1072

Preliminary safety and efficacy of GX-I7, a long-acting interleukin-7, in combination with pembrolizumab in patients with refractory or recurrent metastatic triple negative breast cancer(mTNBC): Dose escalation period of Phase 1b/2 study(KEYNOTE-899)

Joohyuk Sohn[1], Kyong Hwa Park[2], Hee Kyung Ahn[3], Keun Seok Lee[4], Jee Hyun Kim[5], Sung-Bae Kim[6], Kyoung Eun Lee[7], Jee Hung Kim[8], Gun Min Kim[1], Sung Hoon Sim[4], Se Hwan Yang[9], NgocDiep T. Le[9], Jiwon Kim[10], Minkyu Heo[10], JungWon Woo[10], Young Chul Sung[10], and Young Hyuck Im[11]

[1]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea. [2]Division of Oncology/Hematology, Department of Internal Medicine, Korea University Anam Hospital, Seoul, Korea. [3]Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea. [4]Center for Breast Cancer, National Cancer Center, Goyang, Korea. [5]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea. [6]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. [7]Department of Hematology and Oncology, Ewha Womans University School of Medicine, Seoul, Korea. [8]Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. [9]NeoImmuneTech, Inc., Rockville, USA. [10]Genexine, Inc., Seongnam, Korea. [11]Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, Korea.

BACKGROUND

Pembrolizumab monotherapy showed 5.3% ORR as ≥2nd-line treatment for mTNBC (KEYNOTE-086[1]) and did not significantly improve OS as 2L or 3L treatment for mTNBC compared to standard chemotherapy in phase 3 study (KEYNOTE-119[2]) leading to high unmet needs of a new drug that could enhance the activity of pembrolizumab when it is combined with. Recent studies showed that higher lymphocyte count is an independent factor which correlates with better response to checkpoint blockade in cancer patients[3]. GX-I7, a long-acting interleukin-7, potentially provides synergistic anti-tumor efficacy with pembrolizumab by increasing number of T cells both in tumor microenvironment (TME) and peripheral blood (PB).

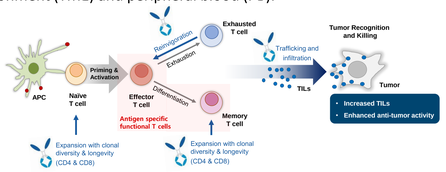


Figure 1. Proposed MoA of GX-I7 in cancer immunotherapy[4),5)]

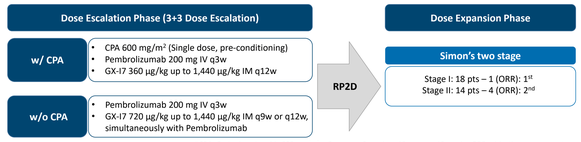
STUDY OBJECTIVES AND METHODS

Study objectives

- **Primary Objectives:**
  - ✓ To evaluate safety and tolerability of GX-I7 in combination with pembrolizumab and determine recommended phase 2 dose (RP2D); Phase 1b
  - ✓ To evaluate objective response rate (ORR) by RECIST v1.1; Phase 2
- **Secondary Objective:**
  - ✓ iORR as assessed by iRECIST and DoR, DCR, PFS, and OS by RECIST v1.1 and iRECIST as determined by the investigator and IRC

Study design and patients

- This is an open-label, phase 1b/2 study in patients with refractory or recurrent TNBC who failed standard chemotherapy from 1st to 3rd line treatment in metastasis setting.
- Dose escalation phase includes cohorts with or without pretreatment of cyclophosphamide (CPA) after entry to the trial. Patients pretreated with CPA received GX-I7 from 360 μg/kg up to 1,440 μg/kg every 9 weeks or 12 weeks and patients without CPA pretreatment received GX-I7 from 720 μg/kg up to 1,440 μg/kg every 12 weeks. After RP2D determination dose expansion phase is planned as Figure 2. Recruitment for 1440 μg/kg dose groups are ongoing.
- Tumor assessment is to be conducted every 9 weeks.



CPA; Cyclophosphamide 600 mg/m², q9w; every 9 weeks, q12w; every 12 weeks, ORR; objective response rate

Figure 2. Phase 1b/2 study design

RESULTS

Patient Disposition and Characteristics

- Total 45 patients had been enrolled (As of April 30, 2020).
- 30 patients were available for the assessment of safety and efficacy.
- All patients had received at least and more than one line of chemotherapy for recurrent and metastatic TNBC.

