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SUPPLEMENTAL DATA

Updated survival outcomes of SYHX2011 versus albumin-bound paclitaxel in advanced breast cancer: A randomized double-blind phase III trial

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Full article is available at the following link: Updated survival outcomes of SYHX2011 versus albumin-bound paclitaxel in advanced breast cancer: A randomized double-blind phase III trial

Supplemental methods

Methods in brief

Study design and participants

This multicenter, double-blind, randomized phase 3 trial was conducted at 56 centers in China. Eligible patients were aged 18 years or older with histologically or cytologically confirmed unresectable locally advanced or metastatic breast cancer and were considered candidates for single-agent albumin-bound paclitaxel treatment according to the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guideline 2022 at the investigator's discretion. Only patients with HER2-negative breast cancer were eligible for enrollment, as the CSCO Breast Cancer Guideline 2022 provides no recommendation for single-agent albumin-bound paclitaxel in HER2-positive breast cancer. The protocol imposed no prespecified restrictions on prior systemic therapy or prior taxane exposure, and eligibility was assessed by the investigator in accordance with the guideline. Additional inclusion criteria included having at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[14] an Eastern Cooperative Oncology Group performance status of 0–1, and a life expectancy of at least 3 months. Patients were required to have adequate organ function within 7 days before the first dose, including an absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, hemoglobin ≥90 g/L, aspartate aminotransferase and alanine aminotransferase ≤10 × the upper limit of normal (ULN), total bilirubin ≤1.5 × ULN, serum creatinine ≤1.5 × ULN, creatinine clearance ≥30 mL/min, and activated partial thromboplastin time, prothrombin time, and international standardized ratio ≤1.5 × ULN. Patients with previously treated brain metastases were eligible if they had stable intracranial disease (radiographic stability for at least 4 weeks before the first study-drug administration, no new neurological symptoms [or neurological symptoms returned to baseline], no requirement for corticosteroid therapy within 14 days before treatment initiation), and no evidence of new or enlarging brain metastases. Key exclusion criteria included a history of hypersensitivity reactions to taxanes or human serum albumin (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, grade ≥3), malignancy within the previous 5 years except for carcinoma in situ or basal cell carcinoma, untreated active brain metastases (including symptomatic brain metastases

or leptomeningeal disease), and unresolved toxicities from previous anti-tumor therapies.

The study was approved by the Independent Ethics Committee at each participating site and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent before enrollment. This study is registered with ClinicalTrials.gov: NCT05753865.

Randomization and masking

SYHX2011 is a modified formulation of albumin-bound paclitaxel designed to reduce rash during drug preparation and administration while maintaining the rapid in vivo disintegration properties, pharmacokinetic characteristics, and efficacy profile of the reference product. Because Abraxane was suspended from importation and use in China in 2020 due to GMP-related issues, albumin-bound paclitaxel for injection (Keaili®, PAB; CSPC Ouyi Pharmaceutical Technology Co., Ltd.), a generic formulation with comparable composition, pharmacokinetic, and safety profiles,[15] was selected as the comparator.

Patients were randomly assigned in a 1:1 ratio to receive SYHX2011 or PAB through an interactive web-response system. Randomization was performed centrally and stratified according to previous taxane exposure and rash occurrence (previous taxanes with rash, previous taxanes with no rash, or no previous taxanes), as well as previous chemotherapy for advanced disease (0 vs ≥1 line), to ensure balance between treatment groups with respect to factors potentially associated with rash risk and treatment outcomes.[16,17]

SYHX2011 and PAB had the same appearance but differed slightly in their solvent. Study drugs were prepared by independent unblinded nurses, who were not involved in patient care, efficacy or safety evaluations, or data analysis. Investigators, patients, sponsors, outcome assessors, data management staff, statisticians, and other study staff were blinded to treatment assignment. Any differences in reconstitution procedures were confined to the independent unblinded preparation nurses and were not disclosed to investigators, patients, outcome assessors, or other blinded study personnel.

