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Clinical Evaluation of Fast-In-Time (FIT) anti-CD19 CAR T—a Non-Viral, 2-day Rapid Manufacture CAR T-cell Therapy for B-Cell Malignancies

Ping Li, MD[1], Jian Ge, PhD[2], Shiguang Ye, MD[1], Lili Zhou, MD[1], Yiming Gong, MD[3], Huaying Ruan, MN[3], Hosein Kouros-Mehr, MD, PhD[3], and Aibin Liang, MD[1]

1. Department of Hematology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China
2. First Affiliated Hospital of Anhui Medical University, Hefei, China
3. Shanghai First Song Therapeutics, Shanghai, China

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy has shown promise in the treatment of hematologic malignancies, but access barriers exist globally. FIT™, a non-viral, 2-day rapid manufacture autologous CAR T platform, aims to address limitations associated with current CAR T-cell therapies.

Features of the FIT platform include

- Non-viral gene delivery (based on proprietary transposase)
- No ex vivo patient T-cell activation or expansion
- 2-day manufacturing process with high CAR T-cell yield
- < 2-week vein-to-vein time
- Low cost of goods ($20-30k)
- Random gene delivery (away from gene elements and towards gene safe harbor regions)

AIM

To investigate the preliminary clinical safety, cellular kinetics, and efficacy of FIT-CD19-CAR-T, a 2nd generation CD28-CD3ζ CAR T utilizing a humanized anti-CD19 binder

METHOD

This investigator-initiated trial (IIT) in China evaluated the safety, pharmacokinetics (PK), and preliminary efficacy of FIT-CD19-CAR-T cells in 3 patients (pts) with relapsed or refractory B-cell malignancies, including a B-ALL patient (pt) with 9 prior lines of therapy (LOT) and 50% bone marrow (BM) blasts, a B-ALL pt with 2 LOT and 0.5% BM blasts, and an FL patient with 4 LOT and moderate tumor burden (sum of product of diameters [SPD] 3440 mm^2).

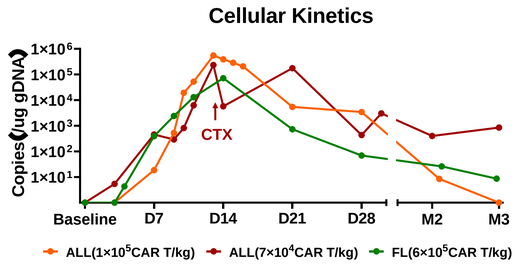
Pts underwent apheresis for CAR T-cell manufacturing and began lymphodepleting (LD) chemotherapy (2-3 days of cyclophosphamide 250-300 mg/m^2/day and fludarabine 25-30 mg/m^2/day) within one day of apheresis.

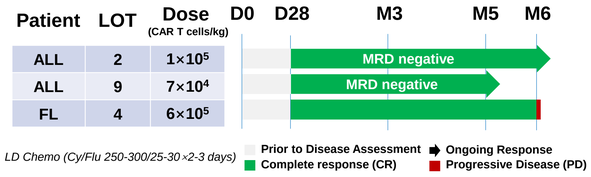
RESULTS

All 3 patients received 2-3 days of LD chemotherapy at the investigator's discretion and received fresh (non-frozen) FIT-CD19-CAR-T cells with a 5-day vein-to-vein time. Two ALL pts received 70k and 100k CAR T cells/kg, while the FL patient received 600k CAR T cells/kg. Peak CAR-T copy numbers were comparable to approved CD19 CAR-T products with Cmax occurring on days 13-14 after CAR T treatment. Overall, the treatment exhibited an acceptable safety profile with manageable cytokine release syndrome (CRS; G3 and G2 in ALL pts; no CRS in FL patient) and immune effector cell-associated neurotoxicity syndrome (ICANS; 1 case of G3 in ALL patient). All three patients experienced complete responses (MRD-CR in 2 ALL pts; CMR in FL patient).

