Abstract 354: HLX22 plus HLX02 and XELOX for first-line treatment of HER2-positive locally advanced or metastatic gastric/gastroesophageal junction cancer: a randomized, double-blind, multicenter phase 2 study

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Background

- Gastric/gastroesophageal junction (G/GEJ) cancer represents a global healthcare challenge. With more than 1 million new cases estimated in 2020, it ranked fifth among all cancers.[1]
- G/GEJ cancer is often diagnosed at the advanced stage, and the prognosis of advanced G/GEJ cancer is poor, with a 5-year relative survival rate of only 6%.[2, 3]
- Around 12–23% of patients with gastric cancer have HER2-positive disease, whose prognosis used to be worse than patients with HER2-negative disease.[2, 4]
- This is a randomized phase 2 study evaluating the efficacy and safety of HLX22 (a monoclonal antibody targeting HER2) in combination with HLX02 (a trastuzumab biosimilar) and XELOX as first-line treatment for HER2-positive locally advanced or metastatic G/GEJ adenocarcinoma.

Methods

- This ongoing, randomized, double-blinded, phase 2 trial screened patients at 28 study sites in China. The study consisted of two stages, of which Stage 1 was a single-arm safety run-in study. Stage 2 was further divided into a double-blind part (Part 1) and an open-label part (Part 2). The present report will focus on Part 1 of Stage 2.
- In Part 1, patients were randomized 1:1:1 to receive different doses of HLX22 plus HLX02 and XELOX or HLX22 placebo plus HLX02 and XELOX (Figure 1).
- Tumor imaging by computed tomography or magnetic resonance imaging was scheduled at screening, once every 6 weeks for 48 weeks from the first dose of study drugs, and every 9 weeks thereafter. Tumor response was assessed per RECIST v1.1.

Figure 1. Study design

Key inclusion criteria:

- Age 18–80 years; ECOG PS 0 or 1;
- Histologically confirmed locally advanced or metastatic HER2-positive G/GEJ adenocarcinoma that could not be cured by surgery, and had not received prior systemic antitumor therapy for this advanced or metastatic disease;
- Should be confirmed by the central laboratory as HER2-positive (i.e., HER2 3+ by IHC or HER2 2+ by IHC and positive by FISH).

Group A Q3W
- HLX22[a], IV, 25 mg/kg
- HLX02[b], IV, 6 mg/kg
- XELOX[c]

Group B Q3W
- HLX22[a], IV, 15 mg/kg
- HLX02[b], IV, 6 mg/kg
- XELOX[c]

Group C Q3W
- HLX22 placebo[d], IV
- HLX02[b], IV, 6 mg/kg
- XELOX[c]

Primary endpoints:
PFS and ORR assessed by IRRC per RECIST v1.1

Secondary endpoints:

- PFS assessed by investigator
- ORR assessed by investigator
- OS
- DOR
- Quality of life
- Safety
- Pharmacokinetics
- Immunogenicity

[a] Up to 2 years; [b] Initial loading dose of 8 mg/kg; [c] IV oxaliplatin (up to 8 cycles) + oral capecitabine (up to 2 years); [d] Dose equivalent to HLX22 25 mg/kg. DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IRRC, independent radiological review committee; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W: every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

- Between November 29, 2021 and June 6, 2022, 82 patients were screened in Part 1. 53 patients (ITT population) were enrolled and randomized to group A (n=18), B (n=17), and C (n=18).
- As of July 30, 2023 (data cutoff), the median follow-up duration was 14.3 months.
- The median age of all patients was 60.0 years. 30 (56.6%) patients had an ECOG PS score of 1. All patients had stage IV disease, and had distant metastases.