Procedures

SYHX2011 and PAB were administered intravenously over 30 minutes at a dose of 260 mg/m^2 on day 1 of each 21-day treatment cycle under the supervision of physicians experienced in the administration of anticancer agents. Treatment

continued until disease progression, unacceptable toxicity, initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death, whichever occurred first. To prevent chemotherapy-related vomiting and myelosuppression, patients received intravenous ondansetron (8 mg) before study drug administration and subcutaneous polyethylene glycol recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF; 6 mg) 48 hours after treatment administration. A maximum of two dose reductions was permitted during treatment. Dose interruption was required for grade 3 neurotoxicity, and treatment could be resumed at a reduced dose after recovery to grade 2 or lower. Treatment delay beyond one cycle was not permitted. The initial dose of SYHX2011 or PAB was 260 mg/m^2 and could be reduced to 220 mg/m^2 in the event of severe neutropenia (absolute neutrophil count $<0.5 \times 10^9$/L for $\geq$1 week) or severe peripheral sensory neuropathy. For recurrent events requiring further dose modification, the dose was reduced from 220 mg/m^2 to 180 mg/m^2. Premedication with corticosteroids and antihistamines was prohibited before the first study treatment administration but was permitted thereafter when clinically indicated at the investigator's discretion.

Tumor assessments were performed by investigators and the independent review committee (IRC) based on RECIST version 1.1 and performed by enhanced CT or MRI every 6 weeks until disease progression, withdrawal of consent, loss to follow-up, death, or initiation of a new anti-tumor treatment (whichever occurred first). IRC assessments and data on post-progression anticancer therapies (**Supplemental Table 5**) were collected up to the primary analysis data cutoff on September 21, 2024. Survival follow-up was conducted every 12 weeks after the end of treatment.

Outcomes

The primary endpoint was confirmed objective response rate (ORR) assessed by the IRC per RECIST version 1.1, defined as the proportion of patients achieving confirmed complete or partial responses as their best overall response. Other secondary endpoints included confirmed investigator-assessed ORR, progression-free survival (PFS; time from randomization to disease progression or all-cause death), time to progression (TTP), overall survival (OS; time from randomization until death from any cause), safety, and investigational drug reconstitution time (dissolution completeness). Here, we report updated investigator-assessed PFS and OS outcomes.

Statistical analysis

Efficacy was assessed in the intention-to-treat population (all randomized patients), and safety was assessed in all patients who received at least one dose of study treatment.

This report presents an exploratory extended follow-up analysis of the phase III trial to evaluate investigator-assessed long-term survival outcomes. PFS and OS were estimated using the Kaplan-Meier method. Patients who were alive without progression or lost to follow-up were censored for PFS at the last tumor assessment. Patients still alive or lost to follow-up were censored for OS at the last day known alive. Differences in PFS and OS between treatment groups in the overall population were assessed using a one-sided stratified log-rank test. Hazard ratios and corresponding 95% confidence intervals were estimated using stratified Cox proportional hazards models based on the randomization stratification factors. Statistical comparisons in the overall population are presented for descriptive purposes. The reported one-sided p-values are nominal, were not adjusted for multiplicity, and should be interpreted descriptively in the context of this exploratory extended follow-up analysis rather than as confirmatory evidence. Exploratory subgroup analyses were conducted in patients with hormone receptor-positive disease, triple-negative breast cancer, first-line therapy, and second- or later-line therapy and were not powered for formal statistical comparisons or interaction testing.

Table S1. Demographic and clinical characteristics at baseline

	SYHX2011 (N=229)	PAB (N=230)
Age, years		
Median (range)	57.0 (27–84)	56.0 (28–84)
<65	183 (79.9)	187 (81.3)
≥65	46 (20.1)	43 (18.7)
Sex		
Male	2 (0.9)	0
Female	227 (99.1)	230 (100)
ECOG PS		
0	85 (37.1)	95 (41.3)
1	144 (62.9)	135 (58.7)
Menopause *		
Yes	177 (78.0)	172 (74.8)
No	50 (22.0)	58 (25.2)
Molecular subtype		
Hormone receptor-positive †	173 (75.5)	166 (72.2)
Triple-negative breast cancer	56 (24.5)	64 (27.8)
Clinical stage (TNM staging system)		
Stage IV (metastatic)	228 (99.6)	223 (97.0)
Stage IIIB/IIIC (unresectable locally advanced)	1 (0.4)	7 (3.0)
Metastatic organs ǂ		
Bone	136 (59.4)	140 (60.9)
Lymph	117 (51.1)	109 (47.4)
Lung	108 (47.2)	102 (44.3)
Liver	105 (45.9)	109 (47.4)
Brain	3 (1.3)	7 (3.0)
Others	74 (32.3)	75 (32.6)
Previous chemotherapy for advanced disease		
0	165 (72.1)	167 (72.6)
≥1	64 (27.9)	63 (27.4)
Previous taxanes use and rash occurrence		

