Interim Phase I Clinical Data of FT819-101, a Study of the First-Ever, Off-the-Shelf, iPSC-Derived TCR-Less CD19 CAR T-Cell Therapy for Patients with Relapsed/Refractory B-Cell Malignancies

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INTRODUCTION

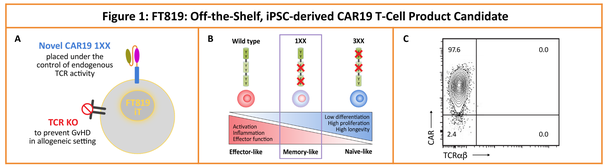
Background

- Autologous chimeric antigen receptor (CAR) T cells targeting CD19 (CAR19) have been shown to provide significant clinical benefit for patients with relapsed/refractory B-cell malignancies.
- However, significant barriers remain to their broad application, including lack of product consistency and purity following genetic engineering, manufacturing timelines necessitating the administration of bridging therapy, and risk of manufacturing failure.
- Clonal master engineered induced pluripotent stem cell (iPSC) lines can serve as a renewable source for the mass production of immune effector cells and offer distinct advantages over existing patient- and donor-derived therapeutic approaches, notably off-the-shelf availability enabling on-demand administration.

FT819

- FT819 is a first-of-kind, off-the-shelf CAR T-cell therapy derived from a renewable master iPSC line engineered to uniformly contain the following (**Figure 1**; **Panel A**):
  - **1XX CAR19:** Novel CAR construct consisting of CD28 costimulatory domain and modified CD3ζ signaling domain, which promotes effector cell persistence and anti-tumor potency (**Panel B**; Feucht et al. 2018)
  - **TRAC-integrated CAR:** Precise insertion of the CAR construct into the T-cell receptor alpha constant (TRAC) locus, which results in uniform CAR expression (**Panel C**)
  - **TCR null:** Bi-allelic disruption of TRAC for complete removal of TCR expression, which eliminates the risk of graft-versus-host disease (GvHD; **Panel C**)
- FT819 exhibits antigen-specific cytolytic activity *in vitro* against CD19+ leukemia and lymphoma cell lines comparable to that of primary CAR T cells and persists and maintains tumor clearance in the bone marrow *in vivo* in a disseminated xenograft model of B-cell acute lymphoblastic leukemia (Valamehr et al. 2020).

Figure 1: FT819: Off-the-Shelf, iPSC-derived CAR19 T-Cell Product Candidate

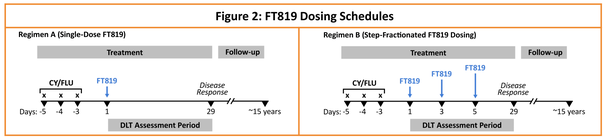


CAR = Chimeric antigen receptor; GvHD = Graft-versus-host disease; iPSC = Induced pluripotent stem cell; iT = iPSC-derived T-cell; KO = Knockout; TCR = T-cell receptor

METHODS

- FT819-101 is an open-label, multicenter, Phase I clinical trial designed to assess the safety and activity of 2 dosing schedules of FT819 in subjects with B-cell malignancies (ClinicalTrials.gov: NCT04629729).
- Primary objectives: Assess safety and tolerability; determine the recommended Phase II dose and dose schedule of FT819
- Key secondary objectives: Assess anti-tumor activity and pharmacokinetics
- Study treatment (**Figure 2**):
  - Conditioning chemotherapy (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2) given intravenously (IV) for 3 days prior to the first dose of FT819
  - FT819 administered IV in the following dosing regimens:
    - **Regimen A:** Single dose on Day 1; **Regimen B:** Step-fractionated doses on Days 1, 3, and 5
- FT819 dose escalation based on a standard 3 + 3 dose-escalation design, with a starting dose of 90 million cells/dose in Regimen A and 30 million cells/dose in Regimen B
- Disease response assessed using Lugano 2014 classification
- Subject to FDA approval, patients with evidence of clinical benefit may receive an additional cycle of study treatment

Figure 2: FT819 Dosing Schedules



CY = Cyclophosphamide; DLT = Dose-limiting toxicity; FLU = Fludarabine

Key Eligibility Criteria

Inclusion	Exclusion
• Documented surface CD19 expression after relapse following most recent CD19-directed therapy or within 6 months of study enrollment in absence of prior CD19-directed therapy	• Inadequate end-organ function
• ≥2 prior lines of immunochemotherapy	• ECOG PS ≥2
• Measurable disease	• Requirement for systemic immunosuppressive therapy
• Prior CD19-targeted CAR T-cell therapy permitted	• Known active CNS involvement
	• Clinically significant infections

CAR = Chimeric antigen receptor; CNS = Central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status

RESULTS

FT819-101 Phase I Study

- We report clinical data from the ongoing dose-escalation study from the first 15 patients treated with FT819 for relapsed/refractory B-cell lymphoma, based on a data cutoff date of 28 September 2022 (except where otherwise indicated).

