Combining FT536, a pan-Tumor Targeting CAR NK Cell Therapy, with CD16 Engagers Provides a Coordinated Strategy to Overcome Tumor Heterogeneity

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INTRODUCTION & GRAPHICAL ABSTRACT

- Tumor heterogeneity, the paucity of tumor-specific antigens and pervasive immune evasion remain a significant challenge to the development of efficacious solid tumor immunotherapies.
- Immune checkpoint inhibition and bi-specific engagers are increasingly utilized in combination to enhance therapeutic applications against solid tumors.
- FT536 is a multiplexed-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 (MICA/B).
- We have previously presented that FT536 can overcome multiple tumor immune evasion mechanisms; eliciting significant and broad CAR-mediated anti-tumor cytotoxic effector function; and contains the ability for multi-antigen targeting through its expression of high-affinity, non-cleavable CD16 (hCD16) Fc receptor.
- We here demonstrate that combining FT536 with monoclonal antibodies (mAbs) targeting EGFR, HER2, and a bi-specific c-met/EGFR mAb (amivantamab) results in potent antibody dependent cellular cytotoxicity (ADCC) and provides additional evidence that multi-antigen-specific tumor targeting affords potent cytotoxicity responses in models of tumor heterogeneity.
- We hypothesize that multi-antigen targeting of solid tumors could provide a novel approach to minimize antigen selection and immune escape through antigen-sculpting.
- To assess the potency of multi-antigen targeting and combinatorial therapeutic application 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).

Off-the-shelf Multiplex-Engineered Cell Therapy Platform

- Multiplexed Engineered iPSC clones selected
- Clones with copy number & locus-targeted
- Clones maintaining pluripotency
- Clones free of reprogramming vectors
- Clones demonstrating genomic stability
- Clones without off-target effects
- Clones with ideal propensity to become NK cells
- Clones with desired functional activity & specificity
- Selected FT536 MCB passing all test criteria

Fate Therapeutics’ induced pluripotent stem cell (iPSC) product platform enables mass production of off-the-shelf, engineered, homogeneous cell products that can be administered with multiple doses to deliver more effective pharmacologic activity, including in combination with cycles of other cancer treatments.

FT536: Off-the-Shelf Multi-Antigen-Targeting NK Cell Immunotherapy

MICA/B CAR: Novel Chimeric antigen receptor targeting the membranous a3 domain of MICA/B. Ferrari de Andrade et al. Science 30 Mar 2018. DOI: 10.1122/science.aaq0059


Cohort A (autologous): Locally advanced or metastatic non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer, ovarian cancer or pancreatic cancer.

Cohort B (allogeneic): NSCLC, pemetrexed-sensitve adenocarcinoma, head and neck squamous cell carcinoma, or urothelial carcinoma with documented PD-L1 expression. Microsatellite unstable/mismatch repair deficient CRC.

Cohort C (allogeneic): Any solid tumor cancer with HER2 IHC 3+ or Average HER2 copy number ≥ 24 per cell.

Cohort D (allogeneic): CRC that has relapsed or progressed following prior EGFR mAb treatment or has KRAS/NRAS mutation HNSCC that has relapsed or progressed following prior retinoblast treatment.

NSCLC with EGFR driver mutation and progression or were not candidates for EGFR TKI. MET exon 14 skipping mutation progressed or were not candidates for MET TKI. MET amplification with MET/CYP2B11 ratio ≥ 1.8 or gene copy number ≥ 5.

Exclusion: ECOG ≥ 2; Insufficient hematologic, renal, hepatic, pulmonary, or cardiac function; Requiring systemic steroids or history of autoimmune disease; Uncontrolled infection.

Eligibility Criteria

Inclusion: Disease relapse or progression after at least one line of therapy; Measurable disease by RECIST

Cohort specific inclusion criteria:

Cohort A

Cohort B & C (allogeneic): HNSCC, colorectal cancer (CRC), breast cancer, ovarian cancer or pancreatic cancer.

Cohort D (allogeneic): CRC that has relapsed or progressed following prior EGFR mAb treatment or has KRAS/NRAS mutation HNSCC that has relapsed or progressed following prior retinoblast treatment.

NSCLC with EGFR driver mutation and progression or were not candidates for EGFR TKI. MET exon 14 skipping mutation progressed or were not candidates for MET TKI. MET amplification with MET/CYP2B11 ratio ≥ 1.8 or gene copy number ≥ 5.

Exclusion: ECOG ≥ 2; Insufficient hematologic, renal, hepatic, pulmonary, or cardiac function; Requiring systemic steroids or history of autoimmune disease; Uncontrolled infection.

Table 1: First monotherapy FT536 escalation cohort (100 million cells/dose)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Type</th>
<th>Prior Lines of Therapy</th>
<th>Activity to Last Therapy</th>
<th>Number of FT536 Doses</th>
<th>DLT &amp; CR</th>
<th>Change in Tumor</th>
<th>Change in CR</th>
<th>Change in PD</th>
<th>Change in NR</th>
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Phase 1 Clinical Trial Interim Summary

- Three patients treated with one cycle of starting dose of 100 million cells/dose x 3 doses.
- No DLTs, CRs or ICANS were reported.
- Monotherapy escalation continuing at 300 million cells/dose.
- Dose escalation in combination with mAbs has been initiated at 100 million cells/dose.

SUMMARY

- MICA and MICB stress antigens are ubiquitously expressed in solid tumors and in combination with other tumor associated antigens, such as EGFR, represent a comprehensive approach to targeting bulky tumors that are often heterogeneous.
- FT536 efficiently targets MICA and MICB stress antigens and provides broad anti-tumor reactivity and superior efficacy relative to peripheral blood NK cells and primary T cells expressing NKKG2D or HER2 CAR.
- The combination of FT536 with multiple CD16 engagers, including therapeutic mAbs, results in additive functional activity between CAR and ADCC, eliciting durable tumor growth inhibition and mitigating antigen escape seen with heterogeneous tumors.
- FT536:101 Phase I Clinical Trial has safely administered 1 cycle of FT536 at 100 million cells/dose to 3 patients without any detected DLT, CRs or ICANS with plans to combine with ADCC-competent mAbs.