The Breast 80 (2025) 104413

Contents lists available at ScienceDirect

The Breast

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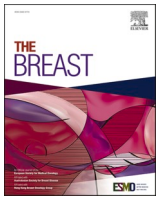

Updated efficacy and safety of HLX02 versus reference trastuzumab in metastatic HER2-positive breast cancer: A randomized phase III equivalence trial

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ARTICLE INFO

Keywords:
HLX02
Trastuzumab
HER2
Metastatic breast cancer

ABSTRACT

Aim: Equivalence between HLX02 and trastuzumab sourced from the European Union (EU-trastuzumab), in combination with docetaxel, was demonstrated in a phase III study. This study aimed to evaluate the long-term efficacy and safety data after 3 years of follow-up.

Methods: Patients with previously untreated, HER2-positive metastatic breast cancer received intravenous HLX02 or EU-trastuzumab (initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for up to 12 months) in combination with docetaxel. Primary endpoint was the overall response rate up to week 24 (ORR_{24}). Secondary endpoints including updated overall survival (OS), progression-free survival (PFS), safety and immunogenicity are reported in this long-term follow-up analysis.

Results: After a median follow-up duration of 35.0 months, 270 out of the 649 enrolled patients had died; 128 (39.5 %) in the HLX02 and 142 (43.7 %) in the EU-trastuzumab group. Median OS was 37.3 (95 % CI 36.2, not evaluable [NE]) months and not reached (95 % CI 34.2, NE) (stratified HR 0.86 [95 % CI 0.68, 1.10]; $p = 0.229$), with a 3-year OS rate of 57.5 % and 54.0 %, respectively. Median PFS at this long-term follow-up assessment was 11.7 (95 % CI 11.5, 12.1) months for the HLX02 group and 10.6 (95 % CI 9.5, 11.7) months for the EU-trastuzumab group (stratified HR 0.86 [95 % CI 0.69, 1.06]; $p = 0.158$). No new safety concerns were reported until the end of the survival follow-up.

Conclusion: Long-term efficacy and safety were consistent with the previous findings. No clinically meaningful differences between HLX02 and reference trastuzumab were demonstrated.

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https://doi.org/10.1016/j.breast.2025.104413
Received 22 August 2024; Received in revised form 1 December 2024; Accepted 3 February 2025
Available online 4 February 2025

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

1. Introduction

Breast cancer is the most common cancer worldwide, accounting for more than 2.2 million cases and 680,000 deaths in 2020 [1]. Approximately 15–20 % of primary breast cancers and 10 % of estrogen receptor (ER)-positive breast cancers exhibit overexpression of the oncogenic human epidermal growth factor receptor 2 (HER2) [2,3]. Its overexpression is predominantly attributed to the amplification of the *HER2* gene, and has been correlated to a more aggressive tumor growth, and poorer prognosis, decreased overall survival, and shorter time to relapse [4–7].

The current gold standard for HER2-positive breast cancer patients is trastuzumab-based treatments. Trastuzumab, a humanized anti-HER2 monoclonal antibody, in combination with chemotherapy has demonstrated significant survival benefits and improvements in tumor responses compared to chemotherapy alone for HER2-positive, advanced or metastatic breast cancer patients in several pivotal clinical studies [8–10]. It is currently approved as treatment for early and advanced breast cancer, as well as metastatic gastric and gastroesophageal junction adenocarcinoma that overexpress HER2 or exhibit *HER2* gene amplification [11]. Despite the tremendous improvements with trastuzumab-based therapies, the relatively high cost of trastuzumab, along with the issue of its availability in various geographical regions, render many eligible breast cancer patients limited accessibility to effective treatments [12].

The development of biosimilars, biologic medicines that have nearly equal efficacy and no clinically meaningful differences in safety as their respective approved reference product, may help to address the aforementioned concern and potentially increase patients' access to efficacious drugs [13]. HLX02 is the first trastuzumab biosimilar manufactured in China that has been approved by the European Medicines Agency (EMA) and National Medical Products Administration (NMPA) of China. Preclinical research and clinical studies have demonstrated its similarity to trastuzumab in terms of structure and function, as well as safety, tolerability and pharmacokinetics [14,15].

At the previous interim analysis (data cut-off: 10 July 2019) performed and published after a median follow-up duration of 15.0 months, the primary objective of efficacy equivalence was demonstrated between HLX02 and EU-trastuzumab; the overall response rate at up to 24 weeks was 71.3 % in the HLX02 group and 71.4 % in the EU-trastuzumab group, with an intergroup difference of −0.1 % (95 % CI, −7.0, 6.9), which was fully contained in the predefined equivalence margins [16]. HLX02 and EU-trastuzumab were also comparable in terms of safety profile and immunogenicity. Here we report the long-term secondary efficacy endpoints, including OS alongside safety and immunogenicity findings performed 24 months after the previous interim analysis (data cut-off: 28 September 2021).

