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ORIGINAL RESEARCH ARTICLE

Efficacy, Safety, and Immunogenicity of HLX02 Compared with Reference Trastuzumab in Patients with Recurrent or Metastatic HER2-Positive Breast Cancer: A Randomized Phase III Equivalence Trial

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Abstract

Background HLX02 is an approved biosimilar of trastuzumab.

Objective This study aimed to evaluated the efficacy, safety, and immunogenicity of HLX02 compared with reference trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic breast cancer.

Patients and Methods This randomized, double-blind, phase III study was conducted at 89 centers in China, the Philippines, Poland, and Ukraine. Eligible patients were randomized (1:1) to receive HLX02 or European Union (EU)-sourced trastuzumab (initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for up to 12 months) in combination with docetaxel intravenously. The primary endpoint was overall response rate up to week 24 (ORR_{24}). Equivalence was declared if the 95% confidence interval (CI) of difference was within ± 13.5%. Safety and immunogenicity were evaluated in patients who received at least one dose of study medication.

Results Between 11 November 2016 and 10 July 2019, a total of 649 patients were enrolled. The ORR_{24} was 71.3 and 71.4% in the HLX02 ($n = 324$) and EU-trastuzumab ($n = 325$) groups, with a difference of − 0.1% (95% CI − 7 to 6.9), which fell entirely in the predefined equivalence margins. No statistically significant differences were observed in all secondary efficacy analyses. Safety profiles and immunogenicity were comparable in HLX02 and EU-trastuzumab groups. In total, 98.8% of patients in each group experienced at least one treatment-emergent adverse event (TEAE), 23.8 and 24.9% experienced serious TEAEs, and 0.6% in each group had antidrug antibodies.

Conclusions Among patients with HER2-positive recurrent or metastatic breast cancer, HLX02 demonstrated equivalent efficacy and similar safety and immunogenicity to reference trastuzumab.

Clinical Trial Registration Chinadrugtrials.org CTR20160526 (12 September 2016), ClinicalTrials.gov NCT03084237 (20 March 2017), EudraCT 2016-000206-10 (27 April 2017).

Plain Language Summary

Trastuzumab is a biologic drug used to treat patients with certain types of breast cancer and stomach cancer. Biosimilars are medications that are almost identical to and indistinguishable from original biologic drugs but usually less expensive

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Binghe Xu, Qingyuan Zhang contributed equally to this work.

Investigators of HLX02-BC01 are listed in Supplementary Table 1.

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and more accessible. The main purpose of this study was to evaluate the efficacy (treatment effects) of HLX02 (trastuzumab biosimilar) compared with reference trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic breast cancer. Other objectives were to evaluate the safety of HLX02 by monitoring adverse events and assessing its potential to induce antibody production (which can prevent a drug from being effective). Patients with HER2-positive recurrent or metastatic breast cancer were randomly allocated to receive HLX02 ($n = 324$) or European Union (EU)-sourced trastuzumab ($n = 325$). Study drugs (HLX02 or EU-trastuzumab) were given intravenously, with an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for up to 12 months. Statistical analyses showed that HLX02 was equivalent to trastuzumab in efficacy evaluations. Adverse events observed in the HLX02 treatment group were consistent with those seen with trastuzumab in the current and previous clinical studies. Additionally, no statistically significant differences were seen in the tendency to stimulate antibody production between the two study drugs. To conclude, HLX02 and reference trastuzumab had similar efficacy and safety profiles. These data support the approval of HLX02 as a trastuzumab biosimilar.

Key Points

This is the first China-manufactured trastuzumab biosimilar investigated in a global setting.

This comparative phase III study demonstrated that HLX02 had equivalent efficacy, and the safety and immunogenicity profiles were similar to those of reference trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic breast cancer.

The results support the clinical development of HLX02 as an affordable treatment option for patients with HER2-positive breast cancer.

1 Introduction

As the most common cancer in women and the second most common cancer overall, more than 2 million new cases of breast cancer were reported worldwide in 2018 [1]. Approximately 20% of patients with breast cancer have human epidermal growth factor receptor 2 (HER2) overexpression [2–4], resulting in aggressive tumor cell growth, poor prognosis, unresponsiveness (to common therapies), and shorter survival [5, 6].

Trastuzumab (Herceptin®, Genentech/Roche, Inc.), a humanized monoclonal antibody targeting the extracellular domain of HER2, in combination with chemotherapy has greatly improved the treatment of metastatic HER2-positive breast cancer compared with chemotherapy alone (overall response rate [ORR] 50 vs. 32%) [7–9]. It is currently approved for the treatment of early, advanced breast cancer and metastatic gastric and gastroesophageal junction adenocarcinoma with HER2 overexpression or *HER2* gene amplification [10]. However, the high cost of trastuzumab limits treatment access for many eligible patients [11].

Biosimilars are biologic medicines with no clinically meaningful differences in safety or efficacy compared with approved reference products and can potentially increase patient access [12]. Several trastuzumab biosimilars have been approved by the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and/or the China National Medical Products Administration (NMPA), including HLX02 (Zercepac®, Henlius Biotech, Inc.), approved by both the EMA and the NMPA [13–15].

A biosimilar must demonstrate similarity to the reference product stepwise, starting with analytical and nonclinical comparisons of quality characteristics and biological activity, including toxicity [16, 17]. HLX02 is the first China-manufactured, globally evaluated trastuzumab biosimilar, and the amino acid sequence is identical to that of trastuzumab. Structural, functional, and preclinical similarities between HLX02 and trastuzumab have been demonstrated both in vitro and in vivo [18]. A phase I study in healthy Chinese male volunteers demonstrated the equivalent safety, tolerability, and pharmacokinetics of HLX02 and China- and EU-sourced trastuzumab (NCT02581748) [19, 20]. This study was designed to assess the clinical similarity of HLX02 and reference trastuzumab for the treatment of recurrent or metastatic HER2-positive breast cancer. The safety, tolerability, and immunogenicity of HLX02 and reference trastuzumab were monitored throughout the study.

