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# Phase 1b/2 Study of GX-I7 plus pembrolizumab in patients with refractory or recurrent (R/R) metastatic triple negative breast cancer (mTNBC): The KEYNOTE-899 Study

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## BACKGROUND

Pembrolizumab showed 5.3% objective response rate (ORR) (KEYNOTE-086)[1] and 9.6% ORR (KEYNOTE-119)[2] in monotherapy setting, and failed to improve overall survival (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. GX-I7 (efineptakin alfa) is a hybrid Fc-fused long-acting recombinant human IL-7 which plays an essential role in the development and homeostasis of T-cells. GX-I7 can potentially enhance the anti-tumor effect of pembrolizumab via induction of T-cell activity. Here, we report results of phase 1b/2 study of GX-I7 plus pembrolizumab in patients with refractory or recurrent (R/R) mTNBC.

## 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; Phase 2
- **Secondary objective:**
  - ✓ DoR, DCR, PFS, and OS by RECIST v1.1 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 a metastasis setting (**Figure 1**).

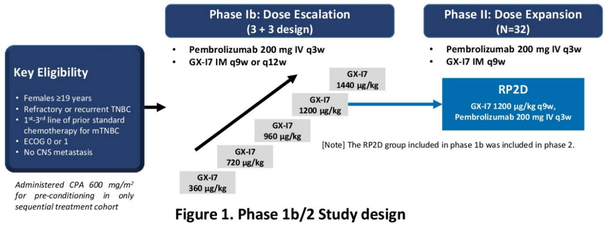


**Figure 1. Phase 1b/2 Study design**

### Patient disposition and characteristics

- A total of 84 patients were enrolled from 10 institutions from March 2019 to July 2021.
- At data cutoff (January 17, 2022), median (range) follow-up was 10.4 (0.7–24.0) months among all patients; 3 patients (3.6%) continued to receive study treatment.
- 53.6% (45/84) of patients received 2nd to 3rd lines of previous therapy, and 86.9% of patients had up to three metastatic locations.

## RESULTS

- Of the 25 patients who had evaluable PD-L1 from a biopsy sample, 40.0% (10/25) were PD-L1 positive (CPS≥10) (**Table 1**).

**Table 1. Baseline characteristics**

| N(%) | | Total N=84 | *Phase 1b* N=51[†] | *Phase 2* N=33[‡] |
|---|---|---|---|---|
| **Age, year, median (range)** | - | 50.0 (29.0-75.0) | 49.0 (29.0 – 75.0) | 51.0 (29.0-67.0) |
| **ECOG PS** | *0*<br>*1* | 46 (54.8)<br>38 (45.2) | 25 (49.0)<br>26 (51.0) | 21 (63.6)<br>12 (36.4) |
| **No. of metastatic organ sites** | *1*<br>*2*<br>*3*<br>*≥4* | 18 (21.4)<br>29 (34.5)<br>26 (31.0)<br>11 (13.1) | 13 (25.5)<br>17 (33.3)<br>17 (33.3)<br>4 (7.8) | 5 (15.2)<br>12 (36.4)<br>9 (27.3)<br>7 (21.2) |
| **Visceral metastasis** | - | 77 (91.7) | 45 (88.2) | 32 (97.0) |
| **LDH concentration** | *<1xULN*<br>*≥1x~<2.5xUL N*<br>*≥2.5xULN* | 41 (48.8)<br>30 (35.7)<br>13 (15.5) | 25 (49.0)<br>17 (33.3)<br>9 (17.6) | 16 (48.5)<br>13 (39.4)<br>4 (12.1) |
| **PD-L1 Status (CPS Score)[§],n=25** | *<10*<br>*≥10* | 15 (60.0)<br>10 (40.0) | NA | 15 (60.0)<br>10 (40.0) |
| **Absolute lymphocyte count** ≤ 1,000 cells/mm³ | - | 26 (31.0) | 12 (23.5) | 14 (42.4) |
| **No. of previous lines of therapy for recurrent/ metastatic disease** | 0<br>1<br>2<br>3<br>≥4 | 0 (0.0)<br>39 (46.4)<br>27 (32.1)<br>17 (20.2)<br>1 (1.2) | 0 (0.0)<br>20 (39.2)<br>16 (31.4)<br>14 (27.5)<br>1 (2.0) | 0 (0.0)<br>19 (57.6)<br>11 (33.3)<br>3 (9.1)<br>- |
| **Previous (neo)adjuvant therapy** | - | 68 (81.0) | 44 (86.3) | 24 (72.7) |
| **Prior taxane & anthracycline Therapy** | - | 84 (100.0) | 51 (100.0) | 33 (100.0) |