2. Materials and methods

2.1. Study design and participants

The study design and patients' eligibility criteria of this randomized, double-blind, phase III study have been previously described [16]. Briefly, adult patients with previously untreated HER2-positive metastatic breast cancer, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1, and measurable disease assessed by central imaging review (CIR) were recruited from 89 centers across China, Philippines, Poland, and Ukraine. Key exclusion criteria included previously or on-treatment (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, prior exposure to doxorubicin (>360 mg/m2 or equivalent), and residual non-hematologic grade ≥2 toxicity from prior therapies.

2.2. Randomization and masking

Enrolled patients were randomized 1:1 to receive either HLX02 or EU-trastuzumab, in combination with docetaxel. Randomization was carried out using a block randomization scheme and patients were assigned to treatment groups using an interactive web response system as per a predefined randomization code. Stratification factors included ER/PgR status, prior neo-/adjuvant therapy with trastuzumab, and ethnicity. Study participants, investigators, or any personnel at each study site had no prior knowledge of the randomization codes until the locking of all final clinical data into the database and the release for analysis. The reviewers were blinded during their assessments of efficacy outcomes.

2.3. Treatments

Patients received an initial dose of 8 mg/kg of either HLX02 or EU-trastuzumab over a 90-min intravenous infusion on day 1, cycle 1, followed by 6 mg/kg of HLX02 or EU-trastuzumab once every 3 weeks up to a maximum of 12 months. Administration of docetaxel at 75 mg/m^2 was carried out over a 60-min intravenous infusion on day 2 of cycle 1, then 60 min after the infusion of HLX02 or EU-trastuzumab in the subsequent cycles up to a maximum of 12 months at the investigator's discretion. Infusions were administered in accordance with site-specific protocols, local guidelines, and product information for EU-trastuzumab.

2.4. Endpoints and assessments

The primary endpoint was the objective response rate up to week 24 (ORR_{24}), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) from the initial assessment up to week 24. Secondary efficacy endpoints included ORR at weeks 6, 12, 18, and 24, disease control rate (DCR) for ≥12 weeks, clinical benefit rate (CBR), defined as the proportion of patients who achieved CR, PR, or durable stable disease (SD) i.e. 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 imaging by computed tomography scan or magnetic resonance imaging was scheduled at screening, weeks 6, 12, 18, and 24, and then every 9 weeks thereafter. Tumor response was assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [17] by the blinded CIR up until week 24, and subsequently by the principal investigator.

All adverse events (AEs) were monitored from the time of the first dose of study drugs up to ≤ 30 days (±2) after the last dose. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Cardiac function, the most common safety concern with the use of trastuzumab, was monitored by echocardiogram (ECG) or multigated acquisition scan at screening (within 42 days prior to randomization) and after every 3 cycles (or more frequently if

clinically indicated). Cardiac AEs were recorded for a maximum of 12 months following randomization, as with the LVEF calculations. Pharmacokinetic (PK) blood samples were collected at cycle 1 (within 7 days before infusion), and every 3 cycles starting on cycle 3 (i.e. cycles 3, 6, 9, 12, and 15). Assessment of immunogenicity by antidrug antibody (ADA) and neutralizing ADA (NADA) was evaluated at screening, cycles 3, 6, 9, 12, 15, as well as the safety follow-up visit. Samples were sent to the central laboratory (WuXi AppTec bioanalytical services department, Shanghai, China) for measurement with validated assays.

2.5. Statistical analysis

Sample size estimation and statistical assumption of equivalence between HLX02 and EU-trastuzumab have been previously described [16]. Briefly, enrolment of 608 patients was required such that 578 patients (289 in each group) randomly received study treatments for the evaluation of equivalence between HLX02 and EU-trastuzumab with an approximate 84 % power. Median DOR, 12-month PFS rate, OS rate at 12, 24, and 36 months, and updated median OS as of the data cut-off date, along with their 95 % CIs, were analyzed using the Kaplan-Meier method. Hazard ratio (HR) for the treatment difference between the two groups was calculated using a stratified Cox proportional hazards model factoring ER/PgR status, prior (neo)/adjuvant therapy with trastuzumab, and ethnicity as covariates. All data analyses, summaries, and outputs were produced using the Statistical Analysis Software (SAS) (version 9.4 or later, SAS Institute Inc., Cary, NC, USA). An independent monitoring committee was established for the monitoring of this study along with all the generated data.