Table 1. Patient Demographics and Baseline Characteristics

Regimen/ Dosing Schedule	Patient #	FT819 (Millions of Cells/Dose)	Age / Sex	Histology	# of Prior Therapies	# of Prior Anti-CD20 Regimens	Prior HSCT	Prior CAR-T (BOR)	Refractory to Last Treatment
Regimen A: Day 1	1	90	64 / M	RT	8	5	N	N	Y
	2	90	47 / M	DLBCL	5	2	Y	Y (PR)	Y
	3	90	41 / M	DLBCL	7	4	Y	Y (PD)	N
	4	90	60 / M	DLBCL	3	3	N	N	Unknown
	5	90	73 / F	DLBCL	4	2	N	Y (PR)	Y
	6	90	29 / F	DLBCL	3	2	N	Y (CR)	N
	7	180	65 / M	RT	3	1	N	N	N
	8	180	60 / M	G3A FL	5	3	Y	Y (CR)	N
	9	180	25 / F	DLBCL	5	3	N	Y (SD)	Y
	10	360	68 / M	HGBCL	4	2	N	Y (CR)	Y
	11	360	73 / M	DLBCL	5	3	Y	N	N
Regimen B: Days 1, 3, 5	12	30	68 / F	RT	9	6	N	N	Y
	13	30	59 / M	DLBCL	3	2	Y	N	N
	14	30	65 / F	DLBCL	3	2	N	Y (PD)	Y
	15	60	66 / M	RT	2	2	N	N	Y

BOR = Best overall response; CAR-T = Chimeric antigen receptor T-cell; CR = Complete response; DLBCL = Diffuse large B-cell lymphoma; F = Female; G3A FL = Grade 3A follicular lymphoma; HGBCL = High-grade B-cell lymphoma; HSCT = Hematopoietic stem cell transplantation; M = Male; N = No; PD = Progressive disease; PR = Partial response; RT = Richter transformation; SD = Stable disease; Y = Yes

Table 2. Patient Safety, Response, and Disposition

Patient #	FT819 (Millions of Cells/Dose)	Safety: DLTs	CRS	ICANS	Related Grade ≥3 AEs	Related SAEs	Best Overall Response	Follow-Up Time (Days)[a]
Regimen A: Single-Dose Day 1								
Aggressive Lymphoma (DLBCL and HGBCL), CAR T-Cell Therapy Naïve								
4	90	N	N	N	N	N	SD	72
11[b]	360	N	N	N	N	N	CR	25+
Aggressive Lymphoma (DLBCL and HGBCL), Prior CAR T-Cell Therapy								
2	90	N	N	N	N	N	PD	29
3	90	N	N	N	N	N	CR	113
5[b,c]	90	N	N	N	N	N	PR	163+
6[d]	90	N	N	N	N	N	SD	136
9	180	N	Gr 2	N	N	Gr 2 CRS	PD	28
10	360	N	N	N	N	N	PD	22
Other (Grade 3A FL, Richter Transformation)								
1	90	N	Gr 2	N	N	N	PD	29
7	180	N	N	N	N	N	PD	28
8	180	N	N	N	N	N	CR	121
Regimen B: Multi-dose Days 1, 3, and 5								
Aggressive Lymphoma (DLBCL, HGBCL), CAR T-Cell Therapy Naïve								
13	30	N	N	N	N	N	SD	86
Aggressive Lymphoma (DLBCL, HGBCL), Prior CAR T-Cell Therapy								
14	30	N	N	N	N	N	PD	31
Other (Grade 3A FL, Richter Transformation)								
12	30	N	Gr 2	N	N	N	SD	38
15[b]	60	N	N	N	N	N	PD	29

[a] For subjects who have progressed, died, or started subsequent anti-systemic cancer therapy, the follow-up is from Day 1 to the earliest date of progression, death, or start of subsequent anti-systemic cancer therapy, whichever occurred 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.

[b] Clinical data for patient based on data cutoff date of 08 November 2022.