[†]*Phase1b: 360, 720, 960, 1200 and 1440 ug/kg, q12w or q9w, n=3 or 6 or 9, respectively*
[‡]*Phase2: 1200 ug/kg, q9w, n=33*
[§]*PD-L1 expression was measured in 25 patients of phase 2 trial (n=33) with available biopsy samples at baseline.*

### Clinical response

- The ORRs were 15.7% (8/51) for phase 1b and 21.2% (7/33) for phase 2. Interestingly, the ORR in PD-L1 positive (CPS≥10%) and negative patients were 60% (6/10) and 0.0% (0/15), respectively.
- The mDoR was of 3.9 months, the mPFS was 2.6 months, and mOS was 16.0 months for phase 2 (**Table2**).

**Table 2. Objective response rates based on RECISTv1.1 per investigator**

| RECIST v1.1 N (%),[95% CI] | Total N=84 | Phase 1b, n=51 Dose escalation 360 ~ 1,440 ug/kg | Phase 2, n=33 RP2D 1,200 ug/kg, q9w |
|---|---|---|---|
| **Objective response rate** | 15 (17.9),[10.4–27.7] | 8 (15.7),[7.0–28.6] | 7 (21.2),[9.0–38.9] |
| *CPS ≥10, n=10*<br>*CPS <10, n=15* | *6 (60.0)*<br>*0 (0.0)* | *NA*<br>*NA* | *6 (60.0)*<br>*0 (0.0)* |
| **Disease control rate[a]** | 28 (33.3) | 18 (35.3) | 10 (30.3) |
| Complete response | - | - | - |
| Partial response | 15 (17.9) | 8 (15.7) | 7 (21.2) |
| Stable disease | 13 (15.5) | 10 (19.6) | 3 (9.1) |
| Progressive disease | 54 (64.3) | 33 (64.7) | 21 (63.6) |
| Non-Evaluable | 2 (2.4) | - | 2 (6.1) |
| median DoR, months [95% CI] | 3.9m [0.0 – 14.9] | 2.9m [1.5– 4.3] | 3.9m [0.3 – 7.4] |
| median PFS, months [95% CI] | 2.4m [2.1 – 2.7] | 2.3m [2.2– 2.5] | 2.6m [2.2 – 3.0] |
| median OS, months [95% CI] | Not reached | Not reached | 16.0m [11.2 – 20.8] |

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

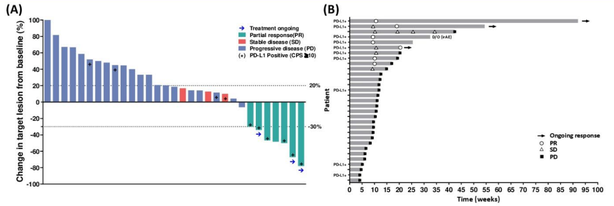


**Figure 2. Best overall response** (A) Waterfall plot, and (B) Swimmer plot of 31 patients (not included 2 patients not evaluable for tumor response) who received GX-I7 1,200 μg/kg with 9 weeks interval plus pembrolizumab with 3 weeks.

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

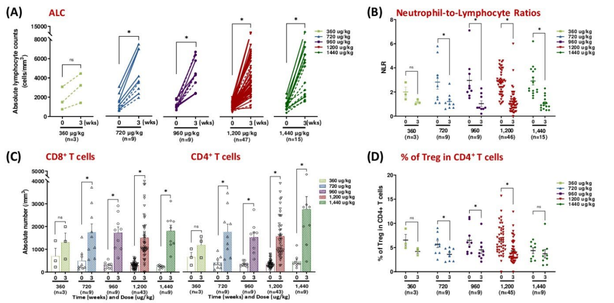


**Figure 3. Change of (A) ALC, (B) NLR, (C) CD4, CD8 and (D) Treg in peripheral blood by GX-I7 (360 μg/kg to 1,440 μg/kg with or without CPA.** Absolute lymphocyte counts (ALCs) and the number of CD4⁺ and CD8⁺ T cells were significantly increased, while Neutrophil-to-Lymphocyte ratios (NLRs) and frequency of Treg were decreased in all treated groups receiving GX-I7 720 μg/kg or higher. *The bar represents Mean ±SEM at baseline (0w) and at 3w for each dose level of GX-I7. An asterisk (*) indicate statistically significant difference between 3 weeks and 0 weeks (baseline) by Wilcoxon matched-pairs signed rank test.*

### Safety and tolerability

- Treatment-related AEs (TRAEs) occurred in 100% (84/84) of patients, and grade 3/4 TRAEs were reported in 31% (26/84) (**Table 3**).
- TRAEs of any grade in ≥10% of patients were injection site reaction (64%, n=54), rash (54%, n=45), ALT increase (49%, n=41), AST increase (43%, n=36), pyrexia (38%, n=32), GGT increase (36%, n=30), pruritus (23%, n=19) and hypothyroidism (21%, n=18).
- Immune-mediated AEs (irAEs) occurred in 71% (60/84) patients; the most common were rash (52%) and pruritus (23%), and the most common of grade 3-4 severity was rash (6%).