3. Results

3.1. Patients disposition and baseline characteristics

Between November 11, 2016 and July 10, 2019, a total of 649 patients were enrolled, randomized to receive HLX02 (n = 324) or EU-trastuzuamb (n = 325), and included in the ITT population (Fig. 1). Baseline characteristics of the enrolled patients have been previously described and were similar between the two treatment arms [16].

The updated efficacy and safety analyses hereafter are based on the data cut-off of September 28, 2021, after a median follow-up duration of 35.0 (range 0.1, 42.3) months (median duration of 35.4 months in the HLX02 group and 32.2 months in the EU-trastuzumab group). In total, 292 (45.0 %) patients had completed the study treatment (155 [47.8 %] in the HLX02 group and 137 [42.2 %] in the EU-trastuzumab group), and 357 (55.0 %) patients had discontinued the study treatment (169 [52.2 %] in the HLX02 group and 188 [57.8 %] in the EU-trastuzuamb group). (Fig. 1). 345 (53.2 %) patients had discontinued the study (163 [50.3 %] in the HLX02 group and 182 [56.0 %] in the EU-trastuzmab group), most commonly due to death (total 285 [43.9 %] patients: 132 [40.7 %] in the HLX02 group and 153 [47.1 %] in the EU-trastuzumab group).

3.2. Drug exposure

The exposure to study drugs (HLX02/EU-trastuzumab) were comparable between the two treatment arms (ESM Table 1); mean (standard deviation [SD]) treatment cycles completed were 12.4 (5.4), and 11.8 (5.4) for the HLX02, and EU-trastuzumab groups, respectively while the median total exposure duration was 10.3 months (range 0.7, 13.4), and

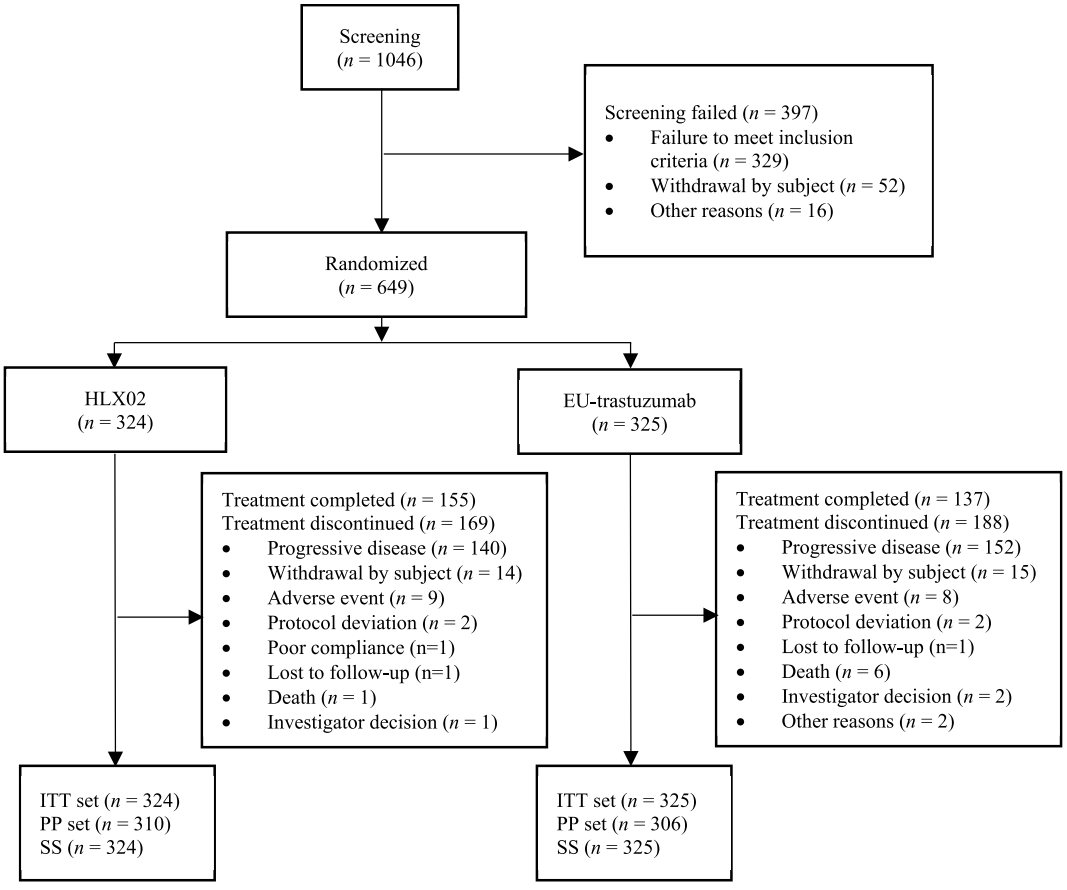

Fig. 1. Trial profile.
ITT intent-to-treat, *PPS* per protocol, *SS* safety set.

