Poster #493b

A randomized, double-blind, international phase 3 trial comparing HLX22 in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy with or without pembrolizumab for first-line treatment for HER2-positive locally advanced or metastatic G/GEJC

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Background

- Trastuzumab plus chemotherapy is the first-line systemic treatment for human epidermal growth factor receptor 2 (HER2)-positive advanced gastric or gastroesophageal junction cancer (G/GEJC)[1]. Treatment options also include pembrolizumab plus trastuzumab and chemotherapy[2] for patients whose tumors express programmed death ligand 1 (PD-L1; defined as combined positive score ≥ 1). However, survival outcomes remain unsatisfactory despite these advances.
- HLX22 is a novel anti-HER2 antibody targeting a different epitope than trastuzumab. HLX22 has shown promise in treating HER2-positive G/GEJC in the first-line setting[3,4]. In the phase 2 study HLX22-GC-201 (NCT04908813), 62 patients were randomly assigned to receive first-line HLX22 (15 mg/kg) or placebo combined with oxaliplatin and capecitabine (XELOX) and trastuzumab[4]. At respective median follow-up duration of 28.5 and 28.7 months, the median progression-free survival (PFS) was not reached (95% confidence interval [CI], 16.2–not evaluable) in the HLX22 group vs. 8.3 months (95% CI, 5.7–21.4) in the placebo group (hazard ratio 0.20, 95% CI, 0.09–0.54; **Figure 1**)[5]. The median PFS with HLX22 + trastuzumab + XELOX in HLX22-GC-201 was longer than the historical data of dual HER2 treatment and trastuzumab + chemotherapy, with or without pembrolizumab (**Figure 2**).

The HLX22-GC-301 phase 3 trial was initiated based on the promising results from HLX22-GC-201 phase 2 trial

Figure 1. Kaplan–Meier curve of PFS in the HLX22-GC-201 study

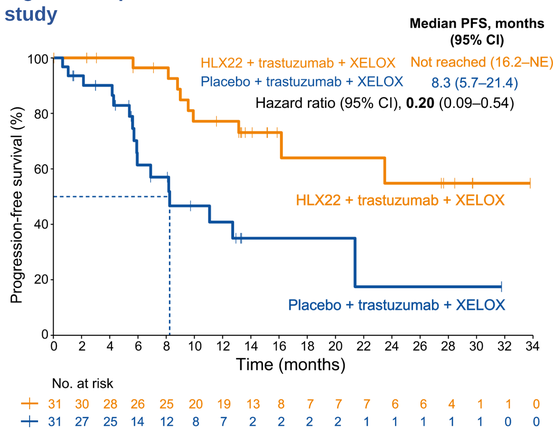
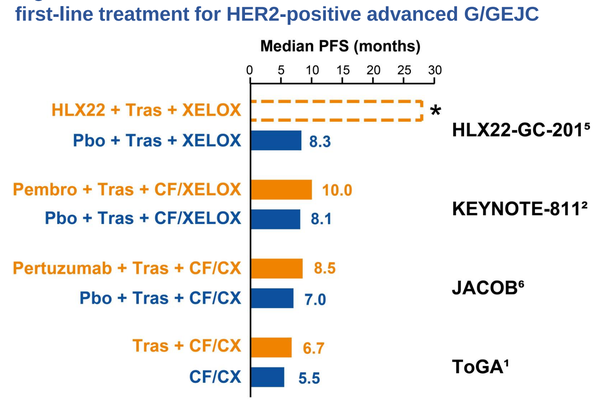


Figure 2. Median PFS in HLX22-GC0201 and other studies of first-line treatment for HER2-positive advanced G/GEJC



* Median PFS was not reached at 28.5 months of median follow-up.

CF, cisplatin and fluorouracil; CI, confidence interval; CX, cisplatin and capecitabine; G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; NE, not evaluable; Pbo, placebo; Pembro, pembrolizumab; PFS, progression-free survival; Tras, trastuzumab; XELOX, oxaliplatin and capecitabine.

- Here, we present HLX22-GC-301, an ongoing global, randomized, double-blind phase 3 study to evaluate HLX22 + trastuzumab + XELOX ± placebo for pembrolizumab vs. placebo for HLX22 + trastuzumab + XELOX ± pembrolizumab as first-line treatment for HER2-positive advanced G/GEJC (NCT06532006).

Objective

Primary

- To evaluate the efficacy of HLX22 in combination with trastuzumab + XELOX ± placebo for pembrolizumab vs. placebo for HLX22 + trastuzumab + XELOX ± pembrolizumab as first-line treatment for patients with locally advanced/metastatic G/GEJC.

Secondary

- To evaluate the safety of HLX22 in combination with trastuzumab + XELOX ± placebo for pembrolizumab vs. placebo for HLX22 + trastuzumab + XELOX ± pembrolizumab as first-line treatment for patients with locally advanced/metastatic G/GEJC.
- To investigate the pharmacokinetic characteristics of HLX22.

