Preliminary Safety and Efficacy Results of KN046 (an anti-PD-L1/CTLA-4 Bispecific Antibody)in combination with KN026 (a HER2-targeted Bispecific Antibody) in Patients with Metastatic HER2-positive Breast Cancer: a Phase II Trial

Jieqiong Liu[1,#], Chuangui Song[2,#], Xiangcai Wang[3], Mingli Ni[4], Xujuan Wang[5], Lei Chen[6], Hongwei Yang[7], Rusen Zhao[8], Ting Xu[9], Johannes Nippgen[9], Long Xiao[9], Lin Shen[10,*]

[1]Guangdong Provincial Key Laboratory of Malignant Tumo r Epigenetics and Gene Regulation, Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; [2]Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian, China; [3]Department of Oncology, The First Affiliated Hospital of Gannan Medical College, Ganzhou, Jinagxi, China; [4]Department of Oncology, Luoyang Central Hospital, Luoyang, Henan, China; [5]Department of Breast, Neijiang Second People's Hospital,Neijiang,Sichuan, China; [6]Department of Oncology, Cancer Hospital Affiliated to Shantou University Medical College,Shantou, Guangdong, China; [7]Department of Breast and Thyroid Surgery, Suining Central Hospital, Suining Sichuan, China; [8]Department of Oncology, Zibo Municipal Hospital, Zibo, Shandong, China; [9]Jiangsu Alphamab Biopharmaceuticals Co., Ltd., Suzhou, China; [10]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China

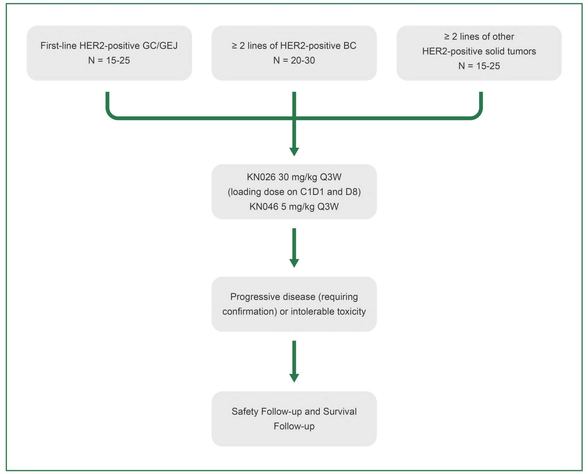
*Correspondence to Dr. Lin Shen: shenlin@bjmu.edu.cn [#]Jieqiong Liu and Chuangui Song contributed equally to this work

BACKGROUND

- HER2-targeted therapies combined with chemotherapy have improved survival outcomes for patients with metastatic HER2-positive breast cancer. However, some patients progressed after several lines of anti-HER2 combinational therapies, and the overall survival (OS) of these patients remained unfavorable.
- Prior studies showed that immunotherapy in combination with chemotherapy or targeted therapy could significantly prolong OS of metastatic breast cancer patients, especially in patients with triple-negative breast cancer. Reports of immunotherapy combined with HER2-targeted therapy are still limited.
- Here we reported the preliminary results from an ongoing phase II trial assessing the safety and efficacy for KN046 (a bispecific antibody blocks both PD-L1 interaction with PD-1/CD80 and CTLA-4 interaction with CD80/CD86) in combination with KN026 (a bispecific antibody that binds to two different HER2 epitopes, same domains as trastuzumab and pertuzumab) in patients with HER2-positive metastatic breast cancer who have progressed after prior anti-HER2 combinational therapies.

STUDY DESIGN

- **Methods:** Female patients with metastatic HER2-positive breast cancer who were previously treated with at least one line of HER2-targeted combinational therapy were enrolled from multiple academic hospitals in China to receive KN046 (iv. 5 mg/kg Q3W) plus KN026 (iv. 30 mg/kg Q3W) until progression, unacceptable toxicities or patient withdrawal. Efficacy evaluation was evaluated Q6W per RECIST 1.1. The primary endpoint was objective response rate (ORR).



RESULTS

- As of the August 10th, 2021, 36 patients with the median age of 53.0 years (range: 33-67) were enrolled. 30 of 36 patients (83.3%) received > 2 lines of HER2-targeted combinational therapies in the metastatic setting. 33 and 36 patients were evaluable for overall response and safety, respectively.
- The ORR was 48.5% (16 of 33, 95% CI: 30.8-66.5), and one patient achieved complete response (CR) (intention-to-treat analysis). And the disease control rate (DCR) was 78.8% (26 of 33, 95% CI 61.1-91.0). The median progression-free survival (PFS) was 6.9 (95%CI 4.2-not reached) months.
- 32 of 36 (88.9%) patients suffered from treatment-related adverse events (TRAEs) of any grade, while 5 of 36 (13.9%) patients had experienced ≥ grade 3 TRAEs. The most common (≥ 10%) TRAEs were infusion related reaction (41.7%), pruritus (22.2%), diarrhea (19.4%), rash (16.7%), alanine aminotransferase increased (16.7%), aspartate aminotransferase increased (16.7%), and Hypothyroidism (13.9%) ,Weight decreased (11.1%), Hepatic function abnormal (11.1%). No treatment-related deaths were observed.