**Table 3. Summary of treatment-related AEs (≥10%) and irAE (≥5%)**

| N(%) | Total, n=84 | | Phase 1b, N=51 | | Phase 2, N=33 | |
|---|---|---|---|---|---|---|
| | Any grade | ≥Gr3 | Any grade | ≥Gr3 | Any grade | ≥Gr3 |
| **Subjects with TRAEs** | **84 (100%)** | **26 (31%)** | **51 (100%)** | **13 (25%)** | **33 (100%)** | **13 (39%)** |
| Injection site reaction | 54 (64%) | - | 39 (76%) | - | 15 (46%) | - |
| Rash | 45 (54%) | 5 (6%) | 25 (49%) | 2 (4%) | 20 (61%) | 3 (9%) |
| ALT increased | 41 (49%) | 9 (11%) | 21 (41%) | 4 (8%) | 20 (61%) | 5 (15%) |
| AST increased | 36 (43%) | 7 (8%) | 20 (39%) | 3 (6%) | 16 (49%) | 4 (12%) |
| Pyrexia | 32 (38%) | 1 (1%) | 19 (37%) | 1 (2%) | 13 (39%) | - |
| GGT increased | 30 (36%) | 11 (13%) | 12 (24%) | 4 (8%) | 18 (55%) | 7 (21%) |
| Pruritus | 19 (23%) | - | 5 (10%) | - | 14 (42%) | - |
| Hypothyroidism | 18 (21%) | 1 (1%) | 9 (18%) | 0 (0.00%) | 9 (27%) | 1 (3%) |
| Nausea | 17 (20%) | 1 (1%) | 11 (22%) | 1 (2%) | 6 (18%) | - |
| Myalgia | 16 (19%) | - | 11 (22%) | - | 5 (15%) | - |
| Decreased appetite | 15 (18%) | - | 6 (12%) | - | 9 (27%) | - |
| ALP increased | 14 (17%) | 2 (2%) | 9 (18%) | 1 (2%) | 5 (15%) | 1 (3%) |
| Constipation | 12 (14%) | - | 9 (18%) | - | 3 (9%) | - |
| **Subjects with irAEs** | **60 (71%)** | **9 (11%)** | **34 (67%)** | **5 (10%)** | **26 (79%)** | **4 (12%)** |
| Rash | 44 (52%) | 5 (6%) | 24 (47%) | 2 (4%) | 20 (61%) | 3 (10%) |
| Pruritus | 19 (23%) | - | 5 (10%) | - | 14 (42%) | - |
| Hypothyroidism | 18 (21%) | 1 (1%) | 9 (18%) | - | 9 (27%) | 1 (3%) |
| Hyperthyroidism | 7 (8%) | - | 3 (6%) | - | 4 (12%) | - |

[Note] Data are presented as n (%) where n is the number of patients who experienced ≥1 episode of a given event. Relatedness to treatment was determined by the investigator.

## CONCLUSIONS

- GX-17 plus pembrolizumab combination therapy showed tolerable and manageable toxicity profiles in this phase Ib/II trial with recommended dose of GX-I7 1,200 μg/kg with 9 weeks interval combined with Pembrolizumab 200mg q 3 weeks.
- The GX-17 plus pembrolizumab combination therapy showed higher ORR (21.2%) compared to historical data with pembrolizumab alone even though it is a small sample-sized study with different polulation[1-2].
- **Notably, ORRs in patients with CPS≥10 were 60% (6/10) compared to 0% (0/15) with CPS<10. Further study of combination regimen for patients with CPS≥10 is warranted.**
- Absolute lymphocyte count and the number of CD4⁺ and CD8⁺ T cells were significantly increased, while NLRs and proportion of Treg in CD4⁺ T cells were significantly decreased in patients receiving GX-I7 720 μg/kg or higher.
- GX-I7 in combination with pembrolizumab demonstrated a promising anti-tumor activity with a manageable safety profile in patients with R/R metastatic TNBC.

## ACKNOWLEDGEMENTS

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## REFERENCES

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