References

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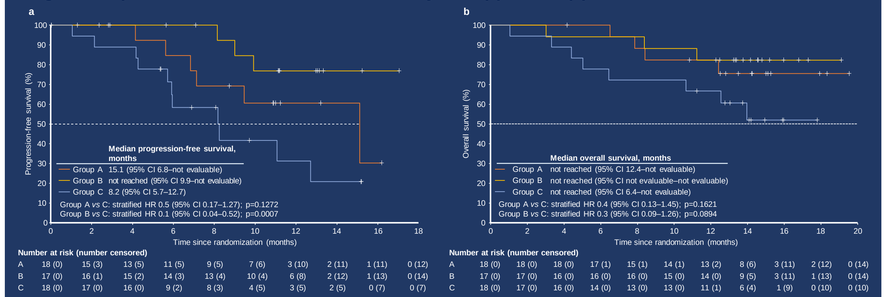
Adding HLX22 to HLX02 + XELOX improved survival and antitumor response in patients with HER2-positive G/GEJ cancer in the first-line setting.

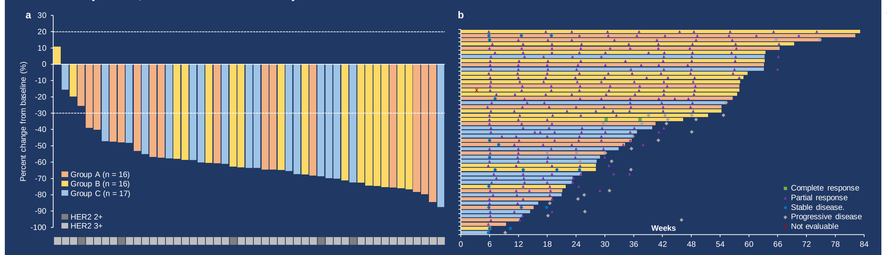
Efficacy

Figure 2. Kaplan–Meier curves of PFS as assessed by IRRC (a) and OS (b)



CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee.

Figure 3. Antitumor activity assessed by IRRC per RECIST v1.1 in the ITT population. (a) Waterfall plot of best percentage change from baseline in target lesion size. (b) Swimmer plot showing time on treatment, time to best response, and duration of response.



Excluding patients with no post-baseline tumor assessment. IRRC, independent radiological review committee.

Table 2. Tumor response[a] assessed by IRRC per RECIST v1.1

	Group A (n = 18)	Group B (n = 17)	Group C (n = 18)
Complete response	0	1 (5.9)	0
Partial response	14 (77.8)	13 (76.5)	16 (88.9)
Stable disease	1 (5.6)	2 (11.8)	0
Progressive disease	0	0	1 (5.6)
NE	3 (16.7)	1 (5.9)	1 (5.6)
ORR, % (95% CI)	77.8 (52.4–93.6)	82.4 (56.6–96.2)	88.9 (65.3–98.6)
Odds ratio[b] (95% CI)	0.4 (0.07–2.73)	0.6 (0.09–4.32)	NA
ORR at week 18, % (95% CI)	55.6 (30.8–78.5)	82.4 (56.6–96.2)	66.7 (41.0–86.7)
ORR at week 36, % (95% CI)	44.4 (21.5–69.2)	64.7 (38.3–85.8)	27.8 (9.7–53.5)
ORR at week 48, % (95% CI)	38.9 (17.3–64.3)	58.8 (32.9–81.6)	16.7 (3.6–41.4)
DCR, % (95% CI)	83.3 (58.6–96.4)	94.1 (71.3–99.9)	88.9 (65.3–98.6)
Odds ratio[b] (95% CI)	0.6 (0.09–4.32)	2.1 (0.17–26.33)	NA
Median DOR, month (95% CI)	12.4 (5.5–NE)	NR (8.6–NE)	6.8 (4.4–NE)
Hazard ratio[b] (95% CI)	0.6 (0.20–1.62)	0.1 (0.02–0.50)	NA

[a] Confirmed tumor response; [b] Odds ratio and hazard ratio were estimated between group A and group C, as well as between group B and group C. CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRRC, independent radiological review committee; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate.

- Baseline demographics and characteristics of group A , B and C are shown in Table 1.