2 Methods

2.1 Study Design and Participants

This randomized, multicenter, double-blind phase III equivalence study was designed to compare the efficacy and safety of HLX02 with reference trastuzumab in adult patients with HER2-positive recurrent or metastatic breast cancer. Patients were recruited from 89 centers in China, the Philippines, Poland, and Ukraine (Table 1 in the Electronic Supplementary Material [ESM]).

Eligible patients were aged ≥ 18 years, had histologically or cytologically confirmed breast adenocarcinoma, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1. Other key inclusion criteria were HER2 positivity (defined as fluorescence in situ hybridization amplification ratio ≥ 2 or immunohistochemistry score 3+), known estrogen-receptor (ER) and progesterone-receptor (PgR) status at study entry, measurable disease assessed by central imaging review (CIR), normal (within institutional range of normal) left ventricular ejection fraction (LVEF), and adequate hematologic, hepatic, and renal function. Key exclusion criteria were previously or on-treated (with systemic chemotherapy, biological, or targeted agent, or any other anticancer agent except hormonal therapy) metastatic breast cancer, symptomatic or untreated brain metastasis or any other central nervous system metastases, uncontrolled systemic disease that in the investigator's opinion made the administration of study drug hazardous, prior exposure to doxorubicin (> 360 mg/m^2 or equivalent), and residual non-hematologic grade 2 or higher toxicity from prior therapies. Full inclusion and exclusion criteria are listed in Table 2 in the ESM.

The study protocol was reviewed and approved by the relevant independent ethics review board at each study site. All patients provided written informed consent before inclusion. This trial was conducted in accordance with the principles outlined in the Declaration of Helsinki, good clinical practice guidelines, and all applicable local regulatory requirements. Study design details are illustrated in Fig. 1 in the ESM.

2.2 Randomization and Masking

After confirmation of eligibility, patients were randomized 1:1 to receive either HLX02 or EU-trastuzumab in combination with docetaxel. Randomization was conducted using a block randomization scheme and stratified by ER/PgR status, prior neo-/adjuvant therapy with trastuzumab, and ethnicity. An interactive web response system was used to assign patients to study groups as per a predefined randomization code. Randomization codes were not revealed to study participants, investigators, or study site personnel until all final clinical data had been entered into the database and the database had been locked and released for analysis. ORR and other outcomes were also assessed by blinded reviewers.

2.3 Treatments

The study consisted of a 28-day screening period and a treatment period. In the treatment period, patients received HLX02 or EU-trastuzumab at an initial dose of 8 mg/kg over 90-min intravenous infusion on day 1, cycle 1, followed by 6 mg/kg study drugs once every 3 weeks for a maximum of 12 months. Docetaxel 75 mg/m^2 was administered over 60-min intravenous infusion on day 2 of cycle 1 and then 60 min after the infusion of HLX02 or EU-trastuzumab in the following cycles at the investigator's discretion for a maximum of 12 months. Infusions were administered in line with site-specific protocols, local guidelines, and product information for reference trastuzumab.

2.4 Endpoints and Assessments

The primary efficacy endpoint of this study was ORR up to week 24 (ORR_{24}), defined as the proportion of patients with a best response of complete response (CR) or partial response (PR) from the first assessment up to week 24. Secondary efficacy endpoints included ORR at weeks 6, 12, 18, and 24; disease control rate (DCR; the proportion of patients who achieved CR, PR, or stable disease [SD] for ≥ 12 weeks); clinical benefit rate (CBR; the proportion of patients who achieved CR, PR, or durable SD [SD sustained for ≥ 24 weeks]); duration of response (DoR); 12-month progression-free survival (PFS) rate; and 12-, 24-, and 36-month overall survival (OS) rate. Tumor response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by blinded CIR until week 24, after which it was evaluated by the principal investigator. Tumor assessments were performed at screening, weeks 6, 12, 18, and 24, and then every 9 weeks with computed tomography (CT) scan or magnetic resonance imaging (MRI). The method used was consistent throughout the entire study. Bone scans or X-rays and brain CT scan/MRI were performed at screening and during the treatment period if clinically indicated.

The safety and tolerability of HLX02 or EU-trastuzumab were evaluated in this study by recording the incidence, severity, and causality of treatment-emergent adverse events (TEAEs), serious TEAEs, serious adverse events (SAEs) and adverse events (AEs) of special interest (AESIs). TEAEs were defined as AEs that began or worsened in severity during or following the first administration of study medication and ≤ 30 days (± 2) following the last dose of study medication. As the most common safety issue with trastuzumab, cardiac function was monitored by echocardiogram (ECG) or multigated acquisition scan at screening (within 42 days before randomization) and after every 3 cycles (or more frequently if clinically indicated). Patients who permanently discontinued the study drug because of a drop in LVEF (for a persistent [> 8 weeks] decline of LVEF or for suspension of HLX02/trastuzumab dosing on more than three occasions for cardiomyopathy [21]) continued to undergo assessments until the LVEF values returned to ≥ 50%.

All AEs, physical examinations, vital signs, ECGs, and laboratory tests were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 and classified according to the

Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Cardiac AEs were collected up to 12 months after randomization, in line with LVEF calculations. Routine laboratory tests were performed by the local laboratory at screening, during treatment, at the end of the study, and 30 days after the end of the last administration.

Pharmacokinetic blood samples were collected from all patients at cycle 1 (within 7 days prior to infusion) and every 3 cycles starting at cycle 3 (cycles 3, 6, 9, 12, and 15). Extended pharmacokinetic collections were collected from all patients in cycle 1 (at the end of infusion) and cycles 4 (prior to infusion) and 8 (prior to and after infusion). Immunogenicity (as assessed by antidrug antibody [ADA] and neutralizing ADA [NADA]) was evaluated with ADA and NADA at screening, cycles 3, 6, 9, 12, 15, and at the safety follow-up visit. The samples were submitted to the central laboratory (WuXi AppTec bioanalytical services department, Shanghai, China) and measured using validated assays.

