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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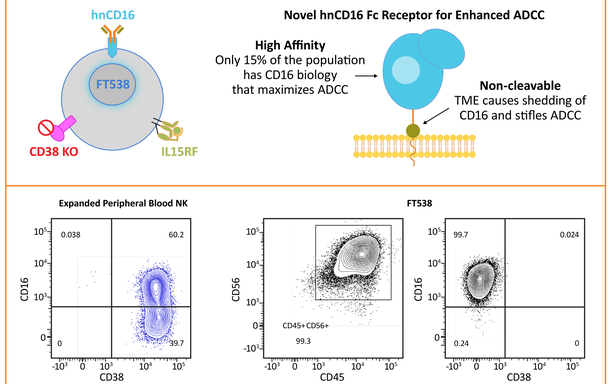
BACKGROUND

- Clonal master engineered induced pluripotent stem cell (iPSC) lines serve as a renewable source for mass production of immune cells, enabling multiplexed-engineered cell therapies that are uniform in composition to be administered off-the-shelf in multi-dose regimens, including in combination with other anti-cancer agents, to patients.
- FT538 is a first-of-kind, multiplexed-engineered natural killer (NK) cell therapy generated from a clonal master engineered iPSC line that incorporates 3 synthetic elements for enhanced innate immunity (**Figure 1**).
  (1) High-affinity 158V, non-cleavable CD16 (hnCD16) Fc receptor to synergize with monoclonal antibodies (mAbs) and enhance antibody-dependent cellular cytotoxicity (ADCC).
  (2) Interleukin-15 (IL-15)/IL-15 receptor fusion that promotes cytokine-autonomous persistence, which obviates the need for exogenous cytokine support.
  (3) CD38 knockout that provides improved metabolic fitness and resistance to oxidative stress within the tumor microenvironment (Woan et al. 2021).
- In preclinical solid tumor models, FT538 was observed to promote ADCC when combined with mAbs to enhance anti-tumor activity (**Figure 2**).
- Next-generation therapies based on the FT538 backbone expressing chimeric antibody receptors (CARs) targeting B-cell maturation antigen (BCMA) (FT576, ClinicalTrials.gov: NCT05182073) and major histocompatibility complex class I chain-related proteins A and B (MICA/B) (FT536, ClinicalTrials.gov: NCT05395052) have been developed and are currently under clinical investigation.

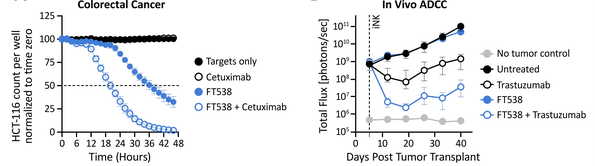
Figure 1. FT538 (hnCD16; IL-15 Receptor Fusion; CD38 Knockout)



The phenotype of FT538 is characterized by uniformly high expression levels of CD16 and absence of CD38 expression, in contrast to the phenotype of expanded peripheral blood NK cells.

ADCC = Antibody-dependent cellular cytotoxicity; hnCD16 = High-affinity 158V, non-cleavable CD16; IL-15RF = Interleukin-15 receptor fusion; NK = Natural killer; TME = Tumor microenvironment

Figure 2. FT538 Cells Mediate ADCC Against Solid Tumor Targets when Combined with Monoclonal Antibodies



FT538 elicits potent activity when combined with the ADCC-competent mAbs trastuzumab and cetuximab in vivo and in vitro, respectively. **Panel A:** FT538 cells were co-cultured with HCT-116 colorectal cancer cells for 48 hours in the presence or absence of cetuximab to elicit ADCC. Cytotoxicity of the HCT-116 cells was assessed using the Incucyte® imaging system. **Panel B:** NSG mice were transplanted intraperitoneally with the SKOV-3 ovarian cancer line. Five days post-transplant, mice were treated with 2.5E6 FT538 cells, 5 mg/kg trastuzumab, or the combination of FT538 and trastuzumab to elicit ADCC. Tumor progression was monitored by weekly bioluminescence imaging.

