Results of a Phase I Trial of FT500, a First-in-Class, Off-the-Shelf, iPSC-Derived NK Cell Therapy Combined with PD-1/PD-L1 Checkpoint Blockade Therapy and IL-2 in Patients with Advanced Solid Tumors

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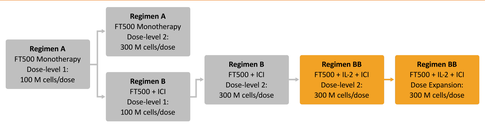
BACKGROUND

- FT500 is an allogeneic natural killer (NK) cell-based cancer immunotherapy derived from a clonal master induced pluripotent stem cell (iPSC) line.
  - Designed for off-the-shelf, on-demand administration to patients in multi-dose regimens
- In preclinical studies, FT500 has been shown to recruit and activate T cells, increasing response to checkpoint inhibition for enhanced inflammatory cytokine production and tumor elimination.
- Study FT500-101 (ClinicalTrials.gov NCT03841110) is the first-ever clinical investigation of iPSC-derived NK cell therapy.
  - Open-label, multicenter, Phase I, dose-escalation and dose-expansion study in patients with advanced solid tumors and lymphomas
  - Dose-escalation phase of the study designed to assess the safety and tolerability of FT500 and to determine the dose level of FT500 appropriate for further assessment in dose expansion
- We report results from 12 patients with classical Hodgkin lymphoma (cHL) or non-small cell lung cancer (NSCLC) who were relapsed/refractory to prior anti-PD-1/PD-L1 immune checkpoint inhibitor (ICI) therapy and received FT500 combined with ICI therapy and interleukin-2 (IL-2) (Regimen BB), based on a data cutoff date of 08 August 2022.

Figure 1. Dose-Escalation/Expansion Study Design



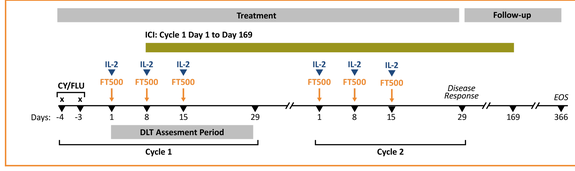
During dose escalation, FT500 was investigated as a monotherapy in patients who were candidates for salvage therapy (Regimen A); and, in patients who had previously failed or progressed on ICI therapy, FT500 was investigated in combination with the ICI on which the patient failed or progressed (Regimen B). Regimen BB (orange), the focus of this presentation, investigates FT500 at dose-level 2 (300 million cells/dose) in combination with IL-2 (6 MIU/dose) and an ICI.

ICI = Immune checkpoint inhibitor; IL-2 = Interleukin-2; M = Million; MIU = Million international units

METHODS

- Up to 2 cycles of treatment (Regimen BB: FT500 + IL-2 + ICI; Figure 2):
  - Conditioning chemotherapy (cyclophosphamide 300 mg/m^2 and fludarabine 25 mg/m^2) for 2 days, Cycle 1 only
  - FT500 (300 million cells/dose) and subcutaneous IL-2 (6 MIU); 3 once-weekly doses/cycle
  - ICI therapy: nivolumab, pembrolizumab, or atezolizumab; dosed per US prescribing information
- No mandatory hospitalization was required for study treatment administration.
- Disease response was assessed using RECIL (for cHL) or iRECIST (for NSCLC).
- Patients were followed routinely for safety and anti-tumor activity up to 1 year, after which patients were followed in a non-interventional observational study.

Figure 2. Dosing Schedule: FT500 + IL-2 + ICI



CY = Cyclophosphamide; DLT = Dose-limiting toxicity; EOS = End of study; FLU = Fludarabine; ICI = Immune checkpoint inhibitor; IL 2 = Interleukin-2

Key Eligibility Criteria for Regimen BB

Inclusion	Exclusion
• Advanced cHL or NSCLC • Disease relapse or progression on a prior ICI • Measurable disease by RECIL or iRECIST	• ECOG PS ≥2 • Insufficient hematologic, renal, hepatic, pulmonary, or cardiac function • Requiring systemic steroids or history of autoimmune disease • Uncontrolled infection

cHL = Classical Hodgkin lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICI = Immune checkpoint inhibitor; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; NSCLC = Non-small cell lung cancer; RECIL = Response Evaluation Criteria in Lymphoma

RESULTS

Table 1. Demographics and Baseline Characteristics

Regimen BB: FT500 + IL-2 + ICI (N = 12)			
Characteristic		**Prior Therapies**	
Age (years), median (min, max)	60.5 (32, 73)	**Prior number of therapies, median (min, max)**	
<65, n (%)	7 (58.3)	cHL	10 (3, 11)
≥65, n (%)	5 (41.7)	NSCLC	4 (1, 8)
Gender, n (%)		**Prior anti-PD-1/PD-L1 therapy, n (%)**	
Male	7 (58.3)	Yes	12 (100)
Female	5 (41.7)	No	0
Tumor type, n (%)		**Prior number of anti-PD-1/PD-L1 regimens, median (min, max)**	
cHL	5 (41.7)	cHL	2 (1, 3)
NSCLC	7 (58.3)	NSCLC	2 (1, 3)
Stage at study entry, n (%)		**Number of patients refractory to most recent anti-PD-1/PD-L1 therapy [a]**	
Stage III	1 (8.3)	cHL	4
Stage IV	11 (91.7)	NSCLC	6