2.5 Statistical Analysis

Assuming a 5% dropout rate, a sample size of 608 was required to ensure that 578 patients (289 in each group) randomly received treatments to evaluate the equivalence between HLX02 and EU-trastuzumab with approximately 84% power. Equivalence was defined as the 95% confidence interval (CI) for the treatment difference being fully contained in the margins of ± 13.5%. These margins were derived by reviewing historical data from two randomized studies of trastuzumab in patients with HER2-positive metastatic breast cancer [8, 10] and estimated with the Der Simonian–Laird [22] random effect.

The intention-to-treat (ITT) set was defined as all patients randomly allocated to study drug, regardless of whether a dose of study drug was given. The per-protocol (PP) set comprised all patients who received ≥ 8 cycles of treatment and had one or more tumor assessment after treatment, or who discontinued treatment early because of disease progression or intolerable toxicity without major protocol deviations. The safety set included all patients who were randomly allocated and received at least one dose of study drug (HLX02 or EU-trastuzumab). The pharmacokinetic set comprised all patients who received study drug and had at least one measured concentration at a scheduled pharmacokinetic time point with no protocol deviations or other pharmacokinetics-affecting events.

The ITT and PP population sets were used for efficacy analyses. Per ITT set, patients with missing ORR assessments were regarded as nonresponders in the primary analysis. The difference (95% CI) in ORR_{24} between the treatment groups was assessed for statistical significance with a chi-squared test. Sensitivity analyses of ORR between the two treatment groups (HLX02 and EU-trastuzumab) were conducted using a stratified Cochran–Mantel–Haenszel (CMH) test (95% Wald CI). The stratification factors for CMH tests were ER/PgR status, prior neo-/adjuvant therapy with EU-trastuzumab, and ethnicity. The CMH test used for the primary efficacy analysis was repeated for the PP set.

For the secondary efficacy endpoints, ORR, CBR, and DCR were analyzed using the same method as for the primary efficacy endpoint. Other secondary efficacy endpoints, such as DoR; PFS up to 12 months; OS rate at 12, 24, and 36 months; and OS at the cut-off date in the two treatment groups were presented graphically using Kaplan–Meier curves along with a summary of associated statistics (i.e., the probability of being event free) and the corresponding two-sided 95% CIs. Furthermore, the treatment difference, which was characterized by the "HLX02/EU-trastuzumab" hazard ratio (HR), was calculated using a stratified Cox proportional hazards model with ER/PgR status, prior (neo)/adjuvant therapy with trastuzumab, and ethnicity as covariates.

All analyses, summaries, and listings were calculated using SAS® software (version 9.4 or later, SAS Institute Inc., Cary, NC, USA). This study and all data were monitored by an independent monitoring committee.

3 Results

3.1 Patient Disposition

Between 11 November 2016 and 10 July 2019, a total of 1046 patients were screened, of whom 649 were randomized to receive HLX02 ($n = 324$) or EU-trastuzumab ($n = 325$) and included in the ITT set (Fig. 1). The PP set comprised 616 patients: 310 in the HLX02 group and 306 in the EU-trastuzumab group (Fig. 1). A total of 12 patients had one or more major protocol deviations: four (1.2%) in the HLX02 group and eight (2.5%) in the EU-trastuzumab group. Major protocol deviations in each group are listed in detail in Table 3 in the ESM.

Patient demographics and baseline characteristics were well-balanced between the treatment groups in the ITT set (Table 1) and the PP set (data not shown). Patients in the HLX02 and EU-trastuzumab groups had a mean age of 53.6 and 52.8 years, respectively. Around half of the patients were ER/PgR receptor positive (46 vs. 48%). The majority of patients in both treatment groups were Asian (> 75%). The proportion of patients aged > 50 years was slightly lower in the HLX02 group than in the EU-trastuzumab group (30.2 vs. 36.9%). The mean LVEF levels at baseline were 64.7 and 64% in the HLX02 and EU-trastuzumab groups, respectively.