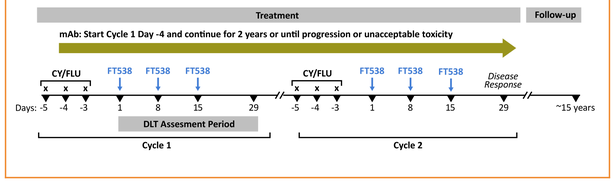
ADCC = Antibody-dependent cellular cytotoxicity; mAb = Monoclonal antibody; NSG = NOD scid gamma

METHODS

FT538 Phase I Study

- Study FT538-102 (ClinicalTrials.gov: NCT05069935) is a multi-arm, dose-escalating Phase I study of FT538 combined with anti-PD-1/L1 or ADCC-competent mAbs in patients with advanced solid tumors.
- FT538 dose escalation is ongoing to evaluate FT538 at up to 1.5 billion cells/dose.
- Patients will receive 2 cycles of initial treatment (**Figure 3**):
  - Conditioning chemotherapy (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2) for 3 days at the start of each cycle
  - 3 once-weekly doses/cycle of FT538
    - FT538 dose escalation utilizing a modified toxicity probability interval algorithm dose-escalation design
    - FT538 dose levels ranging from 100 million cells/dose up to 1.5 billion cells/dose
  - mAb (anti-PD-1/PD-L1 antibody, trastuzumab, cetuximab) administered at standard dose and schedule
  - No exogenous cytokine support
  - Patients whose disease progressed or relapsed following initial objective response to FT538 have the option to receive 2 additional treatment cycles (Cycles 3 and 4).
- No mandatory hospitalization required for study treatment administration
- Disease response assessed using RECIST v1.1 (Eisenhauer et al. 2009)

Figure 3. Dosing Schedule: FT538 + Monoclonal Antibody



CY = Cyclophosphamide; DLT = Dose-limiting toxicity; FLU= Fludarabine; mAb = Monoclonal antibody

Key Eligibility Criteria

Inclusion

- Advanced or metastatic solid tumor
- Disease relapse or progression after at least one line of therapy
- No currently approved therapies expected to improve survival are available or have been declined
- Measurable disease by RECIST

Exclusion

- ECOG PS ≥2
- Insufficient hematologic, renal, hepatic, pulmonary, or cardiac function
- Requiring systemic steroids or history of autoimmune disease
- Active bacterial, fungal or viral infection

Diagnosis of one of the following:

FT538 + anti-PD-1/PD-L1 antibody:
- NSCLC, gastroesophageal adenocarcinoma, HNSCC, TNBC, or UC with documented PD-L1 expression

FT538 + trastuzumab:
- Any solid tumor with documented HER2 IHC ≥2+; or
- Average HER2 copy number ≥4 signals per cell by in situ hybridization

FT538 + cetuximab:
- CRC that has relapsed or progressed following prior EGFR mAb treatment or has KRAS/NRAS mutation
- HNSCC that has relapsed or progressed following prior cetuximab treatment
- Squamous cell or EGFR-mutated NSCLC

CRC = Colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = Epidermal growth factor receptor; HER2 = Human epidermal growth factor receptor 2; HNSCC = Head and neck squamous cell carcinoma; IHC = Immunohistochemistry; mAb = Monoclonal antibody; NSCLC = Non-small cell lung cancer; PD-L1 = Programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; TNBC = Triple-negative breast cancer; UC = Urothelial carcinoma

- We report initial clinical data from 8 patients who were treated at the first dose level of FT538 (100 million cells/dose) in combination with avelumab, trastuzumab, or cetuximab, based on a data cutoff date of 15 August 2022, unless otherwise noted.

References:
Eisenhauer EA, Therasse P, Bogaerts J, et al. *Eur J Cancer.* 2009;45:228-47.
Goulding J, Hancock B, Blum R, et al. SITC Annual Meeting. 2022 (Abstract 204).
Woan KV, Kim H, Bjordahl R, et al. *Cell Stem Cell.* 2021;28(12):2062-2075.e5.

