P425

Phase 1b study of GX-I7, a long-acting interleukin-7, evaluating the safety, pharmacokinetics and pharmacodynamics profiles in patients with advanced solid cancers

Minkyu Heo[1], Joohyuk Sohn[2], Myung Ah Lee[3], Eui-Cheol Shin[4], Su-Hyung Park[4], So Jeong Kim[4], Yeon-Kyung Oh[1], Sohee Jeong[1], JungWon Woo[1], Young Chul Sung[1], and Tae Won Kim[5]

[1]Genexine, Inc., 700, Daewangpangyo-ro, Korea Bio-Park Bldg. Bundang-gu, Seongnam-si, Gyeonggi-do, Korea, [2]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea., [3]Division of Medical Oncology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea., [4]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea., [5]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

BACKGROUND

Cancer and treatment-related lymphopenia is associated with higher mortality in patients with various oncologic malignancies. Interleukin-7 (IL-7), a homeostatic cytokine of T lymphocytes, plays a critical and non-redundant role in T cell development and homeostasis of mature T lymphocytes. IL-7 is a potent amplifier of naïve and memory T cells, thereby correcting T cell deficiency and contributing to immune reconstitution (Mackall CL et al. Nat. Rev. Immunol. 2011, 11:330). This may result in significant clinical benefit when combined with lymphopenia-inducing radiation/chemotherapy or immunotherapy where anti-tumor effects are mediated by T cells.

GX-I7 is a long-acting form of human IL-7 fused with hybrid Fc (hIL-7-hyFc™). In animal studies, GX-I7 increased ALC and TIL, yielding high CD8⁺ T/Treg and CD8+ T/MDSC ratios in the tumor microenvironment and enhanced anti-tumor effects in combination with various Checkpoint Blockades (*Lee SW et. al. AACR 2018, 2019*). In Phase 1 trial in healthy volunteers, GX-I7 was shown to increase ALC and various subsets of T cells except Treg and induce expression of CCR5 (Lee H et. al, AACR 2019). CCR5-ligand, CCL5 is known to be expressed by tumors such as TNBC and induces CD8⁺ T cell infiltration and associated with an improved outcome (Karnoub AE et. al. Nature, 2007, 449:557. Araujo JM et. al. Science Reports, 2018, 8:4899).

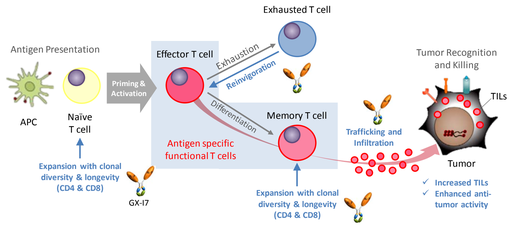


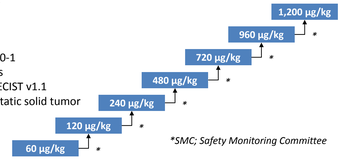
Figure 1. Proposed MoA of GX-I7 in Cancer Immunotherapy

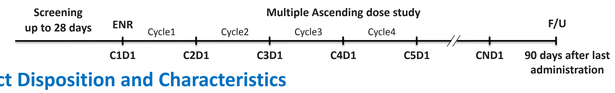
OBJECTIVES AND METHODS

Phase 1b Overall Study Design

3+3 study design per cohort

Eligibility
- Age ≥ 19 years
- ECOG performance status 0-1
- Life expectancy ≥ 12 weeks
- Measurable disease per RECIST v1.1
- Locally advanced or metastatic solid tumor





Study Objectives

- **Primary objective**
  - ✓ Safety and tolerability of GX-I7
  - ✓ RP2D, MTD and DLTs
- **Secondary objective**
  - ✓ Pharmacokinetics and pharmacodynamics
  - ✓ Immunogenicity
  - ✓ Exploratory biomarkers

➢ GX-I7 given as intramuscular administration
➢ Patients received GX-I7 every 3 weeks

