Title: Preliminary results of an ongoing phase I trial of FT500, a first-in-class, off-the-shelf, induced pluripotent stem cell (iPSC) derived natural killer (NK) cell therapy in advanced solid tumors

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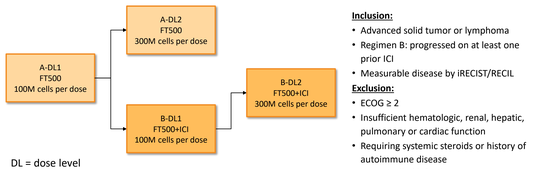
Background

FT500 Phase 1 Clinical Trial

- FT500 is a first-of-kind, allogeneic NK cell product candidate derived from a human clonal master iPSC line. The master iPSC line serves as a renewable cell source from which FT500 is mass produced, cryopreserved, stored and made available off-the-shelf for patient administration.
- FT500 is being investigated in an open-label, multi-center Phase 1 clinical trial as a salvage therapy for adult patients with advanced solid tumors and lymphomas (NCT03841110). The Phase 1 clinical trial is the first-ever study in the U.S. to evaluate an iPSC-derived cell product. In addition, the Phase 1 clinical trial is the first-ever study to evaluate a multi-dose treatment schedule of an iPSC-derived cell product.
- The dose-escalation phase of the FT500 Phase 1 study was designed to assess the safety and tolerability of FT500. The trial includes two treatment regimens: FT500 as a monotherapy in patients that are candidates for salvage therapy (Regimen A); and, in patients who have previously failed or progressed on checkpoint inhibitor therapy, FT500 in combination with the checkpoint inhibitor on which the patient failed or progressed (Regimen B) (see Figure 1). FT500 is administered in three once-weekly doses (Day 1, Day 8, Day 15) in the outpatient setting following lympho-conditioning. For those patients that are clinically stable at Day 29, a second outpatient treatment cycle of three once-weekly doses may be administered without lympho-conditioning (see Figure 2).

Figure 1: FT500 Dose-Escalation Study Design

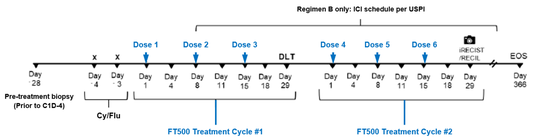


DL = dose level
ICI = immune checkpoint inhibitor

Inclusion:
- Advanced solid tumor or lymphoma
- Regimen B: progressed on at least one prior ICI
- Measurable disease by iRECIST/RECIL

Exclusion:
- ECOG ≥ 2
- Insufficient hematologic, renal, hepatic, pulmonary or cardiac function
- Requiring systemic steroids or history of autoimmune disease
- Uncontrolled infections

Figure 2: FT500 Dosing Schedule



- *FT500 Treatment Cycle 1*. Fludarabine (Flu) 25 mg/m^2 and cyclophosphamide (Cy) 300 mg/m^2 given days -4 and -3 followed by three once-weekly doses of FT500 starting on Day 1 as an outpatient.
- *FT500 Treatment Cycle 2*. If clinically stable following FT500 Treatment Cycle 1, retreatment may proceed without lympho-conditioning with three-once weekly doses of FT500 as an outpatient.
- In Regimen B, ICI is administered per manufacturer's prescribing information (USPI) starting with Day 8 of FT500 Treatment Cycle 1.
- Response was assessed by iRECIST (for solid tumors) and RECIL (for lymphoma) starting at Day 29 of FT500 Treatment Cycle 2 and then every 8 weeks. Patients were followed to PD or the end of study (EOS) at ~1 year, whichever occurred first.
- Tumor biopsy was performed prior to Day -4 of FT500 Treatment Cycle 1 and on-treatment Day 18 of FT500 Treatment Cycle 1 (when feasible).

Phase 1 Dose-Escalation Clinical Results

Table 1: Patient Demographics and Baseline Characteristics

Cohort / Cell Dose	Patient #	Age / Sex	Tumor Type	# Lines of Prior Therapy	Refractory to Last Prior Therapy	Refractory to Last Prior ICI
A1 100M cells / dose	1	54 / M	Colon	4	Yes	Yes
	2	57 / M	Metastatic salivary gland carcinoma	2	Yes	N/A
	3	61 / F	Ovary	5	Yes	N/A
A2 300M cells / dose	1	43 / M	Colon	4	N/E	N/E
	2	52 / F	Colorectal	1	No	N/A
	3	57 / M	Squamous cell carcinoma, left tonsil	2	Yes	Yes
	4	62 / M	Floor of mouth cancer	4	N/E	Yes
	5	53 / F	Pancreas	3	Yes	N/A
	6	53 / M	Metastatic melanoma of orbit	4	No	N/E
B1 100M cells / dose	1	59 / F	Non-small cell lung cancer	7	Yes	Yes
	2	54 / F	Non-small cell lung cancer	4	Yes	Yes
	3	61 / M	Hepatocellular carcinoma	2	Yes	Yes
B2 300M cells / dose	1	71 / F	Primary peritoneal mesothelioma	5	No	No
	2	29 / M	Hodgkin lymphoma	14	Yes	Yes
	3	65 / M	Malignant neoplasm of the esophagus	5	N/E	Yes

