Abstract # 4040: A phase II study evaluating KN026 monotherapy in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancers

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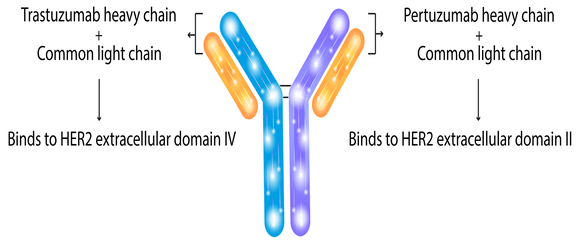
Background

- Outcomes of second or later-line treatment for pts with advanced gastroesophageal junction cancers (GC/GEJC) remain inferior.[1]
- Human epidermal growth factor receptor 2 (HER2) is recognized as a prognostic factor associated with poor outcomes and a treatment target for GC/GEJC.[2]
- KN026 is a novel HER2-targeted bispecific antibody composed of VH regions of Trastuzumab and Pertuzumab, targeting the HER2 juxtamembrane domain (IV) and the dimerization domain (II) simultaneously (Figure 1).[3]
- Here we present the results of this multicenter, single-arm open-label, phase II study (NCT03925974) designed to evaluate the efficacy and safety of KN026 in patients with previously-treated advanced HER2-expressing GC/GEJC.

Figure 1 . Structure of KN026



Study Methods

This was a two-cohort, two-part, non-randomized, open-label, phase II study conducted in 15 study sites in China (Figure 2).

Figure 2 . Study design

Enrollment

Patients with advanced HER2-expressing GC/GEJC who failed from at least one prior line of standard treatment.

High-level HER2 (Cohort 1): IHC3+ or IHC2+/ISH+;
Low-level HER2 (Cohort 2): IHC2+/ISH-, IHC1+, or IHC0/ISH-.

Part 1 (lead-in period): Patients were enrolled regardless of the cohort per HER2 level.

Part 2 (dose expansion): Patients were enrolled according to HER2-level cohort.

Treatment

Part 1 : KN026 was given intravenously in 10 mg/kg QW first, then 20 mg/kg Q2W, and 30 mg/kg Q3W.

No significant issues on safety

Part 2 : KN026 was given intravenously in 20 mg/kg Q2W or 30 mg/kg Q3W based on the recommendation of the Study Monitoring Committee.

Treatment continued until the withdrawal of consent, intolerable toxicity, progressive disease or death

Endpoints

Primary endpoints:
Objective response rate (ORR);
Duration of response (DoR) assessed by investigators per RECIST 1.1.

Secondary endpoints:
Disease control rate (DCR);
Clinical benefit rate (CBR);
Progression-free survival (PFS);
Overall survival (OS);
Safety outcomes.

Other key eligibility criteria:

- Both sexes, 18–75 years (inclusive);
- ECOG score of 0 or 1;
- Adequate hematologic, hepatic, and renal function;
- A life expectancy of at least three months;
- Standard treatment was not limited to Trastuzumab-based treatment (for high-level HER2 patients).

Results

- Data cut-off date: Oct. 29, 2021
- Baseline demographics and clinical characteristics are summarized in Table 1.

Table 1 . Baseline demographics and clinical characteristics

Characteristics	All (n=45)	Cohort 1: high-level HER2 (n=27)	Cohort 2: low-level HER2 (n=14)
Median age, years, (IQR)	62.0 (55.0–67.0)	62.0 (54.0–64.0)	61.5 (53.0–70.0)
Male/ Female	38 (84%)/ 7 (16%)	25 (93%)/ 2 (7%)	10 (71%)/ 4 (29%)
ECOG score 0/1	9 (20%)/ 36 (80%)	8 (30%)/ 19 (70%)	0/ 14 (100%)
Prior lines of systemic treatments			
1 line	26 (58%)	16 (59%)	8 (57%)
2 lines	12 (27%)	8 (30%)	3 (21%)
≥3 lines	7 (15%)	3 (11%)	3 (21%)
Prior types of systemic treatments			
prior chemotherapy	45 (100%)	27 (100%)	14 (100%)
prior Trastuzumab treatment	23 (51%)	16 (59%)	5 (36%)
prior radiotherapy	3 (7%)	1 (4%)	1 (7%)