Table 1
Summary of tumor response by the blinded CIR for the intent-to-treat population.

	HLX02 (n = 324)	EU-trastuzumab (n = 325)	Difference % (95 % CI)	Stratified difference % (95 % CI)[a]
Primary endpoint, n (%)				
ORR_{24}	231 (71.3)	232 (71.4)	−0.1 (−7.0, 6.9)	0.1 (−6.9, 7.0)
Response up to week 24[b]				
Complete response	17 (5.2)	12 (3.7)		
Partial response	214 (66.0)	220 (67.7)		
Noncomplete/ nonprogressive	5 (1.5)	3 (0.9)		
Stable disease	48 (14.8)	65 (20.0)		
Progressive disease	24 (7.4)	16 (4.9)		
Not evaluable	16 (4.9)	9 (2.8)		
Secondary endpoints, n (%)				
Week 24 DCR[c]	274 (84.6)	285 (87.7)	−3.1 (−8.4, 2.2)	−3.3 (−8.6, 2.1)
Week 24 CBR[c]	263 (81.2)	263 (80.9)	0.2 (−5.8, 6.3)	0.3 (−5.8, 6.3)
ORR by week				
Week 6[b]	146 (45.1)	139 (42.8)	2.3 (−5.3, 9.9)	
Week 12[b]	190 (58.6)	187 (57.5)	1.1 (−6.5, 8.7)	
Week 18[b]	199 (61.4)	189 (58.2)	3.3 (−4.3, 10.8)	
Week 24[b]	192 (59.3)	175 (53.8)	5.4 (−2.2, 13.0)	
Week 33[c]	162 (50.0)	134 (41.2)	8.8 (1.1, 16.4)	
Week 42[c]	139 (42.9)	116 (35.7)	7.2 (−0.3, 14.7)	
Week 51[c]	90 (27.8)	86 (26.5)	1.3 (−5.5, 8.2)	

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 derived using the stratified CMH test with hormone receptor status, prior neo-/adjuvant therapy with trastuzumab and ethnicity as stratification factors (sensitivity analysis).

[b] Assessed by blinded CIR according to RECIST v1.1.

[c] Assessed by the investigator.

Table 2
Summary of adverse events (safety set).

	HLX02 (n = 324)	EU-trastuzumab (n = 325)
Number of TEAEs	6831	7001
Any TEAE, n (%)	320 (98.8)	321 (98.8)
Grade 1	3 (0.9)	7 (2.2)
Grade 2	39 (12.0)	33 (10.2)
Grade 3	84 (25.9)	95 (29.2)
Grade 4	191 (59.0)	181 (55.7)
Grade 5	3 (0.9)	5 (1.5)
TEAEs related to study drugs, n (%)	236 (72.8)	232 (71.4)
TEAEs leading to drug withdrawal, n (%)	10 (3.1)	11 (3.4)
Serious TEAEs, n (%)	77 (23.8)	80 (24.6)
Grade 1	0	1 (0.3)
Grade 2	12 (3.7)	7 (2.2)
Grade 3	22 (6.8)	31 (9.5)
Grade 4	40 (12.3)	36 (11.1)
Grade 5	3 (0.9)	5 (1.5)
Serious TEAEs related to study drugs, n (%)	31 (9.6)	29 (8.9)
Deaths, n (%)	3 (0.9)	5 (1.5)
Treatment-related AEs (≥5 % of patients), n (%)		
Neutrophil count decreased	105 (32.4)	108 (33.2)
White blood cell count decreased	102 (31.5)	110 (33.8)
Anaemia	61 (18.8)	74 (22.8)
Alopecia	39 (12.0)	49 (15.1)
Alanine aminotransferase increased	38 (11.7)	35 (10.8)
Infusion related reaction	34 (10.5)	24 (7.4)
Aspartate aminotransferase increased	33 (10.2)	32 (9.8)
Diarrhoea	32 (9.9)	27 (8.3)
Pyrexia	22 (6.8)	25 (7.7)
Rash	22 (6.8)	20 (6.2)
Oedema peripheral	21 (6.5)	17 (5.2)
Malaise	19 (5.9)	15 (4.6)
Gamma-glutamyl transferase increased	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 (≥5 % of patients), n (%)	260 (80.2)	258 (79.4)
White blood cell count decreased	225 (69.4)	224 (68.9)
Neutrophil count decreased	214 (66.0)	209 (64.3)
Anaemia	122 (37.7)	133 (40.9)
Infusion related reaction	41 (12.7)	32 (9.8)
Myelosuppression	20 (6.2)	23 (7.1)
Platelet count decreased	19 (5.9)	23 (7.1)
Febrile neutropenia	16 (4.9)	20 (6.2)

