Phase I Results of FT516, an Off-the-Shelf, iPSC-Derived NK Cell Therapy Expressing a High-Affinity, Non-cleavable CD16 (hnCD16) Combined with Avelumab in Patients with Advanced Solid Tumors

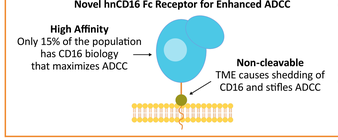
Martin E. Gutierrez, MD[1]; Manish R. Patel, DO[2]; Feng Liu, PhD[3]; Peter Szabo, MD, PhD[3]; Bahram Valamehr, PhD[3]; Yu-Waye Chu, MD[3]; Brandon Beagle, PhD[3]; Jeffrey Chou, MD, PhD[3]; and David S. Hong, MD[4]

[1]Hackensack University Medical Center, John Theurer Cancer Center, Hackensack, NJ; [2]Division of Hematology, Oncology and Transplantation, Masonic Cancer Center, University of Minnesota, Minneapolis, MN; [3]Fate Therapeutics, Inc., San Diego, CA; [4]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

BACKGROUND

- FT516 is an allogeneic, off-the-shelf natural killer (NK) cell-based cancer immunotherapy derived from a clonal master engineered induced pluripotent stem cell (iPSC) line incorporating a novel high-affinity 158V, non-cleavable CD16 (hnCD16) Fc receptor (**Figure 1**).
- FT516 mediates enhanced antibody-dependent cellular cytotoxicity (ADCC) and promotes prolonged survival in preclinical lymphoma xenograft models when compared to ex vivo expanded peripheral blood NK cells (Zhu et al. 2020).
- The clonal master engineered iPSC line serves as a renewable cell source from which FT516 can be:
  - Mass produced as a uniformly engineered NK cell product, cryopreserved, and stored; and
  - Made available off-the-shelf for broad patient access and multi-dose administration in the outpatient setting.

Figure 1. High-Affinity, Non-cleavable CD16 Fc Receptor



- CD16a (FcγRIIIa) binds the Fc region of IgG antibodies, resulting in NK-cell activation and induction of ADCC. The high-affinity variant encoded by the 158 V/V polymorphism is associated with superior clinical outcomes in patients with cancer treated with monoclonal antibodies (Bibeau et al. 2009; Cartron et al. 2002; Musolino et al. 2008).
- The high-affinity receptor has been modified to prevent its down-regulation by ADAM17-mediated cleavage upon NK-cell activation and to enhance its binding to tumor-targeting antibodies.

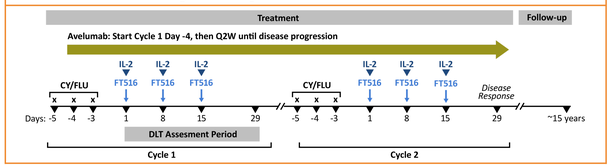
ADCC = Antibody-dependent cellular cytotoxicity; hnCD16 = High-affinity, non-cleavable CD16; IgG = Immunoglobulin G; NK = Natural killer; TME = Tumor microenvironment

- Interim clinical data from a Phase I dose-escalation study of FT516 in combination with rituximab and low-dose interleukin (IL)-2 in patients with B-cell lymphomas has shown favorable safety and anti-tumor activity (data cutoff date 18 October 2021; Patel et al. 2021).
  - Up to 6 doses of FT516 through 900 million cells/dose were safety administered in the outpatient setting, with no cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), graft-versus-host disease (GvHD), or dose-limiting toxicities (DLTs) observed.
  - 11 of 18 patients (61%) treated at ≥90 million cells/dose achieved an objective response, including 8 patients (44%) with complete response and 8 patients (44%) with ongoing response (3.7 to 14.2 months from treatment initiation).
- We report results from the Phase I dose-escalation portion of Study FT516-102 (ClinicalTrials.gov NCT04551885): FT516 in combination with low-dose IL-2 and the ADCC-competent anti-PD-L1 monoclonal antibody (mAb) avelumab in patients with advanced solid tumors, based on a data cutoff date of 15 August 2022.
  - **Primary objective:** Identify the DLT and determine the maximum tolerated dose/maximum assessed dose
  - **Additional objectives:** Safety, tolerability, preliminary activity, pharmacokinetics, and immunogenicity

METHODS

- Up to 2 cycles of initial treatment (FT516 + IL-2 + avelumab; **Figure 2**):
  - Conditioning chemotherapy (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2) for 3 days at the start of each cycle
  - FT516 (90-900 million cells/dose) and low-dose subcutaneous IL-2 (6 MIU); 3 once-weekly doses/cycle
    - FT516 dose escalation based on standard 3 + 3 dose-escalation design
  - Avelumab (800 mg) administered every 2 weeks until disease progression
- Patients whose disease progressed or relapsed following initial objective response to FT516 have the option to receive 2 additional treatment cycles (Cycles 3 and 4).
- No mandatory hospitalization required for study treatment administration.
- Disease response was assessed using iRECIST (Seymour et al. 2017).

