699

Efficacy and safety of GX-I7 plus pembrolizumab for heavily pretreated patients with metastatic triple negative breast cancer: The Phase 1b/2 KEYNOTE-899 Study

Joohyuk Sohn[1], Kyong Hwa Park[2], Hee Kyung Ahn[3], Sung-Bae Kim[4], Keun Seok Lee[5], Jee Hyun Kim[6], Jee Hung Kim[7], Jieun Lee[8], Kyoung Eun Lee[9], Se Hwan Yang[10], NgocDiep T. Le[10], Jiwon Kim[11], Minkyu Heo[11], JungWon Woo[11], Young Chul Sung[11], and Young Hyuck Im[12]

[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]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. [5]Center for Breast Cancer, National Cancer Center, Goyang, Korea. [6]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea. [7]Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. [8]Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea. [9]Department of Hematology and Oncology, Ewha Womans University School of Medicine, Seoul, Korea. [10]NeoImmuneTech, Inc., Rockville, USA. [11]Genexine, Inc., Seongnam, Korea. [12]Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, Korea.

BACKGROUND

Pembrolizumab monotherapy showed 5.3% ORR (KEYNOTE-086)[1] in a phase 2 study and failed to improve OS as ≥2L treatment for mTNBC, compared to standard chemotherapy. Thus, there is still an unmet need for a new drug able to enhance the activity of pembrolizumab when used in combination. Low level of peripheral blood and tumor infiltrating T cells correlates with poor response to checkpoint blockade in cancer patients[2]. Based on the mechanism of action of GX-I7, which increases T cell numbers in both peripheral blood and within the tumor microenvironment, we evaluated the efficacy of the combination treatment with GX-I7 and pembrolizumab in patients with mTNBC who failed in at least one line of treatment.

STUDY OBJECTIVES AND METHODS

Study objectives

- **Primary Objectives:**
  - ✓ To evaluate safety and tolerability of GX-I7 in combination with pembrolizumab and to determine the recommended phase 2 dose (RP2D); Phase 1b
  - ✓ To evaluate the objective response rate (ORR) by RECIST v1.1 and immune-ORR by iRECIST; Phase 2
- **Secondary Objective:**
  - ✓ 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.
- Tumor assessment is to be conducted every 9 weeks.
- Two treatment regimens are tested. Regimen A. sequential treatment with GX-I7 and Pembrolizumab with single dose of cyclophosphamide; Regimen B. simultaneous treatment with GX-I7 and pembrolizumab (Figure 1).

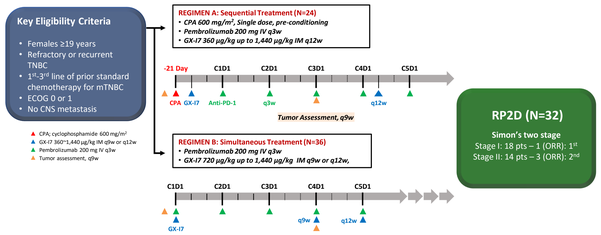

Figure 1. Phase 1b/2 study design

RESULTS

Patient Disposition and Characteristics

- A total of 60 patients had been enrolled and treated with GX-I7 in combination with pembrolizumab with or without CPA. (As of Sept 30, 2020).
- 60 patients were available for the assessment of safety and efficacy.
- All patients had received at least one line of chemotherapy for recurrent and metastatic TNBC (Table 1).

Table 1. Baseline characteristics

N(%)		CPA/GX-I7/Pembrolizumab *Sequential Treatment* N=24	GX-I7/Pembrolizumab *Simultaneous Treatment* N=36
Age, year, median(range)	-	46.0 (29 - 69)	50.5 (29 – 75)
Postmenopausal	-	11 (45.8)	19 (52.8)
ECOG PS	0 1	11 (45.8) 13 (54.2)	23 (63.9) 13 (36.1)
LDH concentration	<1xULN ≥1x~<2.5xULN ≥2.5xULN	9 (37.5) 12 (50.0) 3 (12.5)	12 (33.3) 16 (44.4) 8 (22.2)
TL size, mm, median(range)	-	30 (10 - 261)	58.5 (10.1 - 203)
No. of metastatic organ sites	1 2 3 ≥4	9 (37.5) 8 (33.3) 7 (29.2) -	7 (19.4) 10 (27.8) 12 (33.3) 7 (19.4)
Prior taxane & anthracycline Therapy	-	24 (100.0)	36 (100.0)
Visceral metastasis	-	19 (79.2)	28 (77.8)
Previous (neo)adjuvant therapy	-	21 (87.5)	28 (77.8)
No. of previous lines of therapy for recurrent/metastatic disease	0 1 2 3 4	- 11 (45.8) 4 (16.7) 8 (33.3) 1 (4.2)	- 17 (47.2) 12 (33.3) 7 (19.4) -