AE adverse event, *TEAE* treatment-emergent AE.

9.6 (range 0.7, 13.7) months, respectively. Exposure to chemotherapy docetaxel was also comparable between the two treatment arms (ESM Table 2); mean (SD) cycles completed were 8.2 (3.5), and 8.1 (3.5) for the HLX02, and EU-trastuzumab groups, respectively.

3.3. Efficacy results

Consistent with the previous efficacy data reported in the previous interim analysis, ORR_{24} as assessed by the CIR was 71.3 % and 71.4 % in the HLX02 and EU-trastuzumab groups, respectively; with an intergroup difference of −0.1 % (95 % CI -7, 6.9). 17 (5.2 %) patients in HLX02 group and 12 (3.7 %) in the EU-trastuzumab group achieved CR, while 214 (66.0 %) patients in HLX02 group and 220 (67.7 %) in the EU-trastuzumab group had PR (Table 1). No difference in ORR_{24} was found between the two treatment arms ($p = 0.983$). Furthermore, there were no marked differences between the two treatment arms in the analyses of various secondary efficacy endpoints and sensitivity analyses (Table 1); similar ORRs at weeks 6, 12, 18, 24, and 51, DCRs, and CBRs were observed between the two treatment groups. Median DOR assessed by the investigator was comparable at 10.6 (95 % CI 10.2, 11.7), and 10.3 (95 % CI 9.0, 11.5) months for the HLX02, and EU-trastuzumab groups, respectively (stratified HR 0.86 [95 % CI 0.65, 1.12]; $p = 0.262$) (ESM Fig. 1). Median PFS was also comparable between the HLX02 and EU-trastuzumab groups (11.7 (95 % CI 11.5, 12.1) and 10.6 (95 % CI 9.5, 11.7) months; stratified HR, 0.86 [95 % CI 0.69, 1.06]; $p = 0.158$) (Fig. 2a), with 171 (52.8 %) patients with events in the HLX02 group versus 184 (56.6 %) patients with events in the EU-trastuzumab group.

After a median follow-up of 35.0 months, 128 (39.5 %), and 142 (43.7 %) patients had died in the HLX02, and EU-trastuzumab group, respectively. Median OS was 37.3 (95 % CI 36.2, not evaluable [NE]) months in the HLX02 group and not reached (95 % CI 34.2, NE) in the EU-trastuzumab group (stratified HR, 0.86 [95 % CI 0.68, 1.10]; $p = 0.229$) (Fig. 2b), indicating a similar OS benefit with the HLX02 and EU-trastuzumab treatments. 12-month, 24-month, and 36-month OS rate was similar between the two treatment arms (12-month rate: 88.9 % vs. 88.4 %; 24-month rate: 71.4 % vs. 67.6 %; 36-month rate: 57.5 % vs. 54.0 %).