Table 1. Patient demographics and baseline characteristics

	Group A (n = 18)	Group B (n = 17)	Group C (n = 18)
Median age, years (range)	63.0 (49–74)	57.0 (26–71)	62.0 (28–72)
Male, n (%)	13 (72.2)	16 (94.1)	15 (83.3)
Median BMI, kg/m^2 (range)	21.2 (17.6–27.8)	24.1 (19.0–29.4)	22.2 (18.6–27.5)
ECOG PS, n (%)			
0	9 (50.0)	6 (35.3)	8 (44.4)
1	9 (50.0)	11 (64.7)	10 (55.6)
LVEF, median, %(range)	62.0 (58–69)	65.0 (56.5–74)	63.8 (61–71)
≥ 55%, n (%)	18 (100)	17 (100)	18 (100)
HER2 IHC, n (%)			
2+	2 (11.1)	1 (5.9)	2 (11.1)
3+	16 (88.9)	16 (94.1)	16 (88.9)
HER2 FISH (required for IHC 2+ tumors), n (%)			
Positive	17 (94.4)	11 (64.7)	12 (66.7)
Negative	0	0	0
Unsure	0	0	1 (5.6)
Not tested	1 (5.6)	6 (35.3)	5 (27.8)
Tumor site, n (%)			
Gastric	17 (94.4)	13 (76.5)	14 (77.8)
Gastroesophageal junction	1 (5.6)	4 (23.5)	4 (22.2)
Previous gastrectomy, n (%)	2 (11.1)	4 (23.5)	0
Previous chemotherapy, n (%)	2 (11.1)	1 (5.9)	0

Safety

- Safety results in group A , B and C are summarized in Table 3.
- HLX22 + HLX02 + XELOX as first-line therapy was well tolerated in HER2-positive G/GEJ cancers.

Table 3. Summary of adverse events

n (%)	Group A (n = 18)		Group B (n = 17)		Group C (n = 18)	
Any TEAE	18 (100)		16 (94.1)		18 (100)	
Grade ≥3	13 (72.2)		7 (41.2)		8 (44.4)	
Grade 5	2 (11.1)		0		3 (16.7)	
Leading to treatment discontinuation	4 (22.2)		1 (5.9)		3 (16.7)	
Any TRAE	18 (100)		16 (94.1)		17 (94.4)	
Related to HLX22/placebo	17 (94.4)		15 (88.2)		11 (61.1)	
Grade ≥3	10 (55.6)		3 (17.6)		3 (16.7)	
Leading to treatment discontinuation	1 (5.6)		1 (5.9)		1 (5.6)	
Related to HLX02	18 (100)		16 (94.1)		12 (66.7)	
Grade 5	0		0		1 (5.6)	
Related to HLX22/placebo	0		0		1 (5.6)	
Related to HLX02	0		0		1 (5.6)	
Adverse event of special interest	6 (33.3)		11 (64.7)		3 (16.7)	
Infusion-related reaction	6 (33.3)		11 (64.7)		3 (16.7)	
Cardiac-related	1 (5.6)		1 (5.9)		0	
Most common TEAEs (≥ 40% in any group)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Neutrophil count decreased	13 (72.2)	3 (16.7)	11 (64.7)	2 (11.8)	10 (55.6)	2 (11.1)
White blood cell count decreased	13 (72.2)	4 (22.2)	9 (52.9)	0	11 (61.1)	1 (5.6)
Anemia	12 (66.7)	2 (11.1)	10 (58.8)	2 (11.8)	13 (72.2)	0
Platelet count decreased	10 (55.6)	5 (27.8)	13 (76.5)	3 (17.6)	15 (83.3)	2 (11.1)
Aspartate aminotransferase increased	8 (44.4)	1 (5.6)	9 (52.9)	0	4 (22.2)	0
Chills	5 (27.8)	0	9 (52.9)	0	2 (11.1)	0
COVID-19	4 (22.2)	0	7 (41.2)	0	1 (5.6)	0

AESI, adverse event of special interest; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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