Previous taxanes with rash	3 (1.3)	1 (0.4)
Previous taxanes with no rash	158 (69.0)	159 (69.1)
No previous taxanes	68 (29.7)	70 (30.4)

Data are presented as *n* (%) unless otherwise specified.* The SYHX2011 group included two male patients; percentages for menopausal status were calculated exclusively among female patients. † Hormone receptor-positive breast cancer was defined as tumors exhibiting positive immunohistochemical staining in >1% of cells for estrogen receptors and/or progesterone receptors. ǂ Patients may have presented with one or more metastatic sites. **Abbreviations**: ECOG PS, Eastern Cooperative Oncology Group performance status; PAB, approved albumin-bound paclitaxel for injection; TNM, tumor–node–metastasis.

Table S2. Baseline characteristics of clinically relevant subgroups

	SYHX2011	PAB	Total
Hormone receptor-positive breast cancer	173	166	339
Prior endocrine therapy	133 (76.9)	120 (72.3)	253 (74.6)
Prior CDK4/6 inhibitor exposure	67 (38.7)	55 (33.1)	122 (36.0)
Triple-negative breast cancer	56	64	120
Prior immunotherapy	1 (1.8)	2 (3.1)	3 (2.5)

Data are presented as n (%). Percentages for subgroup-specific treatments were calculated using the corresponding subgroup population as the denominator. **Abbreviations**: CDK4/6, cyclin-dependent kinase 4/6; PAB, approved albumin-bound paclitaxel for injection; SYHX2011, novel albumin-bound paclitaxel formulation.

Table S3. Reasons for censoring of progression-free survival in the intention-to-treat population

	SYHX2011	PAB
Any reasons	99	85
Started new anticancer treatment before event	61 (61.6)	55 (64.7)
Continued in trial without event	9 (9.0)	6 (7.0)
Event occurred after ≥2 consecutive missing tumor assessments	4 (4.0)	2 (2.4)
Lost to follow-up / withdrew consent / other	17 (17.1)	17 (20.0)
No baseline or post-baseline imaging, and no death recorded	8 (8.1)	5 (5.9)

Data are presented as n (%). Percentages were calculated using the number of censored patients within each treatment group as the denominator.

Abbreviations: PAB, approved albumin-bound paclitaxel for injection; SYHX2011, novel albumin-bound paclitaxel formulation.

Table S4. Reasons for censoring overall survival data in the intention-to-treat population

	SYHX2011	PAB
Any reasons	131	122
Alive	112 (85.5)	93 (76.2)
Lost to follow-up	19 (14.5)	29 (23.8)

Data are presented as n (%). Percentages were calculated using the number of censored patients within each treatment group as the denominator.

Abbreviations: PAB, approved albumin-bound paclitaxel for injection; SYHX2011, novel albumin-bound paclitaxel formulation.

Table S5. Post-progression anticancer therapies (cutoff date: September 21, 2024)

	SYHX2011 (*n*=229)	PAB (*n*=230)	Total (*n*=459)
Drug therapy	57 (24.9)	72 (31.3)	129 (28.1)
Radiotherapy	6 (2.6)	8 (3.5)	14 (3.1)
Surgery	3 (1.3)	6 (2.6)	9 (2.0)
Other therapies*	1 (0.4)	4 (1.7)	5 (1.1)

Data are presented as *n* (%). *Other therapies included: unknown therapies for patients S09001 and S09002 (PAB group); hepatic arteriography, hepatic arterial infusion chemotherapy, and embolization for patient S38001 (PAB group); transcatheter hepatic arterial embolization under local anesthesia combined with chemotherapy infusion, abdominal arteriography, and focused ultrasound ablation of liver tumors for patient S41004 (PAB group); and percutaneous abdominal arteriography, superselective hepatic arteriography, infusion chemotherapy, and embolization for patient S36006 (SYHX2011 group).

