FT536 PATH TO IND: UBIQUITOUS TARGETING OF SOLID TUMORS WITH AN OFF-THE-SHELF, FIRST-OF-KIND MICA/B-SPECIFIC CAR-INK CELLULAR IMMUNOTHERAPY

¹John Goulding, ¹Bryan Hancock*, ¹Robert Blum, ¹Moyar Ge, ¹Svetlana Gaidarova, ¹Paul Rogers, ¹Sajid Mahmood, ¹Rina Mbofung, ¹Wen-I Yeh, ¹Bi-Huei Yang, ¹Chia-Wei Chang, ¹Brian Groff, ¹Soheila Shirinbak, ¹Joy Grant, ¹Martin Hosking, ¹Mochtar Pribadi, ¹Yijia Pan, ¹Hui-Yi Chu, ¹Shohreh Sikaroodi, ¹Lauren Fong, ¹Nicholas Brookhouser, ¹Fernanda Rodrigues Cugola, ¹Ramzey Abujarour, ¹Janel Huffman, ¹Pei-Fang Tsai, ¹Antonio Fernandez-Perez, ¹Karina Palomares, ¹Natalie Marquez-Solorzano, ¹Riya Kanherkar, ¹Andrew Burns, ¹Aidan Keefe, ¹Samvel Nazaretyan, ¹Christine Chen, ¹Raedun Clarke, ¹Thomas Dailey, ¹Miguel Meza, ¹Jason O'Rourke, ¹Jerome Bressi, ¹Tom Lee, ¹Ryan Bjordahl, ²Lucas Ferrari de Andrade, ³Kai Wucherpfennig, ¹Bahram Valamehr. ¹Fate Therapeutics, San Diego, CA, USA; ²Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³Dana-Farber Cancer Institute, Boston, MA, USA

Background Chimeric antigen receptor (CAR)-T cell therapy has revolutionized cancer treatment, but it is associated with significant dose-limiting toxicities, restricted tumor targeting (limited by specific antigen expression), and, notably, a lack of multi-antigen targeting capability to mitigate tumor associated immune evasion and heterogeneity. Furthermore, dysfunctional starting material, product inconsistency, and small manufacturing lot size limits the application and on-demand availability of CAR-T cell therapy.

Methods To overcome these considerable limitations, we have developed FT536, a first-of-kind, induced pluripotent stem cell (iPSC)-derived NK (iNK) cell with a novel CAR that ubiquitously targets cancer cells through canonical stress ligand recognition. We have previously reported FT536 recognizes the conserved $\alpha 3$ domain of the pan-tumor associated antigens MICA and MICB (MICA/B), and is derived from a renewable master iPSC line that contains multiplexed genetic edits to enhance effector cell functionality, persistence, and multi-antigen targeting capabilities via high affinity non cleavable CD16 (hnCD16) mediated antibody dependent cellular cytotoxicity (ADCC). Here we preview the nonclinical study for the investigational new drug (IND) application for FT536.

Results Utilizing a manufacturing process analogous to pharmaceutical drug product development, we demonstrate FT536 can be consistently and uniformly produced with a greater than 4×10^7 fold cellular expansion per manufacturing campaign. Furthermore, FT536 can be cryopreserved at clinical scale to support off-the-shelf clinical application, with rapid product thaw and immediate patient infusion in an out-patient setting. Functional evaluation demonstrated that FT536 uniquely possesses potent and persistent antigen specific cytolytic activity against an array of solid and hematological tumor lines. Through its hnCD16 modality, FT536 can be utilized in combination with monoclonal antibodies to provide multi-antigen targeting capabilities and in conjunction with chemotherapeutics and/or radiation that augment surface MICA/B expression. In addition, directly thawed and infused FT536 demonstrated significant tumor growth inhibition in multiple solid and liquid in vivo xenograft models, in which tumor control was further enhanced in combination with a therapeutic antibody (figure 1). Finally, ongoing studies utilizing a lung adenocarcinoma model have highlighted the sustained persistence of FT536 in lung tissue up to 33 days following a single dose infusion without the need for exogenous cytokine support.

Abstract 117 Figure 1 FT536 provides statistically significant in vivo anti-tumor activity which is enhanced in combination with ADCC active monoclonal antibody therapy. (A-B) FT536 significantly reduced the number of lung and liver (not shown) metastases compared to CAR negative iNK control cells in a murine metastatic melanoma model using B16-F10 cells engineered to overexpress human MICA. (C-D) FT536 alone, and in combination with Herceptin, demonstrate significant tumor growth inhibition (TGI) compared to Herceptin alone in an orthotopic xenograft model of human lung adenocarcinoma.

Conclusions Collectively, these studies demonstrate that FT536 is a highly potent, multi-tumor targeting CAR-iNK cell product that is uniform in composition and can be effectively and safely used off-the-shelf for on-demand treatment of multiple solid and hematological malignancies. An IND submission is planned for 2021, with an initial Phase 1 clinical trial to follow.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.117>