

## INTERIM PHASE I CLINICAL DATA OF FT538, AN OFF-THE-SHELF, MULTIPLEXED-ENGINEERED, iPSC-DERIVED NK CELL THERAPY, COMBINED WITH MONOCLONAL ANTIBODIES IN PATIENTS WITH ADVANCED SOLID TUMORS

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**Background** Clonal induced pluripotent stem cell (iPSC) lines serve as a renewable source for mass production of immune cells, enabling engineered cell therapies to be administered off-the-shelf in multi-dose regimens to patients, including in combination with other anti-cancer agents. In preclinical solid tumor models, iPSC-derived natural killer (NK) cells have been observed to synergize with monoclonal antibodies (mAbs), including anti-PD-1/L1 checkpoint blockade and antibody-dependent cellular cytotoxicity (ADCC)-competent mAbs, resulting in greater anti-tumor activity. FT538, a first-of-its-kind, multiplexed-engineered NK cell therapy generated from a clonal master engineered iPSC line, incorporates 3 synthetic elements for enhanced innate immunity: (1) high-affinity 158V, non-cleavable CD16 Fc receptor that maximizes ADCC; (2) IL-15/IL-15 receptor fusion that promotes cytokine-autonomous persistence; (3) CD38 knockout that provides improved metabolic fitness and resistance to oxidative stress within the tumor microenvironment.<sup>1</sup> We intend to report initial clinical data from a Phase I study of FT538 combined with mAbs in patients with advanced solid tumors.

**Methods** FT538-102 is a Phase I dose-escalation study (ClinicalTrials.gov: NCT05069935) investigating FT538 combined with anti-PD-1/L1 or ADCC-competent mAbs in advanced solid tumors. Treatment consists of two, 29-day treatment cycles, each consisting of 3 days outpatient conditioning chemotherapy (cyclophosphamide 500 mg/m<sup>2</sup> and fludarabine 30 mg/m<sup>2</sup>), followed by 3 outpatient once-weekly doses of FT538; mAbs are administered at standard dose and schedule. Key study endpoints include determining the recommended Phase II dose, safety and tolerability, anti-tumor activity, pharmacokinetics, and anti-product immunogenicity of FT538.

Dose escalation is based on a modified toxicity probability interval algorithm dose-escalation design with a starting dose level of 100 million FT538 cells/dose in combination with avelumab or pembrolizumab in PD-L1-expressing solid tumors; trastuzumab in HER2-expressing tumors; or cetuximab in colorectal cancer, squamous head and neck or lung cancers, or epidermal growth factor receptor-mutated lung cancer.

**Results** As of 14 July 2022, 7 patients were treated at the first dose level of 100 million FT538 cells/dose combined with avelumab (3), trastuzumab (1), or cetuximab (3). No dose-limiting toxicities, and no events of any grade of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or graft vs. host disease, were reported. No FT538 treatment-related Grade  $\geq$ 3 adverse events (AEs), or serious AEs were observed. Dose escalation is ongoing.

**Conclusions** Interim clinical data, including safety and tolerability and initial anti-tumor activity, from the ongoing Phase I dose-escalation study of FT538 combined with anti-PD-1/L1 or ADCC-competent mAbs in advanced solid tumors will be presented at the conference.

### REFERENCE

1. Woan KV, Kim H, Bjordahl R, *et al.* Harnessing features of adaptive NK cells to generate iPSC-derived NK cells for enhanced immunotherapy. *Cell Stem Cell.* 2021;**28**(12):2062–2075.e5. doi:10.1016/j.stem.2021.08.013

**Ethics Approval** This study is being conducted in accordance with the Declaration of Helsinki and was approved by all Institutional Review Boards from each clinical site participating in the study. Specific approval numbers can be provided upon request.

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