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Trastuzumab Rezetecan in ERBB2-Low Advanced Breast Cancer
The HORIZON-Breast06 Randomized Clinical Trial

Ying Fan, MD; Yunjiang Liu, MD; Yongsheng Wang, MD; Quchang Ouyang, MD; Qingyuan Zhang, MD; Jiuwei Cui, MD; Jingruo Li, MD; Qiang Ding, MD; Xinhong Wu, MD; Xiaojia Wang, MD; Zhongsheng Tong, MD; Yinduo Zeng, MD; Wenhui Wang, MB; Min Yan, MD; Yili Wang, MD; Xiaoyu Liu, MD; Kai Li, MD; Zhengkui Sun, MD; Chunxiu Yuan, MD; Ting Wang, MD; Weimin Xie, MM; Jing Yao, MD; Shoubing Zhou, MD; Jialin Hou, MD; Zhong Ouyang, MD; Yijing Li, MS; Sisi Cui, MM; Xia Zhang, MM; Xiaoyu Zhu, MD; Binghe Xu, MD, PhD

IMPORTANCE Trastuzumab rezetecan (SHR-A1811) has demonstrated encouraging antitumor activity in a global phase 1 trial involving heavily pretreated patients with erythroblastic oncogene B (ERBB2)–low metastatic breast cancer.

OBJECTIVE To compare trastuzumab rezetecan vs physician's choice of chemotherapy in patients with ERBB2-low metastatic breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This open-label, randomized, multicenter phase 3 trial was conducted at 73 hospitals across China. Eligible patients were females aged 18 to 75 years with centrally confirmed ERBB2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in-situ hybridization [ISH]–negative) unresectable locally recurrent or metastatic breast cancer who had received 1 or fewer prior lines of chemotherapy for metastatic disease, with prior endocrine therapy required for hormone receptor–positive disease. Enrollment began on June 30, 2023, and ended on August 20, 2025. The last day of follow-up for the final analysis for progression-free survival in the current study was March 20, 2026.

INTERVENTIONS Patients were randomly assigned (1:1) to receive trastuzumab rezetecan (6.4 mg/kg intravenously every 3 weeks; n = 277) or physician's choice of chemotherapy (n = 274).

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival assessed by blinded independent central review in chemotherapy-naive patients and the overall population.

RESULTS Between June 30, 2023, and August 20, 2025, a total of 551 patients were randomized, with a mean (SD) age of 54.9 (9.9) years. At the data cutoff (March 20, 2026), trastuzumab rezetecan significantly prolonged progression-free survival compared with chemotherapy in the chemotherapy-naive patients (median, 16.6 [95% CI, 14.0-19.4] months vs 6.8 [95% CI, 5.7-7.0] months; hazard ratio, 0.25 [95% CI, 0.19-0.33]; $P < .001$) and the overall population (median, 16.4 [95% CI, 14.0-16.8] months vs 6.8 [95% CI, 5.7-6.9] months; hazard ratio, 0.27 [95% CI, 0.21-0.34]; $P < .001$). The benefit was consistent in hormone receptor–negative disease (median progression-free survival: 16.5 vs 6.8 months; hazard ratio, 0.34, [95% CI, 0.22-0.54]) and hormone receptor–positive disease (median progression-free survival: 16.4 vs 6.7 months; hazard ratio, 0.24 [95% CI, 0.18-0.33]). Grade 3 or greater treatment-related adverse events occurred in 84.1% of patients (232/276) with trastuzumab rezetecan and 67.9% (184/271) with chemotherapy, most commonly decreased neutrophil count (180 [65.2%] vs 147 [54.2%]).

CONCLUSIONS AND RELEVANCE Trastuzumab rezetecan provided significant progression-free survival benefit over physician's choice of chemotherapy in patients with ERBB2-low advanced breast cancer, with benefit observed across all key subgroups. It exhibited the potential as a new treatment option with a distinct safety profile in this setting.

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Visual Abstract
Research Summary
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Binghe Xu, MD, PhD, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Innovative Drug Research and Translational Study for Breast Cancer and State Key Laboratory of Advanced Medical Materials and Devices, 17 Panjiayuan South Lane, Chaoyang District, Beijing, 100021, China (xubinghe@medmail.com.cn).

