Efficacy and safety results of KN026, a HER2-targeted bispecific antibody combined with docetaxel in first-line treatment of HER2-positive recurrent/metastatic breast cancer

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BACKGROUND

- The 3-drug combination therapy, trastuzumab, pertuzumab, and taxane chemotherapy is one of the standard treatment options for the first-line treatment of HER2-positive recurrent/metastatic breast cancer.
- KN026 is a novel bispecific HER2-targeted antibody(Figure 1)：
  - Fully humanized, IgG1-like antibody binds to two distinct HER2 epitopes, recognized by transtuzumab and pertuzumab. KN026 targets juxtamembrane domain (IV) and the dimerization domain (II) on HER2.
  - KN026 induces clustering of HER2, leads to faster internalization and mediates potent ADCC.
- Preliminary safety and efficacy results from Phase 1 study data (data as of Jan.22, 2020) of KN026 monotherapy in HER2-positive advanced breast cancer were presented at ASCO 2020[1], showed promising efficacy and well tolerated safety. Herein, we present the results from the phase 2 trial.

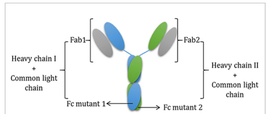


Figure 1 Structure of KN026

METHODS

- Study design is shown in Figure 2.
- Eligible subjects with HER2-positive and first-line systemic treatment-naïve.
- Recurrent or metastatic breast cancer were enrolled in this study.
- Subjects received KN026 30 mg/kg combined with docetaxel 75 mg/m² Q3W until disease progression, unacceptable toxicity, or other circumstances that require drug discontinuation.
- The primary endpoints were ORR and DoR per investigator assessment according to RECIST v1.1. The secondary endpoints included PFS, safety, and OS.
- The data cut-off date was Aug 18, 2022.

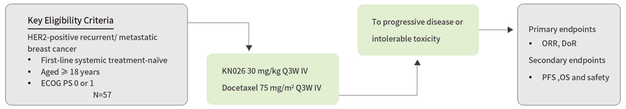


Figure 2 Study Design

RESULTS

- 57 subjects were enrolled, the median age was 52 years, 100% were female, and 91.2 % (52/57) were stage Ⅳ.
- The confirmed ORR within 55 evaluable subjects was 76.4% (95% CI: 62.98, 86.77) and DoR was 24.0 months (95% CI: 18.070, NE). （Table 1,Figure 3）

Table 1 Objective response rate-Efficacy Analysis Set

	Efficacy Analysis Set (N=55) ,n(%)	Visceral metastasis (N=32) ,n(%)	No-visceral metastasis (N=23) ,n(%)	IHC1+¢/IHC2+ (N=9) , n(%)	IHC3+ (N=46) , n(%)
Best of response rate, BOR					
CR	3 (5.5)	2 (6.3)	1 (4.3)	0	3 (6.5)
PR	39 (70.9)	23 (71.9)	16 (69.6)	5 (55.6)	34 (73.9)
SD	13 (23.6)	7 (21.9)	6 (26.1)	4 (44.4)	9 (19.6)
PD	0	0	0	0	0
NE	0	0	0	0	0
ORR (95%CI)	42 (76.4) (62.98, 86.77)	25 (78.1) (60.03, 90.72)	17 (73.9) (51.59, 89.77)	5 (55.6) (21.20, 86.30)	37 (80.4) (66.09, 90.64)
DCR (95%CI)	55 (100) (93.51, 100)	32 (100) (89.11, 100)	23 (100) (85.18, 100)	9 (100) (66.37, 100)	46 (100) (92.29, 100)

- The disease control rate was 100% in 55 evaluable subjects.
- ORR was similar between subjects with and without visceral metastasis.
- Compared to IHC3+ subjects, ORR was lower in subjects with IHC1+ or IHC2+ HER2 positive expression.

¢:There was only one IHC1+ subject and this subject was enrolled in the study due to a positive HER2 (FISH) result.