Figure 2. Dosing Schedule: FT516 + IL-2 + Avelumab



CY = Cyclophosphamide; DLT = Dose-limiting toxicity; FLU = Fludarabine; IL 2 = Interleukin-2; Q2W = Every 2 weeks

Key Eligibility Criteria

Inclusion	Exclusion
• Advanced solid tumor where treatment with anti-PD-L1 mAbs are approved • Disease relapse or progression after at least one line of therapy • Measurable disease by iRECIST	• ECOG PS ≥2 • Insufficient hematologic, renal, hepatic, pulmonary, or cardiac function • Requiring systemic steroids or history of autoimmune disease • Clinically significant infections

ECOG PS = Eastern Cooperative Oncology Group Performance Status; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; mAb = Monoclonal antibody

RESULTS

Phase I Dose-Escalation Clinical Results

Table 1. Patient Demographics and Baseline Characteristics

FT516 Cells/Dose	Patient No.	Age / Sex	Tumor Types	# Lines of Prior Therapy	Refractory to Last Prior Therapy[a]	Refractory to Last Prior ICI[a]
90 Million Cells/Dose	1	65 / F	Uveal melanoma	2	Yes	Yes
	2	75 / F	NSCLC	7	No	No
	3	65 / F	Uveal melanoma	1	Yes	Yes
300 Million Cells/Dose	1	72 / F	Melanoma	3	Yes	Yes
	2	48 / M	Melanoma	4	NE	NE
	3	54 / M	Uveal melanoma	5	Yes	Yes
900 Million Cells/Dose	1	44 / F	Mucosal melanoma	2	Yes	Yes
	2	67 / F	Melanoma	1	Yes	Yes
	3	61 / M	Melanoma	2	Yes	Yes
	4	79 / F	Melanoma	3	Yes	Yes
	5	60 / F	TNBC	6	No	NA
	6	66 / M	Mucosal melanoma	5	Yes	Yes

[a] Refractory disease is defined as best overall response of stable disease/no response or progressive disease.

F = Female; ICI = Immune checkpoint inhibitor; M = Male; NA = Not applicable; NE = Not evaluable; No. = Number; NSCLC = Non-small cell lung cancer; TNBC = Triple-negative breast cancer

Table 2. Patient Safety, Response, and Disposition

FT516 Cells/Dose	Patient No.	FT516 Doses Received	Safety			Best Overall Response (iRECIST)	Disposition	
			DLTs	Related Grade ≥3 AEs	Related SAEs		Days on Study Treatment	Reason for Treatment Discontinuation
90 Million Cells/Dose	1	6	None	None	None	iCPD	108	iCPD
	2	6	None	None	None	iSD	129	Alternative anti-cancer therapy
	3	6	None	None	None	iSD	337	iCPD
300 Million Cells/Dose	1	6	None	None	None	iSD	120	Clinical progression
	2	6	None	None	None	iCPD	106	iCPD
	3	6	None	None	None	iSD	316	iCPD
900 Million Cells/Dose	1	6	None	None	None	iCPD	92	iCPD
	2	5	None	None	None	iSD	199	iCPD
	3	9	None	None	None	iPR	246	iCPD
	4	6	None	None	None	iSD	120	Death[a]
	5	6	None	None	None	iUPD	73	Consent withdrawn
	6	3	None	None	None	iUPD	16	Clinical progression

[a] Primary cause of death due to disease progression.

AE = Adverse event; DLT = Dose-limiting toxicity; iCPD = Immune confirmed progressive disease; iPR = Immune partial response; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; iSD = Immune stable disease; iUPD = Immune unconfirmed progressive disease; No. = Number; SAE = Serious adverse event

Baseline Characteristics

- 10 of 12 patients (83%) had Stage IV disease at the time of entry.
- Patients were heavily pre-treated with median of 3 prior lines of therapy.
- 11 of 12 (92%) patients received a median of 2 prior anti-PD-1/PD-L1 regimens; 9 of 11 patients were refractory to most recent anti-PD-1/PD-L1 therapy.