3.4. Safety results

At this long-term follow-up analysis, the overall safety profiles of

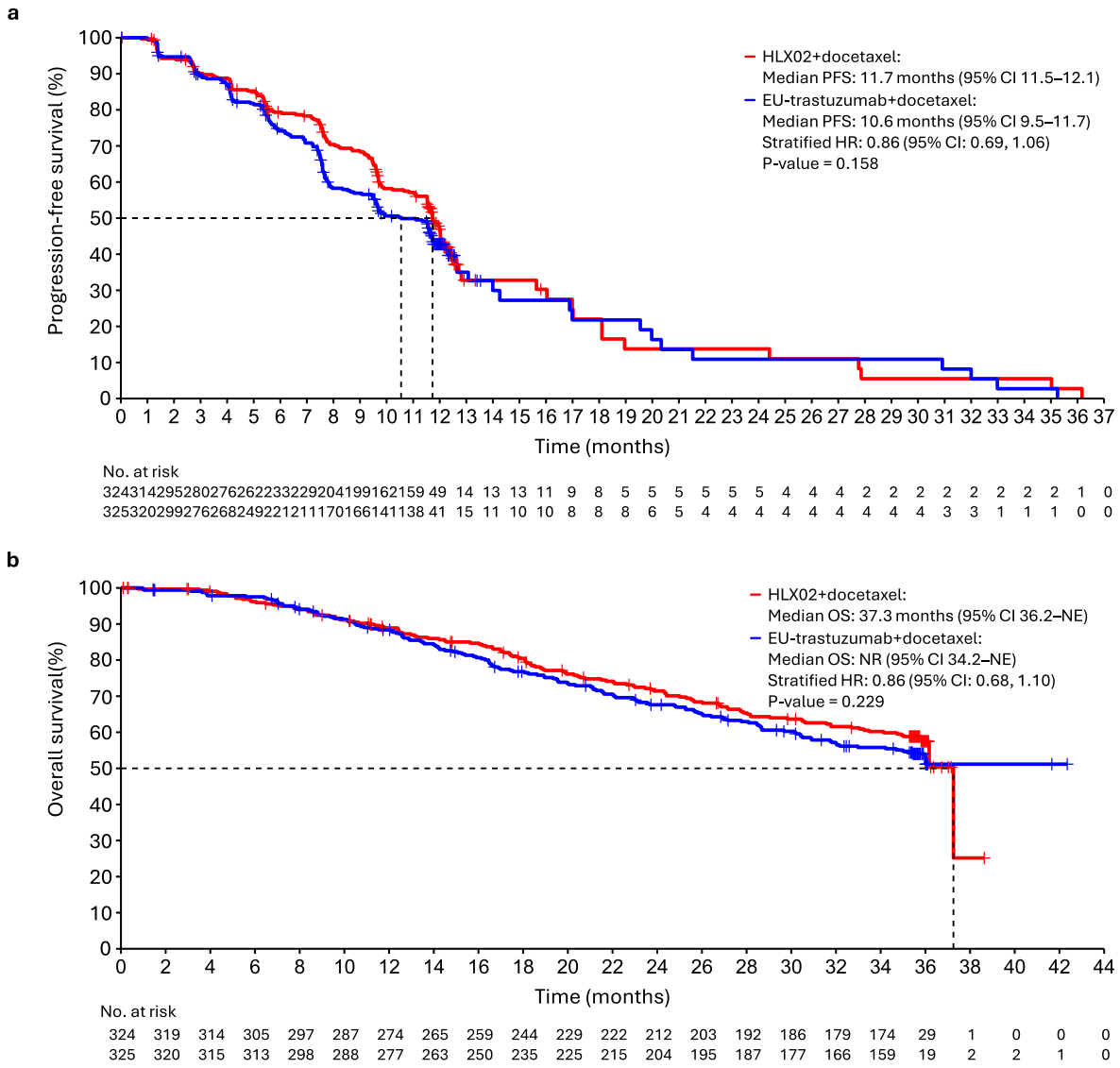

Fig. 2. Kaplan–Meier estimates of investigator-assessed progression-free survival and overall survival.
(a) progression-free survival and (b) overall survival in the intent-to-treat population ($n = 649$); HLX02 ($n = 324$), EU-trastuzumab ($n = 325$). Tick marks indicate censoring of the data at the time of the last imaging assessment for PFS, and censoring of the data at the last known survival date for OS, respectively. Median survival and their 95 % CIs were derived using a Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with trastuzumab, and ethnicity (Asian vs. non-Asian) as covariates. P-values were calculated using the stratified log-rank test.
CI confidence interval, *HR* hazard ratio, *NE* not evaluable, *NR* not reached.

HLX02 and EU-trastuzumab were similar (Table 2); 98.8 % of patients in the HLX02 and EU-trastuzumab groups experiencing at least one treatment-emergent adverse event (TEAE), most commonly white blood cell count decreased, neutrophil count decreased, alopecia, and anaemia. Incidences of Grade 3 or higher TEAEs (85.8 vs. 86.4 %) and serious TEAEs (23.8 vs. 24.6 %) were reported in a similar proportion of patients in both groups. TEAEs leading to treatment discontinuation were reported in 3.1, and 3.4 % of patients in the HLX02, and EU-trastuzumab groups, respectively. Three, and five patients in the HLX02, and EU-trastuzumab groups experienced TEAEs leading to death; one case each due to lung infection, dyspnea, and pneumonia in the HLX02 group and 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 in the EU-trastuzumab group.

