A Phase I Study of FT538, an Off-the-Shelf, Multiplexed-Engineered, iPSC-Derived NK Cell Therapy in Combination with Daratumumab in Relapsed/Refractory Multiple Myeloma

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INTRODUCTION

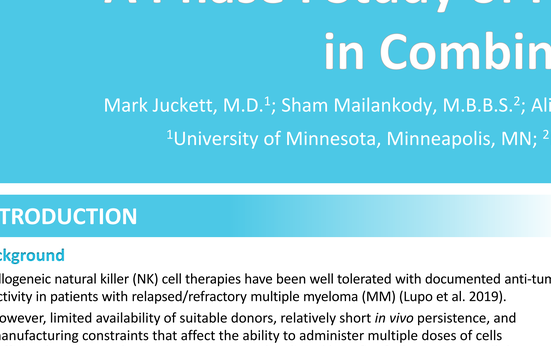
Background

- Allogeneic natural killer (NK) cell therapies have been well tolerated with documented anti-tumor activity in patients with relapsed/refractory multiple myeloma (MM) (Lupo et al. 2019).
- However, limited availability of suitable donors, relatively short *in vivo* persistence, and manufacturing constraints that affect the ability to administer multiple doses of cells sufficiently are major barriers to maximizing the clinical benefit of allogeneic NK cell therapy.
- Induced pluripotent stem cell (iPSC)-derived immune effector cells offer distinct advantages over existing patient- and donor-derived therapeutic approaches, notably the use of a clonal master engineered iPSC line as a renewable source for the mass production of multiplexed-engineered immune cells of uniform composition for off-the-shelf availability, repeated dosing, and broad patient access.

FT538

- FT538 is a first-of-kind, multiplexed-engineered NK cell therapy generated from a clonal master engineered iPSC line that incorporates 3 synthetic elements designed 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 prevents fratricide when FT538 is combined with daratumumab and also provides improved metabolic fitness and resistance to oxidative stress within the tumor microenvironment (Woan et al. 2021).
- In preclinical studies, FT538 displays increased persistence without the need for exogenous cytokine support and, when combined with daratumumab against MM targets, demonstrates avoidance of daratumumab-mediated fratricide and significantly enhanced ADCC *in vitro* in a serial stimulation cytotoxicity assay compared with peripheral blood NK cells.
  - The combination of FT538 and daratumumab led to highly effective tumor control compared with daratumumab alone in an *in vivo* MM xenograft model (Bjordahl et al. 2019; **Figure 2**).

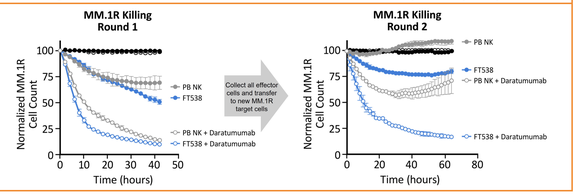
Figure 1. FT538 (hnCD16; IL-15 Receptor Fusion; CD38 Knockout)



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; KO = Knockout; NK = Natural killer; TME = Tumor microenvironment

Figure 2. FT538 Cells Persist and Mediate ADCC in a Restimulation Cytotoxicity Assay



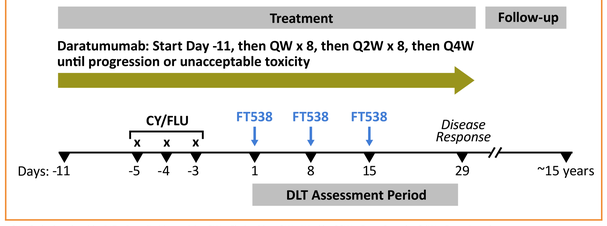
FT538 or PB NK cells were used as effectors in the presence or absence of daratumumab in a 42-hour cytotoxicity assay against the MM1.R cell line. After the 42-hour co-culture period, all remaining effector cells were collected and transferred to new MM1.R target cells. In contrast to PB NK, FT538 cells maintained ADCC in both co-cultures with MM1.R target cells.
Solid black circles = MM.1R target cells alone, which is normalized to 100%. Open black circles = MM.1R target cells + daratumumab. All groups are normalized against the MM.1R target cells alone. ADCC = Antibody-dependent cellular cytotoxicity; MM.1R = Multiple myeloma cell line; NK = Natural killer; PB = Peripheral blood