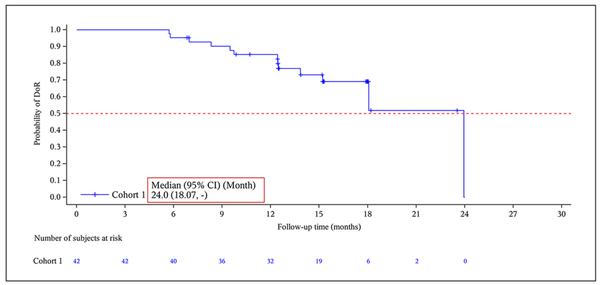


Figure 3 Kaplan - Meier Curve for Duration of Response- Efficacy Analysis Set

- The median follow-up for PFS was 16.6 months (95%CI：15.15,19.29). Median PFS was 25.4 months (95% CI: 16.53, NE) （Figure 4）and median OS was not reached. The median PFS was not yet mature.
- The 12-, 18-and 24-month OS rates were 93.0 % (95% CI: 82.37, 97.31), 91.2 % (95% CI: 80.05, 96.22) and 91.2 % (95% CI: 80.05, 96.22), respectively. （Figure 5）

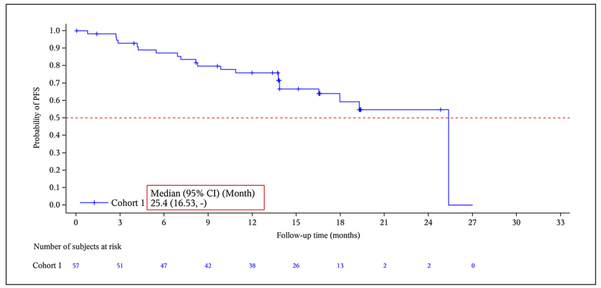
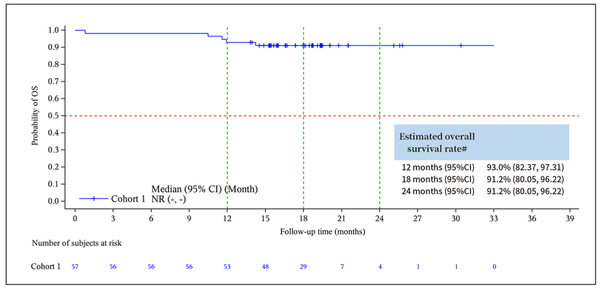


Figure 4 Kaplan - Meier Curve for Progression Free Survival-Intent to Treat Analysis Set



#: Overall survival and 95% confidence intervals were estimated for each time point based on the Kaplan-Meier method.

Figure 5 Kaplan - Meier Curve for Overall Survival-Intent to Treat Analysis Set

- No-visceral metastases, No-brain metastases and IHC3+ are Stratification factors for longer PFS. （Figure 6-8）

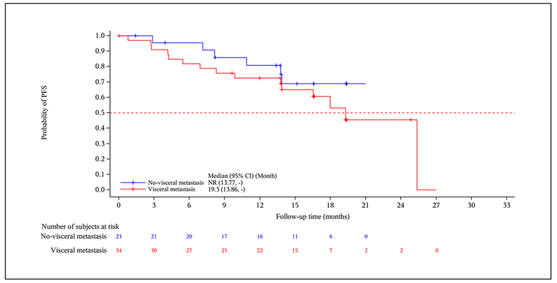


Figure 6 Kaplan - Meier Curve for
Subgroup Analysis of Progression Free Survival by Visceral Metastasis

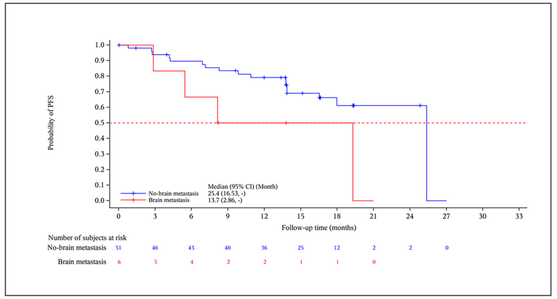


Figure 7 Kaplan - Meier Curve for
Subgroup Analysis of Progression Free Survival by Brain Metastasis

