SIM1811-03 in participants with advanced solid tumor and cutaneous T cell lymphomas : preliminary results from an on-going first-in-human phase I trial in China

#696P

F. Liu[1], N. Yang[2], J.Wang[3], R.Wang[4], Z.Han[5],C. Yang[6] , J .Li[6], Z. Liu[6], Y. Li[6], J.Tang[7] ,A. Cui[8], R. Xu[9]

[1] Clinical Research,Sun Yat-sen University Cancer Center, Guangzhou, China; [2] Lung & Gastrointestinal Oncology Deportment, Hunan Cancer Hospital,Changsha,china; [3] Digestive Department, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University ,Zhengzhou, China; [4] Phase I Clinical Trial Laboratory, Anhui Chest Hospital , Hefei, China; [5]Oncology Department ,The Affiliated Hospital of Xuzhou Medical University Xuzhou, China;; [6] Clinical Science, Shandong Simcere Biopharmaceutical Co., Ltd. Shandong, China ; [7] Translational Medicine, Shandong Simcere Biopharmaceutical Co., Ltd. Shandong, China; [8]Clinical Pharmacology, Shandong Simcere Biopharmaceutical Co., Ltd. Shandong, China;[9] Medical Oncology Department , Sun Yat-sen University Cancer Center, Guangzhou, China

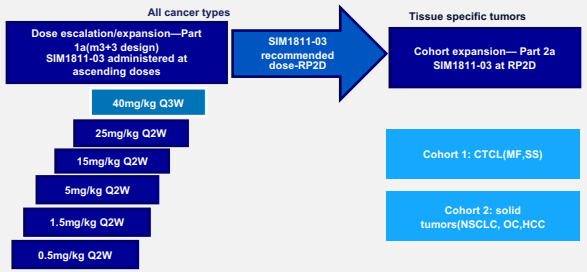
BACKGROUND

Tumor necrosis factor receptor-2(TNFR2) drives immune escape and tumor proliferation, and is highly expressed on tumor cells, immunosuppressive cells in the tumor microenvironment, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). SIM1811-03 is a humanized IgG1 monoclonal antibody that targeting TNFR2,which demonstrated antitumor activity in preclinical models as single agent. SIM1811-03 is being evaluated in the First-in-Human study in patients with advanced solid tumors and cutaneous T-cell lymphoma (CTCL), here we report the data based on Chinese population

METHODS

The study enrolled participants with advanced solid tumors who were not eligible for standard of care treatment. Participants received one dose of SIM1811-03 in cycle 0 and subsequently once every 2 weeks (Q2W) in dose from 0.5mg/mg to 25mg/mg. Based on emerging data, every 3 weeks(Q3W) schedule in 40mg/kg was tested for single agent. The primary objectives were to determine the maximum-tolerated dose (MTD) or recommended dose (RD) in the dose escalation part for expansion and to evaluate preliminary anti-tumor activity using either RECIST v1.1 for solid tumors or the global response score for CTCL (Olsen 2011) in expansion part. The secondary objectives were to assess safety and tolerability and to characterize pharmacokinetics (PK) and pharmacodynamics (PD) profiles of SIM1811-03.

Figure1:Study design



Solid tumors: Objective response rate (ORR) assessed by Investigator per RECIST 1.1
CTCL: ORR assessed by Investigator per global response (Olsen 2011)

MF:Mycosis Fungoides, SS: Sézary syndrome

RESULTS

As of April 18, 2023, 22 patients in dose escalation part received SIM1811-03 monotherapy at doses of 0.5 mg/kg (n=3), 1.5 mg/kg (n=4), 5 mg/kg (n=4), 15 mg/kg (n=4), 25 mg/kg (n=4) Q2W and 40 mg/kg Q3W (n=3). Median age was 51 years (range: 30-68) (Table 1). No dose-limiting toxicity (DLT) was observed and the MTD was not reached. Majority of adverse events were Grade 1 or 2.There were two subjects with Grade 3/4 treatment-related adverse event (TRAE). Two patients experienced treatment-related serious adverse event (SAE), one had peripheral edema and the other platelet count increase (Table 2,Table3)

