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SHR-A1811 versus pyrotinib plus capecitabine in human epidermal growth factor receptor 2-positive (HER2+) advanced/metastatic breast cancer (BC): A multicenter, open-label, randomized, phase III study (HORIZON-Breast01)

E. Song[1], H. Yao[2], H. Li[3], Y. Yin[4], Q. Zhang[5], S. Wang[6], Q. Ouyang[7], T. Sun[8], X. Wang[9], W. Xie[10], B. Wang[11], W. Li[12], M. Yan[13], C. Geng[14], Y. Peng[15], Y. Yang[16], F. Dong[17], Y. Zhang[18], L. Cheng[18], X. Zhu[18]

[1] Department of Breast Tumor Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [2] Phase I Clinical Trial Centre, Department of Medical Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [3] Department of Breast Oncology, Beijing Cancer Hospital, Beijing, China, [4] Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [5] Department of Breast and Lymphoma, Harbin Medical University Cancer Hospital, Harbin, China, [6] Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China, [7] Department of Medical Oncology, Hunan Cancer Hospital, Changsha, China, [8] Department of Breast Medicine 1, Cancer Hospital of Dalian University of Technology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, China, [9] Breast Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China, [10] Dept. of Breast and Bone Soft Tissue Tumors, Guangxi Medical University Cancer Hospital, Nanning, China, [11] Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, [12] Department of Oncology, The First Hospital of Jilin University, Changchun, China, [13] Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China, [14] Breast Center, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [15] Special Medical Care Department, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China, [16] Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [17] Department of Biometrics, Jiangsu Hengrui Pharmaceutical Co., Ltd., Shanghai, China[18] Oncology Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background

SHR-A1811, a HER2-targeted antibody-drug conjugate, proved substantial single agent antitumor activity in heavily pretreated solid tumors as shown in a global phase 1 trial (*J Clin Oncol. 2024*). Here, we first report the interim analysis of SHR-A1811 versus pyrotinib plus capecitabine in HER2+ advanced/metastatic BC from the pivotal phase 3 HORIZON-Breast01 study.

Methods

Taxane- and trastuzumab-pretreated patients (pts) with HER2+ advanced/metastatic BC were randomized (1:1) to receive intravenous SHR-A1811 or oral pyrotinib plus capecitabine. The primary endpoint was PFS by blinded independent central review (BICR).

Results

As of Jun 30, 2025, 287 pts were randomized (SHR-A1811, n=142; pyrotinib plus capecitabine, n=145; IHC 3+: 76.1% vs. 71.7%; HR+: 47.9% vs. 47.6%; median lines of prior systemic treatments: 1 vs.1; prior pertuzumab: 71.8% vs. 72.4%), with median follow-up of 15.9 months (95% CI 14.6–17.1) for SHR-A1811, and 15.3 months (95% CI 14.3–16.6) for pyrotinib plus capecitabine. The PFS by BICR was significantly improved in the SHR-A1811 group than in the pyrotinib plus capecitabine group (30.6 months vs. 8.3 months; HR 0.22 [95% CI 0.15–0.34]; p<0.0001; table). Although the median OS was not yet reached, SHR-A1811 showed a clear OS benefit trend. Median treatment duration was 19.5 months (95% CI 17.3–NR) with SHR-A1811, 7.1 months (95% CI 5.6–9.2) with pyrotinib, and 7.5 months (95% CI 5.7–9.6) with capecitabine. Similar rates of TRAEs were observed. Interstitial lung disease (ILD) occurred only in 4 pts (2.8%) receiving SHR-A1811 (grade 1/2: 3 [2.1%]; grade 3: 1 [0.7%]).Table: LBA19

Summary of results

Efficacy	SHR-A1811 (n=142)	Pyrotinib [a] plus capecitabine (n=145)
PFS events by BICR, n (%)	37 (26.1)	87 (60.0)
Median PFS by BICR, months (95% CI)	30.6 (16.8–NR)	8.3 (6.9–11.0)
HR (95% CI); p [b]	0.22 (0.15–0.34); p<0.0001	
12-months PFS rates by BICR, % (95% CI)	84.7 (77.0–90.0)	35.5 (26.8–44.2)
Median OS, months (95% CI)	NR (NR–NR)	NR (NR–NR)
HR (95% CI); p [b]	0.31 (0.14–0.69); p=0.0012	
confirmed ORR by BICR, % (95% CI)	81.7 (74.3–87.7)	55.9 (47.4–64.1)

Efficacy	SHR-A1811 (n=142)	Pyrotinib [a] plus capecitabine (n=145)
TRAEs [c]	SHR-A1811 (n=142)	Pyrotinib plus capecitabine (n=144)
Grade ≥3, n (%)	100 (70.4)	90 (62.5)
Serious, n (%)	19 (13.4)	17 (11.8)
Leading to death, n (%)	0	1 (0.7)

[a]pan-HER TKI, commonly used 2L SOC for HER2+ BC in China. [b]1-sided c. assessed in treated pts.

Conclusions

SHR-A1811 exhibited significant PFS benefit and strong trend in OS benefit versus pyrotinib plus capecitabine in the second-line therapy in HER2+ advanced/metastatic BC, with favorable safety profile of low ILD occurrence.

Clinical trial identification

NCT05424835.

Legal entity responsible for the study

Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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Disclosure

F. Dong, Y. Zhang, L. Cheng, X. Zhu: Financial Interests, Personal, Full or part-time Employment: Jiangsu Hengrui Pharmaceuticals Co., Ltd. All other authors have declared no conflicts of interest.