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Clinical Trial

KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer

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Abstract ***Background:*** KN026 is a novel human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody that binds two distinct domains of HER2. We report the safety and efficacy results of the phase 2 trial in patients with advanced HER2-expressing gastric or gastroesophageal junction cancer who failed from at least one prior line of standard treatment.

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Material and methods: In this open-label, multicentre, phase 2 trial, eligible patients were enrolled in the high-level HER2 cohort or low-level HER2 cohort and assigned to receive KN026 10 mg/kg (once a week), 20 mg/kg (once every two weeks) or 30 mg/kg (once every three weeks) intravenously. The primary end-points were the objective response rate (ORR) and duration of response assessed according to Response Evaluation Criteria in Solid Tumours (version 1.1).

Results: Between 17th June 2019 and 23rd August 2021, 45 patients were enrolled and received at least one dose of KN026, including 27 patients in the high-level HER2 cohort, 14 patients in the low-level HER2 cohort and four patients who had no HER2 expression. The ORR in the high-level HER2 cohort was 56% (95% confidence interval [CI] 35%–76%), with a durable response duration of 9.7 months (95% CI 4.2–not evaluable); while for the patients with low-level HER2, the ORR was 14% (95% CI 2%–43%). The most frequent ≥ grade 3 treatment-emergent adverse events were gastrointestinal disorders (five patients, 11%). No drug-related deaths were reported.

Conclusions: KN026 showed a favourable safety profile and promising anti-tumour activity. Our results support further studies evaluating KN026 and the combination treatment with other active drugs in patients with advanced gastric or gastroesophageal junction cancer having high-level HER2 expression.

1. Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, having approximately one million new cases reported in 2020 and responsible for an estimated 769,000 deaths, according to the latest GLOBOCAN [1]. Gastroesophageal junction cancer (GEJC) is an aggressive disease of the upper gastrointestinal tract with the fastest-growing incidence and mortality rate in recent years [2]. Despite the advances in diagnostic technology, most patients with GC/GEJC are diagnosed at an advanced stage [1,3]. Fluoropyrimidine-based or platinum-based chemotherapy is still the main option for patients with metastatic or recurrent disease; the prognosis in this setting is inferior. The median survival was about one year with optimal systemic chemotherapy and supportive care [4,5].

Human epidermal growth factor receptor 2 (HER2) is recognised as a prognostic factor associated with poor outcomes and a treatment target for GC/GEJC. The high-level HER2 expression was reported in approximately 10%–20% of advanced GC/GEJC cases [6]. Anti-HER2 therapy was introduced in the treatment armamentarium of GC/GEJC in 2010. In combination with chemotherapy, Trastuzumab, an anti-HER2 antibody, significantly improved the survival outcome and is approved as the first-line therapy for HER-positive metastatic GC/GEJC [7]. However, more often in the metastatic setting, most patients developed tumour progression around eight months after the first-line Trastuzumab-based chemotherapy [7]. More recently, a new candidate for the first-line combination treatment emerged for patients with HER2-positive GC/GEJC. Pembrolizumab added to Trastuzumab and chemotherapy as first-line therapy (KEYNOTE 811 study) showed an impressive objective response rate (ORR) of 74% in HER-positive metastatic GC/GEJC. However, the difference in the median duration of response (DOR) was only 1.1 months compared with Trastuzumab plus chemotherapy. The long-term benefits, including progression-free survival (PFS) and overall survival (OS) need further observation [8]. For HER2-negative patients, by adding Nivolumab in chemotherapy as the first-line treatment, the median OS was prolonged to 13–17 months [9,10].

Although much progress has been made to improve the outcomes of patients with advanced GC/GEJC and who failed the standard therapy, the second-line or subsequent treatment options are still limited. Regardless of HER2 expression, systemic chemotherapy in the later-line setting only offered an ORR of 13%–27% [5]. Ramucirumab-based therapy resulted in an ORR of 28% [11,12]. For HER2-positive patients, RC48, a HER2-targeted antibody–drug conjugate, offered a modest ORR of 25%; while Trastuzumab deruxtecan, another HER2-targeted antibody–drug conjugate, significantly improved the ORR to 51% [13,14].

Here, we introduce a novel HER2-targeted approach. KN026 is a bispecific anti-HER2 antibody consisting of the heavy chain variable domain of Trastuzumab and Pertuzumab on each arm with the fragment crystallisable region from Trastuzumab. The unique design of KN026 allowed simultaneous bindings of HER2 domains II (Pertuzumab binding site) and IV (Trastuzumab binding site) and inherited Trastuzumab's antibody-dependent cellular cytotoxicity and phagocytic killing effect [15]. In our preclinical study, KN026 demonstrated impressive anti-tumour activity over cell lines with different HER2 expression levels [17]. In the phase 1 study, KN026 has shown encouraging efficacy in patients with previously treated metastatic breast cancer (including 96.8% of Trastuzumab-pretreated

patients); the ORR was 28%, and median PFS was 6.9 months [18]. Treatment-related adverse events (TRAEs) were mainly mild; only 4 (6%) patients reported reversible grade 3 TRAEs [18].

Given these promising results from previous studies, we aimed to evaluate the safety and efficacy of KN026 in patients with HER2-expressing advanced GC/GEJC who failed from at least one prior line of standard treatment.