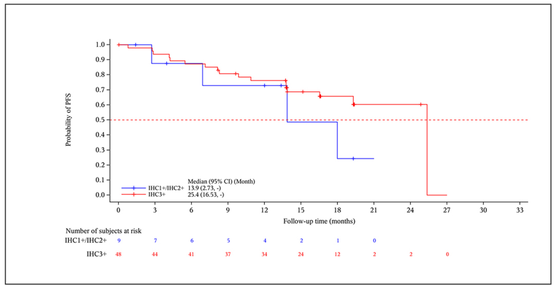


Figure 8 Kaplan - Meier Curve for
Subgroup Analysis of Progression Free Survival by HER2 - positive Expression

- TEAE ⩾Grade 3 and SAE associated with KN026 occurred in 38.6% (22/57) and 8.8% (5/57) of subjects. There were no deaths due to KN026 drug-related AEs in this study. （Table 2）
- The incidence of serious adverse events was 15.8%(9/57), including 5.3%（3/57） for febrile neutropenia, 3.5%（2/57）for white blood cell count decreased, and less than 2% for other SAEs. （Table 3）

Table 2 Safety summary

	(N=57) n (%)
Any TEAE	57 (100)
associated with any study drug	55 (96.5)
associated with KN026	52 (91.2)
associated with Docetaxel	54 (94.7)
TEAE Grade⩾ 3	33 (57.9)
associated with any study drug	31 (54.4)
associated with KN026	22 (38.6)
associated with Docetaxel	30 (52.6)

	(N=57) n (%)
Serious Adverse Event（SAE）	9 (15.8)
associated with any study drug	8 (14.0)
associated with KN026	5 (8.8)
associated with Docetaxel	6 (10.5)
TEAE leading to death	1 ##(1.8)
associated with any study drug	0
associated with KN026	0
associated with Docetaxel	0

##: Medical records related to the death of this subject could not be obtained, so the death reason was determined to be unknown and unrelated to KN026 and docetaxel, which was determined by the investigator.

Table 3 Summary of Serious Adverse Events

SOC PT	(N=57) n (%)
Any SAEs	9 (15.8)
Blood and lymphatic system disorders	3 (5.3)
Febrile neutropenia	3 (5.3)
Infections and infestations	3 (5.3)
Appendicitis	1 (1.8)
Peritonitis	1 (1.8)
Sepsis	1 (1.8)
Tonsillitis	1 (1.8)
Gastrointestinal disorders	2 (3.5)
Diarrhoea	1 (1.8)
Intestinal obstruction	1 (1.8)
Vomiting	1 (1.8)

SOC PT	(N=57) n (%)
Investigations	2 (3.5)
White blood cell count decreased	2 (3.5)
Cardiac disorders	1 (1.8)
Arrhythmia	1 (1.8)
General disorders and administration site conditions	1 (1.8)
Death	1 (1.8)
Metabolism and nutrition disorders	1 (1.8)
Hypokalaemia	1 (1.8)
Vascular disorders	1 (1.8)
Venous thrombosis limb	1 (1.8)

CONCLUSIONS

- KN026 in combination with docetaxel is well tolerated and has shown promising clinical benefit as 1L treatment for HER2-positive advanced breast cancer. At data cut-off date (Aug 18, 2022)，median PFS was 25.4 months while 24-month OS rate was 91.2 %， which is very encouraging. Efficacy and safety require large-scale phase III studies to verify. A phase III study with Transtuzumab/Pertuzumb and docetaxel combo as control arm is in planning stage, to confirm the efficacy and safety of KN026.

REFERENCE

1 DM Ji et al. Preliminary Safety, Efficacy and Pharmacokinetics (PK) Results of KN026, a HER2-targeted Bispecific Antibody in Patients (pts) with HER2-positive Metastatic Breast Cancer. 2020ASCO, Abstract # 1041

CONFLICT OF INTEREST

- The first author has no conflicts of interest.

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