[c] Patient #5 received 2 cycles of treatment: PR was reported after the first treatment cycle on Day 30, with disease progression occurring on Day 72; second treatment cycle following disease progression resulted in PR on Day 163.

[d] Patient #6 received 2 cycles of treatment: SD was reported after the first treatment cycle on Day 29, with disease progression occurring on Day 56; second treatment cycle following disease progression resulted in SD on Day 106. The patient started subsequent anti-cancer therapy on Day 136.

AE = Adverse event; CAR-T = Chimeric antigen receptor T-cell; CR = Complete response; CRS = Cytokine release syndrome; DLBCL = Diffuse large B-cell lymphoma; DLT = Dose-limiting toxicities; FL = Follicular lymphoma; Gr = Grade; G3A FL = Grade 3A follicular lymphoma; HGBCL = High-grade B-cell lymphoma; ICANS = Immune effector cell-associated neurotoxicity syndrome; N = No; NA = Not applicable; PD = Progressive disease; PR = Partial response; SAE = Serious adverse event; SD = Stable disease

Baseline Characteristics

- 14 of 15 patients had relapsed/refractory diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, or Richter transformation; 1 patient had relapsed/refractory Grade 3A follicular lymphoma (FL).
- All 15 patients were heavily pre-treated with median of 4 prior lines of therapy (range 2-9), with 14 of 15 patients receiving at least 2 prior anti-CD20 treatment regimens.
- 8 patients (6 with DLBCL, 1 with HGBCL, and 1 with Grade 3A FL) relapsed or progressed on prior CAR T-cell therapy.
- 8 patients were refractory to last prior therapy.

Safety

- No dose-limiting toxicities (DLTs) and no events of immune effector-cell associated neurotoxicity syndrome (ICANS) or GvHD were observed.
- No patients experienced Grade ≥3 cytokine release syndrome (CRS).
  - Grade 2 CRS was observed in 3 patients, characterized by fever, hypotension, and hypoxia.
  - All 3 events resolved with single-dose tocilizumab and supportive care.
- No Grade ≥3 treatment-emergent adverse events (AEs) related to FT819.
  - 1 patient had a serious AE related to FT819 (Grade 2 CRS).
- Grade ≥3 treatment-emergent AEs not related to FT819 occurring in ≥2 patients included: neutropenia, anemia, leukopenia, thrombocytopenia, neutrophil count decreased, and platelet count decreased.

Tolerability

- All patients received the prescribed doses of FT819.
- No study discontinuations or deaths due to treatment-emergent AEs, other than 1 patient (#12) who died due to Grade 5 sepsis on Day 38, not considered related to FT819 by the study investigator.
- 2 patients (#5, #6) who had clinical benefit following an initial cycle of treatment at 90 million cells received a second cycle of treatment at a higher dose level (180 million cells), with no evidence of new or worsening toxicity following the second treatment cycle.

Anti-tumor Activity

- Of 15 efficacy-evaluable patients, 4 patients achieved an objective response, including 3 patients with complete responses (CRs) and 1 patient with a partial response (PR).
- In the single-dose regimen (Regimen A):
  - Of the 2 patients with aggressive lymphoma naïve to CD19-targeted CAR T-cell therapy, 1 patient had an objective response (CR).
  - Of the 6 patients with aggressive lymphoma previously treated with CD19-targeted CAR T-cell therapy, 2 patients had an objective response (1 CR, 1 PR).
  - 1 patient with follicular lymphoma had a CR.
  - 2 patients with Richter transformation had progressive disease.
- In the step-fractionated dose regimen (Regimen B):
  - 1 patient with aggressive lymphoma naïve to CD19-targeted CAR T-cell therapy had stable disease characterized by a 49% decrease in tumor burden by computed tomography (CT) imaging with no decrease in positron emission tomography (PET) uptake.
  - 1 patient with Richter transformation had stable disease characterized by a 44% decrease in tumor burden by CT-imaging and with no decrease in PET-uptake.

Pharmacokinetics & Immunogenicity

- Dose-dependent pharmacokinetics (PK) were observed.
- Early data suggest that a Day 1, 3, and 5 multi-dose schedule provides better PK exposure over the first 2 weeks.
- Anti-product recognition by patient lymphocytes measured by enzyme-linked immunosorbent spot (ELISpot) was detected in a single patient (#6) on Day 29 of the first treatment cycle. The signal was not detected prior to or after the second treatment cycle.
- No detection of anti-product human leukocyte antigen (HLA) Class I antibodies in patients' serum.