2. Material and methods

2.1. Study design

This was a two-cohort, two-part, non-randomised, open-label, single-arm, multicentre phase 2 study conducted in 15 study sites in China between 17th June 2019 and 23rd August 23 2021, in patients with HER2-expressing advanced GC/GEJC who failed from at least one prior line of standard treatment. HER2 level was determined by immunohistochemistry (IHC) combined with in-situ hybridisation (ISH) and classified into two categories: high-level and low-level. High-level HER2 expression was defined as IHC3+ or IHC2+/ISH-positive. Low-level HER2 expression was defined as either IHC2+/ISH-negative, IHC1+ or IHC0/ISH-positive.

In general, patients with high-level HER2 expression were included in the high-level HER2 cohort, and patients with low-level HER2 expression were assigned to the low-level HER2 cohort. Tumour tissue samples from surgery or biopsy of the primary tumour were used to test HER2 status. The enrolment was according to the HER2 test results from the local study site, and then, tissue sections were set to the central laboratory for a re-test. Data analysis was based on re-tested HER2 results from the central laboratory.

In part 1, patients were enrolled regardless of the cohort according to HER2 level. First, atleast six patients were enrolled in the 10 mg/kg once a week (QW) group to assess the safety and tolerability of KN026. Upon a satisfactory review of the data from the 10 mg/kg QW group by the Study Monitoring Committee (SMC), three to six patients were enrolled in 20 mg/kg once every two weeks (Q2W) group, then three to six patients in 30 mg/kg once every three weeks (Q3W) group. In part 2, patients were enrolled in a high-level HER2 cohort or a low-level HER2 cohort according to HER2 level. A dose expansion on the recommended dose of 20 mg/kg Q2W or 30 mg/kg Q3W was conducted to evaluate further the safety, tolerability and efficacy of KN026 [18].

The SMC monitored the study results on a pre-planned schedule. This preliminary analysis was planned to conduct after 44 patients were treated, and the 44th patient underwent two post-treatment response evaluations approximately 12 weeks after the first administration.

Based on the review of all the available results, the SMC could suggest terminating a certain study cohort or the whole study due to the analysis suggesting significant effectiveness, futility, safety issue or problems with the study conduct.

2.2. Patients

Eligible patients were 18–75 years (inclusive) with locally advanced or metastatic HER2-expressing GC/GEJC confirmed by histopathological and/or cytological examinations. Patients were required to provide tumour tissue samples from surgery or biopsy of the primary tumour to check the HER2 expression. If the archived sample was not available, a tumour biopsy was performed before the enrolment to obtain a fresh sample. Additional major eligibility criteria included patients must receive at least one prior line of standard treatment (patients in the high-level HER2 cohort may receive prior treatment with or without Trastuzumab); with at least one measurable lesion at baseline as per Response Evaluation Criteria in Solid Tumours version 1.1; an Eastern Cooperative Oncology Group performance status of 0 or 1; a life expectancy of at least three months; adequate haematological, hepatic, cardiac and renal function.

This study was approved by the Independent Ethics Committee at each study site and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained from all patients before enrolment. This study is registered with ClinicalTrials.gov: NCT03925974.

2.3. Procedures

KN026 was administered via an intravenous infusion on day-1 of each cycle. Treatment with KN026 continued until the withdrawal of consent, intolerable toxicity, progressive disease or death. Patients were followed up for survival status every 12 weeks until the initiation of new anti-tumour treatment, withdrawal of consent, loss of follow-up or death.

Tumour assessments by contrast-enhanced computed tomography or magnetic resonance imaging were arranged at baseline, then approximately every six weeks for the first 24 weeks of treatment and every 12 weeks during the rest of the treatment period and the end of treatment visit. Tumour response was evaluated by the investigators as per Response Evaluation Criteria in Solid Tumours 1.1 criteria. If a patient has a complete response or partial response, a repeated assessment should be performed around six weeks after the initial assessment to confirm the response.

Safety assessments included the documentation of treatment-emergent adverse events (TEAEs), laboratory examinations, vital signs monitoring, physical examinations, 12-lead ECG and echocardiography. TEAEs and concomitant medications were continuously recorded throughout the study period. The predefined adverse event of special interest was cardiotoxicity (such

as ventricular arrhythmia and reduced left ventricular function). Dose interruptions and permanent discontinuation of KN026 were allowed, depending on the type and severity of toxicity.

2.4. End-points

The primary end-points were ORR evaluated by the investigators and DOR. Secondary efficacy end-points included disease control rate (DCR); clinical benefit rate (CBR); time to response (TTR); OS; PFS; PFS rate at six and nine months. The definition of efficacy end-points is provided in the supplementary methods. Safety end-points included the incidence and severity of TEAEs graded according to the Common Terminology Criteria for Adverse Events (version 5.0). Adverse events were coded using Medical Dictionary for Regulatory Activities (version 23.1).

2.5. Statistical analysis

The referenced ORR was 16%–20% in the second-line chemotherapy for GC based on published results [12,19,20]. Assuming a true ORR of 42% in both high-level and low-level HER2 cohorts, a sample size of 22 could provide approximately 70% power to detect a statistically significant difference between the ORR of KN026 and the threshold ORR of 20%, at the 0.05 (two-sided) significance level. Assuming a 15% dropout rate, the number of patients with high-level HER2 was expected to be 25, including no less than 15 patients previously treated with Trastuzumab, and the number of patients with low-level HER2 was expected to be 25. The planned total sample size was set to 50.

The safety analysis set included all patients who received at least one full or partial dose of the study drug and served as the primary analysis set for all the data analysis unless otherwise specified. The efficacy analysis set included all patients who received at least one full or partial dose of the study drug and had at least one post-baseline tumour assessment, which was used for the analysis of ORR, DCR, CBR and DOR.