Table 1: Demographic and baseline characteristics

	0.5mg/kg Q2W(N = 3)	1.5mg/kg Q2W(N = 4)	5mg/kg Q2W(N = 4)	15mg/kg Q2W(N = 4)	25mg/kg Q2W(N = 4)	40mg/kg Q3W(N = 3)	Total (N = 22)
Age (years)							
Median(Range)	53.0(43~63)	50.0(32~65)	47.5(40-49)	58.0(49-63)	60.0(52-68)	44.0(30-50)	51.0(30-68)
Sex, n(%)							
Male	2(66.7%)	3(75.0%)	1(25.0%)	1(25.0%)	2(50.0%)	1(33.3%)	10(45.5%)
Female	1(33.3%)	1(25.0%)	3(75.0%)	3(75.0%)	2(50.0%)	2(66.7%)	12(54.5%)
ECOG PS , n(%)							
0	1(33.3%)	2(50.0%)	0	0	0	2(66.7%)	5(22.7%)
1	2(66.7%)	2(50.0%)	4(100%)	4(100%)	4(100%)	1(33.3%)	17(77.3%)
Prior lines of drug therapy,n(%)							
1 line	0	0	1(25.0%)	0	0	1(33.3%)	2(9.1%)
2 line	2(66.7%)	0	1(25.0%)	0	1(25.0%)	0	4(18.2%)
3 line	0	2(50.0%)	0	1(25.0%)	1(25.0%)	1(33.3%)	5(22.7%)
≥4 line	1(33.3%)	2(50.0%)	2(50.0%)	3(75.0%)	2(50.0%)	1(33.3%)	11(50.0%)
Type of cancer, n(%)							
Colon	2(66.7%)	1(25.0%)	0	2(50.0%)	2(50.0%)	1(33.3%)	8(36.4%)
Ovarian	0	1(25.0%)	2(50.0%)	1(25.0%)	1(25.0%)	1(33.3%)	6(27.3%)
Cervical	0	0	1(25.0%)	0	0	1(33.3%)	2(9.1%)
Lung	0	0	0	0	1(25.0%)	0	1(4.5%)
Other *	1(33.3%)	2(50.0%)	1(25.0%)	1(25.0%)	0	0	5(22.7%)

Other: 1 Pancreatic cancer, 1 unknow solid tumor, 1 Endometrial cancer,2 Nasopharynx cancer

Table 2 Summary of safety

Event n (%)	0.5mg/kg Q2W (N = 3) n(%)	1.5mg/kg Q2W (N = 4) n(%)	5mg/kg Q2W (N = 4) n(%)	15mg/kg Q2W (N = 4) n(%)	25mg/kg Q2W (N = 4) n(%)	40mg/kg Q3W (N = 3) n(%)	Total (N = 22) n(%)
TEAE	3(100%)	4(100%)	4(100%)	4(100%)	4(100%)	3(100%)	22(100%)
Grade≥3 TEAE	0	2(50.0%)	0	2(50.0%)	2(50.0%)	0	6(27.3%)
TRAE	2(66.7%)	2(50.0%)	2(50.0%)	4(100%)	4(100%)	1(33.3%)	15(68.2%)
Grade≥3TRAE	0	0	0	1(25.0%)	1(25.0%)	0	2(9.1%)
TEAE leading to interruption	0	1(25.0%)	0	2(50.0%)	4(100%)	0	7(31.8%)
TEAE leading to discontinue	0	0	0	0	1(25.0%)	0	1(4.5%)
Serious TEAE	0	2(50.0%)	0	2(50.0%)	2(50.0%)	0	6(27.3%)
Serious TRAE	0	0	0	1(25.0%)	1(25.0%)	0	2(9.1%)

No patient experienced a grade 5 TRAE
TEAE leading to interruption: 1 Infusion related reaction,1 Oedema peripheral, 1 Platelet count increased, 4 COVID-19 (Not related to SIM1811-03)
Both in Grade ≥3 TRAE and Serious TRAE: Edema peripheral, anemia and platelet count increased

Table 3: TRAEs Occurring in >10% Patients by Grade (Treatment Related to SIM1811-03): Pooled 6 dose cohorts

AE by PT n,%	Total(N = 22)n(%)	
	Any Grade	≥Grade 3 *
Any treatment related TEAE	15(68.2%)	2(9.1%)
Blood creatinine increased	4(18.2%)	0
Anaemia	4(18.2%)	2(9.1%)
Nausea	3(13.6%)	0
Hyponatraemia	3(13.6%)	0