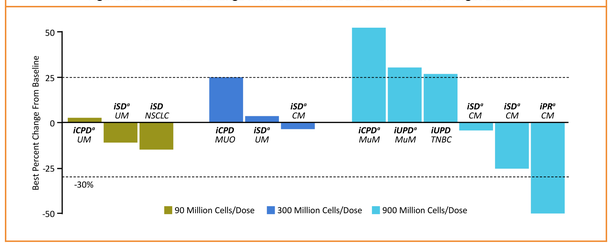
Safety

- No DLTs, GvHD, ICANS, FT516-related Grade ≥3 adverse events (AEs), or FT516-related serious AEs were reported.
- Grade 1 CRS was reported in 1 patient following administration of FT516 on Days 8 and 15 of Cycle 1.
  - Manifested as fever and managed symptomatically without the need for anti-IL-6 receptor antibodies, pressors, or steroids
- Grades 3 to 4 treatment-emergent AEs reported in ≥2 patients, all of which were considered unrelated to FT516, were neutrophil count decreased (n = 10), anemia (8), white blood cell count decreased (8), platelet count decreased (3), neutropenia (2), and lymphocyte count decreased (2).

Multi-dose Tolerability

- Of the 12 patients, 10 patients received 2 treatment cycles with FT516, 1 patient received 1 cycle, and 1 patient received 3 cycles.
- No patient discontinued treatment due to toxicity from study treatment.

Figure 3. Best Percent Change From Baseline in Sum of Diameters of Target Lesions

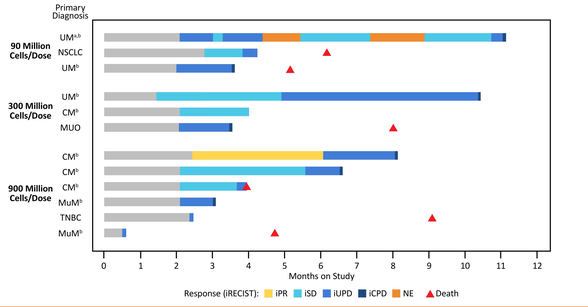


[a] Refractory to last prior anti PD-1/PD-L1 therapy.

CM = Cutaneous melanoma; iCPD = immune confirmed progressive disease; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; MuM = Mucosal melanoma; MUO = Melanoma of unknown origin; NSCLC = Non-small cell lung cancer; TNBC = Triple-negative breast cancer; UM = Uveal melanoma

- Tumor reduction from baseline was observed in 6 patients.

Figure 4. Patient Status and Time on Study



[a] Patient had overall objective response assessment of NE at indicated times due to non-target lesions not evaluated.

[b] Refractory to last prior anti-PD1/anti-PDL1 therapy.

CM = Cutaneous melanoma; iCPD = Immune confirmed progressive disease; iPR = Immune partial response; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; iSD = Immune stable disease; iUPD = Immune unconfirmed progressive disease; MuM = Mucosal melanoma; MUO = Melanoma of unknown origin; NE = Not evaluable; NSCLC = Non-small cell lung cancer; TNBC = Triple-negative breast cancer; UM = Uveal melanoma

- 1 patient treated at 900 million cells/dose achieved an immune partial response (iPR) through 6.2 months from initiation of treatment.
- 6 patients had immune stable disease (iSD) with a median duration of disease control of 4.7 months (3.8, 8.7 months).

Pharmacokinetics

- FT516 cells were not detected consistently at 90 and 300 million cells/dose. At 900 million cells/dose, FT516 cells persisted in the peripheral blood for 7 days after the first dose in 3 of 6 patients.

Immunogenicity

- No evidence of emerging humoral immunogenicity was observed as assessed by anti-FT516 Class I human leukocyte antigen (HLA) using a panel-reactive antibody assay. Pre-existing Class I HLA antibody (Ab)+ was detected in 1 patient (1 Ab <5000 MFI and 1 Ab >5000 MFI) at screening and the end of Cycle 2.
- Evidence of cellular recognition of FT516 was observed in 1 of 11 (9%) tested patients who developed a de novo anti-product response during Cycle 2 as assessed by ELISpot assay. None of the patients exhibited cellular immunogenicity against FT516 cells at baseline.

