Interim Phase I Clinical Data of FT576 as Monotherapy and in Combination with Daratumumab in Subjects with Relapsed/Refractory Multiple Myeloma

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INTRODUCTION

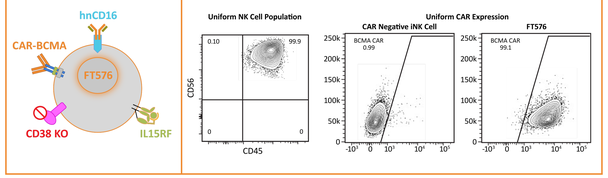
Background

- Despite the recent FDA approval of autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA), relapsed/refractory multiple myeloma (MM) remains an incurable disease and is an area of high unmet medical need.
- Additionally, patient access to autologous CAR T-cell therapies is currently limited due to manufacturing constraints, the need for bridging therapy, and potentially life-threatening toxicities, including cytokine release syndrome (CRS) and neurologic toxicities (Munshi et al. 2021).
- Off-the-shelf natural killer (NK) cell therapies may offer an improved therapeutic profile and broader patient access than autologous CAR T-cell therapies.

FT576

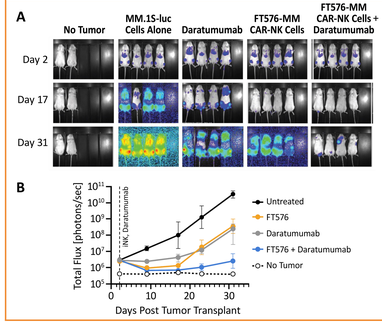
- FT576 is a first-of-kind, multiplexed-engineered, BCMA-targeted CAR NK cell therapy generated from a clonal master engineered induced pluripotent stem cell (iPSC) line, which can be used as a renewable source for the mass production of off-the-shelf NK cells of uniform composition.
- FT576 is engineered with 4 modalities to combine multi-faceted innate immunity with multi-antigen-targeting capability (**Figure 1**):
  - **(1) hnCD16:** High-affinity 158V, non-cleavable CD16 Fc receptor to synergize with monoclonal antibodies (mAbs) and enhance antibody-dependent cellular cytotoxicity (ADCC)
  - **(2) IL-15RF:** Interleukin-15 receptor fusion that promotes cytokine-autonomous persistence, which obviates the need for exogenous cytokine support
  - **(3) CD38 KO:** Mitigates NK cell fratricide by CD38-directed mAbs and provides improved metabolic fitness and resistance to oxidative stress within the tumor microenvironment
  - **(4) CAR-BCMA:** Novel CAR construct that targets B-cell maturation antigen
- These modalities are designed to enhance potency and persistence and to enable multi-antigen targeting when combined with tumor-targeting mAbs.
- In preclinical studies, FT576 combined with the anti-CD38 mAb daratumumab demonstrated highly effective tumor control compared to either treatment alone or to primary CAR T cells in a disseminated MM xenograft model (**Figure 2**; Goodridge et al. 2020), suggestive that limitations in MM treatment confounded by clonal heterogeneity and antigen loss can be overcome with a dual antigen-targeting approach.

Figure 1. FT576: Off-the-Shelf, iPSC-Derived, CAR-BCMA NK Cell Product Candidate



BCMA = B-cell maturation antigen; CAR = Chimeric antigen receptor; hnCD16 = High-affinity 158V, non-cleavable CD16; IL = Interleukin; iNK = iPSC-derived natural killer; iPSC = Induced pluripotent stem cell; KO = Knockout; NK = Natural killer

Figure 2. FT576 Mediates Superior In Vivo Tumor Control



NSG mice were engrafted with 2×10^5 luciferase-transduced MM.1S cells. After 2 days, groups of mice received either no treatment, daratumumab alone, 1×10^7 FT576-MM CAR-NK cells, or 1×10^7 FT576-MM CAR-NK cells with daratumumab.

(A) Bioluminescence imaging of mice on Days 2, 17, and 31.

(B) Graphical representation of the bioluminescence data.