Baseline and disease characteristics, drug exposure and TEAEs were summarised by descriptive statistics. The ORR, DCR and CBR were based on the confirmed best overall response and calculated along with 95% Clopper—Pearson confidence intervals (CIs). The Kaplan–Meier method was used to estimate time-to-event variables, and corresponding 95% CIs were calculated by the Brookmeyer—Crowley method. The pooled analysis of efficacy end-points per HER2 cohort was based on predictions of the population pharmacokinetic model. Further details of the population pharmacokinetic model are provided in the supplementary methods. Subgroup analysis was performed for ORR based on baseline and disease characteristics. All analyses were done with SAS software (version 9.4).

3. Results

3.1. Patient disposition

Between 17th June 2019 and 23rd August 2021, a total of 45 patients with previously treated, advanced HER2-expressing GC/GEJC were enrolled in 15 study sites across China and received at least one dose of KN026 at 10 mg/kg QW, 20 mg/kg Q2W or 30 mg/kg Q3W. The data cutoff date for this pre-planned analysis was 29th October 2021. Of the 45 enrolled patients, 27 patients were with high-level HER2 expression, 14 had low-level HER2 expression, and four had no HER2 expression (IHC0/ISH-negative) based on central laboratory testing. Five of the high-level HER2 patients were assigned to receive KN026 at 10 mg/kg QW, four at 20 mg/kg Q2W and 18 at 30 mg/kg Q3W; while for the low-level HER2 patients, six received 10 mg/kg QW, two with 20 mg/kg Q2W and six with 30 mg/kg Q3W. At data cutoff, 37 patients discontinued the treatment, and eight patients were still on treatment. Most of the patients discontinued (29, 78%) due to progressive disease. All 45 patients were included in the safety analysis set. And 39 patients were included in the efficacy analysis, excluding the four patients with no HER2 expression and two patients without post-treatment response results (Fig. 1).

3.2. Patient and disease characteristics

The baseline characteristics of the patients are summarised in Table 1. Overall, the median age of enrolled patients was 62 years, with an interquartile range (IQR) of 55–67. 84% of patients were male. Most patients (43, 96%) were diagnosed with advanced gastric adenocarcinoma. 19 out of 45 patients (42%) underwent two or more lines of previous systemic anti-cancer treatments. Among the 27 patients with high-level HER2, 16 (59%) patients have progressed on the prior Trastuzumab treatment.

3.3. Efficacy

In the efficacy analysis set, the ORR was 56% (95% CI 35%–76%) in the high-level HER2 cohort with 14 partial responses and 14% (95% CI 2%–43%) with two partial responses in the low-level HER2 cohort (Table 2). The higher DCR and CBR were also observed in the high-level HER2 cohort (76%, 95% CI 55%–91% and 72%, 95% CI 51%–88%, respectively) compared to that of the low-level HER2 cohort (29%, 95% CI 8%–58% and 21%, 95% CI 5%–51%) (Table 2). Among the responders, the objective responses were observed quickly after the initiation of KN026; the median TTR was 1.4 months (IQR 1.4–1.5) in the high-level HER2 cohort. However, the median TTR was longer in the low-level HER2 cohort (4.2 months, IQR 2.8–5.7). As shown in the waterfall plot (Fig. 2), 19