Baseline Disease Characteristics

	HER2-positive Breast Cancer (N = 36)
ECOG score	
0	29 (80.6%)
1	7 (19.4%)
Sex	
F	36 (100%)
M	0
Age Group	
< 50 years	11 (30.6%)
≥ 50 years	25 (69.4%)
Distant metastasis or not	
Yes	33 (91.7%)
No	3 (8.2%)
Number of metastatic sites	
< 3	23 (63.9%)
≥ 3	10 (27.8%)
Prior Anticancer Therapy	
Radiation	13 (36.1%)
Surgery	29 (80.6%)
Chemotherapy	36 (100%)
Number of previous treatment lines	
1st-line treatment	4 (11.1%)
2nd-line treatment	12 (33.3%)
3rd-line treatment	6 (16.7%)
>3rd-line treatment	14 (38.9%)

Cutoff date 2021/8/10

Safety overview

	HER2+BC (N=36)	
	All	Grade≥3
Number of TEAE	275	46
Subjects with at least 1 TEAE	35 (97.2%)	6 (16.7%)
Related to KN046	31 (86.1%)	5 (13.9%)
Related to KN026	30 (83.3%)	4 (11.1%)
Related to KN046 or KN026	32 (88.9%)	5 (13.9%)
Subjects with at least 1 IRR	16 (44.4%)	1 (2.8%)
Related to KN046	8 (22.2%)	1 (2.8%)
Related to KN026	13 (36.1%)	1 (2.8%)
Subjects with at least 1 irAE	6 (16.7%)	0
Related to KN046	6 (16.7%)	0
Subjects with at least 1 SAE during treatment	3 (8.3%)	3 (8.3%)
Related to KN046	2 (5.6%)	2 (5.6%)
Related to KN026	1 (2.8%)	1 (2.8%)
Subjects with at least 1 TEAE Leading to KN046 Withdrawn	3 (8.3%)	2 (5.6%)
Related to KN046	3 (8.3%)	2 (5.6%)
Related to KN026	3 (8.3%)	2 (5.6%)
Subjects with at least 1 TEAE Leading to KN026 Withdrawn	3 (8.3%)	2 (5.6%)
Related to KN046	3 (8.3%)	2 (5.6%)
Related to KN026	3 (8.3%)	2 (5.6%)
Subjects with at least 1 TEAE Leading to Death	0	0
Related to KN046	0	0
Related to KN026	0	0

Cutoff date 2021/8/10

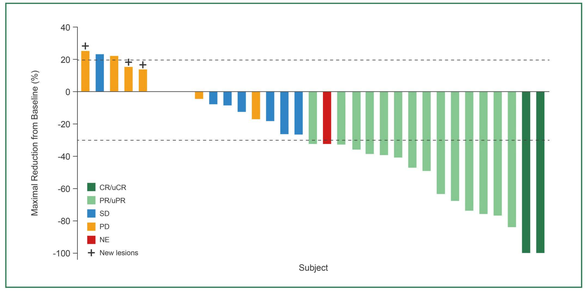
Summary of incidence ≥10% KN046 or KN026 related Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set)

	HER2+BC (N=36)
Infusion related reaction	15 (41.7%)
Alanine aminotransferase increased	6 (16.7%)
Diarrhoea	7 (19.4%)
Aspartate aminotransferase increased	6 (16.7%)
Pruritus	8 (22.2%)
Weight decreased	4 (11.1%)
Rash	6 (16.7%)
Hypothyroidism	5 (13.9%)
Hepatic function abnormal	4 (11.1%)

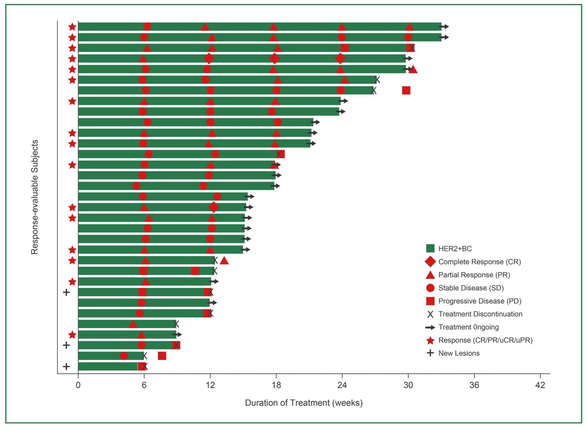
Efficacy overview

	Total (N=33)
DCR, n (%)	**26 (78.8%)**
95%CI	61.1%, 91.0%
ORR, n (%)	**16 (48.5%)**
95%CI	30.8%, 66.5%
PR	12 (36.4%)
uPR	2 (6.1%)
CR	1 (3.0%)
uCR	1 (3.0%)

Figure 4.1.1.1.3 Waterfall Plot by Best Overall Response of BC Cohort (Evaluable Analysis Set)



Efficacy-swimming lane



CONCLUSION

- **Conclusions:** This chemo-free regime that KN046 in combination with KN026 has shown favorable clinical efficacy with manageable toxicities in heavily pre-treated patients with metastatic HER2-positive breast cancer. This trial is currently ongoing.
- ClinicalTrials.gov number, NCT04521179