KN026 in combination with docetaxel as neoadjuvant treatment for HER2-positive early or locally advanced breast cancer: A single arm, multicenter, phase 2 study

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BACKGROUND

- Despite the use of targeted therapy has revolutionized the treatment in the neoadjuvant setting for early, locally advanced, HER2-positive breast cancer, these approaches still have limited efficacy[1,2], which calls for persistent exploration for optimized treatment strategy.
- KN026 is a bispecific monoclonal antibody that targets the distinct extra-cellular domains II (Pertuzumab binding site) and IV (Trastuzumab binding site) of HER2 (figure 1) . KN026 has better anti-tumor activity than either Trastuzumab or Pertuzumab used alone and aimed to demonstrate similar or better anti-tumor response than Trastuzumab in combination with Pertuzumab.
- Here we report the preliminary results of KN026 and docetaxel as neoadjuvant treatment in patients with HER2-positive early or locally advanced breast cancer (LABC).

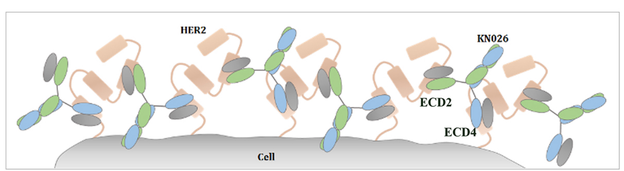

Figure 1 Mechanism of action of KN026

METHODS

- Treatment naive patients with HER2-positive early (T1c or 2, N1, M0; T2 or 3, N0, M0) or locally advanced breast cancer (T1c or 2 or 3, N2, M0; T3N1M0; T1c or 2 or 3, N3a or 3b, M0) were enrolled to receive 4 cycles of KN026 (30mg/kg, ivgtt d1, q3w) and docetaxel (75 mg/m^2 , ivgtt d1, Q3w) neoadjuvant treatment.
- The primary endpoint was total pCR rate (tpCR; defined as absence of any residual invasive cancer in the breast and lymph nodes) [ypT0/is, ypN0]). Secondary endpoints were pCR rate in the breast (bpCR, defined as absence of any residual invasive cancer in the breast [ypT0/is]), ORR (objective response rate), safety，PK (pharmacokinetics) and immunogenicity.
- The study is still ongoing. This study is registered in ClinicalTrials.gov, number NCT04881929. The data cutoff date was Sep 10, 2022.

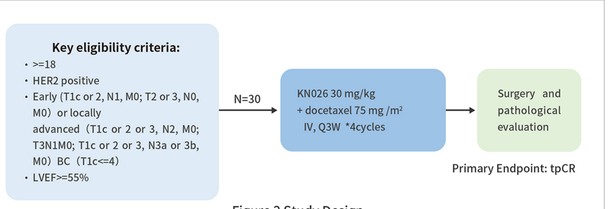

Figure 2 Study Design

RESULTS

- Between August 8, 2021, and Sep 10, 2022, a total of 30 patients were enrolled from 5 sites.
- 16 (53.3%) patients were stage II, and 14 (46.7%) patients were stage III; 26 (86.7%) patients with lymph node metastases, and 4 (13.3%) patients without lymph node metastases; 15 (50.0%) patients were hormone receptor positive, and 15 (50.0%) patients were hormone receptor negative (Table 1).

Table 1 Baseline characteristics

	FAS (N =30)
Age（years），n (%)	
≤40 years	6 (20.0)
41-64 years	22 (73.3)
≥65 years	2 (6.7)
Smoking History, n(%)	
never	0
stopped smoking	0
smoking	30 (100.0)
Alcohol Drinking History, n(%)	
never	0
stopped drinking	0
drinking	30 (100.0)
ECOG, n (%)	
0	29 (96.7)
1	1 (3.3)
T stage, n (%)	
T2	24 (80.0)
T3	6 (20.0)
Lymph Nodes status，n (%)	
cN0	4 (13.3)
cN1	16 (53.5)
cN2	10 (33.3)
Clinical Stage, n (%)	
IIa	3 (10)
IIb	13 (43.5)
IIIa	14 (46.7)
HR status, n (%)	
Positive	15 (50.0)
Negative	15 (50.0)
ER, n(%)	
Positive	15 (50.0)
Negative	15 (50.0)
PR, n(%)	
Positive	13 (43.3)
Negative	17 (56.7)