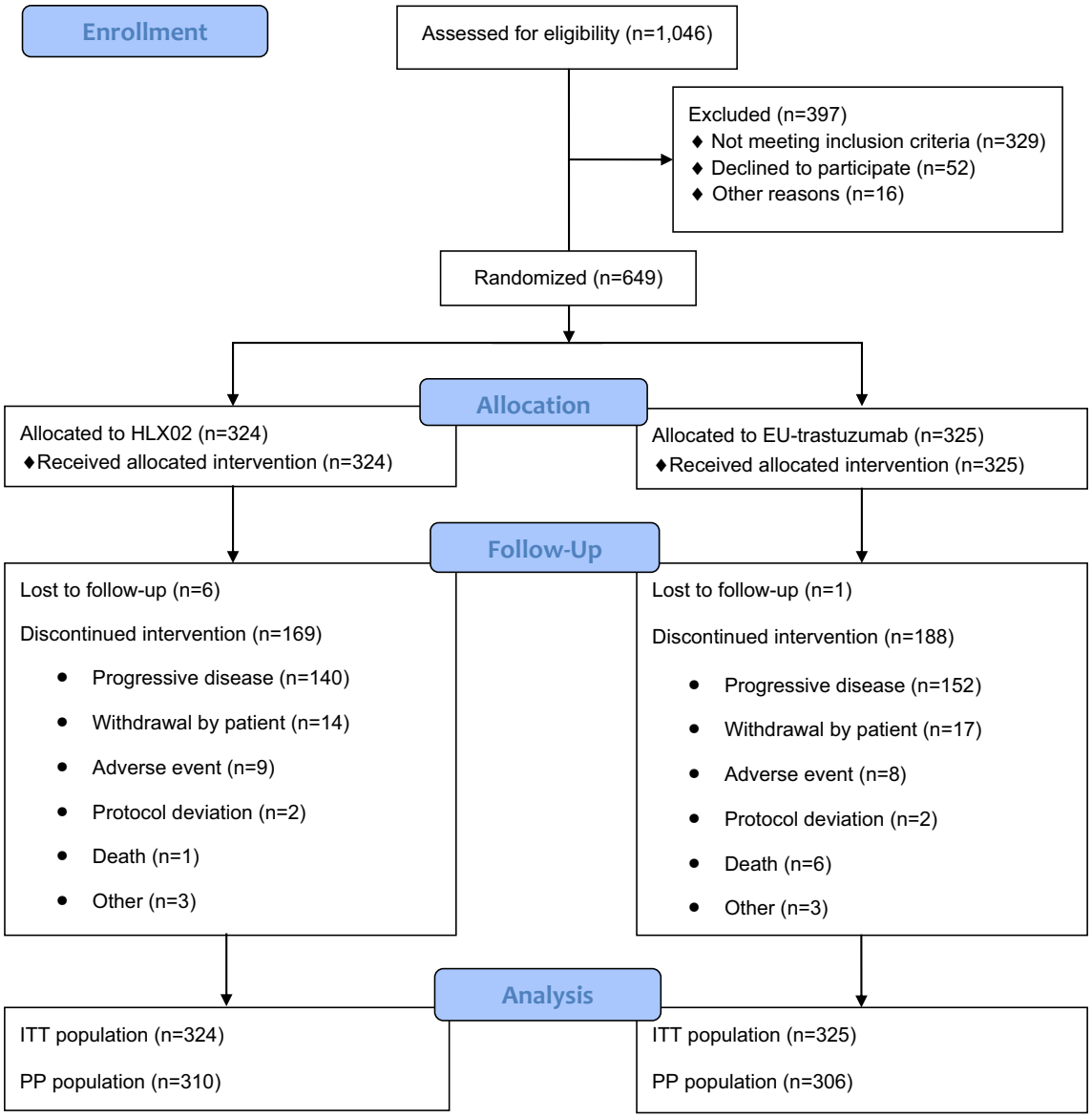


Fig. 1 Patient flow diagram. *ITT* intention-to-treat, *PP* per-protocol

3.2 Drug Exposure

The median follow-up durations were comparable in the HLX02 and EU-trastuzumab groups (457.0 vs. 455.0 days). Exposure to study drug and chemotherapy agent docetaxel were similar between the treatment groups (Tables 4 and 5 in the ESM). The mean number of treatment cycles completed were 12.4 and 11.8; mean days of treatment exposure were 264.6 and 253.4 in the HLX02 and EU-trastuzumab groups, respectively. Exposure to docetaxel was also similar (mean 8.2 vs. 8.1 cycles) between the two treatment groups.

3.3 Efficacy Results

In the ITT set, ORR_{24} was 71.3 and 71.4% in the HLX02 and EU-trastuzumab groups, respectively, with an intergroup difference of − 0.1% (95% CI − 7 to 6.9) (Table 2), and the sensitivity analysis revealed a stratified intergroup difference of 0.1% (95% CI − 6.9 to 7). Both 95% CIs of intergroup differences fell completely in the predefined equivalence margins of ± 13.5%. Results in the PP set were comparable. The difference in ORR_{24} of the HLX02 or EU-trastuzumab groups was 1.0% (95% CI − 6 to 7.9); the intergroup difference produced by a stratified CMH (sensitivity) analysis was 1.3% (95% CI − 5.7 to 8.2) in the PP set.

Table 1 Patient demographics and baseline characteristics (intention-to-treat set)

Variable	HLX02 ($n = 324$)	EU-trastuzumab ($n = 325$)
Age, years		
Mean	53.6 ± 9.7	52.8 ± 10.1
Median (range)	54 (30–80)	53 (26–76)
> 50 years	98 (30.2)	120 (36.9)
≤ 50 years	226 (69.8)	205 (63.1)
Females	324 (100)	325 (100)
Weight, kg		
Mean	64.6 ± 12.6	63.7 ± 12.5
Median (range)	62 (41.5–118)	62 (37.2–120)
BMI, kg/m^2	25.4 ± 4.3	25.2 ± 4.6
Childbearing potential	105 (32.4)	111 (34.2)
Ethnicity		
Asian	248 (76.5)	251 (77.2)
Non-Asian	76 (23.5)	74 (22.8)
Chinese	237 (73.1)	236 (72.6)
Non-Chinese	87 (26.9)	89 (27.4)
Primary tumor status at screening		
TX	81 (25)	86 (26.5)
T0, Tis, T1	78 (24.1)	87 (26.8)
T2	76 (23.5)	70 (21.5)
T3, T4	68 (21)	63 (19.4)
Missing	21 (6.5)	19 (5.8)
ECOG status		
0	138 (42.6)	139 (42.8)
1	186 (57.4)	186 (57.2)
ER/PgR		
Positive for ER, PgR or both	149 (46)	156 (48)
Negative/unknown	175 (54)	169 (52)
Metastatic site number (CIR)		
> 2	123 (38)	104 (32)
≤ 2	190 (58.6)	207 (63.7)
Site of metastatic disease[a] (CIR)		
Liver	157 (48.5)	164 (50.5)
Bone	94 (29)	102 (31.4)
ADA status		
Positive	6 (1.9)	17 (5.2)
Negative	315 (97.2)	307 (94.5)
Unknown	3 (0.9)	1 (0.3)
Prior treatment history		
Trastuzumab	17 (5.2)	20 (6.2)
Taxanes	171 (52.8)	168 (51.7)
Other cytotoxic drugs	212 (65.4)	218 (67.1)
Hormonal therapy	70 (21.6)	81 (24.9)
Prior neo-/adjuvant therapy with trastuzumab		
Yes	16 (4.9)	20 (6.2)
No	308 (95.1)	305 (93.8)
One or more concomitant medication	52 (68.4)	49 (66.2)
Corticosteroids for systemic use	323 (99.7)	325 (100)
Antiemetics and antinauseants	299 (92.3)	309 (95.1)

Table 1 (continued)

Variable	HLX02 ($n = 324$)	EU-trastuzumab ($n = 325$)
Immunostimulants[b]	262 (80.9)	259 (79.7)
Left ventricular ejection fraction, %		
Mean	64.7 ± 5.1	64 ± 4.9
Median (range)	65 (52–82)	64 (50–80)

Values are presented as n (%) or mean ± standard deviation unless otherwise specified