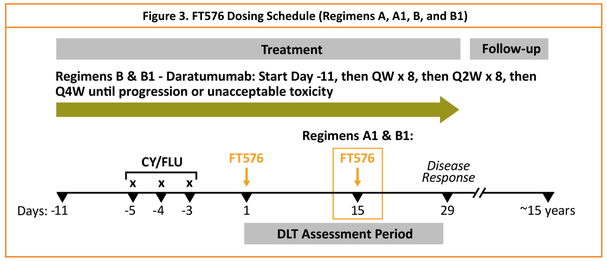
Data on file, Fate Therapeutics, Inc. CAR = Chimeric antigen receptor; MM = Multiple myeloma; NK = Natural killer; NSG = NOD scid gamma

METHODS

FT576-101 Phase I Study

- FT576-101 is an open-label, multicenter, Phase I clinical trial designed to assess the safety and activity of FT576 as monotherapy and in combination with daratumumab in patients with relapsed/refractory MM (ClinicalTrials.gov: NCT05182073).
- We report clinical data from the ongoing dose-escalation study of the first 9 patients treated with FT576 for relapsed/refractory MM, based on a data cutoff date of 07 October 2022.
- Study objectives:
  - **Primary objectives:** Assess safety and tolerability; determine the recommended Phase II dose and dose schedule of FT576
  - **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 FT576
  - FT576 administered IV in the following dosing regimens:
    - **Regimen A:** Single dose of FT576 on Day 1
    - **Regimen B:** Single dose of FT576 on Day 1 in combination with daratumumab
    - **Regimen A1:** Multiple doses of FT576 on Days 1 and 15
    - **Regimen B1:** Multiple doses of FT576 on Days 1 and 15 in combination with daratumumab
- FT576 dose escalation based on a modified toxicity probability interval algorithm dose-escalation design, with a starting dose of 100 million cells
- Daratumumab administered at standard dose and schedule
- Disease response assessed according to the International Myeloma Working Group (IMWG) response criteria and MRD assessment (Kumar et al. 2016)
- Subject to FDA approval, patients with evidence of clinical benefit may be eligible for an additional cycle of study treatment
- Patients followed for up to 15 years for safety, anti-tumor activity, and survival

Figure 3. FT576 Dosing Schedule (Regimens A, A1, B, and B1)



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

Key Eligibility Criteria

Inclusion

- Patients with relapsed/refractory MM who received ≥3 prior therapies, including a PI, an IMiD, and an anti-CD38 mAb (Regimens A, A1)
- Patients with relapsed/refractory MM who received ≥2 prior therapies, including a PI and an IMiD (Regimens B, B1)
  - Prior treatment with an anti-CD38 mAb is permitted; however, the last dose must have been ≥30 days prior to the first dose of FT576
- Prior treatment with BCMA-targeted agents or BCMA-targeted immunotherapies (CAR T cells, bispecific immune-cell engagers) is permitted.
- 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

Exclusion

- ANC <1000/μL
- Platelets <75,000/μL
  - Cytopenias due to significant bone marrow involvement by disease may be eligible with Medical Monitor approval
- 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

FT576 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
Regimen A: FT576 Single Dose, Day 1											
100 Million Cells	1	62 / M	3	Standard	22%	10	Y	Y	Y / N	N	Y
	2	72 / F	1	Standard	1%	6	Y	N	Y / Y	Y	Y
	3	68 / F	2	Standard	0	8	Y	Y	Y / Y	Y	Y
300 Million Cells	4	75 / F	1	Standard	0	5	Y	Y	N / Y	N	Y
	5	81 / M	2	Standard	0	5	Y	Y	Y / Y	Y	Y
	6	74 / M	2	Standard	29%	5	Y	Y	N / N	N	N
Regimen B: FT576 Single Dose, Day 1 + Daratumumab											
100 Million Cells	7	62 / M	1	Standard	95%	3	N	Y	N / N	N	N
	8	65 / M	2	Standard	7%	4	N	Y	N / N	N	N
	9	81 / F	1	High	NE	5	Y	N	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; NE = Not evaluable; PI = Proteasome inhibitor; Y = Yes

Baseline Characteristics

- Patients were heavily pre-treated with a median of 5 prior lines of therapy (range 3-10).
- Of the 9 patients:
  - 7 patients received prior hematopoietic stem cell transplantation (HSCT).
  - 4 patients were triple refractory to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb.
  - 6 patients were refractory to the last prior therapy.