*TL; Target lesion

Safety and tolerability

- Treatment-related AEs of grade 1-2 were observed in 100% of patients (n=60), with 25.0% for grade 3, 1.7% for grade 4, and no grade 5 AE was observed.

Table 2. Summary of adverse events

N (%)	CPA/GX-I7/Pembrolizumab *Sequential Treatment* N=24		GX-I7/Pembrolizumab *Simultaneous Treatment* N=36		Total (n=60)
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade
Injection site reaction	19 (79.2)	0 (0)	25 (69.5)	0 (0)	44 (73.4)
Rash	8 (33.4)	1 (4.2)	18 (50)	2 (5.6)	26 (43.4)
Pyrexia	6 (25.0)	0 (0)	15 (41.7)	1 (2.8)	21 (35.0)
AST increase	5 (20.9)	1 (4.2)	14 (38.9)	3 (8.4)	19 (31.7)
ALT increase	6 (25)	1 (4.2)	13 (36.2)	5 (13.9)	19 (31.7)
GGT increase	3 (12.5)	0 (0)	9 (25)	3 (8.4)	12 (20)
Myalgia	5 (20.9)	0 (0)	7 (19.5)	0 (0)	12 (20)
Nausea	7 (29.2)	1 (4.2)	4 (11.2)	0 (0)	11 (18.4)
ALP increase	3 (12.5)	0 (0)	5 (13.9)	1 (2.8)	8 (13.4)
Pruritus	2 (8.4)	0 (0)	6 (16.7)	0 (0)	8 (13.4)
Decreased appetite	2 (8.4)	0 (0)	5 (13.9)	0 (0)	7 (11.7)
Hypothyroidism	4 (16.7)	0 (0)	2 (5.6)	0 (0)	6 (10)
Platelet count decrease	2 (8.4)	0 (0)	3 (8.4)	0 (0)	5 (8.4)
Hyperthyroidism	1 (4.2)	0 (0)	3 (8.4)	0 (0)	4 (6.7)
Arthralgia	1 (4.2)	0 (0)	3 (8.4)	1 (2.8)	4 (6.7)
Hyperglycemia	1 (4.2)	1 (4.2)	1 (2.8)	0 (0)]	2 (3.4)
Immune-mediated hepatitis	0 (0)	0 (0)	2 (5.6)	0 (0)	2 (3.4)
Pneumonitis	0 (0)	0 (0)	2 (5.6)	1 (2.8)	2 (3.4)

- The most common treatment-related AEs were injection site reaction (n=44, 73.4%), rash (n=26, 43.4%), pyrexia (n=21, 35.0%), ALT/AST increase (n=19, 31.7%), GGT increase (n=12, 20.0%), myalgia (n=12, 20.0%) and nausea (n=11, 18.4%).
- Higher incidence of irAEs were observed in the simultaneous treatment group than the sequential treatment group.
- 1 DLT (skin rash, grade 3) was observed in a patient dosed 1,440μg/kg in the simultaneous treatment group (Table 2).

Clinical response

- Median follow up period of all treated patients (n=60) was 4.32 months (range 0.9–15.3 months) including 16 ongoing patients.
- **Regimen B** showed higher response rate than **Regimen A**; 7/36 (19.4%) vs 2/24 (8.3%).
- Especially, the cohort (18 pts) receiving 1,200 μg/kg GX-I7 with pembrolizumab without CPA showed the highest ORR (27.8%, 5 PR) with DCR of 44.4% (5 PR and 3 SD).