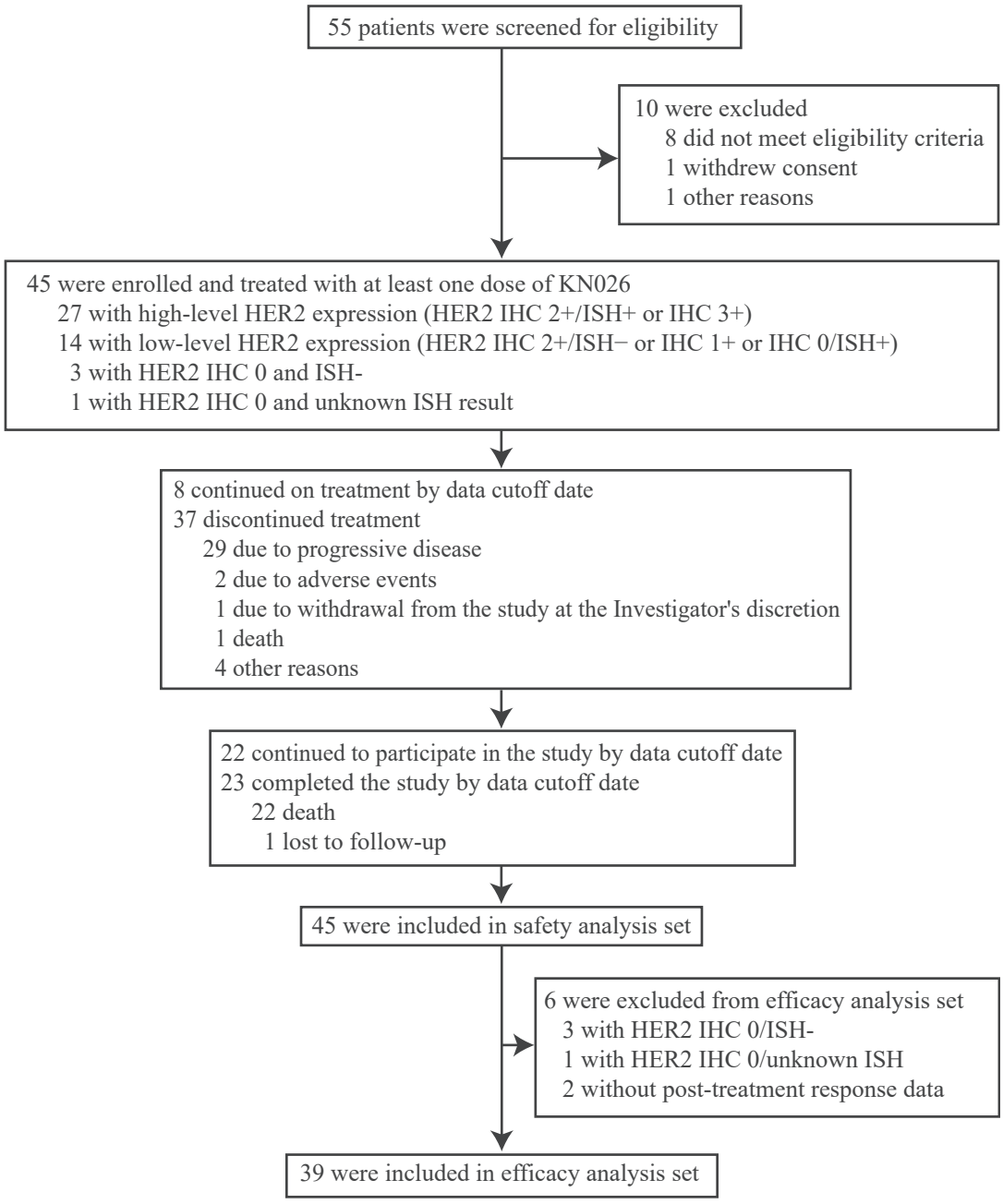

Fig. 1. Trial profile.

(76%) patients in the high-level HER2 cohort had a reduction in the sum of diameters of target lesions and six (43%) patients in the low-level HER2 cohort experienced tumour shrinkage. According to Kaplan–Meier estimation, the median DOR was 9.7 months in the high-level HER2 cohort (95% CI 4.2–not evaluable (NE)), which was about three months longer than that of the low-level HER2 cohort (Table 2, Fig. 3a).

At a median follow-up of 14.7 months (IQR 9.4–16.5), the median PFS was 8.3 months (95% CI 4.2–11.4) in the high-level HER2 cohort. The median PFS of the low-level HER2 cohort was 1.4 months (95% CI 1.4–4.1), with a median follow-up of 27.5 months (IQR 4.1–NE) (Fig. 3b). The Kaplan–Meier estimate of PFS rate was 53% (95% CI 31%–72%) at six months and 44% (95% CI 23%–63%) at nine months in the high-level HER2 cohort; 9% (95% CI 1%–32%) in the low-level HER2 cohort at both of six and nine months. There were ten events of deaths due to any cause in both cohorts. Median OS was 16.3 months (95% CI 11.0–NE) and 9.6 months (95% CI 3.5–14.9) in the high-level HER2 and low-level HER2 cohorts, respectively (Fig. 3c).

The efficacy results of the low-level HER2 cohort suggested no meaningful improvement compared to the current second-line treatment. The probability of

Table 1
Demographic and disease characteristics of patients.

Characteristic	All[a] (n = 45)	High-level HER2 (n = 27)	Low-level HER2 (n = 14)
Age, years, median (IQR)	62.0 (55.0–67.0)	62.0 (54.0–64.0)	61.5 (53.0–70.0)
Sex			
Male	38 (84%)	25 (93%)	10 (71%)
Female	7 (16%)	2 (7%)	4 (29%)
Body mass index, kg/m^2, Median (IQR)	20.8 (19.1–23.2)	21.2 (19.1–23.4)	21.1 (19.4–23.4)
ECOG performance status			
0	9 (20%)	8 (30%)	0
1	36 (80%)	19 (70%)	14 (100%)
Primary site of disease			
Gastric	43 (96%)	26 (96%)	13 (93%)
Gastroesophageal junction	2 (4%)	1 (4%)	1 (7%)
Time from initial diagnosis, months[b], median (IQR)	15.3 (10.8–23.3)	15.9 (10.8–25.5)	11.2 (8.3–18.3)
Differentiation grade			
Well differentiated	1 (2%)	0	1 (7%)
Moderately differentiated	25 (56%)	16 (59%)	6 (43%)
Poorly differentiated	15 (33%)	9 (33%)	6 (43%)
Unknown	4 (9%)	2 (7%)	1 (7%)
Histological classification			
Adenocarcinoma	45 (100%)	27 (100%)	14 (100%)
Metastatic sites[c], *N*			
Visceral	44	28	11
Non-visceral	57	32	21
Tumour size, mm, median (IQR)	48 (33–80)	44 (25–64)	53 (34–92)
Number of prior systemic treatments			
1 line[d]	26 (58%)	16 (59%)	8 (57%)
2 lines	12 (27%)	8 (30%)	3 (21%)
≥3 lines	7 (15%)	3 (11%)	3 (21%)
Type of prior systemic treatments			
Prior chemotherapy	45 (100%)	27 (100%)	14 (100%)
Prior radiotherapy	3 (7%)	1 (4%)	1 (7%)
Prior Trastuzumab treatment	23 (51%)	16 (59%)	5 (36%)

Data are expressed as count (percentage) unless otherwise specified.
IQR: interquartile range; n: count.
[a] 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.
[b] Time from initial diagnosis was calculated from the date of signing the informed consent form to the date of initial diagnosis.
[c] A patient may have more than one metastatic site and may have both visceral and non-visceral metastasis.
[d] Adjuvant/neoadjuvant therapy was considered one prior line of systemic therapy when tumour recurrence or metastasis occurred within ≤24 weeks after the prior adjuvant/neoadjuvant therapy.

meeting the threshold ORR (20%) was dismal even if the low-level HER2 cohort was fully enrolled. Therefore, the enrolment of the low-level HER2 cohort was closed according to the SMC's suggestion to protect the best interest of patients with low-level HER2 expression.