[a] Refractory disease defined as best overall response of stable disease/no response or progressive disease from most recent anti-PD1/PD-L1 therapy.

cHL = Classical Hodgkin lymphoma; ICI = Immune checkpoint inhibitor; IL-2 = Interleukin-2; Max = Maximum; Min = Minimum; NSCLC = Non-small cell lung cancer

- 11 of 12 (92%) patients had Stage IV disease at enrollment.
- Patients were heavily pre-treated, with a median of 4.5 prior regimens.
- All patients received a median of 2 prior anti-PD-1/PD-L1 regimens, with 10 of 12 (83%) patients refractory to most recent anti-PD-1/PD-L1 therapy.

Safety

Table 2. Adverse Events Occurring in 3 or More Patients

Treatment-Emergent Adverse Event	All Grades N (%)	Grade ≥3 N (%)
	12 (100)	**12 (100)**
Anaemia	7 (58.3)	2 (16.7)
Lymphocyte count decreased	7 (58.3)	7 (58.3)
Chills	5 (41.7)	0
Cough	5 (41.7)	1 (8.3)
Hypokalaemia	5 (41.7)	1 (8.3)
Nausea	5 (41.7)	0
Neutrophil count decreased	5 (41.7)	2 (16.7)
C-reactive protein increased	4 (33.3)	0
Diarrhoea	4 (33.3)	0
Fatigue	4 (33.3)	0
Hypomagnesaemia	4 (33.3)	0
Night sweats	4 (33.3)	0
Pneumonia	4 (33.3)	1 (8.3)
Pyrexia	4 (33.3)	0
White blood cell count decreased	4 (33.3)	0
Dry skin	3 (25.0)	0
Hypophosphataemia	3 (25.0)	0
Injection site erythema	3 (25.0)	0
Injection site induration	3 (25.0)	0
Platelet count decreased	3 (25.0)	0
Rash	3 (25.0)	0
Serum ferritin increased	3 (25.0)	0

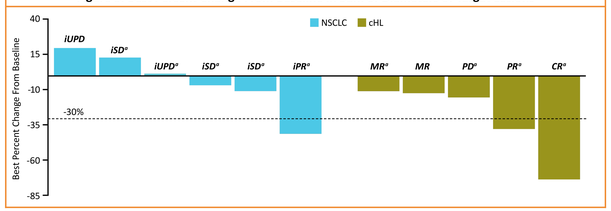
- No events of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) were observed. 5 patients with reported treatment-emergent serious adverse events (AEs); none were assessed as related to FT500 by the Investigator or the Sponsor.
- Only 1 Grade ≥3 FT500-related AE of Grade 3 lymphocyte count decreased was reported.

Multi-dose Tolerability

- 10 patients completed 2 cycles (6 doses) of treatment with FT500.
- 2 patients discontinued early prior to completion of 2 cycles (withdrawal of consent after 3 doses; death from stroke considered unrelated to FT500 or other study drugs after 4 doses).

Efficacy

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



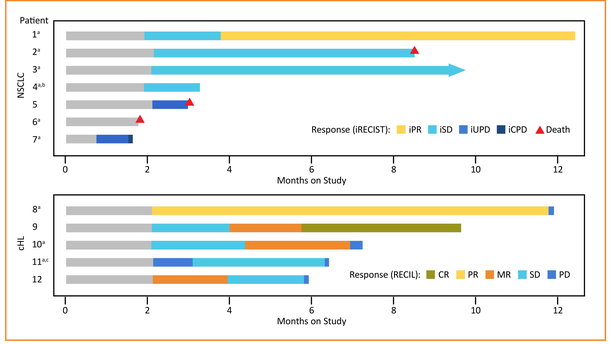
[a] Refractory to most recent anti-PD-1/PD-L1 therapy.

Eleven patients were eligible for efficacy analysis. One patient with NSCLC did not complete a post-treatment response assessment and was not evaluable for efficacy.

cHL = Classical Hodgkin lymphoma; CR = Complete response; iPR/PR = Immune partial response/partial response; iSD = Immune stable disease; iUPD = Immune unconfirmed progressive disease; MR = Minor response; NSCLC = Non-small cell lung cancer; PD = Progressive disease

- Among 6 efficacy-evaluable NSCLC patients, 1 patient had best overall response per iRECIST of immune partial response (iPR) and 3 had immune stable disease (iSD).
- Among 5 cHL patients, 1 patient had a best overall response per RECIL of complete response (CR), 1 patient had partial response (PR), and 2 had minor responses (MRs).