N/A (Not Applicable): Patient did not receive prior ICI
N/E (Not Evaluable): Best objective response to last prior therapy was not determined

Table 2: Patient Safety, Response & Disposition

Cohort / Cell Dose	Patient #	FT500 Doses Received	Safety: Dose Limiting Toxicities	Safety: Related Grade ≥ 3 AEs	Safety: Related SAEs	Best Overall Response (iRECIST) *	Disposition: Days on Study	Disposition: Reason for Study Discontinuation
A1 100M cells / dose	1	6	None	None	None	SD	94	CP
	2	6	None	None	None	UPD	94	CPD
	3	6	None	None	None	SD	83	UPD
A2 300M cells / dose	1	6	None	None	None	SD	70	UPD
	2	5	None	None	None	SD	61	CP
	3	3	None	None	None	SD	33	UPD
	4	6	None	None	None	SD	72	CP
	5	6	None	None	None	SD	90	UPD
	6	6	None	None	None	SD	286	CPD
B1 100M cells / dose	1	3	None	None	None	SD	76	Patient decision
	2	6	None	None	None	SD	98	UPD
	3	6	None	None	None	UPD	85	CPD
B2 300M cells / dose	1	6	None	None	None	SD	300	CPD
	2	4	None	None	None	PD **	61	PD **
	3	6	None	None	None	UPD	72	UPD

* SD = stable disease, UPD = unconfirmed progressive disease, CPD = confirmed progressive disease, CP = clinical progression
** Progressive disease per RECIL

Safety

- No dose-limiting toxicities, and no SAEs or Grade ≥ 3 AEs considered related to FT500, were observed.
- No cases of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or graft-versus-host disease were observed.
- No treatment-related discontinuations or deaths were observed. Grade 3-4 treatment-emergent adverse events (TEAEs), all of which were considered unrelated to FT500, were: in Regimen A, lymphocyte count decreased (n=3); anemia (n=1); white blood cell decreased (n=1); neutrophil count decreased/neutropenia (n=1); in Regimen B, lymphocyte count decreased (n=2); anemia (n=1); fatigue (n=1); back pain (n=1).

Multi-Dose Tolerability

- 15 patients (100%) completed FT500 Treatment Cycle 1. 13 patients (87%) initiated FT500 Treatment Cycle 2, with 11 of 13 patients (85%) completing FT500 Treatment Cycle 2. Discontinuation was due to disease progression in each case.
- In total, 81 doses of FT500 were administered to patients in the outpatient setting with no mandatory hospitalization required during treatment period.

Efficacy

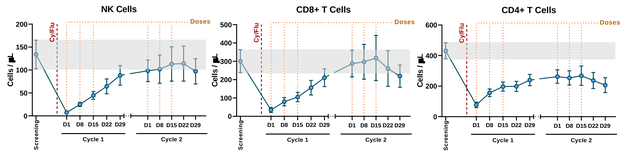
- Among 15 heavily pre-treated patients (9 who were refractory to prior therapy), 11 had a best overall response of SD.

Phase 1 Translational Data

Immune Reconstitution

- Immune reconstitution was assessed following outpatient lympho-conditioning (Flu 25 mg/m^2 and Cy 300 mg/m^2 given days -4 and -3) during the up to six-dose FT500 treatment schedule by immunophenotyping of patient PBMCs collected patients at the specified timepoints (Figure 3). The mean and SEM for each immune subset are shown (n=15), with the range of values at baseline shown in gray and FT500 dosing shown in dashed orange line.

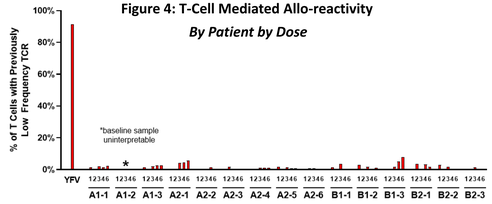
Figure 3: Immune Reconstitution of Lymphocytes



T-Cell Mediated Immunogenicity

- The T-cell compartment of 14 evaluable patients was analyzed for T-cell mediated host-versus-product allo-reactivity. A TCR repertoire analysis for each patient was conducted at multiple time points following FT500 dosing, which showed that no more than 8% of the T-cell clones in the patients' reconstituted T-cell compartment were comprised of pre-existing low-frequency T-cell clones after six FT500 doses, suggesting that a robust anti-FT500 T-cell response was not evident. As a point of contrast, in subjects undergoing immunization for infectious disease (YFV), almost 90% of the T-cell clones that emerge existed in low frequency prior to immunization (Figure 4).