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RESULTS

Interim Phase I Dose-Escalation Clinical Data

Table 1. Patient Demographics and Baseline Characteristics

Cohort	Patient No.	Age / Sex	Tumor Type	No. Lines of Prior Therapy	Refractory to Last Prior Therapy[a]	Refractory to Last Prior mAb with Similar Target[a,b]
FT538 100 Million Cells/Dose + mAb						
FT538 + Avelumab	1	59 / F	NSCLC	4	Yes	Yes
	2	69 / F	HNSCC	4	Yes	No
	3	67 / M	NSCLC	3	Yes	Yes
FT538 + Trastuzumab	1	77 / M	Extramammary Paget Disease	0	NA	NA
	2	66 / M	GEJ Cancer	5	Yes	Yes
FT538 + Cetuximab	1	61 / F	Colon Cancer[c]	4	No	No
	2	65 / F	Colon Cancer[c]	3	Yes	NA
	3	49 / M	Colon Cancer[c]	3	Yes	NA

[a] Refractory disease defined as best overall response of stable disease/no response or progressive disease.
[b] Last prior mAb with similar/same target as the assigned cohort.
[c] NRAS/KRAS mutation.

F = Female; GEJ = Gastroesophageal junction; HNSCC = Head and neck squamous cell carcinoma; M = Male; mAb = Monoclonal antibody; NA = Not applicable; No. = Number; NSCLC = Non-small cell lung cancer

Table 2. Patient Safety, Response, and Disposition

Cohort	Patient No.	FT538 Doses Received	Safety: DLTs	Safety: Related Grade ≥3 AEs	Safety: Related SAEs	Best Overall Response (RECIST)	Disposition: Days on Study Treatment	Disposition: Reason for Treatment Discontinuation
FT538 100 Million Cells/Dose + mAb								
FT538 + Avelumab	1	3	None	None	None	NE	43	Disease Progression[c]
	2	4[a]	None	None	None	SD	71+	NA
	3	3	None	None	None	SD	98	PI Decision
FT538 + Trastuzumab	1[b]	6	None	None	None	PR	65+	NA
	2	6	None	None	None	PD	64	Disease Progression
FT538 + Cetuximab	1	3	None	None	None	PD	50	Subject Decision
	2	6	None	None	None	SD	107	Disease Progression
	3	6	None	None	None	SD	123	Disease Progression

[a] Patient had 2 doses of FT538 withheld in Cycle 2 because of Grade 3 SAEs of nausea and vomiting considered related to conditioning chemotherapy and considered not related to FT538.
[b] Clinical data for subject based on data cutoff date of 27 September 2022.
[c] Discontinued due to clinical progression not assessed radiographically.

AE = Adverse event; DLT = Dose-limiting toxicity; mAb = Monoclonal antibody; NA = Not applicable; NE = Not evaluable; PD = Progressive disease; PI = Principal Investigator; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = Serious adverse event; SD = Stable disease

Baseline Characteristics

- 6 of 8 patients had Stage IV disease at the time of entry.
- Patients were heavily pre-treated with a median of 3 prior lines of therapy.
- 5 of 8 patients received prior cohort-specific mAbs; 3 were refractory to prior mAb-containing treatment.

Safety

- No dose-limiting toxicities (DLTs), serious adverse events (SAEs), or Grade ≥3 adverse events (AEs) considered related to FT538 were observed.
- No cases of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) were observed.
- No FT538- or mAb-related treatment discontinuations or deaths were observed.
- Grade ≥3 treatment-emergent AEs in ≥2 patients, all of which were considered unrelated to FT538 or mAb, included neutrophil count decreased (7), white blood cell count decreased (5), lymphocyte count decreased (2), and platelet count decreased (2).

Multi-dose Tolerability

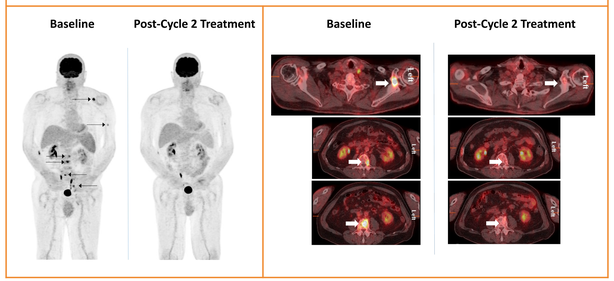
- All 8 patients completed at least 1 cycle (3 doses) of treatment with FT538.
- 5 patients continued to a second cycle of FT538, with 4 patients completing 2 cycles (6 doses) of treatment. One patient received 4 doses of FT538, with 2 doses withheld in Cycle 2 because of nausea and vomiting considered related to conditioning chemotherapy and considered not related to FT538.
- 6 patients discontinued study treatment due to disease progression, investigator decision, or subject decision.