Table 2. Patient Safety, Response, and Disposition

	Patient #	FT576 (Millions of Cells/Dose)	Safety: DLTs	Safety: CRS	Safety: ICANS	Safety: Related Grade ≥3 AEs	Safety: Related SAEs	Best Overall Response	Follow-up Time (Days)[a]
Regimen A	1	100	N	N	N	Y	N	PD	29
	2	100	N	N	N	Y	N	PD	159
	3	100	N	N	N	N	N	SD	130
	4	300	N	N	N	N	N	SD	200+
	5	300	N	N	N	N	N	VGPR	88
	6	300	N	N	N	N	N	SD	29
Regimen B	7	100	N	N	N	N	N	MR	101
	8	100	N	N	N	N	N	PR	151+
	9	100	N	N	N	N	N	SD	89

[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, the 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 effector cell-associated neurotoxicity syndrome; MR = Minimal response; N = No; PD = Progressive disease; PR = Partial response; SAE = Serious adverse event; SD = Stable disease; VGPR = Very good partial response; Y = Yes

Safety

- No dose-limiting toxicities and no events of any grade of CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) were observed.
- 2 patients had Grade ≥3 treatment-emergent adverse events (AEs) related to FT576:
  - 1 patient had Grade 3 diarrhea.
  - 1 patient experienced 2 episodes of Grades 3 through 4 neutropenia and 3 episodes of Grade 3 anemia.
  - All episodes of Grade ≥3 treatment-emergent AEs related to FT576 resolved; there were no serious AEs related to FT576.
- Grade ≥3 treatment-emergent AEs not related to FT576 in ≥2 patients included: anemia, neutropenia, and white blood cell decreased.

Tolerability

- There were no study discontinuations or deaths due to treatment-emergent AEs.

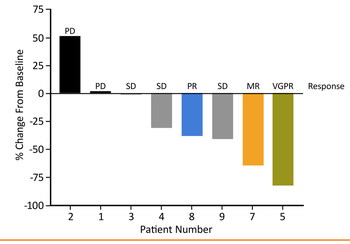
Anti-tumor Activity

- Of the 9 efficacy evaluable patients, 3 patients had a decrease in their myeloma disease burden (38%-97% decrease), with 2 subjects with a confirmed objective response.
- 1 patient who had been treated with 5 prior lines of therapy and was triple refractory to an IMiD, a PI, and an anti-CD38 mAb was treated with FT576 as monotherapy in the second dose cohort (300 million cells) and achieved a very good partial response (VGPR).

Immunogenicity & Pharmacodynamics

- No anti-product recognition by patient lymphocytes was detected by ELISpot.
- No detection of anti-product human leukocyte antigen (HLA) Class I antibodies in patients' serum.

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



sBCMA levels were measured at baseline and on Day 29 after treatment with FT576 ± daratumumab. The percent change from baseline is graphed based on patient response after 1 cycle of treatment.
Sample quantity is not sufficient for testing of Patient #6.
MR = Minimal response; PD = Progressive disease; PR = Partial response; sBCMA = Soluble B-cell maturation antigen; SD = Stable disease; VGPR = Very good partial response

- Evidence of FT576 activity further demonstrated by treatment-induced decreases in soluble B-cell maturation antigen (sBCMA), including in patients with objective response by IMWG response criteria.

CONCLUSIONS & FUTURE DIRECTIONS

- Administration of a single dose of FT576 as monotherapy and in combination with daratumumab is safe and well tolerated:
  - There were no events of any grade of CRS, ICANS, or GvHD.
  - 2 patients had Grade ≥3 treatment-emergent AEs related to FT576:
    - 1 patient with Grade 3 diarrhea, and 1 patient with 2 episodes of Grades 3 through 4 neutropenia and 3 episodes of Grade 3 anemia.
    - All episodes of Grade ≥3 treatment-emergent AEs related to FT576 resolved.
  - There were no serious AEs related to FT576.
  - There were no study discontinuations or deaths due to treatment-emergent AEs.
- Administration of a single dose of FT576 as monotherapy and in combination with a CD38-targeted mAb shows evidence of anti-myeloma activity.
  - 1 patient who had been treated with 5 prior lines of therapy and was triple refractory to an IMiD, a PI, and an anti-CD38 mAb was treated with FT576 as monotherapy and achieved a VGPR.
- Given the favorable safety and tolerability profile observed to date, dose escalation is ongoing in the multi-dose regimens as monotherapy (Regimen A1) and in combination with daratumumab (Regimen B1).

References:
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