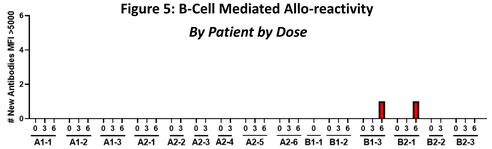
Figure 4: T-Cell Mediated Allo-reactivity
By Patient by Dose



B-Cell Mediated Immunogenicity

- The antibody repertoire of 15 evaluable patients was analyzed for B-cell mediated host-versus-product allo-reactivity. Patient serum samples were assessed for the six HLA class I types expressed by FT500 at screening, after Cycle 1 (after 3 doses), and after Cycle 2 (after 6 doses) using a panel reactive antibody screen with reflex testing by ELISA for positive results. Among the 15 patients, single FT500 anti-HLA antibodies with mean fluorescence intensity (MFI) levels of ≥ 5,000 were detected in two patients, suggesting that a robust anti-FT500 B-cell response was not evident (Figure 5). As a point of reference, in patients undergoing haplo-identical hematopoietic stem cell transplant, an MFI level ≥ 5,000 has been correlated with a 5-fold increase in risk of graft rejection (*EBMT Guidelines on Donor Specific Antibodies; Ciuria et al, BMT, 2018*).

Figure 5: B-Cell Mediated Allo-reactivity
By Patient by Dose



Cohort B2 Patient 2 Case Study

R/R Classical Hodgkin Lymphoma Resistant to anti-PD1 Therapy

- 29 y/o male with relapsed / refractory classical Hodgkin lymphoma, who had received 14 prior therapies including FDA-approved ICI therapies. Refractory to last prior therapy of CSF-1 inhibitor plus experimental anti-PD-1 therapy.
- Response assessment demonstrated an 84% reduction in size of a lymphonodal mass (Figure 6) and a 58% reduction in size of all target lesions following three doses of FT500 plus anti-PD-1 therapy, however, new bone lesion was observed. IHC staining of the lymphonodal mass demonstrates post-treatment increases in the number of CD3$^+$ and CD8$^+$ cells per high power field (hpf) as well as in the ratio of CD3$^+$ and CD8$^+$ cells to tumor cells, indicative of T-cell trafficking to the responding tumor bed (Figure 7).

Figure 6: Tumor Regression

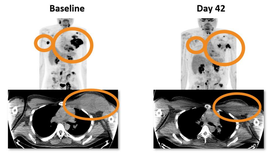
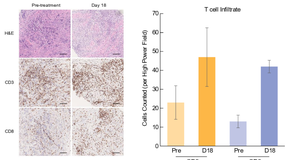


Figure 7: Increased T-cell Infiltration

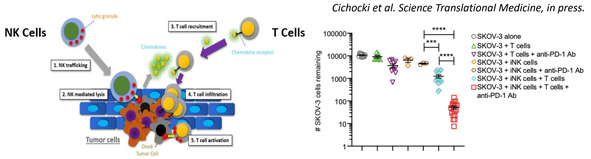


Conclusions & Future Directions

- In the dose-escalation phase of the FT500 Phase 1 clinical trial:
  - Up to six doses of FT500 were safely administered in the outpatient setting. The multi-dose, two-cycle treatment schedule was well-tolerated, and there were no treatment discontinuations due to adverse events.
  - At dose levels of up to 300M cells per dose, FT500 was well-tolerated as a monotherapy and in combination with anti-PD-1/PD-L1 checkpoint inhibitor therapy. No dose-limiting toxicities and no FT500-related SAEs or Grade ≥ 3 AEs were observed.
  - Immunological response to FT500 was not suggestive of host-versus-product B-cell or T-cell mediated rejection.
- In Regimen B2, clinical and pharmacodynamic anti-tumor activity were observed in a heavily pre-treated patient with classical Hodgkin lymphoma resistant to checkpoint inhibitor therapy, supportive of the NK cell-mediated cancer immunity cycle. In preclinical studies, iPSC-derived NK cells (iNK) have demonstrated the potential to mediate anti-tumor activity in tumors resistant to checkpoint inhibitor therapy, where T-cell response may be impaired due to loss of antigen presentation, T-cell inactivation and/or reduced numbers of proliferating CD8$^+$ T cells in the tumor microenvironment (Figure 8).

Figure 8: NK Cell-mediated Cancer Immunity Cycle

Cichocki et al. Science Translational Medicine, in press.



- The dose-expansion stage of the FT500 clinical trial is ongoing in up to 15 patients with either non-small cell lung cancer or classical Hodgkin lymphoma who are refractory to, or have relapsed on, checkpoint inhibitor therapy. Each patient in the dose-expansion stage is to receive three once-weekly doses of FT500 at 300 million cells per dose, each with IL-2 cytokine support for each dose, for up to two 30-day cycles in combination with the same checkpoint inhibitor on which the patient failed or relapsed.