Table 1. Baseline characteristics

N(%)		GX-I7-CA-006, N=30 GX-I7/Pembrolizumab±CPA	KEYNOTE-086[1], N=170 Pembrolizumab
Age, year, median(range)	-	48.5(29-75)	53.5(28-85)
Postmenopausal	-	14(46.7)	140(82.4)
ECOG PS	*0*	16(53.3)	90(52.9)
	1	14(46.7)	80(47.1)
LDH concentration	*<1xULN*	9(30.0)	82(48.2)
	≥1x~<2.5xULN	16(53.3)	85(50.0)
	≥2.5xULN	5(16.7)	2(1.2)
	Unknown	-	1(0.6)
TL size, mm, median(range)	-	45.6(10-203)	51.0(10-531)
No. of metastatic organ sites	*1*	7(23.3)	46(27.1)
	2	13(43.3)	68(40.0)
	3	3(10.0)	56(32.9)
	≥4	7(23.3)	
Prior taxane & anthracycline Therapy	-	30(100.0)	125(73.5)
Visceral metastasis	-	26(86.7)	125(73.5)
Previous (neo)adjuvant therapy	-	25(83.3)	141(82.9)
No. of previous lines of therapy for recurrent/metastatic disease	*0*	-	-
	1	15(50.0)	53(31.2)
	2	7(23.3)	43(25.3)
	3	7(23.3)	31(18.2)
	4	-	22(12.9)
	≥5	1(3.3)	21(12.4)

Safety and tolerability

- Treatment related AEs (TEAEs) occurred in 100% of patients (n=30) with grade 1-2 and 23% with grade 3 (no grade 4).
- The most common TEAEs were injection site reaction (n=22, 73%), fever (n=12, 40%), rash (n=10, 33%), ALT/AST increased (n=11, 37%), and GGT increased (n=4, 13%), hypothyroidism (n=3, 10%), hyperthyroidism (n=2, 7%), hepatitis (n=2, 7%).
- Grade 3 toxicities were 'increased hepatic enzyme' and 'infusion related reaction', reported from 1 patient each (3.3%).
- No DLT was observed in patients with dose escalation of up to 1,200μg/kg.

Table 2. Summary of adverse events

N(%)	360μg/kg (n=3)		720μg/kg (n=9)		960μg/kg (n=9)		1,200μg/kg (n=9)	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Most frequently reported TEAEs								
Injection site reaction	2 (67)	0 (0)	7 (78)	0 (0)	7 (78)	0 (0)	6 (66)	0 (0)
Pyrexia	1 (33)	0 (0)	5 (56)	0 (0)	4 (44)	0 (0)	2 (22)	0 (0)
Rash	0 (0)	0 (0)	2 (22)	0 (0)	5 (55)	0 (0)	3 (33)	0 (0)
ALT increased	2 (67)	0 (0)	2 (22)	0 (0)	0 (0)	0 (0)	4 (44)	0 (0)
AST increased	2 (67)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	4 (44)	0 (0)
GGT increased	1 (33)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)
Oedema peripheral	0 (0)	0 (0)	2 (22)	0 (0)	2 (22)	0 (0)	1 (11)	0 (0)
ALP increased	1 (33)	0 (0)	2 (22)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)
Nausea	1 (33)	0 (0)	1 (11)	0 (0)	1 (11)	0 (0)	1 (11)	1 (11)
Hyperthyroidism	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)
Hepatitis	0 (0)	0 (0)	1 (11)	0 (0)	1 (11)	0 (0)	1 (11)	0 (0)
Hypothyroidism	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)
Increased hepatic enzyme	0 (0)	0 (0)	1 (11)	1 (11)	1 (11)	0 (0)	0 (0)	0 (0)
Infusion related reaction	0 (0)	0 (0)	1 (11)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)

*GGT; Gamma-glutamyltransferase

Clinical response

- Median follow up period was 3.53 months (range 0.7–9.6 months) including 11 ongoing patients.
- A total of 30 mTNBC patients treated with GX-I7 in combination with pembrolizumab with or without CPA showed ORR of 0% in 360 μg/kg and 720 μg/kg, 11.1% in 960 μg/kg and, 33.3% in 1,200 μg/kg.
- Of note, a cohort (9 pts) received 1,200 μg/kg of GX-I7 with pembrolizumab with or without CPA showed 3 PR and 4 SD.