ADA antidrug antibody, *BMI* body mass index, *CIR* central imaging review, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *PgR* progesterone receptor

[a]Patients may have had metastatic disease at more than one site

[b]Immunostimulants here mainly include granulocyte colony-stimulating factor, filgrastim, and ribonucleic acid

Table 2 Tumor response rates following up to 8 cycles of HLX02 or EU-trastuzumab (intention-to-treat set)

Response	HLX02 ($n = 324$)	EU-trastuzumab ($n = 325$)	Difference % (95% CI)	Stratified difference % (95% CI)[a]
Primary endpoint				
ORR_{24}[b]	231 (71.3)	232 (71.4)	− 0.1 (− 7 to 6.9)	0.1 (− 6.9 to 7.0)
Response type up to week 24[b]				
Complete response	17 (5.2)	12 (3.7)		
Partial response	214 (66)	220 (67.7)		
Noncomplete response/nonprogressive disease	5 (1.5)	3 (0.9)		
Stable disease	48 (14.8)	65 (20)		
Progressive disease	24 (7.4)	16 (4.9)		
Not evaluable	16 (4.9)	9 (2.8)		
Secondary tumor response endpoints				
Week 24 DCR[c]	274 (84.6)	285 (87.7)	− 3.1 (− 8.4 to 2.2)	− 3.3 (− 8.6 to 2.1)
Week 24 CBR[c]	263 (81.2)	263 (80.9)	0.2 (− 5.8 to 6.3)	0.3 (− 5.8 to 6.3)
ORR[b] by week				
Week 6	146 (45.1)	139 (42.8)	2.3 (− 5.3 to 9.9)	
Week 12	190 (58.6)	187 (57.5)	1.1 (− 6.5 to 8.7)	
Week 18	199 (61.4)	189 (58.2)	3.3 (− 4.3 to 10.8)	
Week 24	192 (59.3)	175 (53.8)	5.4 (− 2.2 to 13)	

Data are presented as *n* (%) unless otherwise specified

CBR clinical benefit rate, *CI* confidence interval, *DCR* disease control rate, *ORR* objective response rate, ORR_{24} overall best response rate evaluated at up to week 24

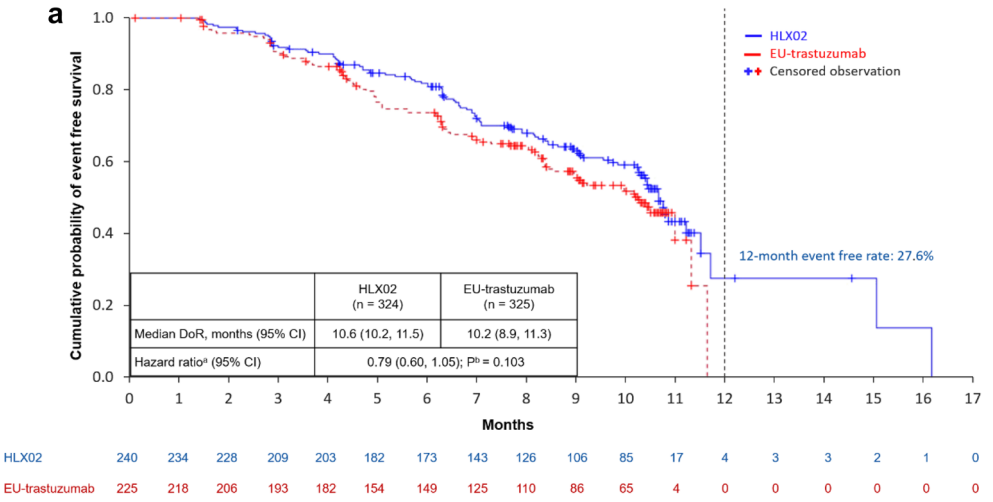
[a]Stratified differences and their 95% CIs were calculated from a stratified Cochran–Mantel–Haenszel, with hormone receptor status, prior neo-/adjuvant therapy with trastuzumab and ethnicity as stratification factors (sensitivity results)

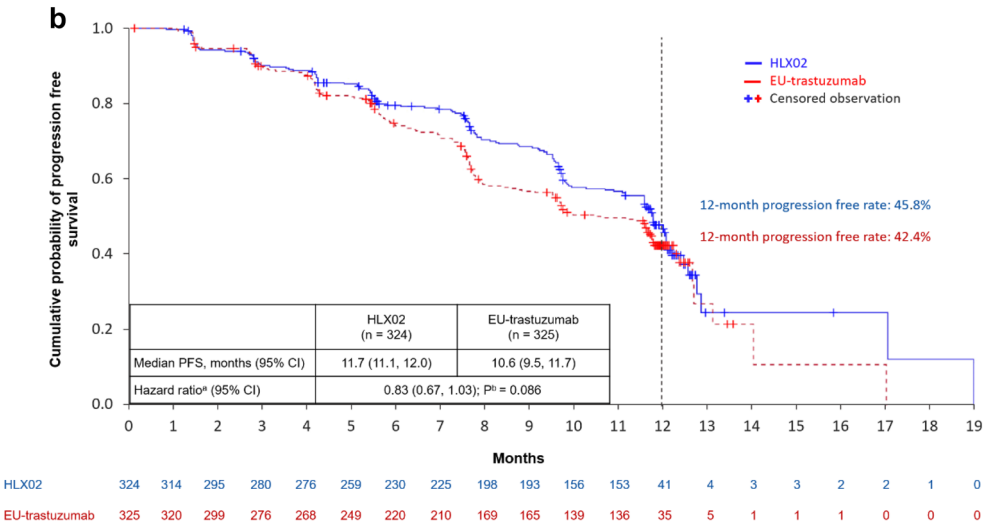
[b]Response rates were evaluated by blinded central imaging review according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