Subject ID		#1 ALL	#2 ALL	#1 FL
Demographic	Age	62	50	43
	Gender	Female	Female	Male
	race/ethnicity	Asian	Asian	Asian
Baseline characteristics	ECOG	0-1	0-1	0-1
	Diagnosis	ALL	ALL	FL Grade 1-2
	Tumor Burden	0.5% BM blasts (MRD 4.9%)	49.5% BM blasts	3440 mm^2
	Baseline LDH	243	174	129
	Prior Treatments	2 lines	9 lines	4 lines
Intervention	LD Regimen	2-day Cy/Flu	3-day Cy/Flu	2-day Cy/Flu
	Cy/Flu LD Dose (mg/m^2/day)	250/25	250/25	300/30
	Dose (CAR T cells/kg)	1.00E+05	7.00E+04	6.00E+05
	CAR+%	33.9%	22.5%	26.0%
AESI	CRS (onset, duration, intervention)	G2 (D8, 5 days, TCZ+DMX+MP)	G3 (D7, 13 days, TCZ+DMX+MP+CTX)	-
	ICANS (onset, duration, intervention)	-	G3 (D11, 9 days, DMX, CTX, ventilation)	-
	Infection	G3 (pneumonia)	G3	G3 (pneumonia)
Cytopenia	anemia	G3	G3	G1
	WBC decreased	G4	G4	G2
	lymphocyte count decreased	G4	G4	G3
	Platelet count decreased	G4	G4	G1
Neural	Headache	-	G1	-
	Dysphasia	-	G2	-
	Depressed level of conciousness	-	G3	-
	Seizure	-	G3	-
	Insomnia	-	-	G1
Coagulation	DIC	-	G3	-
	Fibrinogen decreased	G2	-	-
	FDP increased	G3	-	-
Hepatic	ALT increased	G1	-	-
	AST increased	G3	-	-
	GGT increased	G2	-	-
Efficacy	Best Response	CR	CR	CR
	MRD status	negative	negative	-
	PFS	164+ days Not reached	133+ days Not reached	166 days

AESI, adverse events of special interest; ALT, alanine transaminase; AST, aspartate transaminase; BM, bone marrow; CRS, cytokine release syndrome; CTX/Cy, cyclophosphamide; DIC, disseminated intravascular coagulation; DMX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; FDP, fibrin degradation product; Flu, fludarabine; GGT, Gamma-glutamyltransferase; LD, lymphodepletion; LDH, lactate dehydrogenase; MP, methylprednisolone; MRD, minimal residual disease; TCZ, tocilizumab

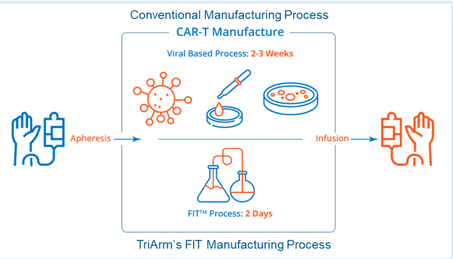




(Top) FIT-CD19-CAR-T cell copy number (copies/ug DNA) as determined by qPCR assay in the 3 patients (D = day; M = month)
(Bottom) Swimmer's plots for 3 patients on study (MRD = minimal residual disease)

CONCLUSIONS

FIT-CD19-CAR-T demonstrates a favorable safety profile and encouraging initial efficacy and pharmacokinetics at relative low doses in patients with heavily pretreated B-cell malignancies, which may be attributable to enhanced expression of naïve & stem cell memory markers on rapidly manufactured FIT-CD19-CAR-T cells. Phase 1 studies are planned for continued investigation.



REFERENCES & ACKNOWLEDGEMENTS

Frame, DG, et al (2024). Comparing 2-day vs 3-day flu-CY lymphodepleting regimens for CD19-CAR T-cell therapy in patients with non-Hodgkin's lymphoma. *Front Immun.* 15: 1403145.

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