A subgroup analysis for the ORR was performed based on sex, age, liver metastasis status, number of prior lines of systemic treatment and prior treatment with Trastuzumab (for the high-level HER2 cohort). No significant differences in ORRs were observed across different subgroups (Supplementary Fig. S1). In the high-level HER2 cohort, seven out of 14 patients who had progressed on the prior Trastuzumab treatment reached partial responses, resulting in an ORR of 50% (95% CI 23%–77%), similar to patients who were naïve to Trastuzumab (ORR 64%, 95% CI 31%–89%). In these patients with disease progression after prior Trastuzumab treatment, the median PFS was 5.5 months (95% CI 1.5–11.0), and median OS was 14.9 months (95% CI 11.0–NE) (Supplementary Table 1). Furthermore, efficacy results in relation to the dose levels are shown in Supplementary Table 2. The distribution into two cohorts was reclassified after the centralised HER2 testing; four patients locally tested as low-level HER2 were re-assessed as no-expression since their centrally tested HER2 results were IHC0 and ISH negative; one patient tested as high-level HER2 at the local site was reclassified to low-level HER2 cohort. Therefore, a sensitivity analysis was performed on efficacy outcomes according to the locally tested HER2 results (Supplementary Table 3), showing consistent results with the primary analysis based on the centralised testing.

Table 2
Tumour response by HER2 level (efficacy analysis set).

	High-level HER2 (n = 25)	Low-level HER2 (n = 14)
Best response		
Complete response	0	0
Partial response	14 (56%)	2 (14%)
Stable disease	5 (20%)	2 (14%)
Progressive disease	5 (20%)	10 (71%)
Not evaluable	1 (4%)	0
Confirmed objective response, n (%; 95% CI)	14 (56%; 35%–76%)	2 (14%; 2%–43%)
Confirmed disease control[a], n (%; 95% CI)	19 (76%; 55%–91%)	4 (29%; 8%–58%)
Confirmed clinical benefit[b], n (%; 95% CI)	18 (72%; 51%–88%)	3 (21%; 5%–51%)
Duration of response, months, Median (95% CI)	9.7 (4.2–NE)	6.2 (3.2–NE)
Time to response[c], months, Median (IQR)	1.4 (1.4–1.5)	4.2 (2.8–5.7)

Data are expressed as count (percentage) unless otherwise specified.
Efficacy analysis set included all patients who received at least one dose of the study drug, and for whom both baseline and post-treatment tumour response data were available.
IQR: Interquartile range; n: count; NE: not evaluable.
[a] Disease control was calculated as the proportion of patients who reached complete response, partial response or stable disease for at least six weeks.
[b] Clinical benefit was calculated as the proportion of patients who reached complete response, partial response or stable disease for at least 12 weeks.
[c] Time to response was calculated for patients who achieved a confirmed objective response.

3.4. Safety

The median duration of treatment was 6.2 weeks (IQR 3.6–26.4) in the 10 mg/kg QW group, 26.8 weeks (IQR 5.9–48.0) in the 20 mg/kg Q2W group and 17.9 weeks (IQR 5.9–36.0) in the 30 mg/kg Q3W group (Supplementary Table 4). TEAEs (>10% of patients) for all 45 patients are summarised in Table 3. In total, 42 (93%) patients experienced at least one TEAE. Grade ≥ 3 TEAEs were reported in 14 (31%) patients, in which only one case of hyperuricemia was rated as grade 4, and no grade 5 TEAEs occurred. Gastrointestinal disorders were the most common class of TEAEs (Table 3). The most common TEAEs were increased aspartate aminotransferase (16, 36%), decreased weight (15, 33%), anaemia (15, 33%), increased alanine aminotransferase (11, 24%) and diarrhoea (10, 22%), which were all mild to moderate (Table 3). TEAEs led to dose interruption were observed in seven (16%) patients (Supplementary Table 5) and discontinuation in two (4%) patients (one grade 2 upper abdominal pain, one grade 3 infusion-related reaction) (Supplementary Table 6).

TRAEs were observed in 37 (82%) patients, and only four patients reported grade 3 TRAEs (Supplementary Table 7). No grade 4 or 5 TRAEs were reported. The most common TRAEs were increased aspartate aminotransferase (12, 27%), increased alanine aminotransferase (9, 20%), rash (7, 16%), anaemia (7, 16%) and infusion-related reaction decreased white (7, 16%) (Supplementary Table 7).

We observed an incidence of 20% for serious adverse events. Four cases of treatment-related serious adverse events were reported by three (7%) patients, which were upper gastrointestinal haemorrhage, interstitial lung disease, renal hydrocele and ureteral stenosis (one each) (Supplementary Table 8). Cardiotoxicity infrequently happened in the total population. Only one (2%) grade 1 left ventricular failure and one (2%) grade 1 ventricular arrhythmia were observed; both were mild and transient (Supplementary Table 9). At data cutoff, a total of 22 deaths occurred during our study; 19 were due to disease progression, and three were due to unknown causes. No deaths were attributed to KN026.