Efficacy

- Of the 8 patients, 7 patients were assessed radiographically for response:
  - 1 achieved best response of partial response (PR)
  - 4 achieved best response of stable disease (SD)
  - 2 patients were reported to have progressive disease (PD)
- 1 patient was reported to have clinical progression in the absence of radiographical assessment.

Patient Case Study

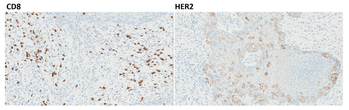
Figure 4. Partial Response Following FT538 + Trastuzumab Treatment in Extramammary Paget Disease



Images courtesy of Tanner M. Johanns, MD, PhD, Division of Oncology, Washington University, St. Louis, MO.

- 77-year-old male diagnosed with metastatic extramammary Paget disease that failed initial surgical control and with multi-focal lymph node and bone lesions at baseline.
- Treatment with 2 cycles (6 doses) of FT538 at 100 million cells/dose in combination with trastuzumab was well tolerated; no events of CRS, ICANS, or GvHD of any grade were observed.
- Achieved PR on Study Day 65 with complete resolution of all lesions except bone lesions; patient continues on study.

Figure 5. CD8 and HER2 IHC Staining of Pre-treatment Biopsy

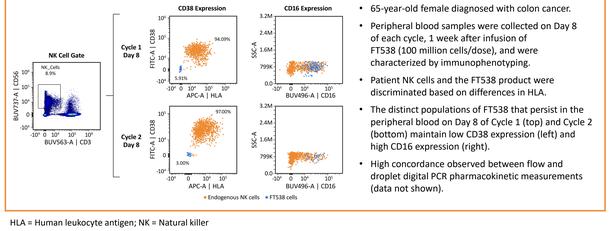


IHC analysis of pre-treatment tumor biopsy showed high CD8+ T-cell infiltration (13.9%), 2+ HER2 expression, PD-L1 expression detected on 1% of immune cells but not on tumor cells, and 90% tumor MHC-I positivity.

HER2 = Human epidermal growth factor 2; IHC = Immunohistochemistry; MHC-I = Major histocompatibility complex class I; PD-L1 = Programmed death-ligand 1

Translational Data

Figure 6. Detection of FT538 Cells in Peripheral Blood after Infusion of 100 Million Cells/Dose



- 65-year-old female diagnosed with colon cancer.
- Peripheral blood samples were collected on Day 8 of each cycle, 1 week after infusion of FT538 (100 million cells/dose), and were characterized by immunophenotyping.
- Patient NK cells and the FT538 product were discriminated based on differences in HLA.
- The distinct populations of FT538 that persist in the peripheral blood on Day 8 of Cycle 1 (top) and Cycle 2 (bottom) maintain low CD38 expression (left) and high CD16 expression (right).
- High concordance observed between flow and droplet digital PCR pharmacokinetic measurements (data not shown).

HLA = Human leukocyte antigen; NK = Natural killer

CONCLUSIONS AND FUTURE DIRECTIONS

- Of 7 patients available for radiographic assessment, 1 patient achieved a best response of PR and 4 patients achieved a best response of SD.
- Up to 6 doses of FT538 (100 million cells/dose), combined with avelumab, cetuximab, and trastuzumab, were safely administered in 8 patients in the outpatient setting.
- The multi-dose treatment schedule was well tolerated, with no events of CRS, ICANS, or GvHD were observed. There were no FT538-related DLTs, SAEs, or Grade ≥3 AEs reported, and dose escalation continues at 300 million cells/dose.
- These data support ongoing evaluation of the next-generation product FT536 (Goulding et al. 2022), which is engineered to express MICA/B CAR on an FT538 backbone, in combination with mAbs in patients with advanced solid tumors.