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Breast cancer, the most prevalent malignancy worldwide, is classified into distinct molecular subtypes based on erythroblastic oncogene B (ERBB2; formerly HER2/neu) expression, a pivotal therapeutic target in breast cancer.[1] Historically, patients with ERBB2-low breast cancer (immunohistochemistry [IHC] 1+ or IHC 2+/in-situ hybridization [ISH]–negative disease)[2,3] long derived little clinical benefit from traditional anti-ERBB2–targeted therapies compared with ERBB2-positive breast cancer (IHC 3+ or ISH-positive) and were associated with a poor prognosis.[4]

The advances in antibody-drug conjugates (ADCs) have revolutionized the therapeutic landscape for ERBB2-low breast cancer, transforming it into a clinically actionable phenotype.[5] Trastuzumab deruxtecan, an ERBB2-targeted ADC, demonstrates cytotoxic activity even in tumors with low ERBB2 expression via its bystander-killing effect. Pivotal trials demonstrated the superiority of trastuzumab deruxtecan over chemotherapy in chemotherapy-treated patients with ERBB2-low metastatic breast cancer in DESTINY-Breast04 trial (median progression-free survival: 9.9 vs 5.1 months)[6,7] and endocrine-resistant disease in DESTINY-Breast06 trial (median progression-free survival: 13.2 vs 8.1 months),[8] supporting its approval in 2025. However, as the DESTINY-Breast06 trial enrolled only patients with hormone receptor (HR)–positive disease, the efficacy of anti-ERBB2 ADCs in HR-negative ERBB2-low disease with no previous chemotherapy for metastatic breast cancer remains unaddressed.[8]

Therapeutic responses further vary depending on HR status. For HR-positive, ERBB2-low advanced disease, the first-line standard treatment remains endocrine therapy combined with a cyclin-dependent kinase (CDK) 4/CDK6 inhibitor.[9-13] Notably, PI3K/AKT/mTOR pathway inhibitors have only been clinically accessible for patients in China since 2025. For triple-negative breast cancer, although options such as the trophoblast cell surface antigen-2–directed ADC sacituzumab govitecan and datopotamab deruxtecan have emerged (median progression-free survival of 9.7 and 10.8 months, respectively),[14,15] frontline treatment typically relies on chemotherapy and immunotherapy with modest efficacy (median progression-free survival range: 7.5-9.7 months).[16,17] Moreover, both groups face limited effective subsequent treatment options.

Trastuzumab rezetecan (SHR-A1811) is an ADC comprising a humanized anti-ERBB2 monoclonal antibody linked via a cleavable tetrapeptide linker to a highly potent topoisomerase I inhibitor.[18] It was recently approved in China for pretreated ERBB2-positive breast cancer based on the phase 3 HORIZON-Breast01 trial, showing superior efficacy over pyrotinib (a small molecule, irreversible, pan-ERBB2 receptor tyrosine kinase inhibitor) plus capecitabine (median progression-free survival: 30.6 vs 8.3 months).[19] Preclinical studies exhibited that its payload demonstrates superior membrane permeability and enhanced cytotoxic activity compared with the payload of trastuzumab deruxtecan.[18] With an optimized drug to antibody ratio of 6, it achieves an improved balance between efficacy, including notable bystander-killing effects, and safety.[18] Promising clinical activity has been observed in a global phase 1 study involving heavily pretreated patients (median of 3 prior treatment regimens) with ERBB2-low advanced breast cancer, with an objective response rate of 60.9%, a duration of response of 12.4 months, and a median progression-free survival of 11.0 months,[20] informing the choice of the 6.4-mg/kg dose for the current phase 3 trial.

This pivotal phase 3 study was designed to evaluate the efficacy and safety of trastuzumab rezetecan in patients with ERBB2-low unresectable and/or metastatic breast cancer, including both HR-positive and HR-negative subtypes, with major focus on patients who received no chemotherapy in the metastatic setting. Given that no indication was ever granted for any anti-ERBB2 ADC in this setting, either in China or worldwide, at the time of study protocol finalization (v1.0; February 10, 2023), the treating physician's choice of chemotherapy was chosen as the control group.