4. Discussion

This study assessed the efficacy and safety of KN026 as second-line or subsequent treatment in advanced HER2-expressing GC/GEJC. In the high-level HER2 cohort, KN026 showed an encouraging ORR of 56% (95% CI 35%–76%) and a median DOR of 9.7 months (95% CI 4.2–NE), which met the primary end-point. In the low-level HER2 cohort, KN026 demonstrated anti-tumour activity comparable with systemic chemotherapy in the later-line treatment, but no meaningful improvement in ORR was detected [5]. Therefore, the patients with high-level HER2 expression were recommended as the target population for KN026 treatment. Overall, KN026 has a well-tolerated safety profile; most TRAEs were low in grade and transient.

For decades, systemic chemotherapy has been the mainstay of later-line treatment in advanced GC/GEJC. One milestone in this setting was the approval of the combination of Ramucirumab and paclitaxel, which significantly increased the median OS to 9.6 months compared to that of the paclitaxel monotherapy (median OS of 7.4 months) [12]. Although the cross-trials comparison may be biased, in the generally similar later-line setting, KN026 demonstrated a similar median

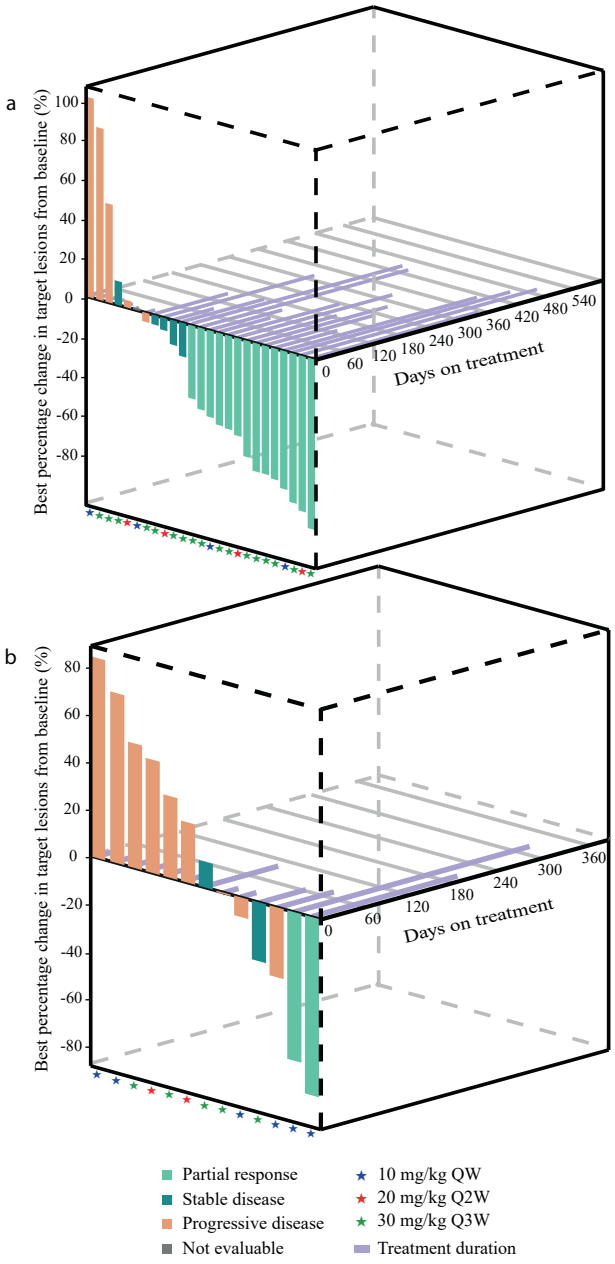

Fig. 2. 3D waterfall plot of best percent change from baseline in the sum of longest diameters of target lesions per RECIST 1.1. (a) The high-level HER2 cohort, (b) the low-level HER2 cohort. QW: once a week, Q2W: once every two weeks, Q3W: once every three weeks. HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumours.

