COMBINING FT536, A PAN-TUMOR TARGETING CAR NK CELL THERAPY, WITH CD16 ENGAGERS PROVIDES A COORDINATED TARGETING STRATEGY TO OVERCOME TUMOR HETEROGENEITY

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Background The hurdles of tumor antigen heterogeneity, a paucity of tumor-specific antigens, and pervasive immune evasion remain as significant challenges to the successful development of solid tumor immunotherapies. Despite clinical success against hematological malignancies, broader clinical application and efficacy of autologous chimeric antigen receptor (CAR)-T cell therapy remains limited. To remedy these intrinsic challenges, CAR-T cell therapy, immune checkpoint inhibition, and bi-specific engagers are being utilized in combination to extend their therapeutic application to solid tumors.

Methods We have previously presented FT536, a multiplex-engineered clonal master induced pluripotent stem cell (iPSC)-derived NK cell product candidate that incorporates a novel CAR targeting the pan-tumor associated MICA and MICB (MICA/B) stress proteins (3MICA/B CAR). FT536 has been shown to overcome multiple tumor immune evasion mechanisms, to elicit significant and broad CAR-mediated anti-tumor cytotoxic effector function, and to provide multi-antigen targeting capability through expression of a high-affinity, non-cleavable CD16 (hnCD16) Fc receptor.

Results In addition to innate cytotoxicity and MICA/B-specific activity against multiple solid tumor targets, we here demonstrate that the combination of FT536 with multiple Fc receptor engagers results in potent ADCC as well as CAR activity. ADCC was established using monoclonal antibodies (mAbs) targeting EGFR and HER2, a bi-specific c-met/EGFR mAb (amivantamab), and bi-specific NK cell engagers. Combining FT536 with conventional mAbs, bi-specific mAbs such as amivantamab, and/or bispecific NK cell engagers provides additional non-clinical evidence that multi-antigen-specific tumor targeting affords potent cytotoxicity responses in preclinical models that recapitulate patient tumor heterogeneity and antigen expression variation. We hypothesize that multi-antigen targeting of solid tumors could provide a novel approach to minimize antigen selection and immune escape.

Conclusions To assess the clinical translation potency of multi-antigen targeting and combinatorial therapeutic application of FT536 in humans, a phase I first-in-human, dose-escalation clinical study of FT536 as monotherapy and in combination with tumor-targeting mAb therapy, including amivantamab, for the treatment of multiple solid tumor indications was designed and is currently enrolling (NCT05395052).