Key Points

Question Is trastuzumab rezetecan an effective treatment for advanced erythroblastic oncogene B (ERBB2)–low breast cancer?

Findings Trastuzumab rezetecan provided a statistically significant improvement in progression-free survival vs chemotherapy by blinded independent central review in both chemotherapy-naive and all patients with ERBB2-low advanced breast cancer; efficacy was also observed in patients with hormone receptor–negative, ERBB2-low disease, a subgroup not previously addressed in clinical trials.

Meaning These findings demonstrate trastuzumab rezetecan as a highly effective treatment for ERBB2-low advanced breast cancer in hormone receptor–positive or –negative disease in patients who had received 1 or fewer prior lines of chemotherapy treatment for metastatic disease.

Methods

Study Design and Patients

This was a randomized, open-label, multicenter, phase 3 trial conducted across 73 hospitals in China (NCT05814354; Supplement 1). Key eligibility criteria included female patients aged 18 to 75 years with pathologically ERBB2-low (centrally confirmed IHC 1+ or IHC 2+/ISH-, based on tumor tissue obtained at the recurrent or metastatic stage) unresectable locally recurrent and/or metastatic breast cancer who received no more than 1 prior line of chemotherapy for metastatic disease (where progression within 6 months after [neo]adjuvant therapy was counted as 1 line) and, for HR-positive disease, had progression while receiving at least 1 line of endocrine therapy (adjuvant endocrine therapy counted as the first line if progression occurred within 24 months of initiation). Patients with active central nervous system metastases, prior anti-ERBB2 therapy, previous treatment with any exatecan derivative–based topoisomerase I inhibitor ADC, or a history of interstitial lung disease were excluded. Additional details regarding the eligibility criteria are provided in the protocol (Supplement 2).

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Trial Oversight

The trial protocol and amendments received approval from ethics committees at each center. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.[21] All patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Procedures

Eligible patients were randomized (1:1) to receive trastuzumab rezetecan (6.4 mg/kg intravenously every 3 weeks) or the treating physician's choice of chemotherapy (taxanes, eribulin, capecitabine, or gemcitabine) in accordance with the local label or guidelines. Per the protocol, the physician's choice of chemotherapy regimen was predefined prior to patient randomization. Dose reductions of trastuzumab rezetecan were allowed to manage toxic effects in a stepwise manner, from 6.4 mg/kg to 5.6 mg/kg and then to 4.8 mg/kg. Tumor assessment by a blinded independent central review and investigators in each participating hospital, based on RECIST 1.1 guidelines, was performed every 6 weeks for the first 48 weeks, then every 12 weeks thereafter; these assessments were performed until disease progression, unacceptable toxicity, death, withdrawal of consent, or investigator decision. All complete responses or partial responses required confirmation at 4 weeks or more after the initial documentation confirmed by a blinded independent central review.

Randomization was performed via an interactive web response system using permuted blocks of size 4, stratified by central ERBB2 status (IHC 1+ vs IHC 2+/ISH−), HR status (HR+ with prior CDK4/6 inhibitor vs HR+ without prior CDK4/6 inhibitor vs HR−), and lines of prior chemotherapy treatment for metastatic disease (0 vs 1).

End Points

The dual primary end points included progression-free survival as assessed by blinded independent central review in 2 populations: the chemotherapy-naive patients (with 0 prior lines of chemotherapy for metastatic disease) and the overall population (all randomized patients). Key secondary end points comprised overall survival in the overall population, overall survival in the chemotherapy-naive patients, and progression-free survival by blinded independent central review in the chemotherapy-treated patients. Other secondary end points included investigator-assessed progression-free survival, objective response rate, duration of response, clinical benefit rate, and safety. The objective response rate, duration of response, and clinical benefit rate were also assessed by blinded independent central review. Exploratory assessments included plasma concentrations of trastuzumab rezetecan and immunogenicity; these analyses are planned for a separate publication.