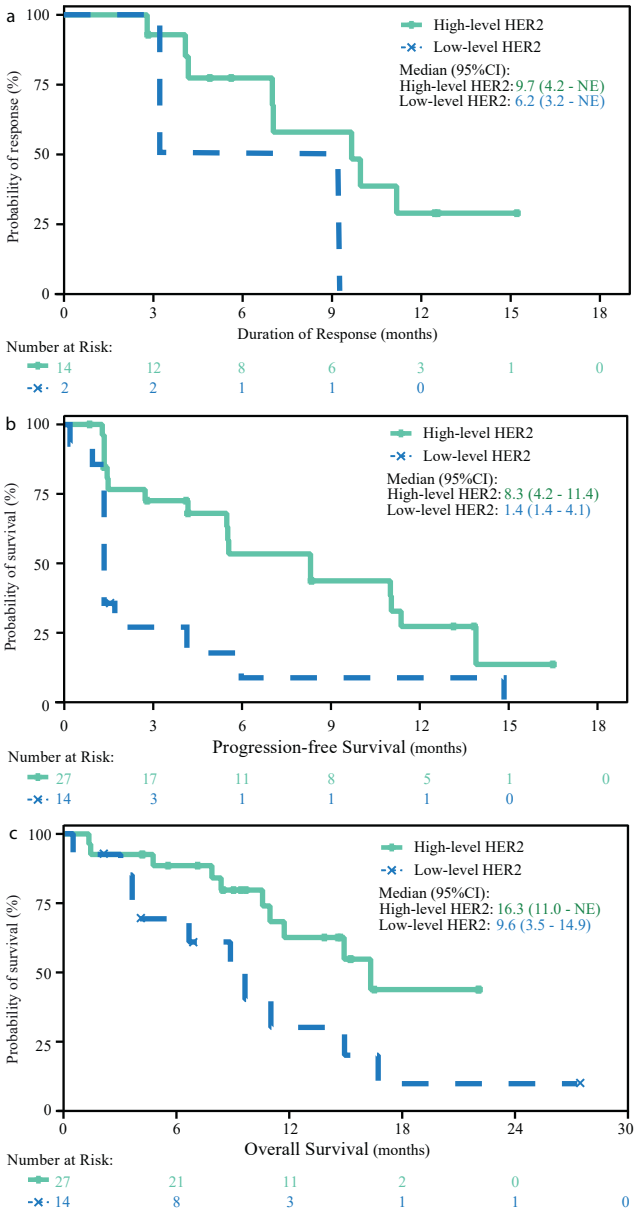

Fig. 3. (a) Kaplan–Meier curve of duration of response (efficacy analysis set). Six patients in the high-level HER2 cohort and no one in the low-level HER2 cohort were censored (tick marks). (b) Kaplan–Meier curve of progression-free survival (safety analysis set). Ten patients in the high-level HER2 cohort and one in the low-level HER2 cohort were censored (tick marks). (c) Kaplan–Meier curve of overall survival (safety analysis set). Seventeen patients in the high-level HER2 cohort and four in the low-level HER2 cohort were censored (tick marks). CI: confidence interval; HER2, human epidermal growth factor receptor 2; NE: not evaluable.

OS of 9.6 months (95% CI 3.5–14.9) in the low-level HER2 cohort. However, the ORR of 14% with KN026 was lower than that of Ramucirumab plus paclitaxel (28%).

Developing new later-line treatment in advanced HER2-positive GC/GEJC seemed more challenging. Lapatinib plus paclitaxel (the TyTAN study), Trastuzumab emtansine (the GATSBY study) and Trastuzumab plus paclitaxel (the T-ACT study) all failed to meet their primary efficacy end-point [20–22].

Several potential resistance mechanisms may explain these negative results. The primary and acquired resistance after the first-line Trastuzumab therapy could be explained mainly from three aspects: the alterations in HER2 biology, the incomplete inhibition of HER2 signalling and the co-occurrence of other oncogenic mutations or pathways. For the HER2 receptor itself, the

Table 3
Treatment-emergent adverse events in >10% of patients (safety analysis set).

	10 mg/kg QW (n = 12)		20 mg/kg Q2W (n = 6)		30 mg/kg Q3W (n = 27)	
	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Any	12 (100%)	5 (42%)	6 (100%)	2 (33%)	24 (89%)	7 (26%)
Investigations						
Increased aspartate aminotransferase	6 (50%)	0	3 (50%)	0	7 (26%)	0
Decreased weight	3 (25%)	0	4 (67%)	0	8 (30%)	0
Increased alanine aminotransferase	2 (17%)	0	2 (33%)	0	7 (26%)	0
Decreased white blood cell count	3 (25%)	0	2 (33%)	0	3 (11%)	0
Decreased platelet count	1 (8%)	0	0	0	4 (15%)	0
Decreased neutrophil count	1 (8%)	0	2 (33%)	0	2 (7%)	0
Increased blood pressure	0	0	0	0	3 (11%)	1 (4%)
Increased γ-glutamyltransferase	0	0	0	0	2 (7%)	1 (4%)
Decreased lymphocyte count	0	0	0	0	2 (7%)	1 (4%)
Gastrointestinal disorders						
Diarrhoea	2 (17%)	0	2 (33%)	0	6 (22%)	0
Vomiting	3 (25%)	0	1 (17%)	0	2 (7%)	0
Upper abdominal pain	1 (8%)	0	2 (33%)	0	2 (7%)	0
Flatulence	0	0	0	0	1 (4%)	1 (4%)
Abdominal discomfort	1 (8%)	1 (8%)	0	0	0	0
Intestinal obstruction	1 (8%)	1 (8%)	0	0	0	0
Haematemesis	1 (8%)	1 (8%)	0	0	0	0
Oesophageal obstruction	0	0	1 (17%)	1 (17%)	0	0
Dysphagia	1 (8%)	1 (8%)	0	0	0	0
Metabolism and nutrition disorders						
Hypokalaemia	3 (25%)	0	1 (17%)	0	4 (15%)	0
Hypoalbuminaemia	4 (33%)	0	1 (17%)	0	2 (7%)	0
Hypocalcaemia	2 (17%)	0	0	0	3 (11%)	0
Decreased appetite	3 (25%)	0	0	0	2 (7%)	0
Hyperuricaemia	1 (8%)	1 (8%)	0	0	2 (7%)	0
Blood and lymphatic system disorders						
Anaemia	5 (42%)	0	2 (33%)	0	8 (30%)	0
Injury, poisoning and procedural complications						
Infusion-related reaction	1 (8%)	1 (8%)	2 (33%)	0	4 (15%)	0
Radiation gastroenteritis	0	0	0	0	1 (4%)	1 (4%)
Humerus fracture	0	0	0	0	1 (4%)	1 (4%)
Skin and subcutaneous tissue disorders						
Rash	1 (8%)	0	2 (33%)	0	4 (15%)	0
Infections and infestations						
Upper respiratory tract infection	2 (17%)	0	2 (33%)	0	2 (7%)	0
Hepatobiliary disorders						
Abnormal hepatic function	1 (8%)	0	1 (17%)	0	2 (7%)	1 (4%)
Renal and urinary disorders						
Renal hydrocele	0	0	1 (17%)	1 (17%)	0	0
Vascular disorders						
Hypertension	0	0	0	0	2 (7%)	1 (4%)