Most commonly reported adverse events of special interest (AESIs) for the HLX02 and EU-trastuzumab groups included white blood cell count decreased (69.4 vs. 68.9 %), neutrophil count decreased (66 vs. 64.3 %), and anaemia (37.7 and 40.9 %). Cardiac disorders of special interest occurred in a similar proportion of patients (4.9 vs. 5.2 %) for both treatment groups; cardiac disorders of special interest classified by preferred terms are listed in ESM Table 3. Shifts in left ventricular ejection fraction (LVEF) from normal to abnormal were observed in 17 (5.2 %) patients in the HLX02 treatment group and in 20 (6.2 %) patients in the EU-trastuzumab group. There were no significant changes in LVEF from baseline to weeks 21 and 48, as well as during follow-up for the two treatment groups (Table 3).

3.5. *Pharmacokinetic and immunogenicity results*

Consistent with the previous interim analysis, the pharmacokinetic profiles were similar between the HLX02 and EU-trastuzumab groups [16]; no noteworthy differences in mean trastuzumab serum concentration were observed between the two treatment groups. The

Table 3
Left ventricular ejection fraction at baseline and weeks 21, 48, and follow-up.

LVEF observed, %	HLX02 (n = 324)	EU-trastuzumab (n = 325)
Baseline		
n (missing)	324 (0)	325 (0)
Mean ± SD	64.7 ± 5.1	64.0 ± 4.9
Median (range)	65.0 (52.0–82.0)	64.0 (50.0–80.0)
Week 21		
n (missing)	256 (68)	253 (72)
Mean ± SD	63.7 ± 4.8	63.8 ± 4.8
Median (range)	63.0 (41.0–77.0)	63.3 (44.0–78.0)
Week 48		
n (missing)	158 (166)	136 (189)
Mean ± SD	64.0 ± 4.6	63.7 ± 5.2
Median (range)	64.0 (53.0–76.0)	63.0 (44.0–79.0)
Follow-up		
n (missing)	265 (59)	264 (61)
Mean ± SD	63.5 ± 4.8	62.9 ± 4.9
Median (range)	63.0 (45.0–78.0)	63.0 (44.0–77.0)
Long-term follow-up		
n (missing)	67 (257)	75 (250)
Mean ± SD	64.2 ± 5.0	64.3 ± 5.1
Median (range)	64.0 (50.0–74.0)	64.0 (53.0–81.0)

LVEF left ventricular ejection fraction, *SD* standard deviation.

immunogenicity profiles for the two groups in this analysis were consistent with that previously published [16]; the overall incidences of ADA- and NADA-positivity were comparable between the patients in the two groups.

4. Discussion

Therapeutic equivalence was previously demonstrated between HLX02 and reference trastuzumab by comparing efficacy endpoints including ORR_{24}, DOR, PFS and OS over 15 months of follow-up [16]. Briefly, there was no difference in ORR_{24} in the ITT population between HLX02 and reference trastuzumab; 71.3 % vs. 71.4 %, intergroup difference of −0.1 % [95 % CI -7, 6.9], $p = 0.983$. Importantly, its 95 % CIs of −7.0 to 6.9 fell completely within the predefined equivalence boundaries of ±13.5 %. Incidences and nature of TEAEs and cardiac disorders of special interest were also similar between the two treatment arms [16].

To date, there are a total of six approved trastuzumab biosimilars by the United States Food and Drug Administration, namely CT-P6, ABP 980, trastuzumab-dkst, SB3, PF-05280014 and HLX02, while several more are being investigated, including BCD-022, EG 12014, TX05, HD201, AryoTrust®, SIBP-01, and DMB-3111 [18]. Among the approved biosimilars, the comparability of CT-P6 [19], ABP 980 [20] and SB3 [21] to reference trastuzumab were examined and demonstrated in the neoadjuvant setting, whereas HLX02 [16] and trastuzumab-dkst [22] were shown to be equivalent to reference trastuzumab in the metastatic setting and that for PF-05280014 was demonstrated in both the neoadjuvant and the metastatic setting [23,24]. While both settings are suitable for comparability studies (since reference trastuzumab is approved for the treatment of early and metastatic breast cancer), the neoadjuvant setting provides a more homogenous and sensitive patient population as these patients tend to have less confounding factors including varying comorbidities and lines of prior treatments [25]. In addition, the selection of clinical endpoint in the neoadjuvant setting i.e. the pathological complete response may be a more desirable endpoint to establish efficacy biosimilarity due to its correlation with a long-term survival outcome in patients with early breast cancer [26–28]. On the other hand, investigations of comparability in the metastatic setting confer advantages including the increased amount of safety data due to the typically longer treatment duration as opposed to that in the neoadjuvant setting. Furthermore, it tends to be a more direct reflection of real-world therapeutic scenarios whereby most patients with metastatic cancer are not candidates for surgery or curative therapies.