METHODS

FT538-101 Phase I Study

- FT538-101 is an open-label, multicenter, Phase I clinical trial designed to assess the safety and activity of multiple doses of FT538 as monotherapy in relapsed/refractory acute myelogenous leukemia and in combination with mAbs in relapsed/refractory MM (ClinicalTrials.gov: NCT04614636).
- We report clinical data from the ongoing dose-escalation study of the first 9 patients treated with FT538 in combination with daratumumab in relapsed/refractory MM (Regimen B), based on a data cutoff date of 13 October 2022.
- Study Objectives
  - **Primary objectives:** Assess safety and tolerability and to determine the recommended Phase II dose of FT538
  - **Additional objectives:** Assess anti-tumor activity, pharmacokinetics, pharmacodynamics, and minimal residual disease (MRD) rate (Adaptive clonoSEQ® assay)
- Study Treatment (**Figure 3**)
  - Conditioning chemotherapy (cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2) given intravenously (IV) for 3 days prior to the first dose of FT538
  - FT538 administered IV in 3 once-weekly doses
  - Daratumumab administered at standard dose and schedule
- FT538 dose escalation based on a standard 3 + 3 dose-escalation design, with a starting dose of 100 million cells/dose in Regimen B
- No mandatory hospitalization required for study treatment administration
- Disease response assessed using the International Myeloma Working Group (IMWG) standard response criteria (Kumar et al. 2016)
- Patients followed for up to 15 years for safety, anti-tumor activity, and survival

Figure 3. FT538 + Daratumumab Dosing Schedule (Regimen B)



CY = Cyclophosphamide; DLT = Dose-limiting toxicity; FLU = Fludarabine; QW = Weekly; Q2W = Every 2 weeks; Q4W = Every 4 weeks

Key Eligibility Criteria

Inclusion	Exclusion
• Patients with relapsed/refractory MM who received ≥2 prior therapies, including a PI and an IMiD	• ANC <1000/µL
• Prior treatment with anti-CD38 mAbs, BCMA-targeted agents, or BCMA-targeted immunotherapies (CAR-T cells, bispecific immune-cell engagers) is permitted	• Platelets <75,000/µL – Cytopenias due to significant bone marrow involvement by disease may be eligible with Medical Monitor approval
• Measurable disease defined by at least one of the following: – Serum M-protein ≥1.0 g/dL – Urine M-protein ≥200 mg/24 hours – Involved serum free light chains ≥10 mg/dL, with an abnormal kappa/lambda ratio, in patients with disease not measurable by serum or urine M-protein	• CrCl <50 mL/min by Cockroft-Gault or other institutional method • Total bilirubin >1.5 × ULN, except for known Gilbert syndrome • AST/ALT >3 × ULN • Active CNS involvement by myeloma

ALT = Alanine transaminase; ANC = Absolute neutrophil count; AST = Aspartate transaminase; BCMA = B-cell maturation antigen; CAR = Chimeric antigen receptor; CNS = Central nervous system; CrCl = Creatinine clearance; IMiD = Immunomodulatory drug; mAb = Monoclonal antibody; MM = Multiple myeloma; PI = Proteasome inhibitor; ULN = Upper limit of normal

RESULTS

Table 1. Patient Demographics and Baseline Characteristics

FT538 Cells/Dose	Patient #	Age / Sex	ISS Stage	Cytogenetic Risk	BMPC %	# of Prior Therapies	Prior Dara[a]	Prior HSCT	IMiD / PI Refractory	Triple Refractory	Refractory to Last Treatment
100 Million Cells	1	73 / F	1	High	9	2	N	Y	Y / N	N	Y
	2	66 / F	1	Standard	90	4	Y	Y	Y / Y	Y	Y
	3	57 / M	3	High	79	2	N	Y	Y / Y	N	N
	4	75 / F	1	High	30	7	Y	Y	Y / Y	Y	Y
300 Million Cells	5	62 / M	1	Standard	20	3	N	Y	Y / N	N	N
	6	61 / M	3	Standard	40	4	N	Y	Y / N	N	N
	7	65 / F	3	Standard	10	4	Y	N	Y / Y	Y	Y
1 Billion Cells	8	77 / M	2	Standard	20	5	Y	Y	Y / Y	Y	N
	9	74 / M	2	High	50	3	Y	Y	Y / Y	Y	Y

[a] All patients who received prior daratumumab were daratumumab refractory.
BMPC = Bone marrow plasma cell; Dara = Daratumumab; F = Female; HSCT = Hematopoietic stem cell transplantation; IMiD = Immunomodulatory drug; ISS = International Staging System; M = Male; N = No; PI = Proteasome inhibitor; Y = Yes

Baseline Characteristics

- Patients were heavily pre-treated with a median of 4 prior lines of therapy (range 2-7).
- Of the 9 patients:
  - 8 patients received prior hematopoietic stem cell transplantation (HSCT).
  - 5 patients were triple refractory to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb.
  - 5 patients were refractory to last prior therapy.

