circular coding RNA platform (oRNA technology) which exhibits significant improvements in production, expression and formulation compared to mRNAs. We have combined oRNA technology with novel immunotropic LNPs to address the limitations of *ex vivo* CAR-T therapies by creating off-the-shelf, yet 'autologous', *in situ* CAR (isCAR™) therapies. The anti-CD19 isCAR candidates were evaluated for in vitro cell killing and tumor regression in a Nalm6CD19+ mouse model.

Results Our immunotropic LNPs show preferential biodistribution to the spleen, with oRNA reporter expression detected in multiple immune cell subsets, including T cells, macrophage and NK cells. Delivery to immune cells is preserved across mice, rats and non-human primates. *In vitro*, expanding human T cells expressing an anti-human CD19 CAR oRNA show potent and sustained cytotoxicity and pro-inflammatory cytokine production compared to controls. Sequence optimization of our oRNA construct drove high levels of CAR expression and cytotoxicity in primary human T cells that were significantly elevated compared to modified mRNA. These optimized IRES elements and coding sequences translated into a 20-fold increase in efficacy in mice treated with the corresponding LNP-oRNAs in a human PBMC-engrafted NALM6 tumor-bearing mouse model. The optimized LNP-oCAR enabled q2w dosing at clinically relevant dose levels producing well-tolerated, robust, and reproducible efficacy across multiple PBMC donors (figure 1).

Conclusions oRNA-enabled isCAR therapies promise a transient, re-dosable and scalable immune cell therapy without requiring immunodepletion for the treatment of cancer. We believe the ability to deliver to multiple immune cell types and large cargo space for multi-targeting provides a differentiated strategy in both hematological malignancies as well as solid tumors.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1205



Abstract 1205 Figure 1 ORN-101 effectively controls leukemia growth when dosed every other week. NSG-MHC I/II double knockout mice were engrafted with Nalm6-fLUC B-ALL cells at D0. On D4, human peripheral blood mononuclear cells (PBMC) were engrafted, followed by LNP-oRNA dosing starting at D5. Animals received 4 doses, every other week, of LNP-CD19CAR at either 0.1 mg/kg or 0.3 mg/kg, or HER2 CAR 0.3 mg/kg (negative control). Animals were imaged twice weekly to monitor Nalm6 burden. Graphs show Nalm6 leukemia burden, based on tumor flux value, in ORN-101 or control treated individual mice.

J Immunother Cancer: first published as 10.1136/jitc-2023-SITC2023.1205 on 2 November 2023. Downloaded from http://jitc.bmj.com/ on November 9, 2024 by guest. Protected by copyright.