The comparisons of HLX02 and the aforementioned biosimilars among patients with metastatic breast cancer have been previously discussed [16]. In the current long-term follow-up analysis, OS as well as safety and immunogenicity, were reported after a follow-up period of up to 36 months. In terms of the updated OS, there was no difference in the OS benefit between HLX02 and reference trastuzumab (median OS, 37.3 months vs. NR, stratified HR, 0.86; $p = 0.229$). Furthermore, the 36-month OS rate was similar with the HLX02 and EU-trastuzumab treatments (57.5 % vs. 54.0 %). Our findings (37.3 months vs. NR) were also comparable to that reported for trastuzumab-dkst (35.0 months vs. 30.2 months) [29], and PF-05280014 (not available [NA] vs. NA) [30]. In terms of PFS, the median PFS of 11.7, and 10.6 months for the HLX02, and reference trastuzumab arms at this long-term follow-up assessment was comparable to that in the trastuzumab-dkst study (trastuzumab-dkst, 11.1 months vs. reference trastuzumab, 11.1 months) [29].

The overall safety profiles of HLX02 and trastuzumab after 36 months of follow-up were similar; no notable differences were observed in terms of TEAE type, incidence, or severity. Safety findings for HLX02 in this study was also comparable to that of the known characteristics for trastuzumab in patients with breast cancer [22,31]. Increased risk of cardiac toxicity has been documented with the use of trastuzumab [8]. In this study, the frequency of cardiac disorders was found to be low and comparable between HLX02 and trastuzumab (three vs. six patients); cardiac disorders that led to treatment interruption or withdraw were only reported in two patients in the HLX02 group (one case each of left ventricular dysfunction and pericardial effusion) and three patients in the trastuzumab group (one case each of congestive cardiac failure, coronary artery disease, and ventricular arrhythmia). Overall, the totality of cardiac disorders experienced by patients receiving HLX02 or trastuzumab in this study resembles that of previously reported trials [22,24]. In terms of immunogenicity, two patients in each treatment group were ADA-positive, thereby indicating similar immunogenicity between HLX02 and reference trastuzumab. Immunogenicity data was also consistent with previously published findings for trastuzumab and other trastuzumab biosimilars [22,24].

4.1. Conclusions

Treatment with HLX02 and reference trastuzumab showed comparable long-term survival data and event-free rate at 36 months. The long-term safety and immunogenicity profiles of the two treatment groups were also similar. Overall, HLX02 and reference trastuzumab are equivalent in patients with previously untreated, HER2-positive metastatic breast cancer.

CRediT authorship contribution statement

Binghe Xu: Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Qingyuan Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Tao Sun:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Wei Li:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Yue'e Teng:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Xichun Hu:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Igor Bondarenko:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Hryhoriy Adamchuk:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Liangming Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Dmytro Trukhin:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Shusen Wang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Hong Zheng:** Writing – review & editing, Writing –

original draft, Formal analysis, Data curation. **Zhongsheng Tong:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Yaroslav Shparyk:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Futang Yang:** Writing – review & editing, Writing – original draft, Formal analysis. **Haoyu Yu:** Writing – review & editing, Writing – original draft, Formal analysis. **Jing Li:** Writing – review & editing, Writing – original draft, Formal analysis. **Qingyu Wang:** Writing – review & editing, Writing – original draft, Formal analysis. **Jun Zhu:** Writing – review & editing, Writing – original draft, Formal analysis.

Data availability

Requests for data from this study should be submitted to Binghe Xu (xubinghe@medmail.com.cn) and are available upon reasonable request.

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. Protocol and all amendments of this study were approved by relevant regulatory authorities and the ethics committees of all participating centers as previously published [16]. 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

Written informed consent was provided by all participants prior to admission and initiation of the study.

Funding

This study was funded by Shanghai Henlius Biotech, Inc., Shanghai, China.

Declaration of competing interest

Futang Yang, Haoyu Yu, Jing Li, Qingyu Wang and Jun Zhu are employees of Shanghai Henlius Biotech, Inc. All other authors have no competing interests to declare.

Acknowledgements

The authors thank all the participants and families who were involved in the HLX02 phase III study, the clinical study teams (Clinical Operation: Liman Zhang; Clinical Pharmacology: Liang Zhou; Statistics: Wenting Qiu, Yi Zhu; Medical Writing: Zhi Hao Kwok, Chen Hu), and Wenjie Zhang of Shanghai Henlius Biotech, Inc., for providing support for the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104413.

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