Table 2. Patient Safety, Response, and Disposition

FT538 Cells/Dose	Patient #	Safety					Best Overall Response	Follow-Up Time (Days)[a]
		DLTs	CRS	ICANS	Related Grade ≥3 AEs	Related SAEs		
100 Million Cells	1	N	N	N	N	N	MR	288
	2	N	N	N	N	N	SD	273
	3	N	N	N	N	N	PR	191
	4	N	N	N	N	N	PR	172+
300 Million Cells	5	N	N	N	Y	N	MR	189
	6	N	N	N	N	N	PR	108+
	7	N	N	N	N	N	SD	44
1 Billion Cells	8	N	N	N	N	N	SD	81+
	9	N	N	N	N	N	PD	29

[a] For subjects who have progressed, died, or started subsequent anti-systemic cancer therapy, follow-up is from Day 1 to the earliest date of progression, death, or start of subsequent anti-systemic cancer therapy, whichever occurs first. For subjects who are ongoing, follow-up is from Day 1 to the last on-study assessment date. The "+" indicates that patients are continuing in active follow-up.

AE = Adverse event; CRS = Cytokine release syndrome; DLT = Dose limiting toxicity; ICANS = Immune cell-associated neurotoxicity syndrome; MR = Minimal response; N = None; PD = Progressive disease; PR = Partial response; SAE = Serious adverse event; SD = Stable disease

Safety

- No dose-limiting toxicities and no events of any grade of cytokine release syndrome (CRS), immune cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) were observed.
- One Grade ≥3 treatment-emergent adverse event (AE) related to FT538 was reported—Grade 4 neutrophil count decreased with a duration of 8 days—and completely resolved.
- There were no serious AEs related to FT538.
- Grade ≥3 treatment-emergent AEs not related to FT538 in ≥2 patients included: neutrophil count decreased, lymphocyte count decreased, and anemia.
- No deaths were related to FT538.

Multi-dose Tolerability

- All patients received all prescribed doses of FT538.
- No study discontinuations or deaths due to treatment-emergent AEs occurred.
- 1 patient died of an unknown cause on Study Day 76, which was not considered related to FT538 by the study investigator.

Anti-tumor Activity

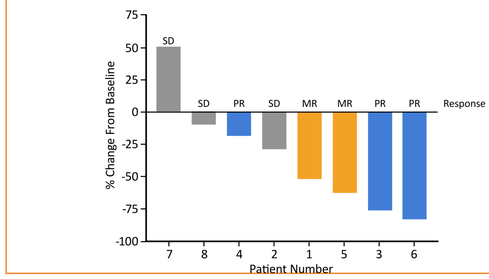
- Of the 9 patients, 5 had a decrease in their myeloma disease burden (40%-75% decrease) with 3 patients with confirmed partial response and 2 patients with minimal response at Day 29.
- 8 of 9 patients showed a treatment-induced decrease in anti-myeloma markers.

Pharmacokinetics & Immunogenicity

- Pharmacokinetic assessment in MM patients detected FT538 after each dose, with persistence at Day 8 after the first dose.
- No anti-product recognition by patient lymphocytes detected by ELISpot.
- No detection of anti-product human leukocyte antigen (HLA) Class I antibodies in patients' serum.

Pharmacodynamics

Figure 4. Percentage Change in sBCMA Levels Day 29 Relative to Baseline By Response



sBCMA levels were measured at baseline and Day 29 after treatment with FT538 in combination with daratumumab. The percent change from baseline is graphed based on patient response after 1 cycle of treatment.
Data pending for Patient No. 9.
MR = Minimal response; PR = Partial response; sBCMA = soluble B-cell maturation antigen; SD = Stable disease

- Treatment-induced decreases in myeloma markers, serum free light chain (sFLC) and soluble B-cell maturation antigen (sBCMA), correlate with response.

CONCLUSIONS & FUTURE DIRECTIONS

- Administration of up to 3 doses of FT538 in combination with daratumumab is safe and well-tolerated:
  - No events of any grade of CRS, ICANS, or GvHD occurred.
  - 1 Grade ≥3 treatment-emergent AE related to FT538 was reported—Grade 4 neutrophil count decreased with a duration of 8 days—and completely resolved.
  - No serious AEs related to FT538 occurred.
- Of 9 patients:
  - 5 patients had a decrease in their myeloma disease burden (40%-75%), with 3 subjects with a confirmed objective response (PR) at Day 29.
  - 8 patients had a treatment-induced decrease in sBCMA levels on Day 29 from baseline, where decrease from baseline correlated with response.
- Dose escalation is ongoing.

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