Table 3. Best Overall Response

Response (RECIST v1.1) N (%)	CPA/GX-I7/Pembrolizumab *Sequential Treatment (N=24)*					GX-I7/Pembrolizumab *Simultaneous Treatment (N=36)*			
	360 μg/kg	720 μg/kg	960 μg/kg	1,200 μg/kg	1,440 μg/kg	720 μg/kg	960 μg/kg	1,200 μg/kg	1,440 μg/kg
ORR	-	-	**1 (33.3)**	-	**1 (11.1)**	**1 (16.7)**	**1 (16.7)**	**5 (27.8)**	-
CR	-	-	-	-	-	-	-	-	-
PR	-	-	1 (33.3)	-	1 (11.1)	1 (16.7)	1 (16.7)	5 (27.8)	-
SD	-	-	-	4 (66.7)	2 (22.2)	1 (16.7)	2 (33.3)	3 (16.7)	1 (16.7)
PD	3 (100)	3 (100)	2 (66.7)	2 (33.3)	6 (66.7)	4 (66.7)	3 (50.0)	10 (55.6)	5 (83.3)
DCR[a]	-	-	**2 (66.7)**	**4 (66.7)**	**3 (33.3)**	**3 (50.0)**	**4 (66.7)**	**8 (44.4)**	**1 (16.7)**

[Abbreviation] *ORR: Objective Response Rate, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease*
[a]*The proportion of patients with complete or partial response or stable disease based on best overall response.*

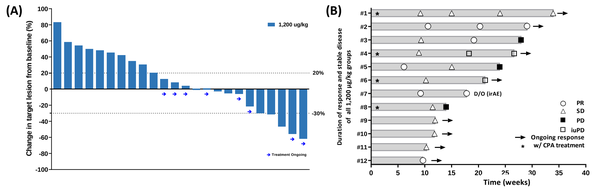

Figure 2. (A) Tumor response and (B) Duration of response and stable disease of all 1,200 μg/kg groups.

Change from baseline in ALC, CD4+ T cells, CD8+ T cells and Treg in PB

- GX-I7 treatment significantly increased ALC and CD4+ and CD8+ T cells in all dose levels ranging from 720 μg/kg to 1,440 μg/kg, with or without CPA (Figure 3).
- % of Treg in CD4+ T cells dropped significantly in 720, 960 and 1,200 μg/kg of GX-I7 but not in 360 and 1,440 μg/kg.

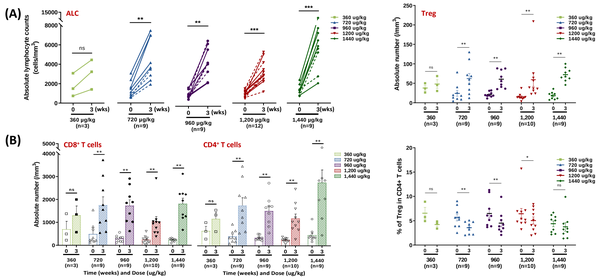

Figure 3. T cell increase in the peripheral blood (PB) by GX-I7 (360 μg/kg to 1,440 μg/kg with or without CPA. (A) Change of individual ALC at 3w post GX-I7 administration from the baseline level. (B) Change of CD4+ T cells and CD8+ T cells at 3w post GX-I7 administration from baseline. (C) Change of absolute number and frequency in Treg 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. Dotted lines indicate 'with CPA' and solid lines, 'without CPA', respectively. *p<0.05, **p<0.01, ***p<0.001 versus baseline (0 week) group by Wilcoxon matched-pairs signed rank test.

CONCLUSIONS

- The combination treatment of GX-I7 and pembrolizumab, with or without CPA, was safe and well tolerated in most study participants and only 1 DLT was observed at the highest dose of 1,440 μg/kg.
- Simultaneous treatment of GX-I7 and pembrolizumab induced higher ORR than sequential treatment of GX-I7 and Pembrolizumab with CPA.
- Absolute lymphocyte count and the number of CD4+ and CD8+ T cells were significantly increased in all treated groups receiving GX-I7 720 μg/kg or higher.
- The ratio of Tregs/CD4+ T cells was significantly decreased due to predominant expansion of CD4+ T cells except in 1,440ug/kg, even though the absolute number of Tregs were increased in patients receiving GX-I7 at 720ug/kg or higher.
- Considering safety, immunogenicity and efficacy, a 1,200ug/kg dose of GX-I7 will be selected to be combined with Pembrolizumab in the next Ph2 study as a RP2D.

ACKNOWLEDGEMENTS

Pembrolizumab 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
2) Delyon J et al Annals of Oncology. 2013