Subject Disposition and Characteristics

Characteristics	Categories	Low dose, n=6 (60~120 μg/kg)	Middle dose, n=6 (240~480 μg/kg)	High dose, n=9 (720~1,200 μg/kg)	Total N=21
Age, Median(Range)	-	58.0(52.0~64.0)	50.0(40.0~75.0)	58.0(46.0~75.0)	58.0(40.0~75.0)
Gender, n(%)	Male	2(33.33)	5(83.33)	5(55.56)	12(57.14)
Histology, n(%)	Adenocarcinoma	3(50.00)	5(83.33)	8(88.89)	16(76.19)
	Infiltrating ductal carcinoma	1(16.67)	0(0.00)	0(0.00)	1(4.76)
	Other	2(33.33)	1(16.67)	1(11.11)	4(19.05)
Performance status, n(%)	0	2(33.33)	1(16.67)	5(55.56)	8(38.09)
	1	4(66.67)	5(83.33)	4(44.44)	13(61.90)
Prior chemotherapy, n(%)	≥ 3	6(100.00)	4(66.67)	9(100.00)	19(90.48)
	< 3	0(0.00)	2(33.33)	0(0.00)	2(9.52)

RESULTS

Safety

- 44 cases of ADRs were reported in dose levels from 60 ~ 1,200 μg/kg and all were Gr1 or Gr2.

n(%),[case]		GX-I7 (hIL-7-hyFc™) 60 μg/kg (n=3)	120 μg/kg (n=3)	240 μg/kg (n=3)	480 μg/kg (n=3)	720 μg/kg (n=3)	960 μg/kg (n=3)	1,200 μg/kg (n=3)	Total (n=21)
Any TEAE*		3(100.0),[13]	3(100.0),[29]	3(100.0),[14]	3(100.0),[18]	3(100.0),[18]	3(100.0),[4]	3(100.0),[14]	21(100.0),[110]
ADR		3(100.0),[6]	2(66.7),[9]	3(100.0),[6]	2(66.7),[6]	1(33.3),[5]	2(66.7),[2]	3(100.0),[10]	16(76.2),[44]
TEAE by Severity	Gr1	2(66.7),[4]	2(66.7),[7]	3(100.0),[4]	2(66.7),[4]	1(33.3),[2]	1(33.3),[1]	2(66.7),[7]	13(61.9),[29]
	Gr2	1(33.3),[2]	2(66.7),[2]	2(66.7),[2]	2(66.7),[2]	1(33.3),[3]	1(33.3),[1]	3(100.0),[3]	12(57.1),[15]
Most frequently reported ADR									
Injection site reaction		3(100.0),[6]	2(66.7),[5]	3(100.0),[3]	2(66.7),[4]	1(33.3),[3]	-	3(100.0),[4]	14(66.7),[25]
Pyrexia			1(33.3),[1]	1(33.3),[1]	1(33.3),[2]	-	1(33.3),[1]	2(66.7),[3]	6(28.6),[8]
Rash / Rash popular			1(33.3),[1]	-	-	1(33.3),[1]	1(33.3),[1]	1(33.3),[1]	4(19.0),[4]
Decreased appetite			1(33.3),[1]	-	-	-	-	1(33.3),[1]	2(9.5),[2]

*TEAE; Treatment emergent adverse event

Pharmacokinetics

- Extended half-life (33~147 hours) compared to other IL-7 derivatives.
  - ✓ CYT 99 007: 6.46~9.80 hours (*Ref: Clin Cancer Res. 2010 Jan 15;16(2):727-35.*)
  - ✓ CYT 107: 8.7~34.6 hours (*Ref: Blood (2012) 120 (24): 4882-4891.*)
- Dose-dependent exposure observed in all doses administered.

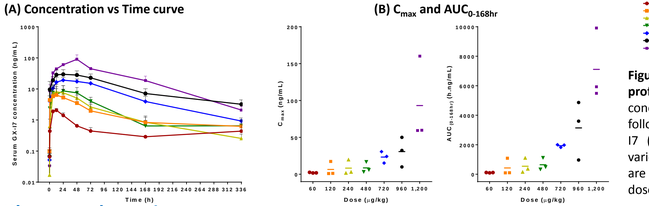


Figure 2. Pharmacokinetic profiles (A) GX-I7 serum concentration-time curves following first dose of GX-I7 (B) C_{max} and AUC at various dose levels. Data are mean±SEM for each dose level.

Pharmacodynamics

- Dose-dependent increase in ALC, CD3⁺, CD4⁺, and CD8⁺ T cells in both lymphopenic/non-lymphopenic cancer patients.