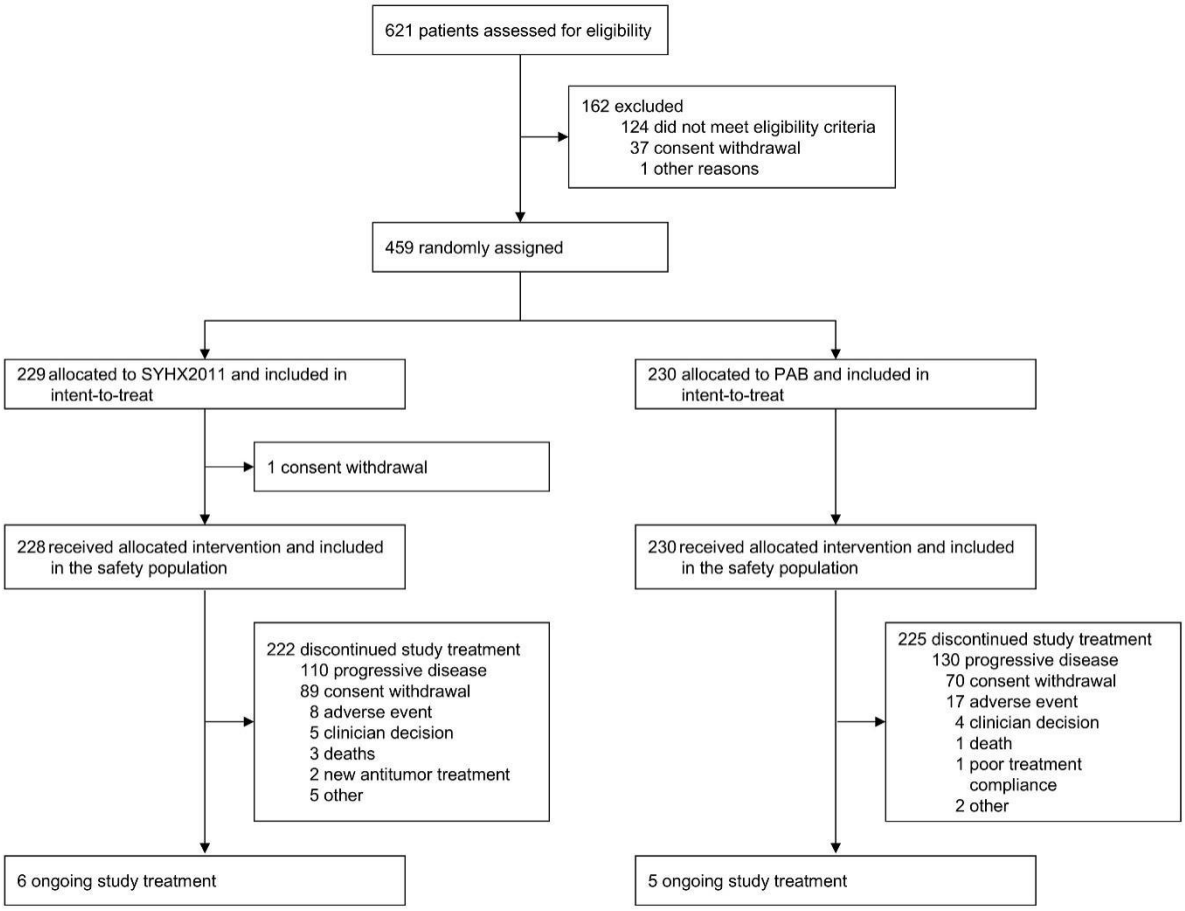


Figure S1. Patient disposition

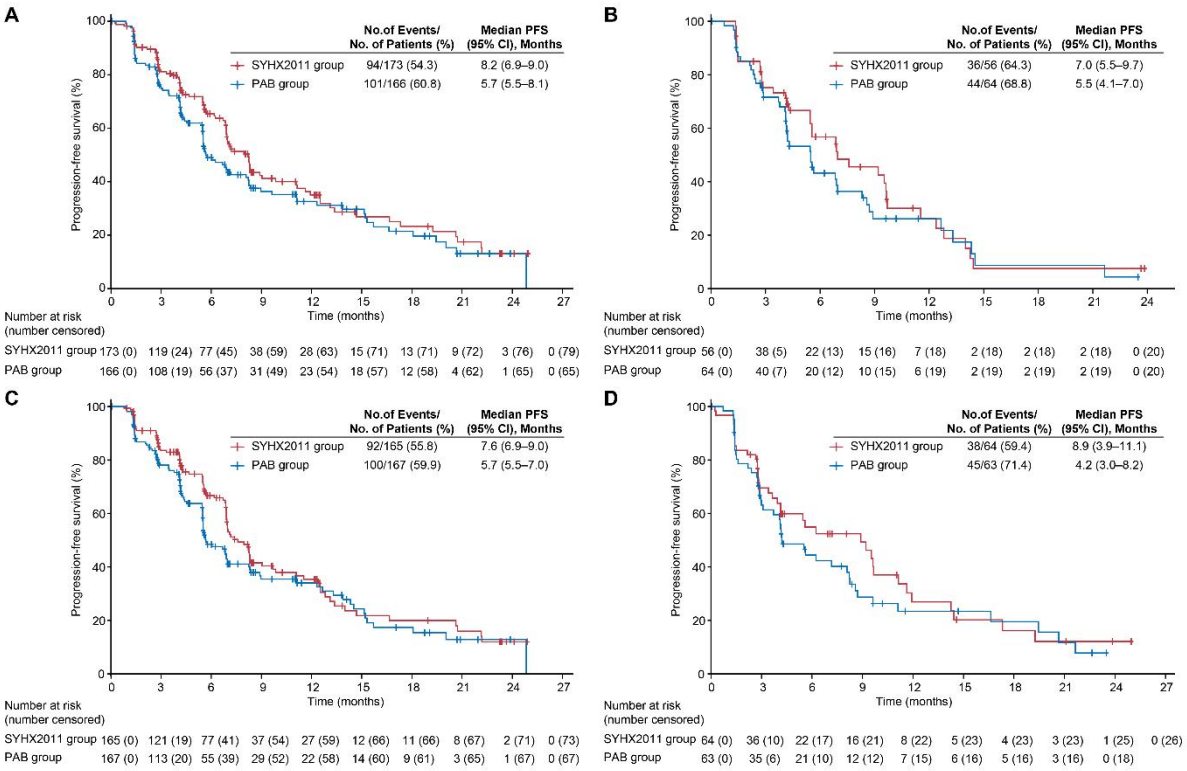


Figure S2. Updated investigator-assessed progression-free survival across clinically relevant subgroups. (A) Kaplan–Meier estimates of progression-free survival in patients with hormone receptor-positive breast cancer. Median progression-free survival was 8.2 months (95% CI: 6.9–9.0) in the SYHX2011 group and 5.7 months (95% CI: 5.5–8.1) in the approved albumin-bound paclitaxel for injection (PAB) group. **(B)** Kaplan–Meier estimates of progression-free survival in patients with triple-negative breast cancer, with median progression-free survival of 7.0 months (95% CI: 5.5–9.7) and 5.5 months (95% CI: 4.1–7.0), respectively. **(C)** Kaplan–Meier estimates of progression-free survival in patients receiving first-line therapy, with median progression-free survival of 7.6 months (95% CI: 6.9–9.0) in the SYHX2011 group and 5.7 months (95% CI: 5.5–7.0) in the PAB group. **(D)** Kaplan–Meier estimates of progression-free survival in patients receiving second- or later-line therapy, with median progression-free survival of 8.9 months (95% CI: 3.9–11.1) and 4.2 months (95% CI: 3.0–8.2), respectively. Tick marks indicate censored observations, and the tables below the plots show the numbers of patients at risk, with cumulative numbers censored in parentheses, at each time point. **Abbreviations**: CI, confidence interval; PAB, approved albumin-bound paclitaxel for injection; PFS, progression-free survival.