Data are expressed as count (percentage) unless otherwise specified. * Four enrolled patients with centrally assessed HER2 results of IHC0 and ISH negative were included in the all-patients group but not included in the High-level HER2 or Low-level HER2 cohort. IQR: Interquartile range; n: count

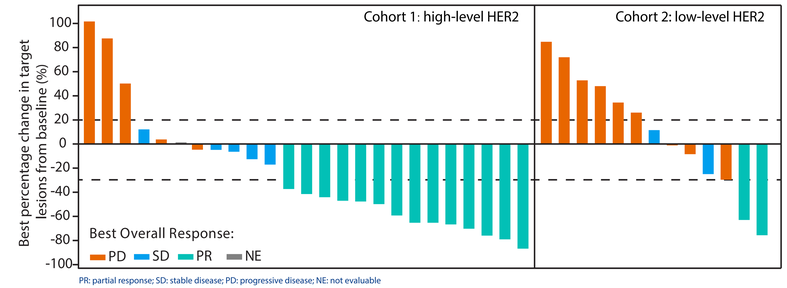
- Efficacy outcomes are summarized in Table 2.
- Tumor reductions are showed in Figure 3.

Table 2 . Efficacy outcomes of KN026

Efficacy outcomes	Cohort 1: high-level HER2 (n=25)	Cohort 2: low-level HER2 (n=14)	Cohort 1- Trastuzumab pretreated (n=14)
ORR, n (%; 95% CI)	14 (56%; 35%–76%)	2 (14%; 2%–43%)	7 (50%; 23%-77%)
Median DOR, months (95% CI)	9.7 (4.2–NE)	6.2 (3.2–NE)	7.0 (2.8-NE)
DCR, n (%; 95% CI)	19 (76%; 55%–91%)	4 (29%; 8%–58%)	11 (79%; 49%-95%)
CBR, n (%; 95% CI)	18 (72%; 51%–88%)	3 (21%; 5%–51%)	10 (71%; 42%-92%)
Median PFS, months (95% CI)	8.3 (4.2-11.4)	1.4 (1.4-4.1)	5.5 (1.5-11.0)
Median OS, months (95% CI)	16.3 (11.0- NE)	9.6 (3.5-14.9)	14.9 (11.0-NE)

Data are expressed as count (percentage) unless otherwise specified. Two patients in Cohort 1 were without post-treatment tumor response data. IQR: Interquartile range; n: count; NE: not evaluable.

Figure 3 . Waterfall plot of tumor reductions



PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable

- The safety outcomes were evaluated in all enrolled patients. The most common treatment-related adverse events (TRAEs) are summarized in Table 3. No grade-4 or grade-5 TRAEs occurred.

Table 3 . Safety outcomes of KN026 (any grade TRAEs ≥10%)

TRAEs	Enrolled patients (n=45)	
	All Grades	Grade 3-5
Any	37 (82%)	4 (9%)*
Increased aspartate aminotransferase	12 (27%)	0
Increased alanine aminotransferase	9 (20%)	0
Rash	7 (16%)	0
Anemia	7 (16%)	0
Infusion related reaction	7 (16%)	1 (2%)*
Decreased white blood cell count	6 (13%)	0
Diarrhoea	6 (13%)	0
Decreased weight	5 (11%)	0
Decreased neutrophil count	5 (11%)	0

Data are expressed as count (percentage). Treatment-related adverse events are summarized by Preferred Term according to MedDRA. * No grade 4 or 5 TRAEs occurred.

Conclusions

- **KN026, a new anti-HER2 agent, yielded promising efficacy in gastric or gastroesophageal junction cancer patients with high-level HER2 expression.**
- **KN026 showed a modest efficacy comparable with the current second-line chemotherapy in gastric or gastroesophageal junction cancer patients with low-level HER2 expression.**
- **KN026 demonstrated a favorable safety profile. Further investigation is warranted.**

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