Method

Study design

Key eligibility criteria

1. Aged ≥ 18 years.
2. **Treatment-naïve**, advanced unresectable, **HER2-positive** G/GEJ adenocarcinoma
3. Life expectancy ≥ 6 months
4. HER2 and PD-L1 expression status assessed by central lab

N = 550

R 1:1

- HLX22 (15 mg/kg) + trastuzumab + XELOX ± placebo for pembrolizumab*, Q3W
- Placebo for HLX22 + trastuzumab + XELOX ± pembrolizumab*, Q3W

Primary Endpoints

- **PFS** (by BICR per RECIST 1.1)
- **OS**

Secondary Endpoints

- PFS by investigator
- ORR by BICR or investigator
- DOR by BICR or investigator
- PFS2 by investigator
- Safety
- Pharmacokinetics
- Immunogenicity
- Quality of life

Stratification factors:

- HER2 status (3+ vs. 2+)
- Region (Asia vs. Europe/North America vs. the rest of the world)
- Primary cancer site (G vs. GEJ)
- PD-L1 status (CPS < 1 vs. 1 ≤ CPS < 10 vs. 10 ≤ CPS)

** For where pembrolizumab is approved for first-line treatment of advanced G/GEJC.*
BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; G, gastric; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, second progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

Current status

Key eligibility criteria

Inclusion	Exclusion
• Histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive G/GEJ adenocarcinoma; • Measurable disease as assessed by BICR according to the RECIST 1.1; the target lesion must not be a bone metastatic lesion only; • ECOG performance status of 0 or 1; • Had HER2-positive tumor, defined as either IHC 3+ or IHC 2+ in combination with ISH+ or FISH+, as assessed by a central laboratory on a primary or metastatic tumor.	• Had other malignant tumors within 2 years prior to randomization; • Received prior treatment for locally advanced unresectable or metastatic G/GEJC; • Received prior HER2-targeted therapy; • Active gastrointestinal bleeding of grade ≥2 according to NCI CTCAE v5.0; • Presence of CNS metastases and/or carcinomatous meningitis; • Had class III or IV cardiac insufficiency according to NYHA classification or LVEF < 55% on color Doppler echocardiogram.

BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; G/GEJ, gastric/gastroesophageal junction; G/GEJC, G/GEJ cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LVEF, left ventricular ejection fraction; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association.

Assessment and follow-up

Assessment	Detail
Tumor response	• Response assessments, including CT/MRI and bone imaging per clinical need, will be performed at baseline and every 6 weeks since randomization until any criteria for discontinuation are met.
Adverse events	• Adverse events will be monitored and assessed by the investigator throughout the study and for 90 days after the last dose of the study treatment or until the initiation of a new anti-cancer treatment, whichever comes first. • Severity will be graded per NCI CTCAE v5.0.

CT, computed tomography; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Analyses

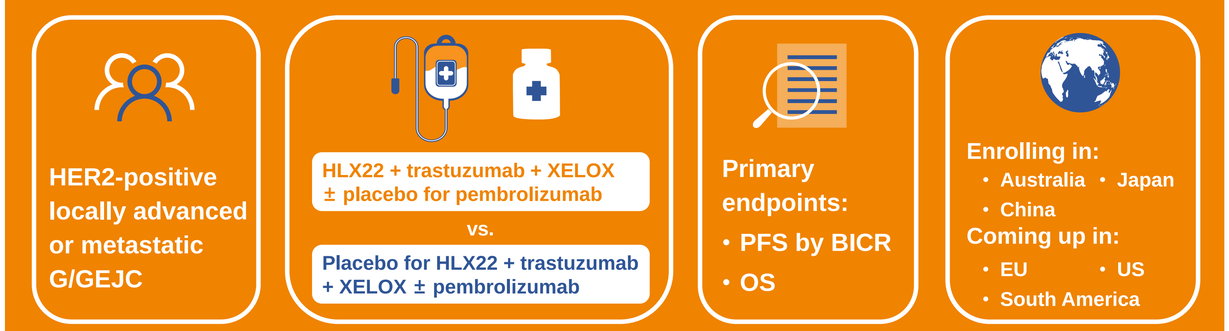
Two interim analyses and one final analysis are planned for this study.

- **The 1st interim analysis** (interim analysis of PFS) will be performed when 50% of expected PFS events (146 events) are observed and serves to allow early stopping of the study for futility of PFS.
- **The 2nd interim analysis** (interim analysis of OS and final analysis of PFS) will be performed when all expected PFS events (292 events) are observed and will evaluate the superiority of HLX22 group vs. control group in PFS and OS.
- **The final analysis** (final analysis of OS) will be performed when all expected OS events (291 events) are observed and will evaluate the superiority of HLX22 group vs. control group in OS.

Analysis	Detail
Efficacy	• Efficacy analyses will be conducted in the intention-to-treat set, which consists of all randomized patients. • Hypothesis testing of differences in OS and PFS between treatment groups will be conducted with the stratified log-rank test. • Median OS and PFS will be estimated using the Kaplan-Meier method; HRs and associated 95% CIs will be calculated using the stratified Cox proportional hazards model. • ORR will be estimated using the Clopper-Pearson method. • Median DOR and PFS2 will be estimated using the Kaplan-Meier method.
Safety	• Safety analyses will be conducted in the safety set, which consists of all patients who received at least one dose of study treatment. • Adverse events will be summarized descriptively.
Pharmacokinetics and immunogenicity	• Serum concentration of HLX22 will be summarized descriptively. • Incidence rates of anti-drug antibody and neutralizing antibody will be summarized descriptively.

CI, confidence interval; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival.

Key takeaways



- **Dual HER2 blockade with HLX22 and trastuzumab combined with XELOX has shown promising efficacy in a phase 2 trial in patients with HER2-positive advanced G/GEJC.**
- **The phase 3 study of HLX22 (HLX22-GC-301) is ongoing. The treatment regimen of HLX22 + trastuzumab + XELOX will alter the treatment landscape of HER2-positive G/GEJC once the study is successful.**

References

1. Lancet. 2010. 376(9742):687.
2. Lancet. 2023. 402(10418):2197.
3. J Transl Med. 2024. 22(1):641.
4. Med. 2024. 5(10):1255.
5. J Clin Oncol. 2025 43(suppl 4):abstr 440.
6. Lancet Oncol. 2018. 19(10):1372.

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ClinicalTrials.gov registration

NCT06532006

Scan to learn more

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