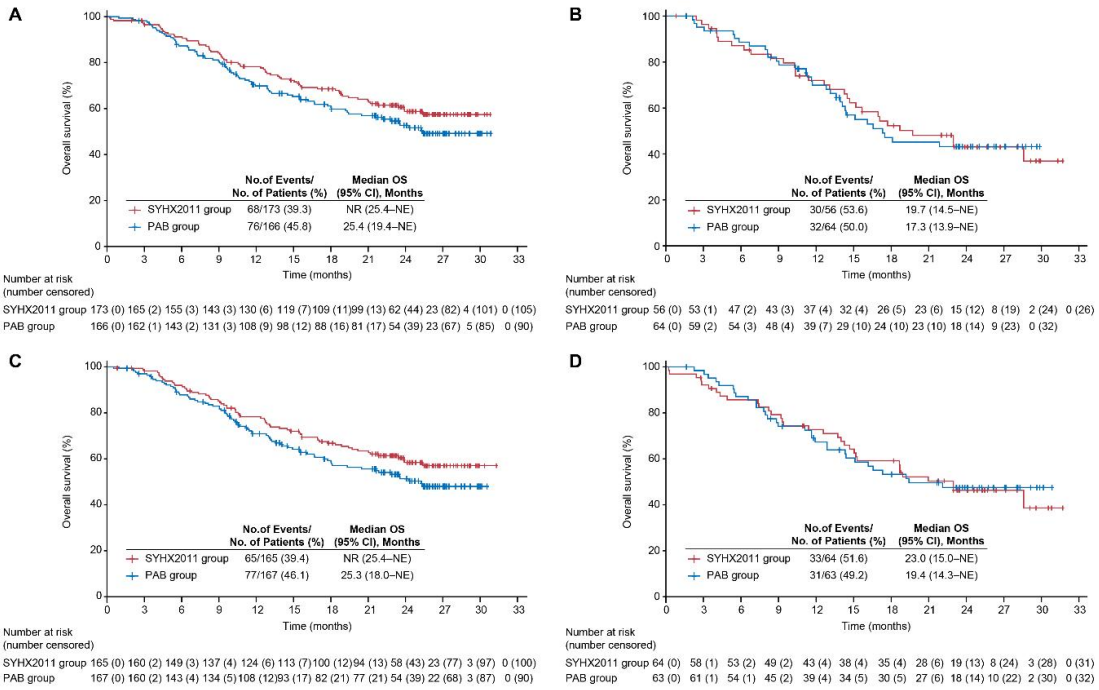


Figure S3. Updated investigator-assessed overall survival across clinically relevant subgroups. (A) Kaplan–Meier estimates of overall survival in patients with hormone receptor-positive breast cancer. Median overall survival was not reached (95% CI: 25.4–NE) in the SYHX2011 group and was 25.4 months (95% CI: 18.4–NE) in the approved albumin-bound paclitaxel for injection (PAB) group. **(B)** Kaplan–Meier estimates of overall survival in patients with triple-negative breast cancer, with median overall survival of 17.7 months (95% CI: 14.5–NE) in the SYHX2011 group and 17.5 months (95% CI: 13.3–NE) in the PAB group. **(C)** Kaplan–Meier estimates of overall survival in patients receiving first-line therapy, with median overall survival not reached (95% CI: 25.4–NE) in the SYHX2011 group and 25.3 months (95% CI: 18.0–NE) in the PAB group. **(D)** Kaplan–Meier estimates of overall survival in patients receiving second- or later-line therapy, with median overall survival of 23.0 months (95% CI: 15.0–NE) in the SYHX2011 group and 19.4 months (95% CI: 14.3–NE) in the PAB group. Tick marks indicate censored observations, and the tables below the plots show the numbers of patients at risk, with cumulative numbers censored in parentheses, at each time point. **Abbreviations**: CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PAB, approved albumin-bound paclitaxel for injection.