Data are expressed as count (percentage).
Treatment-emergent adverse events are summarised by primary System Organ Class and Preferred Term according to MedDRA for events occurring in >10% of patients in the safety analysis set and all ≥grade 3 events that occurred.
Safety analysis set included all patients who received at least one dose of the study drug. QW: once a week, Q2W: once every two weeks, Q3W: once every three weeks.

distribution of the HER2 receptor was mainly basolateral, uneven, and the HER2 receptor might be lost partially or entirely after the first-line Trastuzumab therapy, resulting in a decreased antibody binding in GC [23–25]. Therefore, a new HER2 antibody with higher binding avidity is needed in GC. From the HER2 signalling aspect, Trastuzumab only blocks the ligand-independent HER2 signalling leading to incomplete inhibition of HER2 pathways, which was also a contributor to primary resistance to Trastuzumab [26]. Induced activation of compensating oncogenic pathways has also been implicated as a means of acquired resistance [27,28]. A total blockade of HER2 signalling with dual-antibody therapy or bispecific antibody may reduce the primary resistance and overcome the acquired resistance after the first-line Trastuzumab treatment.

Although the previous JACOB study failed to confer significant improvement in OS, an improvement in PFS and the ORR was observed, strongly suggesting an increased clinical benefit of Pertuzumab and Trastuzumab combination [16]. In principle, the biparatopic antibody KN026 may possess a few advantages over

Pertuzumab and Trastuzumab combination [17]. Regarding binding avidity, KN026 has demonstrated an increased maximum binding density on HER2 than Trastuzumab and Pertuzumab because two KN026 molecules could bind on one HER2 receptor, resulting in more potent inhibition of tumour growth in the preclinical study [17]. In addition, KN026 may offer a more robust receptor-clustering effect than monospecific antibodies, facilitating rapid receptor internalisation and signal down regulation [31].

The last year has witnessed the successful establishment of Trastuzumab deruxtecan as the new second or later-line treatment in advanced HER2-positive GC [32], based on the impressive results of the DESTINY-Gastric01 study [13]. Trastuzumab deruxtecan provided a stunning anti-tumour efficacy as a third-line treatment with an ORR of 51%, median PFS of 5.6 months, and median OS of 12.5 months [13]. Also, in the last year, RC48 was granted conditional marketing approval in China as a third-line treatment for advanced HER2-positive GC [33]. This conditional approval was based on the results of a pivotal phase 2 study that showed an ORR of 25% with median response duration of about five months [14]. Consistent with these studies, KN026 also showed promising efficacy outcomes in the later-line setting by targeting potential resistance mechanisms and improving the drug potency. Moreover, high-level HER2 patients who progressed on the prior Trastuzumab treatment demonstrated an ORR of 50%, median PFS of 5.5 months and median OS of 14.9 months. In terms of safety, KN026 was associated with better safety outcomes. Serious adverse events occurred in 20% of patients having KN026, while serious adverse reactions were reported in 44% of patients receiving Trastuzumab deruxtecan and 36% of patients having RC48 [14,34]. Cardiotoxicity is associated with HER2-targeted therapy [35]. In our study, the cardiotoxicity of special interest was reported by two (4%) patients; but decreased left ventricular ejection fraction was observed in 8% of patients in DESTINY-Gastric01 [34]. It was not entirely fair to compare the safety outcomes between KN026, RC48 and Trastuzumab deruxtecan since cytotoxin was not involved in the treatment with KN026. The absence of a cytotoxin component makes KN026 different from Trastuzumab deruxtecan and RC48, which is why KN026 has the advantage of low toxicity. Moreover, the favourable safety profile of KN026 provided feasibility for combining with other anti-tumour agents (such as chemo agents or immunotherapy agents). A phase 2–3 study of KN026 combined with chemotherapy versus chemotherapy alone in the second-line treatment of HER2 positive advanced or metastatic GC is launched recently (NCT05427383) to further investigate the potential of KN026 in combination therapy. In addition, an exploratory biomarker analysis of patients' blood ctDNA is included in our phase 2–3 study to explore the correlation between biomarkers and efficacy of KN026.

Our study presented several limitations. First, our study adopted a single-arm design with no control group; the number of patients was relatively small, especially when patients were split into subgroups. Some of our results should be interpreted with caution. Second, the primary end-point, ORR, was only assessed by investigators but not by an independent review committee. Third, for most of our patients, HER2 level was assessed using archived samples collected before progression on prior trastuzumab treatment, which may lead to a possible loss of HER2 overexpression. Fourth, Trastuzumab was not contained in previous treatment in a few patients due to no coverage of Trastuzumab in their medical insurance, which poses some limitations in judging the effectiveness. Additionally, we did not conduct a quality-of-life assessment, and we did acknowledge that anti-tumour treatment is not only about clinical response but also aims to improve patients' well-being.

In conclusion, the encouraging results from this single-arm phase 2 study showed that KN026 has promising anti-tumour efficacy in advanced HER2-positive GC/GEJC with a well-tolerated safety profile. The favourable anti-tumour efficacy was also observed in HER2-positive patients who had progressed on the prior Trastuzumab treatment. Our results indicated that KN026 might become a cytotoxic drug-free option and have a great potential to develop combination therapy for advanced HER2-positive GC/GEJC patients who had received at least one line of standard treatment.

Author contributions

Jianming Xu: Conceptualization, data curation, supervision, funding acquisition, investigation, methodology, project administration, writing-original draft, writing-review and editing.

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Rongrui Liu: Data curation, investigation, methodology, writing-review and editing.

Jun Wu: Data curation, investigation, methodology, writing-review and editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YS and QW are employees of CSPC ZhongQi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. BG and XHL are employees of Alphamab Oncology Ltd. All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.10.004.

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