- As of Sep 10, 2022, 20 patients completed the surgery and pathological evaluation, 2 patients withdrew from the study earlier due to AE(not related to KN026) during neoadjuvant treatment period, and the other patients are still in study.
- Of the 20 patients who completed surgery and pathological evaluation, tpCR rate were 50% (10/20, 95% CI: 27.2%-72.8%), bpCR rate were 55.0% (11/20, 95% CI:31.53%-76.94%), and ORR were 100% (20/20, 95% CI: 83.16%-100%) (Table 2) (Figure 3-4).

Table 2 Efficacy after neoadjuvant therapy

	EAS (N =20)
tpCR, n (%)	**10 (50.0)**
95%CI	[27.2-72.8]
bpCR, n (%)	**11 (55.0)**
95%CI	[31.53-76.94]
ORR, n (%)	**20 (100.0)**
95%CI	[83.16-100]
BOR, n (%)	
CR	**4 (20.0)**
PR	**16 (80.0)**
SD	**0**
PD	**0**

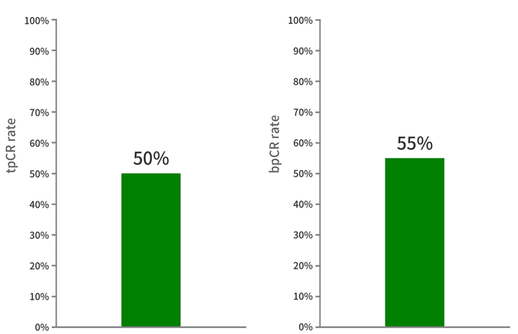

Figure 3 tpCR in EAS

Figure 4 bpCR in EAS

- The incidence of TEAE and CTCAE Grade ⩾3 TEAEs were 100% (30/30) and 53.3% (16/30), respectively. The most common (⩾5%) Grade ⩾3 TEAE were neutrophil count decreased (50%, 15/30), white blood cell count decreased (40%, 12/30), and lymphocyte count decreased (10%, 3/30). The incidence of SAE and CTCAE Grade ⩾3 SAE were both 6.7% (2/30). KN026-Related SAE and docetaxel-Related SAE occurred in only one patient (Table 3).
- Cardiac safety：no patient had left ventricular ejection fraction (LVEF) declines 10 percentage points or more from baseline accompanied with LVEF<50%; and no patient had LVEF declines 15 percentage points or more from baseline.

Table 3 Summary of Adverse Events

	SS (N =30)	
	Total, n(%)	Grade⩾3，n (%)
Treatment-Emergent Adverse Event (TEAE)	30 (100.0)	16 (53.3)
TEAE Leading to KN026 Interruption	4 (13.3)	3 (10.0)
TEAE Leading to KN026 Withdrawal	2 (6.7)	2 (6.7)
TEAE Leading to docetaxel Interruption	0	0
TEAE Leading to docetaxel Withdrawal	2 (6.7)	2 (6.7)
TEAE Leading to Death	0	0
Serious Adverse Event (SAE)	2 (6.7)	2 (6.7)
Treatment-Related SAE	1 (3.3)	1 (3.3)
KN026-Related SAE	1 (3.3)	1 (3.3)
Docetaxel-Related SAE	1 (3.3)	1 (3.3)
TEAE Leading to Death	0	0
TEAE of Grade⩾3		
Neutrophil count decreased		15 (50.0)
White blood cell count decreased		12 (40.0)
Lymphocyte count decreased		3 (10.0)
Alanine aminotransferase increased		1 (3.3)
Dermatitis acneiform		1 (3.3)
Diarrhoea		1 (3.3)
Febrile neutropenia		1 (3.3)
Gamma-glutamyltransferase increased		1 (3.3)
Hepatitis E		1 (3.3)
Hypersensitivity		1 (3.3)

CONCLUSIONS

- KN026 and docetaxel as neoadjuvant treatment has shown promising clinical benefit for patients with HER2-positive early or locally advanced breast cancer with an acceptable and manageable safety profile.
- Further validation in a large-scale randomized controlled trial is warranted.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.