References:

Feucht J, Sun J, Eyquem J, et al. Calibration of CAR activation potential directs alternative T cell fates and therapeutic potency. *Nat Med.* 2019;25(1)82-88.

Valamehr B, Clarke R, van der Stegen, et al. FT819 path to IND: first-of-kind off-the-shelf CAR19 T-cell for B-cell malignancies. *Cancer Res.* 2020;80(16_Supplement): 3245.

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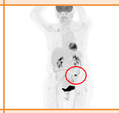
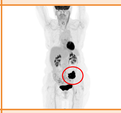
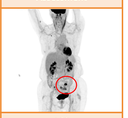
Patient Case Study

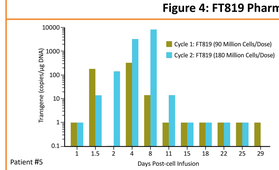
Figure 3: Anti-Tumor Responses with FT819 in a Patient with Relapsed/Refractory DLBCL Previously Treated with CD19-Targeted CAR T-Cell Therapy

Patient #5	Baseline	Post-Cycle 1 Response Assessment	Pre-Cycle 2 Baseline	Post-Cycle 2 Response Assessment
PET Image				
Study Day	-7	30	99	163
SPD (mm^2)	2973	192	2022	792
SUV_{max}	32.7	16.4	23.4	13.6
Objective Response	**NA**	**PR**	**NA**	**PR**

CAR = Chimeric antigen receptor; DLBCL = Diffuse large B-cell lymphoma; NA = Not applicable; PET = Positron emission tomography; PR = Partial response; SPD = Sum of the product of diameters; SUV = Standardized uptake value

- 73-year-old female with DLBCL
  - 4 prior lines of therapy, including commercial autologous CD19-targeted CAR T-cell therapy with best response of PR
  - Refractory to last prior therapy (investigational cord blood-derived natural killer cell therapy)
- Patient received conditioning chemotherapy, followed by a single dose of FT819 at 90 million cells (Regimen A), with PR observed on Day 30
- Following progressive disease on Day 72, and with FDA consent, patient received a second treatment cycle consisting of conditioning chemotherapy followed by a single dose of FT819 (180 million cells) on Day 134, with a PR observed on Day 163
- Treatment was well tolerated:
  - No reported DLTs or serious AEs; no reported CRS, ICANS, or GvHD
  - Grade ≥3 treatment-emergent AEs included leukopenia and neutropenia, which occurred with both treatment cycles and resolved, and were not considered related to FT819
  - No evidence of new or worsening toxicity with the second treatment cycle

Figure 4: FT819 Pharmacokinetics in Peripheral Blood



- PK during the second treatment cycle (180 million cells) was greater than during first treatment cycle (90 million cells), with measurable detection to Day 11.
- No detectable humoral or cellular immunogenicity after Cycle 1 or Cycle 2.

FT819 PK in transgene copies/µg DNA in peripheral blood as measured using a Droplet Digital™ polymerase chain reaction (ddPCR™) assay at indicated timepoints after Cycle 1 (90 million cells; green) and after Cycle 2 (180 million cells; blue).
Levels peaked at Day 4 (Cycle 1) and Day 8 (Cycle 2), with quantifiable PK through Day 8 after Cycle 1 and through Day 11 after Cycle 2.
The smallest PK value of 1 transgene copy/µg DNA implies that no PK signal is detected.

CONCLUSIONS & FUTURE DIRECTIONS

Safety & Tolerability

- FT819 appears safe and well tolerated.
  - Low incidence of CRS (20%), with no patients having Grade ≥3 CRS
  - No DLTs, ICANS, or GvHD reported
  - No Grade ≥3 treatment-emergent AEs or serious AEs related to FT819
  - Most treatment-emergent AEs were hematologic cytopenias
- No evidence of worsening toxicity with multi-dose FT819 administration on Days 1, 3, and 5.
- Second treatment cycle of FT819 at a higher FT819 dose in 2 patients was not associated with new or worsening toxicity.

Anti-tumor Activity

- Evidence of anti-tumor activity, including CRs in aggressive lymphoma, in early dose escalation among patients with relapsed/refractory B-cell lymphoma, including in patients who failed prior CAR T-cell therapy.
- FT819 retreatment may lead to re-induction of objective response in patients whose disease had initial response to FT819 and who had subsequent disease progression.

Future Directions

- Dose escalation is ongoing in cohorts assessing single-dose and multi-dose schedules.