Efficacy, Safety, and Tolerability of KN046 (an anti-PD-L1/CTLA-4 Bispecific Antibody) in combination with Nab-paclitaxel in Metastatic Triple-negative Breast Cancer (mTNBC): Final results of the Phase II trial

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BACKGROUND

- Despite recent FDA approval of immune checkpoint inhibitor pembrolizumab and drug-antibody conjugate in the treatment of mTNBC, the overall survival benefit of these patients remains modest.
- Mechanism of action of KN046 (Figure 1):
  - Blocking CTLA-4 with B7 and PD-L1 with PD-1.
  - Limited peripheral distribution reduces treatment-associated on-target off-tumor toxicity.
  - IgG1 Fc domain, CTLA-4 blocking-mediated Treg cells depletion.

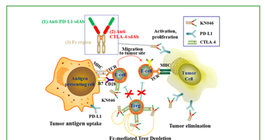

Figure 1 Mechanism of KN046 Action

- Preliminary results have been released in 2021 AACR[1], here we reported the final results of the progression-free survival (PFS) and overall survival (OS) analysis.

METHODS

- Study design is shown in Figure 2.
- Eligible pts received nab-paclitaxel plus KN046 at two dose levels (DL1: KN046 3 mg/kg Q2W or DL2: KN046 5 mg/kg Q2W).
- Tumor response was evaluated Q8W per RECIST 1.1.
- PD-L1 expression on tumor cells was measured using SP142 assay.
- The cut-off date was Aug 21, 2022.

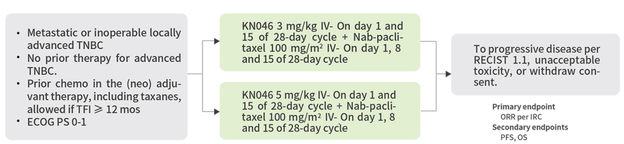

Figure 2 Study Design

RESULTS

- From July 2019 to July 2020, 27 subjects were enrolled, the median age was 50, 100% were female, and 88.9 % (24/27) were stage IV.
- The median follow-up was 27.93 months (IQR: 20.73, 30.46). The ORR and PFS were assessed by IRC. The ORR was evaluated based on the evaluable (EAS) population. The PFS and OS were evaluated based on the Intend-to-treat (ITT) population.

Table 1 Baseline characteristics

	KN046 3 mg/kg Q2W +Nab-paclitaxel	KN046 5 mg/kg Q2W +Nab-paclitaxel	Total N=27 (%)
Number of Patients (n)	16	11	27
Age			
Median	53	45	50
Range	35-70	33-62	33-70
ECOG PS			
0	9(56%)	5(45%)	14(52%)
1	7(44%)	6(55%)	13(48%)
Stage			
IIIb	0	1	1
IIIC	2	0	2
IV	14	10	24
PD-L1 Status			
<1% or UNK	10	8	18(67%)
⩾ 1%	6	3	9(33%)

Table 2 Objective Response Rate per IRC

	KN046 3 mg/kg Q2W +Nab-paclitaxel (N=15)	KN046 5 mg/kg Q2W +Nab-paclitaxel (N=10)	Total* (N=25)
Best Overall Response			
Complete Response (CR)	1 (6.7%)	0	1 (4.0%)
Partial Response (PR)	8 (53.3%)	2 (20.0%)	10 (40.0%)
Stable Disease (SD)	6 (40.0%)	7 (70.0%)	13 (52.0%)
Progressive Disease (PD)	0	1 (10.0%)	1 (4.0%)
Objective Response Rate (ORR)	60.0%	20.0%	44.0%
95% CI	32.3%, 83.7%	2.5%, 55.6%	21.1%, 61.3%
Disease Control Rate (DCR)	100%	90.0%	96.0%
95% CI	78.2%, 100.0%	55.5%, 99.7%	79.6%, 99.9%
Clinical Benefit Rate (CBR)	60.0%	40.0%	52.0%
95% CI	32.3%, 83.7%	12.2%, 73.8%	31.3%, 72.2%
Duration of Response (DoR)	Not reach	11.8 months	11.9 months
95% CI	7.49, NE	5.59, NE	5.59, NE

* 2 patients withdrawal the trial before the first tumor assessment and excluded from the EAS population.

- The median PFS was 7.33 (95% CI, 3.68 - 11.07) months. Among the PD-L1 ⩾1% pts, the median PFS was 8.61 (95%CI, 1.61 - NE) months (seen in Figure 3 & 4).