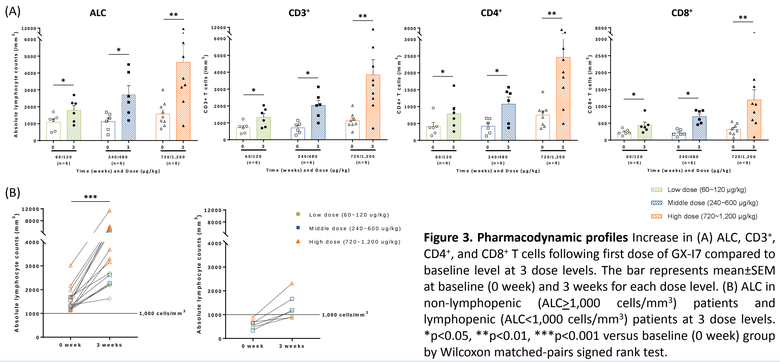


Figure 3. Pharmacodynamic profiles Increase in (A) ALC, CD3⁺, CD4⁺, and CD8⁺ T cells following first dose of GX-I7 compared to baseline level at 3 dose levels. The bar represents mean±SEM at baseline (0 week) and 3 weeks for each dose level. (B) ALC in non-lymphopenic (ALC≥1,000 cells/mm³) patients and lymphopenic (ALC<1,000 cells/mm³) patients at 3 dose levels. *p<0.05, **p<0.01, ***p<0.001 versus baseline (0 week) group by Wilcoxon matched-pairs signed rank test.

Analysis of Ki67, CD127 (IL-7Rα) and Subsets of T cell

- Dose-dependent increase in Ki67 and CD4⁺/Treg & CD8⁺/Treg ratios, and decrease in CD127 (IL-7Rα).

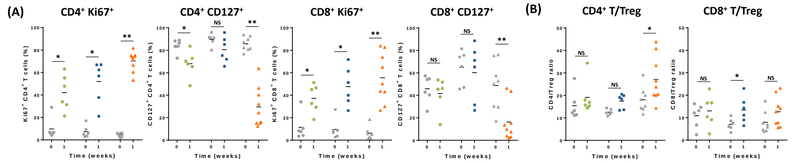


Figure 4. Changes in (A) Ki67, CD127 and (B) Treg ratio in CD4⁺ and CD8⁺ T cells following first dose of GX-I7. NS; p>0.05, *p<0.05, **p<0.01, ***p<0.001 versus baseline (0 week) group by Wilcoxon matched-pairs signed rank test.

- Dose dependent increase in T cell subsets and NK cell but not in B cell.

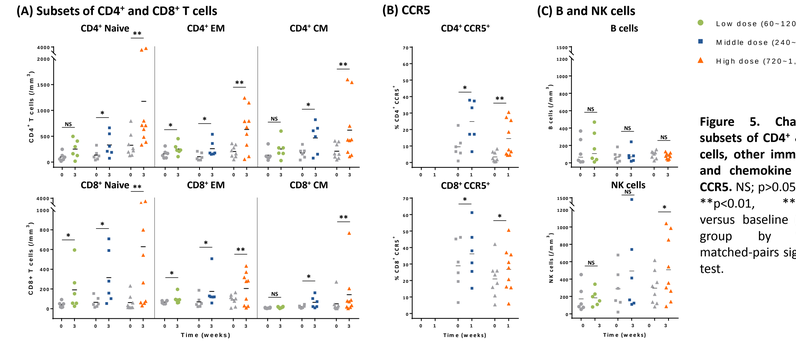


Figure 5. Changes in subsets of CD4⁺ & CD8⁺ T cells, other immune cells and chemokine receptor CCR5. NS; p>0.05, *p<0.05, **p<0.01, ***p<0.001 versus baseline (0 week) group by Wilcoxon matched-pairs signed rank test.

CONCLUSIONS

- Q3W administration of GX-I7 was safe and tolerable in patients with advanced solid tumors.
- No treatment-related serious adverse events were reported and ADRs were mostly mild and transient.
- Injection site reaction was the most frequently reported ADR, and was manageable with conventional use of anti-histamines and/or corticosteroids.
- PK profiles showed dose-dependent increase and significantly longer half-life compared to that of rhIL-7.
- PD profiles showed
  - ✓ Dose-dependent increase of T cell and its subsets in both lymphopenic and non-lymphopenic patients, evidenced by increase of Ki67 and down-regulation of CD127.
  - ✓ Induction of chemokine receptor, CCR5.
  - ✓ Improvement in CD4+ T cell/Treg & CD8+T cell/Treg ratio.
  - ✓ Increase of NK cells in high dose (720 ~ 1,200 μg/kg) but no dose-dependent increase of B cells .
- No ADA-induced interference of PK and PD profiles were observed.
- GX-I7 as T cell amplifier provides a unique opportunity for immuno-oncology combination strategies by reconstituting persistent T cell immunity.