Figure 4. Patient Status and Time on Study



[a] Refractory to most recent anti-PD-1/PD-L1 therapy.

[b] Patient experienced non-radiographically confirmed clinical progression at 3.3 months and died 20.5 months after start of FT500 treatment.

[c] In the setting of regressing target lesions, the patient developed new lesion (shown as PD). However, based on the Investigator's clinical judgement, the patient had potential to derive clinical benefit from continuing treatment, and the patient remained on study.

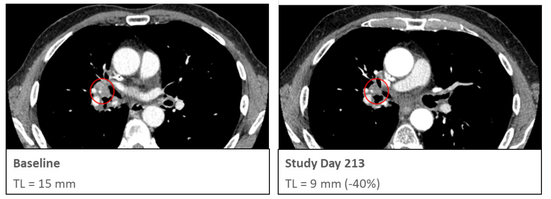
Right arrow indicates that the patient is still being followed routinely for safety and anti-tumor activity (up to 1 year). Subsequently, patients are followed in non-interventional observational study.

cHL = Classical Hodgkin lymphoma; iCPD = Immune confirmed progressive disease; iCR/CR = Immune complete response/complete response; iPR/PR = Immune partial response/partial response; iSD/SD = Immune stable disease/stable disease; iUPD = Immune unconfirmed progressive disease; MR = Minor response (RECIL only); PD = Progressive disease; RECIL = Response Evaluation Criteria in Lymphoma

- Of the NSCLC patients, 4 of 6 efficacy-evaluable patients showed disease control.
  - 1 achieved iPR, which was ongoing through 12 months from initiation of treatment (maximum protocol-specified period for radiographic follow-up).
  - 3 achieved stable disease.
  - Median duration of disease control was 8.6 months (3.4, 12.6 months).
- Of the cHL patients, 4 of 5 efficacy-evaluable patients achieved an objective response (MR or greater).
  - 1 achieved CR and remained in CR until being lost to follow-up at 9.8 months after initiation of treatment.
  - 1 achieved PR, with disease progression 12 months after initiation of treatment.
  - 2 achieved MR, with disease progression 5.9 and 7.2 months after initiation of treatment.
  - Median duration of disease control was 9.6 months (5.9, 12 months).

Case Study: Patient with NSCLC

Figure 5. Partial Response Following FT500 + IL-2 + Pembrolizumab in Patient with NSCLC



NSCLC = Non-small cell lung cancer; TL = Target lesion

- 66-year-old male with Stage IV NSCLC (large cell neuroendocrine carcinoma subtype; *STK11* mutated; PD-L1 tumor proportion score 1%; tumor mutational burden 7.1 mutations/megabase)
- 5 prior systemic therapies
  - Refractory to 2 prior lines of pembrolizumab-containing regimens
  - Confirmed disease progression following most recent line (ipilimumab + pembrolizumab)
  - Tracheal stent placed prior to FT500 treatment
- Disease burden at baseline
  - 1 target lesion (right hilar lymph node)
  - 2 non-target lesions (pre-vascular lymph nodes; infiltrating soft tissue mediastinal mass)
- Treatment with FT500 at 300 million cells/dose in combination with low-dose IL-2 and an ICI was well tolerated; no events of CRS, ICANS, or GvHD of any grade were observed.
- Achieved PR in combination with pembrolizumab
  - Tracheal stent removed after completing FT500 treatment
  - PR up to 1 year from initiation of treatment at which time the patient entered long-term follow-up

CONCLUSIONS & FUTURE DIRECTIONS

When combined with low-dose IL-2 and concurrent ICI therapy, FT500—the first iPSC-derived NK cell product to be administered in patients with advanced relapsed/refractory solid tumors—is safe and tolerable, with evidence of durable anti-tumor activity observed in heavily pre-treated patients resistant to anti-PD-1/PD-L1 therapy.

Anti-tumor Activity

- Anti-tumor activity as reflected by objective responses and evidence of disease control were observed in ICI-relapsed/refractory cHL and NSCLC after treatment with a multi-dose regimen of FT500 in combination with low-dose IL-2 and ICI therapy.

Safety & Tolerability

- Up to 6 doses of FT500 at dose levels through 300 million cells/dose with low-dose IL-2 and ICI therapy were safely administered in an outpatient setting. The multi-dose, 2-cycle treatment schedule was well tolerated.
- No events of CRS, ICANS, or GvHD were observed.
- No FT500-related serious AEs were reported.
- No treatment discontinuations due to treatment-related AEs were reported.

Future Directions

- These results with non-engineered, iPSC-derived NK cells support the development of next-generation, iPSC-derived NK cells engineered with synthetic functional elements designed to synergize with ICI therapy or other antibody therapies and enhance anti-tumor activity in solid tumors.

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