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

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Background

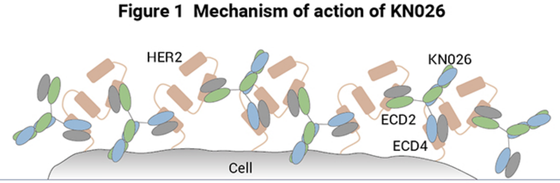
Despite the use of targeted therapy has revolutionized the treatment in the neoadjuvant setting for early, locally advanced, HER2-positive breast cancer, these approaches still have limited efficacy[1,2], which calls for persistent exploration for optimized treatment strategy.

KN026 is a bispecific antibody that targets the distinct extra-cellular domains II (Pertuzumab binding site) and IV (Trastuzumab binding site) of HER2 (figure1). 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.

The superior efficacy had also been validated in a series of clinical trials in late line Her2+ solid tumors as well as the first line Her2+ breast cancer and gastric cancer.

Here we report the 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



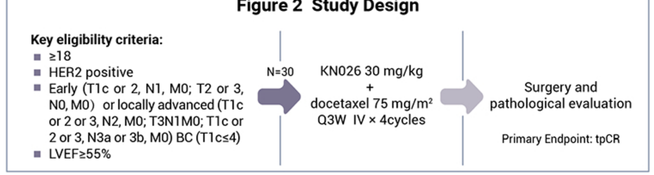
Methods

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, d8 (cycle 1 only), Q3w) and docetaxel (75 mg/m² ivgtt d1, Q3w) as 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 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.

As of Nov 21st, 2022, the study completed the primary outcome. This study is registered in ClinicalTrials.gov, number NCT04881929.

Figure 2 Study Design



Results

From August 9th, 2021, to July 29th, 2022, a total of 30 pts were enrolled from 5 sites.

16 pts (53.3%) were stage II, and 14 pts (46.7%) were stage III; 26 pts (86.7%) with biopsy-confirmed lymph node metastases; all the pts (100.0%) were HER2-positive; 15 pts (50.0%) were hormone receptor positive. (Table 1)

Table 1 Baseline characteristics

		Total (N=30)
Age (years), n (%)	≤ 40 years 41-64 years ≥65 years	6 (20.0) 22 (73.3) 2 (6.7)
ECOG, n (%)	0 1	29 (96.7) 1 (3.3)
T Stage, n (%)	T2 T3	24 (80.0) 6 (20.0)
N Stage, n (%)	N0 N1 N2	4 (13.3) 16 (53.3) 10 (33.3)
M Stage, n (%)	M0	30 (100.0)
Clinical Stage, n (%)	IIa IIb IIIa	3 (10.0) 13 (43.3) 14 (46.7)
HER2 Status, n (%)	Negative Positive	0 30 (100.0)
HR Status, n (%)	Positive Negative	15 (50.0) 15 (50.0)

As of Nov 21st, 2022, the study completed the primary outcome. 28 pts completed the surgery followed by pathological evaluation, and 2 pts discontinued from the study earlier due to AEs.

In FAS, tpCR rate was 56.7% (17/30, 95% CI: 37.43%-74.54%), posterior probability for tpCR>40% was 96.7%; bpCR rate was 60.0% (18/30, 95% CI:40.60%-77.34%); ORR was 90.0% (27/30, 95% CI: 73.47%-97.89%); confirmed ORR was 86.7% (26/30, 95% CI: 69.28%-96.24%). (Table2)

Table 2 Efficacy after neoadjuvant therapy

		FAS (N=30)	EAS (N=28)
tpCR	n (%) 95%CI Posterior probability for tpCR > 40% (%)	17 (56.7) [37.43-74.54] 96.7	17 (60.7) [40.58-78.50] 98.7
bpCR	n (%) 95%CI	18 (60.0) [40.60-77.34]	18 (64.3) [44.07-81.36]
ORR	n (%) 95%CI	27 (90.0) [73.47-97.89]	27 (96.4) [81.65-99.91]
ORR (confirmed)	n (%) 95%CI	26 (86.7) [69.28-96.24]	26 (92.9) [76.50-99.12]

Among the subgroups, the tpCR rate was numerically higher in pts with HR negative vs HR positive; and in patients with stage II vs stage III. The tpCR rate was numerically similar in other subgroups (Age ≥ 65 years was excluded as only two patients were enrolled). (Table 3)

Table 3 Subgroup analysis of tpCR

		FAS	EAS
Age			
≤ 40 years	N tpCR, n (%) 95%CI	6 3 (50.0) [11.81-88.19]	5 3 (60.0) [14.66-94.73]
41-64 years	N tpCR, n (%) 95%CI	22 12 (54.5) [32.21-75.61]	21 12 (57.1) [34.02-78.18]
≥ 65 years	N tpCR, n (%) 95%CI	2 2 (100.0) [15.81-100.00]	2 2 (100.0) [15.81-100.00]
Clinical Stage			
II	N tpCR, n (%) 95%CI	16 11 (68.8) [41.34-88.98]	15 11 (73.3) [44.90-92.21]
III	N tpCR, n (%) 95%CI	14 6 (42.9) [17.66-71.14]	13 6 (46.2) [19.22-74.87]
Primary Tumor Size			
≤ 5cm	N tpCR, n (%) 95%CI	25 14 (56.0) [34.93-75.60]	23 14 (60.9) [38.54-80.29]
> 5cm	N tpCR, n (%) 95%CI	5 3 (60.0) [14.66-94.73]	5 3 (60.0) [14.66-94.73]
Lymph Nodes Status			
Negative	N tpCR, n (%) 95%CI	4 2 (50.0) [6.76-93.24]	3 2 (66.7) [9.43-99.16]
Positive	N tpCR, n (%) 95%CI	26 15 (57.7) [36.92-76.65]	25 15 (60.0) [38.67-78.87]
HR Status			
Positive	N tpCR, n (%) 95%CI	15 6 (40.0) [16.34-67.71]	13 6 (46.2) [19.22-74.87]
Negative	N tpCR, n (%) 95%CI	15 11 (73.3) [44.90-92.21]	15 11 (73.3) [44.90-92.21]

The incidence of TEAE and CTCAE Grade ≥3 TEAE were 100.0% (30/30) and 53.3% (16/30), respectively. The most common (≥5%) Grade ≥3 TEAE were neutrophil count decreased (50.0%, 15/30), white blood cell count decreased (40.0%, 12/30), and lymphocyte count decreased (10.0%, 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 4)

Table 4 Summary of Adverse Event

	FAS (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)
At least One TEAE of Grade ≥ 3	16 (53.3%)	
Neutrophil count decreased	15 (50.0)	
White blood cell count decreased	12 (40.0)	
Lymphocyte count decreased	3 (10.0)	
Gamma-glutamyltransferase increased	1 (3.3)	
Alanine aminotransferase increased	1 (3.3)	
Febrile neutropenia	1 (3.3)	
Hepatitis E	1 (3.3)	
Dermatitis acneiform	1 (3.3)	
Diarrhoea	1 (3.3)	
Hypersensitivity	1 (3.3)	

No patient had left ventricular ejection fraction (LVEF) declines 10% points or more from baseline accompanied with LVEF <50%; and no patient had LVEF declines 15% points or more from baseline.

Conclusions

KN026 combined with 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.

References

1. Luca Gianni, et al Lancet Oncol. 2012 Jan;13(1):2-3
2. Zhimin Shao, et al. JAMA Oncol. 2020;6(3):e193692

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Conflict of Interest

The authors have declared no conflicts of interest.