Statistical Analysis

Assuming median progression-free survival of 5.7 months in the chemotherapy group for the chemotherapy-naive patients and 5.6 months for the overall population with 20% annual dropout rate, 440 patients with 242 events would provide at least 85% power to detect a hazard ratio of 0.68 for progression-free survival in the chemotherapy-naive patients and 530 patients with 296 events would provide at least 91% power to detect a hazard ratio of 0.68 for progression-free survival in the overall population, indicating that an additional 90 chemotherapy-treated patients would be enrolled. For the dual primary progression-free survival end point, superiority was tested hierarchically with a 1-sided α of .025, first in the chemotherapy-naive patients and then in the overall population. The current analysis reported the final analysis for progression-free survival. A descriptive analysis of overall survival was also performed, because overall survival data remained immature. Further analysis of overall survival, including an interim analysis at approximately 70% of events and a final analysis, are planned per the statistical analysis plan (Supplement 2). Time-to-event end points, including progression-free survival, overall survival, and duration of response, were estimated using the Kaplan-Meier method. Comparison between groups were assessed by stratified log-rank tests, and stratified Cox proportional hazards models were used to estimate hazard ratios and 95% CIs. The stratified analyses were based on the prespecified randomization stratification factors including central ERBB2 status (IHC 1+ vs IHC 2+/ISH−), HR status (HR+ with prior CDK4/6 inhibitor vs HR+ without prior CDK4/6 inhibitor vs HR−), and lines of prior chemotherapy for metastatic disease (0 vs 1). Efficacy end points were also analyzed by HR status as exploratory. The homogeneity of treatment effects on the primary end point was evaluated by adding treatment × HR status interaction into a Cox proportional hazards model as an ad hoc analysis. All statistical analyses were performed using SAS version 9.4 or higher (SAS Institute).

Results

Patients

Between June 30, 2023, and August 20, 2025, a total of 551 patients were enrolled and randomized to receive trastuzumab rezetecan (n = 277) or physician's choice of chemotherapy (n = 274) (**Figure 1**). The physician's choice regimens were taxanes (63.5% [172/271]), eribulin (28.8% [78/271]), capecitabine (5.5% [15/271]), and gemcitabine (2.2% [6/271]). At data cutoff (March 20, 2026), the median (IQR) follow-up was 15.5 (9.7-21.5) months for all patients. Treatment discontinuations occurred in 174 patients receiving trastuzumab rezetecan and 249 receiving chemotherapy, primarily due to radiographic progression. Baseline characteristics were well-balanced and typical of ERBB2-low metastatic disease (**Table 1**; eTable 1 and eTable 2 in Supplement 1), including 449 chemotherapy-naive patients (81.5%) and 102 patients (18.5%) who received 1 prior line of chemotherapy for metastatic disease. HR status was positive in 73.0% of patients (402/551) and negative in 27.0% (149/551).