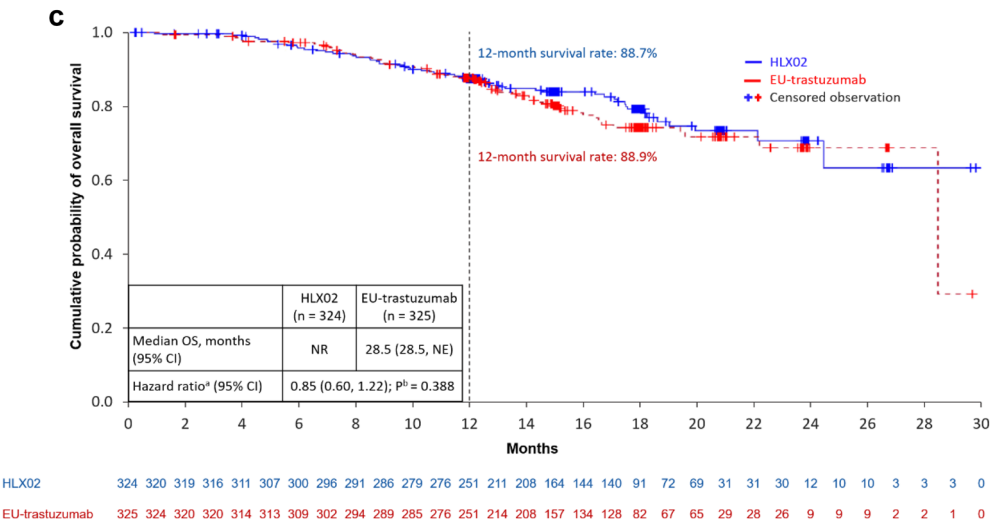
[c]DCR and CBR were evaluated by the investigator

In addition, no statistically significant differences were observed between the two treatment groups in all secondary endpoint efficacy analyses and further sensitivity analyses (Table 2). At up to week 24, a similar proportion of patients in the HLX02 and EU-trastuzumab groups experienced a CR (5.2 vs. 3.7%) or PR (66 vs. 67.7%). ORRs (at weeks 6, 12, 18, and 24), DCRs, and CBRs were similar between the two treatment groups.

The median DoR (10.6 vs. 10.2 months; HR 0.79; $p = 0.103$) and median PFS (11.7 and 10.6 months; HR 0.83; $p = 0.086$) were comparable between the HLX02 and EU-trastuzumab groups (Fig. 2a, b). Median OS was not reached


a
Cumulative probability of event free survival
HLX02
EU-trastuzumab
Censored observation
12-month event free rate: 27.6%
HLX02 (n = 324)
EU-trastuzumab (n = 325)
Median DoR, months (95% CI) 10.6 (10.2, 11.5) 10.2 (8.9, 11.3)
Hazard ratio[a] (95% CI) 0.79 (0.60, 1.05); P[b] = 0.103
Months
HLX02 240 234 228 209 203 182 173 143 126 106 85 17 4 3 3 2 1 0
EU-trastuzumab 225 218 206 193 182 154 149 125 110 86 65 4 0 0 0 0 0 0


b
Cumulative probability of progression free survival
HLX02
EU-trastuzumab
Censored observation
12-month progression free rate: 45.8%
12-month progression free rate: 42.4%
HLX02 (n = 324)
EU-trastuzumab (n = 325)
Median PFS, months (95% CI) 11.7 (11.1, 12.0) 10.6 (9.5, 11.7)
Hazard ratio[a] (95% CI) 0.83 (0.67, 1.03); P[b] = 0.086
Months
HLX02 324 314 295 280 276 259 230 225 198 193 156 153 41 4 3 3 2 2 1 0
EU-trastuzumab 325 320 299 276 268 249 220 210 169 165 139 136 35 5 1 1 1 0 0 0


c
Cumulative probability of overall survival
12-month survival rate: 88.7%
12-month survival rate: 88.9%
HLX02
EU-trastuzumab
Censored observation
HLX02 (n = 324)
EU-trastuzumab (n = 325)
Median OS, months (95% CI) NR 28.5 (28.5, NE)
Hazard ratio[a] (95% CI) 0.85 (0.60, 1.22); P[b] = 0.388
Months
HLX02 324 320 319 316 311 307 300 296 291 286 279 276 251 211 208 164 144 140 91 72 69 31 31 30 12 10 10 3 3 3 0
EU-trastuzumab 325 324 320 320 314 313 309 302 294 289 285 276 251 214 208 157 134 128 82 67 65 29 28 26 9 9 9 2 2 1 0

◂**Fig. 2** Kaplan–Meier plots showing **a** duration of response, **b** progression-free survival, and **c** overall survival in patients with HER2-positive recurrent and metastatic breast cancer who received HLX02 or EU-trastuzumab (ITT). [a]Hazard ratio and 95% CI calculated using a Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with trastuzumab, and ethnicity (Asian vs. non-Asian) as covariates; [b]*P*-values calculated using a stratified log-rank test. *CI* confidence interval, *DoR* duration of response, *HER2* human epidermal growth factor receptor 2, *HR* hazard ratio, *ITT* intention-to-treat, *NE* not evaluable, *NR* not reached, *OS* overall survival, *PFS* progression-free survival

in the HLX02 group and was 28.5 months in the EU-trastuzumab group (Fig. 2c, HR 0.85; $p = 0.388$).

3.4 Safety Results

Overall, the safety profiles of HLX02 and EU-trastuzumab were similar (Table 3), with 98.8% of patients in the HLX02 and EU-trastuzumab groups experiencing one or more TEAEs. The most common TEAEs were decreased neutrophil count, decreased white blood cell count, and anemia. Grade 3 or higher TEAEs (85.8 vs. 86.4%) and serious TEAEs (23.8 vs. 24.9%) were reported in a similar proportion of patients in the HLX02 and EU-trastuzumab treatment groups. TEAEs leading to treatment discontinuation occurred in 3.1 and 3.4% of patients, and death due to TEAEs occurred in three patients in the HLX02 group (one case each due to lung infection, dyspnea, and pneumonia) and six patients in the EU-trastuzumab group (one case each due to dyspnea and cardiovascular event; one case due to electrolyte imbalance, arthralgia, and altered consciousness; and three cases due to general disorders and administration site conditions).