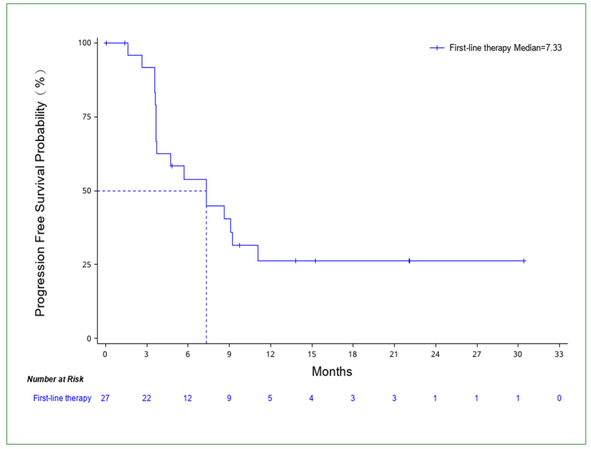

Figure 3 Kaplan - Meier Curve for Progression Free Survival per IRC

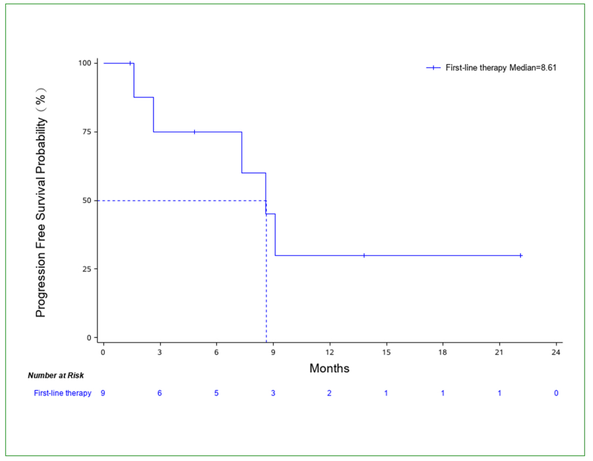

Figure 4 Kaplan - Meier Curve for Progression Free Survival of PD-L1 ⩾1% per IRC

- The median OS is immature, the preliminary result is 27.73 (95% CI, 14.75 - NE) months, and the 2-year OS rate was 60.1% (95%CI, 37.2% - 76.9%). Both PD-L1 negative and positive patients derived OS benefit from the therapy (seen in Figure 5).

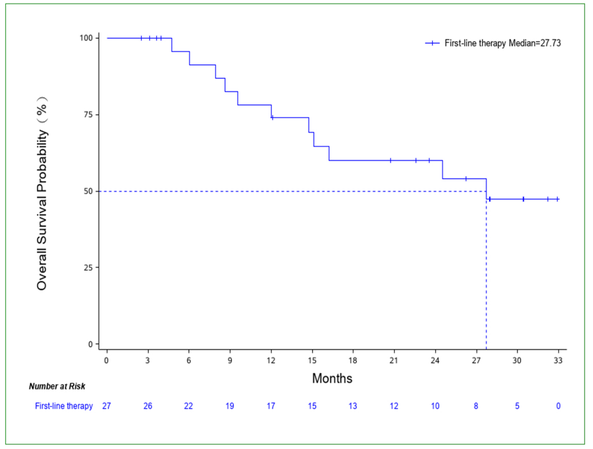

Figure 5 Kaplan - Meier Curve for Overall Survival

- Patients tolerated well to combination therapy. The incidence of SAE was 33.3%, with no TRAE leading to death.

Table 3 Safety Summary (N=27)

	KN046 3 mg/kg Q2W +Nab-paclitaxel N=16 (%)	KN046 5 mg/kg Q2W +Nab-paclitaxel N=11 (%)	Total N=27 (%)
TEAE	16 (100%)	11 (100%)	27 (100%)
TEAE associated with any study drug	16 (100%)	11 (100%)	27 (100%)
TRAE Grade⩾ 3	11 (68.8%)	7 (63.6%)	18 (66.7%)
TEAE Grade⩾ 3 associated with any study drug	11 (68.8%)	7 (63.6%)	18 (66.7%)
Serious Adverse Event (SAE)	6 (37.5%)	3 (27.3%)	9 (33.3%)
SAE associated with any study drug	4 (25.0%)	2 (18.2%)	6 (22.2%)
Immune-related AE	8 (50.0%)	5 (45.5%)	13 (48.1%)
irAE Grade ⩾ 3	0	3 (27.3%)	3 (11.1%)
TRAE leading to death	0	0	0

Table 4 The Most Commonly Reported (⩾20%) Adverse Events

Preferred Term (⩾20%)	KN046 3 mg/kg Q2W +Nab-paclitaxel (N=16)		KN046 5 mg/kg Q2W +Nab-paclitaxel (N=11)		Total (N=27)	
	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades
Subjects with any study drug related TEAE	11 (68.8%)	16 (100%)	7 (63.6%)	11 (100%)	18 (66.7%)	27 (100%)
Neutrophil count decreased	7 (43.8%)	12 (75.0%)	2 (18.2%)	6 (54.5%)	9 (33.3%)	18 (66.7%)
White blood cell count decreased	6 (37.5%)	11 (68.8%)	2 (18.2%)	5 (45.5)	8 (29.6%)	16 (59.3%)
Alopecia	0	7 (43.8%)	0	7 (63.6%)	0	14 (51.9%)
Aspartate aminotransferase increased	2 (12.5%)	7 (43.8%)	1 (9.1%)	6 (54.5%)	3 (11.1%)	13 (48.1%)
Alanine aminotransferase increased	0	8 (50.0%)	0	5 (45.5%)	0	13 (48.1%)
Pyrexia	0	5 (31.3%)	1 (9.1%)	5 (45.5%)	1 (3.7%)	10 (37.0%)
Rash	0	6 (37.5%)	1 (9.1%)	3 (27.3%)	1 (3.7%)	9 (33.3%)
Anemia	0	6 (37.5%)	0	2 (18.2%)	0	8 (29.6%)
γ-glutamyltransferase increased	1 (6.3%)	4 (25.0%)	3 (27.3%)	3 (27.3%)	4 (14.8%)	7 (25.9%)
Vomiting	0	5 (31.3%)	0	1 (9.1%)	0	6 (22.2%)
Hypothyroidism	0	3 (18.8%)	0	3 (27.3%)	0	6 (22.2%)

CONCLUSIONS

- The combination therapy of KN046 plus nab-paclitaxel has shown favorable clinical efficacy in mTNBC, especially in PD-L1 positive patients.
- By the cut-off date, the mOS is not mature and there is still more than half of pts alive, which demonstrated an encouraging 2-year OS rate.
- Pts in this trial tolerated well to the combination therapy and safety profile was manageable.

REFERENCE

- 1. Cancer Res (2021) 81 (13_Supplement): 1660.

CONFLICT OF INTEREST

- The first author has no conflicts of interest.

CONTACT

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