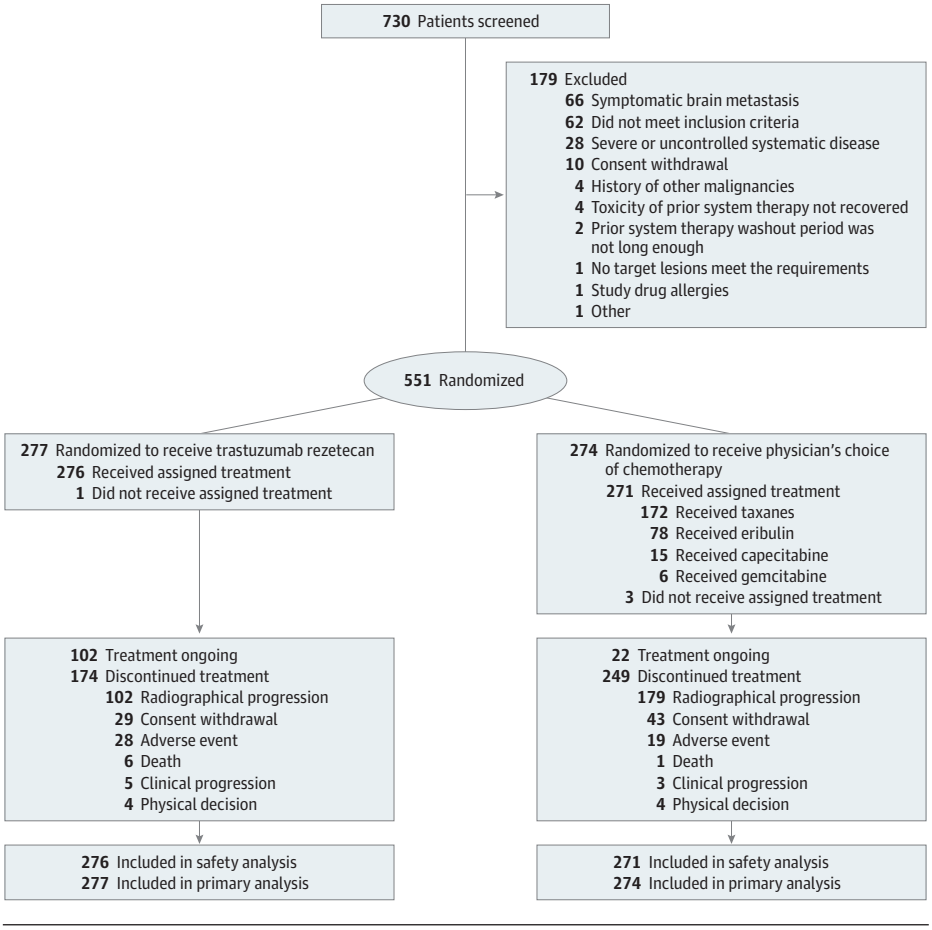
Efficacy

In the chemotherapy-naive patients, the median progression-free survival per blinded independent central review was 16.6 (95% CI, 14.0-19.4) months for trastuzumab rezetecan vs 6.8 (95% CI, 5.7-7.0) months for physician's choice of

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Figure 1. Flowchart of Patients in the Study of Trastuzumab Rezetecan in ERBB2-Low Advanced Breast Cancer



ERBB2 indicates erythroblastic oncogene B.

chemotherapy (hazard ratio, 0.25 [95% CI, 0.19-0.33]; $P < .001$; **Figure 2**B). In the overall population, the median progression-free survival was 16.4 months (95% CI, 14.0-16.8) for trastuzumab rezetecan vs 6.8 months (95% CI, 5.7-6.9) for physician's choice of chemotherapy (hazard ratio, 0.27 [95% CI, 0.21-0.34]; $P < .001$; Figure 2A). The 1-sided log-rank P values for both dual primary end point analyses crossed the prespecified threshold for significance. Across all prespecified subgroups, trastuzumab rezetecan demonstrated consistent progression-free survival benefit (per blinded independent central review) vs physician's choice of chemotherapy, including HR-negative (16.5 vs 6.8 months; hazard ratio, 0.34 [95% CI, 0.22-0.54]) and HR-positive cohorts (16.4 vs 6.7 months; hazard ratio, 0.24 [95% CI, 0.18-0.33]; **Figure 3**; eFigure 2 in Supplement 1), with a P value for interaction of .55 (**Figure 4**; eFigure 1 in Supplement 1). In the chemotherapy-naive patients, sustained and consistent benefit was also observed with trastuzumab rezetecan in HR-positive disease and HR-negative disease (median progression-free survival, 16.5 and 16.8 months; eFigure 2 in Supplement 1).

Ninety patients (32.5%) received subsequent anticancer therapy following discontinuation of trastuzumab rezetecan and 149 (54.4%) after discontinuation of physician's choice of chemotherapy (eTable 3 in Supplement 1). At data cutoff, overall survival data were immature, with fewer deaths in the trastuzumab rezetecan group than the physician's choice of chemotherapy group (23.8% [66/277] vs 28.1% [77/274]). The 12-month overall survival rate was 90.6% (95% CI, 86.2%-93.6%) with trastuzumab rezetecan vs 81.4% (95% CI, 75.9%-85.8%) with physician's choice of chemotherapy (hazard ratio, 0.67 [95% CI, 0.48-0.94]; nominal $P = .01$; eFigure 3 in Supplement 1).