* Include one patient with CRC treated with 15mg/kg with a treatment related SAE of Grade 3 Oedema peripheral and one patient with NSCLC with 25mg/kg with a treatment related SAE of Grade 3 Platelet count increased

Pharmacokinetics

After SIM1811-03 infusion,

- At doses from 0.5 to 15 mg/kg, the drug concentrations decreased rapidly and the PK profile showed a target–mediated drug disposition (TMDD) property (Figure 2);
- At the doses >15 mg/kg, the drug exposure were dose-proportional (Figure 2);
- The terminal elimination half-life was approximately 12 days at doses higher than 15 mg/kg;
- A slight accumulation of SIM1811-03 exposure (1.28 to 2.14 folds) was observed on Cycle 3.

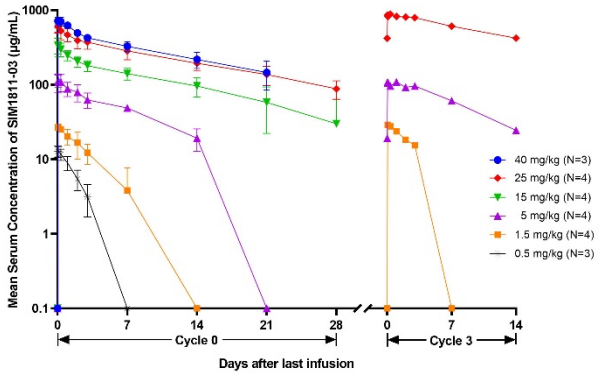


Figure 2. Mean ± SD Serum Pharmacokinetics Profiles (semi-log scale) after Single and Multiple Doses of SIM1811-03 Infusion.

RO and sTNFR2 data

The TNFR2 receptor occupancy (RO) on CD14+ cells or CD16+cells, and sTNFR2 secretion showed a highly consistent trend and showed excellent correlation with the dose levels of SIM1811-03. The TNFR2 RO in peripheral blood was almost saturated (>95% RO) at dose levels of 15 mg/kg and above after multiple doses (Figures 3 and 4).

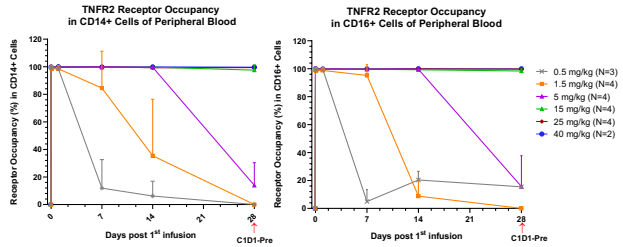


Figure 3. TNFR2 Receptor Occupancy in CD14+ and CD16+ Cells of Peripheral Blood after SIM1811-03 Infusion.

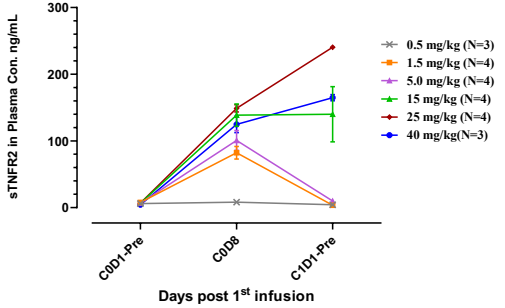


Figure 4. sTNFR2 Release in Plasma after SIM1811-03 Infusion.

CONCLUSIONS

SIM1811-03 was well tolerated without and DLT reported in participants with advanced solid tumors across all dose levels explored and the MTD was not reached. The preliminary PK and PD results supported 40mg/kg every 3-week to be selected as the recommended dose for expansion and for combinations with PD(L)-1 inhibitors. Clinical trial information: NCT05781386

Acknowledgments
We thank the patients and their families who made this trial possible and the clinical study teams involved in this trial. This study is sponsored by Jiangsu Simcere Biological Co., Ltd

Contact information
Ruihua Xu, MD
86-20-8734-3468
xurh@sysucc.org.cn

Disclosure
Dr. Liu confirm that she does not have conflicts of interest to declare