References: **Bibeau F**, Lopez-Crapez E, Di Fiore F, et al. *J Clin Oncol*. 2009;27:1122-29. **Cartron G**, Dacheux L, Salles G, et al. *Blood*. 2002;99:754-8. **Musolino A**, Naldi N, Bortesi B, et al. *J Clin Oncol*. 2008;26:1789-96. **Patel K**, Bachanova V, Goodman A, et al. *Blood*. 2021;138:s1:3873. **Seymour L**, Bogaerts J, Perrone A, et al. *Lancet Oncol*. 2017;18:e143-e152. **Szabo PM**, Lee G, Ely S, et al. *J Clin Oncol*. 2019;37:s15:2594. **Zhu H**, Blum RH, Bjordahl R, et al. *Blood*. 2020;135:399-410.

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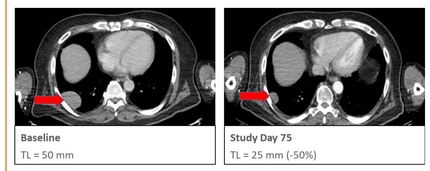
Patient Case Study

Figure 5. Partial Response Following FT516 + IL-2 + Avelumab Treatment in Patient Double Refractory to PD-1-Directed Therapy

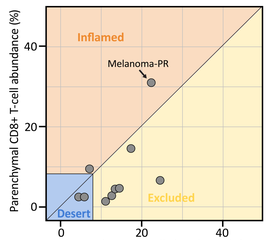


- 61-year-old male with Stage IV cutaneous melanoma
- 2 lines of prior systemic therapy and 1 course of radiation
  - Refractory to 2 prior lines of anti-PD-1 regimens
  - 1L: pembrolizumab (best overall response = progressive disease)
  - 2L: ipilimumab + nivolumab (best overall response = progressive disease)
- Disease burden at baseline
  - 1 target lesion (right lung)
  - 2 non-target lesions (right lung; multiple jejunal lesions)

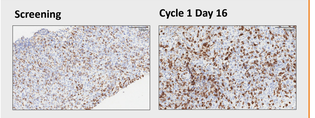
1L = First line; 2L = Second line; IL-2 = Interleukin-2; PD-1 = Programmed death-1; TL = Target lesion

- The patient achieved iPR after initial response to 2 cycles of FT516 + IL-2 + avelumab, and safely received a third cycle of treatment for a total of 9 doses of FT516.
- The patient discontinued study treatment due to disease progression 6.2 months after initiation of treatment.

Figure 6. Immunohistochemistry-Based Immune Phenotyping Demonstrates a Pre-treatment Immune Inflamed Phenotype in Partial Responder



- The CD8 topology in tumor parenchyma and stroma from pre-treatment biopsy samples (n = 10) was characterized from CD8 IHC images using artificial intelligence-powered image analysis and classified as desert, excluded, or inflamed (Szabo et al. 2019).
- Of the 10 available samples at pre-treatment, the sample from the cutaneous melanoma patient with PR was the only sample that was determined to have an inflamed tumor phenotype.



A subsequent biopsy collected from this patient 16 days after first FT516 infusion revealed a further increase in the level of tumor-infiltrating CD8+ T cells.

IHC = Immunohistochemistry; PR = Partial response

CONCLUSIONS AND FUTURE DIRECTIONS

Anti-tumor Activity

- Of the 12 patients, best overall responses of partial response and stable disease were observed in 1 and 6 patients, respectively.
- Response was observed in a patient with cutaneous melanoma who had not responded to prior ICI therapy and had low PD-L1 at baseline. This patient had the only immune inflamed baseline tumor topology. After treatment with the highest dose of FT516 (900 million cells/dose), tumor-infiltrating CD8 T cells were increased, suggesting that response to FT516 therapy depends in part on the ability of immune lymphocytes to enter the tumor microenvironment.

Safety & Tolerability

- Up to 9 doses of FT516 at dose levels through 900 million cells/dose were safely administered in the outpatient setting. The multi-dose, multi-cycle treatment schedule was well tolerated, with no treatment discontinuations due to AEs.
- No DLTs, GvHD, or ICANS were observed; 1 patient experienced Grade 1 CRS, which was of limited duration, and not treatment limiting.

Future Directions

- These findings will inform further clinical development of checkpoint inhibitors and ADCC-enabled antibodies in combination with immune NK cells engineered with hnCD16 and other genetic edits.