The most commonly reported AESIs were decreased white blood cell count (69.4 vs. 68.9%), decreased neutrophil count (66 vs. 64.3%), and anemia (37.7 and 40.9%) in the HLX02 and EU-trastuzumab groups, respectively. Cardiac disorders of special interest occurred in similar proportions of patients (4.9 vs. 5.2%) in each treatment group. Cardiac disorders of special interest classified by preferred terms are listed in Table 6 in the ESM. LVEF shifts from normal to abnormal were observed in 17 (5.3%) patients in the HLX02 treatment group and in 20 (6.2%) patients in the EU-trastuzumab group. LVEF did not show any significant changes from baseline to week 21 and week 48 in the two treatment groups (Table 4).

3.5 Pharmacokinetic and Immunogenicity Results

No notable differences in pharmacokinetic and immunogenicity endpoints were observed between the treatment groups. In the pharmacokinetic set, serum concentration–time profiles were comparable in the HLX02 ($n = 321$) and EU-trastuzumab ($n = 324$) groups (Fig. 2 in the ESM). In the safety set, seven (2.2%) patients in the HLX02 group and 17 (5.2%) patients in the EU-trastuzumab group were ADA positive prior to the initiation of treatments. Of these, four and six were NADA positive, respectively. Four (0.6%) patients (two patients in each treatment group) were considered overall ADA and NADA positive during the study (Tables 7 and 8 in the ESM). No SAEs were reported in these four patients.

4 Discussion

This randomized, multicenter, double-blind phase III trial demonstrated the therapeutic equivalence between HLX02 and reference trastuzumab in patients with recurrent or metastatic breast cancer based on 95% CIs of the intergroup difference of ORR_{24} in relation to the prespecified equivalence margins (± 13.5%). There were no statistically significant differences in all efficacy endpoints, pharmacokinetics, safety, or immunogenicity between the treatment groups.

Trastuzumab was initially approved for the treatment of metastatic HER2-positive breast cancer [7, 23]. Several established equivalence studies of trastuzumab biosimilars, including MYL-1401O [24] (Biocon/Mylan), BCD-022 (BIOCAD) [25], and PF-05280014 (Pfizer) [26], were conducted in patients with metastatic breast cancer. Based on the recent findings of a systematic literature review presented at the 2018 European Society for Medical Oncology congress, both early-stage and metastatic breast cancer are appropriate for the equivalence evaluation of trastuzumab biosimilar drugs to trastuzumab [27]. The efficacy and safety similarity evaluations of HLX02 to trastuzumab were conducted in patients with metastatic breast cancer in this study.

Even though trastuzumab in combination with pertuzumab and chemotherapy is the current standard treatment for HER2-positive breast cancer in many countries [28], trastuzumab, as the first effective therapeutic monoclonal antibody, which revolutionized the treatment of HER2-positive breast cancer [29], remains a fundamental treatment option. To assess the similarity between HLX02 and trastuzumab through between-group ORR comparisons, pertuzumab was not included in the treatment regimen in this study. Another reason for not including pertuzumab is its lack of accessibility worldwide.

The therapeutic equivalence of HLX02 to trastuzumab was statistically demonstrated by the primary efficacy results in both the ITT ($p = 0.983$, risk difference in ORR − 0.1%) and the PP sets ($p = 0.727$, risk difference in ORR 1%). Even through the secondary efficacy analyses results of DoR, PFS, and OS were in favor of HLX02 at some time points according to Fig. 2, no statistically significant differences were

Table 3 Summary of safety data (safety set)

Safety data	HLX02 (n = 324)	EU-trastuzumab (n = 325)
Number of TEAEs	6828	7002
Any TEAE[a]	320 (98.8)	321 (98.8)
Grade 1	3 (0.9)	7 (2.2)
Grade 2	39 (12)	33 (10.2)
Grade 3	84 (25.9)	95 (29.2)
Grade 4	191 (59)	180 (55.4)
Grade 5	3 (0.9)	6 (1.8)
TEAEs related to study drug	236 (72.8)	233 (71.7)
TEAEs leading to drug withdrawal	10 (3.1)	11 (3.4)
Serious TEAEs	77 (23.8)	81 (24.9)
Grade 1	0 (0)	1 (0.3)
Grade 2	12 (3.7)	7 (2.2)
Grade 3	26 (6.8)	31 (9.5)
Grade 4	40 (12.3)	36 (11.1)
Grade 5	3 (0.9)	6 (1.8)
Serious TEAEs related to study drug	32 (9.9)	31 (9.5)
Deaths	3 (0.9)	6 (1.8)
Treatment-related AEs occurring in ≥ 5% of patients		
Decreased neutrophil count	105 (32.4)	108 (33.2)
Decreased white blood cell count	102 (31.5)	110 (33.8)
Anemia	61 (18.8)	74 (22.8)
Alopecia	39 (12)	49 (15.1)
Increased alanine aminotransferase	38 (11.7)	35 (10.8)
Infusion-related reaction	34 (10.5)	24 (7.4)
Increased aspartate aminotransferase	33 (10.2)	32 (9.8)
Diarrhea	32 (9.9)	27 (8.3)
Rash	22 (6.8)	20 (6.2)
Pyrexia	22 (6.8)	25 (7.7)
Edema peripheral	21 (6.5)	17 (5.2)
Malaise	19 (5.9)	15 (4.6)
Increased gamma-glutamyltransferase	18 (5.6)	15 (4.6)
Asthenia	11 (3.4)	19 (5.8)
Decreased appetite	11 (3.4)	18 (5.5)
Nausea	11 (3.4)	25 (7.7)
Fatigue	9 (2.8)	18 (5.5)
AEs of special interest occurring in ≥ 5% of patients	260 (80.2)	258 (79.4)
Decreased white blood cell count	225 (69.4)	224 (68.9)
Decreased neutrophil count	214 (66)	209 (64.3)
Anemia	122 (37.7)	133 (40.9)
Infusion-related reaction	41 (12.7)	32 (9.8)
Bone marrow failure	20 (6.2)	23 (7.1)
Decreased platelet count	19 (5.9)	23 (7.1)
Febrile neutropenia	16 (4.9)	20 (6.2)