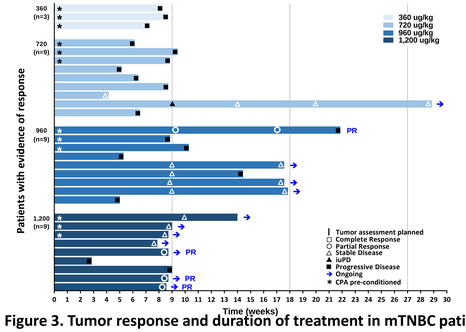


Figure 3. Tumor response and duration of treatment in mTNBC patients

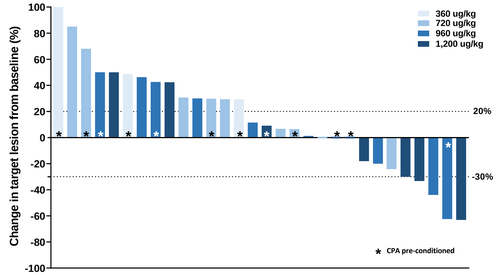


Figure 4. Best percentage change in target lesion from baseline

Table 3. Best Overall Response

RESPONSE (RECIST v1.1) N(%)	360 μg/kg (N=3)	720 μg/kg (N=9)	960 μg/kg (N=9)	1,200 μg/kg (N=9)
Objective Response Rate (ORR)				
Complete Response (CR)	-	-	-	-
Partial Response (PR)	-	-	1(11.1)	3(33.3)
Stable Disease (SD)	-	2(22.2)	3(33.3)	4(44.4)
Progressive Disease (PD)	3(100.0)	7(77.8)	5(55.6)	2(22.2)
Non-Evaluable	-	-	-	-
Disease Control Rate (DCR)	-	2(22.2)	4(44.4)	7(77.8)

[a]The proportion of patients with complete or partial response or stable disease based on best overall response.

Change from baseline in ALC, CD3+ T cells in PB

- GX-I7 treatment increased T cells significantly in all dose levels ranging from 360 μg/kg to 1,200 μg/kg with or without CPA.

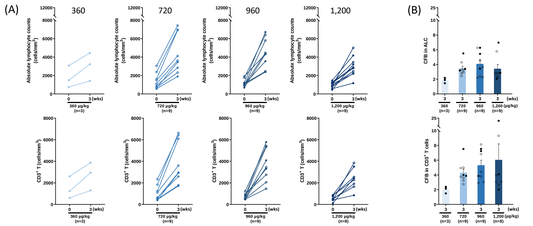


Figure 5. T cell increase in the peripheral blood (PB) by GX-I7 (360 μg/kg~1,200 μg/kg with or without CPA. (A) Change of individual ALC and CD3+ T cell levels at 3w post GX-I7 administration from the baseline level. (B) Fold increase of ALC and CD3+ T cell counts at 3w post GX-I7 administration from baseline. The bar represents Mean±SEM at baseline (0w) and at 3w for each dose level of GX-I7. Closed circles indicate 'with CPA' and open circles, 'without CPA', respectively.

CONCLUSIONS

- GX-I7 in combination with pembrolizumab with or without CPA was safe and well tolerated in most study participants and no DLT was observed in this phase 1b part of the trial.
- GX-I7 significantly increased T cell numbers in combination with pembrolizumab with or without CPA at doses from 360 μg/kg to 1,200 μg/kg.
- Disease control rate (PR+SD) was observed as follows: 0+2/9 (22.2%) in 720ug/kg, 1+3/9 (44.4%) in 960ug/kg and 3+4/9 (77.8%) in 1,200ug/kg of GX-I7 with or without CPA.
- Disease control rate and ORR tend to increase in a dose-dependent manner by GX-I7 administration.
- ORR in 1,200 μg/kg without CPA was 50% (3/6) and, therefore, 1,200 μg/kg without CPA is currently being considered as an RP2D candidate for the expansion phase.
- GX-I7 showed promising results to increase anti-tumor therapeutic effects in combination with checkpoint blockade with or without CPA in metastatic TNBC.

ACKNOWLEDGEMENTS

Pembrolizumab for this research was provided by Merck Sharp & Dohme Corp. This research was funded by Korea Drug Development Fund (Grant No. KDDF-201709-60).

REFERENCES

1) Adams S et al. Annals of Oncology. 2019;30:397-404
2) Cortes J et al. Annals of Oncology. 2019;30(suppl_5):859-860
3) Delyon J et al Annals of Oncology. 2013;24:1697-1703
4) Pauken KE et al. Science. 2016;Dec 2:354(6313)
5) Robb L et al Oncogene. 2007;26:6715-23