Data are presented as n (%) unless otherwise indicated

AE adverse event, *TEAE* treatment-emergent AE

[a]TEAEs were coded using the Medical Dictionary for Regulatory Activities version 21.1 coding dictionary. Severity of adverse events was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events

Table 4 Left ventricular ejection fraction at baseline and weeks 21 and 48 (safety set)

LVEF, %, observed	HLX02 ($n = 324$)	EU-trastuzumab ($n = 325$)
Baseline[a]		
n[b]	324	325
Mean ± SD	64.7 ± 5.1	64 ± 4.9
Median (range)	65 (52–82)	64 (50–80)
Week 21		
n[b]	256	253
Mean ± SD	63.7 ± 4.8	63.8 ± 4.8
Median (range)	63 (41–77)	63.3 (44–78)
Week 48		
n[b]	158	136
Mean ± SD	64 ± 4.6	63.7 ± 5.2
Median (range)	64 (53–76)	63 (44–79)

LVEF left ventricular ejection fraction, *SD* standard deviation

[a]Baseline measurements were taken within 42 days of randomization

[b]Number of patients with available data

observed between the two treatment groups in the ITT and PP sets based on the 1-year results.

The ORR at week 24 (59.3%), median DoR (10.6 months), PFS (11.7 months), and OS (not reached) observed in the HLX02 treatment group in this study were comparable to those observed in patients with metastatic breast cancer treated with trastuzumab in the reference study: ORR at week 24 64%; median DoR 11.1 months; median PFS 11.1 months; median OS not estimable [24]. Sensitivity analyses of primary and secondary efficacy endpoints were performed in the following subgroups: ER/PgR status, prior neo-/adjuvant therapy with trastuzumab, and ethnicity (Asian and non-Asian). Results were consistent with the primary efficacy analysis and supported the conclusion of therapeutic equivalence. Long-term follow-up is important to accurately assess the efficacy outcomes. Efficacy parameters, including DoR and PFS, were followed up to 12 months. OS was estimated up to 12, 24, and 36 months. Long-term OS results will be reported once available.

The primary endpoint ORR is a sensitive endpoint for identifying the differences between a biosimilar candidate and the reference drug through direct measurement of drug activity [16, 17]. The equivalence margins of this study were derived by reviewing the historical ORR of chemotherapy plus trastuzumab and estimating with the Der Simonian–Laird estimate effect model [8, 10]. The intergroup difference in ORR was estimated as 0.2493 (95% CI 0.1579 to 0.3407). To increase assay sensitivity, the margins were defined as ± 13.5%, which was tighter than the lower boundary of the estimated 95% CI. The margins selected for this study were consistent with other phase III equivalence studies of approved trastuzumab biosimilars, including the above-mentioned MYL-1401O [24] and PF-05280014 [26, 30], as well as CT-P6 (Celltrion) [31, 32], ABP980 (Amgen/Allergan) [33], and SB3 (Samsung Bioepis) [34].

There were no notable differences between the two treatment groups regarding the type, incidence, or severity of TEAEs. This study also showed that the safety profiles were comparable with the known safety profiles of trastuzumab in patients with breast cancer [21, 24]. Clinical laboratory evaluations, vital signs, physical examinations, immunogenicity, and other safety observation (ECG, ECOG) results were similar between the two treatment groups. ADAs were detected overall in two patients in each treatment group, indicating similar immunogenicity between HLX02 and reference trastuzumab. The low immunogenic potential was consistent with published data for trastuzumab and trastuzumab biosimilars [24, 26].

Trastuzumab has been reported as related to increased risks of cardiac toxicity [7]. Thus, cardiac disorders in the HLX02 and trastuzumab treatment groups were carefully assessed. The frequency of cardiac disorders was low and similar between the two groups (three vs. six patients). Two patients in the HLX02 group (one case each of left ventricular dysfunction and pericardial effusion) and three patients in the EU-trastuzumab group (one case each of congestive cardiac failure, coronary artery disease, and ventricular arrhythmia) experienced a cardiac disorder that resulted in drug interruption or withdrawal. Two patients in the HLX02 group and three patients in the EU-trastuzumab group had a serious cardiac disorder related to study medication. The cardiac disorders reported in this study were similar to those previously reported [21, 26].

Overall, the safety findings in the current trial were consistent with those expected of trastuzumab and previous studies of trastuzumab biosimilars [10, 24, 26]. A long-term extension study that further monitors the efficacy and safety of HLX02 is under consideration.

5 Conclusions

The primary endpoint ORR_{24} and secondary endpoints were equivalent between HLX02 and reference trastuzumab groups when administrated in combination with docetaxel. Safety, in terms of the type, frequency, and severity of AEs, including cardiac disorders, were not different between the two treatment groups and were consistent with the known safety profiles of trastuzumab. Pharmacokinetic and immunogenicity profiles were similar between the two treatment groups. This study demonstrated similarity between HLX02 and reference trastuzumab in patients with HER2-positive recurrent or metastatic breast cancer.

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Declarations

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Conflicts of interest Qingyu Wang is an employee of Henlius. Binghe Xu, Qingyuan Zhang, Tao Sun, Wei Li, Yue'e Teng, Xichun Hu, Igor Bondarenko, Hryhoriy Adamchuk, Liangming Zhang, Dmytro Trukhin, Shusen Wang, Hong Zheng, Zhongsheng Tong, and Yaroslav Shparyk have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The trial was conducted in accordance with the principles of both good clinical practice from the International Conference on Harmonization and the 1964 Declaration of Helsinki. The protocol and all amendments of this study were approved by regulatory authorities and the ethics committees of all participating centers (Table 1 in the ESM). This study was approved by the National Medical Products Administration (China); the Food and Drug Administration (Philippines); the Ministry of Health (Ukraine); and the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Poland).

Consent to participate All participants provided written informed consent before admission and initiation of the study.

Consent for publication Not applicable.

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Code availability Not applicable.

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