Among chemotherapy-treated patients, the median progression-free survival by blinded independent central review was 13.9 (95% CI, 9.7-16.6) months for trastuzumab rezetecan vs 5.6 (95% CI, 4.0-8.4) months for physician's choice of chemotherapy (hazard ratio, 0.32 [95% CI, 0.19-0.54]; nominal $P < .001$) (Figure 2C). Consistent results were observed for investigator-assessed progression-free survival (eFigure 4 in Supplement 1).

Blinded independent central review confirmed a higher objective response rate with trastuzumab rezetecan (75.5% [95% CI, 69.9%-80.4%]) than with physician's choice of chemotherapy (41.2% [95% CI, 35.4%-47.3%]) in all patients (eTable 4, eFigure 5 in Supplement 1). These efficacy benefits were also observed in both the chemotherapy-naive patients (76.0% vs 43.3%) and chemotherapy-treated patients (73.1% vs 32.0%) (eTable 4 in Supplement 1), as well as both in

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Table 1. Demographic and Clinical Characteristics at Baseline

	Chemotherapy-naive patients		Chemotherapy-treated patients		Overall patients	
	Trastuzumab rezetecan (n = 225)	Physician's choice of chemotherapy (n = 224)	Trastuzumab rezetecan (n = 52)	Physician's choice of chemotherapy (n = 50)	Trastuzumab rezetecan (n = 277)	Physician's choice of chemotherapy (n = 274)
Age, median (IQR), y	56.0 (50.0-62.0)	56.0 (49.0-62.5)	53.5 (45.5-59.0)	54.0 (47.0-60.0)	55.0 (49.0-62.0)	55.0 (49.0-61.0)
Age ≥65 y, No. (%)	48 (21.3)	45 (20.1)	6 (11.5)	5 (10.0)	54 (19.5)	50 (18.2)
Ethnicity, No. (%)						
Han Chinese	218 (96.9)	217 (96.9)	50 (96.2)	48 (96.0)	268 (96.8)	265 (96.7)
Other ethnicity Chinese	7 (3.1)	7 (3.1)	2 (3.8)	2 (4.0)	9 (3.2)	9 (3.3)
ECOG performance status score, No. (%)						
0	117 (52.0)	113 (50.4)	20 (38.5)	19 (38.0)	137 (49.5)	132 (48.2)
1	108 (48.0)	111 (49.6)	32 (61.5)	31 (62.0)	140 (50.5)	142 (51.8)
ERBB2 status, No. (%)[a]						
IHC 1+ and ISH unknown	137 (60.9)	134 (59.8)	33 (63.5)	34 (68.0)	170 (61.4)	168 (61.3)
IHC 2+ and ISH-	78 (34.7)	79 (35.3)	18 (34.6)	16 (32.0)	96 (34.7)	95 (34.7)
IHC 1+ and ISH-	10 (4.4)	11 (4.9)	1 (1.9)	0	11 (4.0)	11 (4.0)
Hormone receptor–positive disease, No. (%)[b]	166 (73.8)	166 (74.1)	35 (67.3)	35 (70.0)	201 (72.6)	201 (73.4)
Visceral metastases, No. (%)	170 (75.6)	180 (80.4)	41 (78.8)	38 (76.0)	211 (76.2)	218 (79.6)
Liver metastases, No. (%)	121 (53.8)	124 (55.4)	28 (53.8)	26 (52.0)	149 (53.8)	150 (54.7)
Lung metastases, No. (%)	80 (35.6)	85 (37.9)	18 (34.6)	17 (34.0)	98 (35.4)	102 (37.2)
Brain metastases, No. (%)	1 (0.4)	5 (2.2)	0	3 (6.0)	1 (0.4)	8 (2.9)
Lines of previous therapy, No. (%)[c]						
0	37 (16.4)	36 (16.1)	0	0	37 (13.4)	36 (13.1)
1	125 (55.6)	116 (51.8)	22 (42.3)	26 (52.0)	147 (53.1)	142 (51.8)
≥2	63 (28.0)	72 (32.1)	30 (57.7)	24 (48.0)	93 (33.6)	96 (35.0)
Median (range)	1 (0-4)	1 (0-4)	2 (1-4)	1 (1-4)	1 (0-4)	1 (0-4)
Treatment in the recurrence and metastasis stage, No. (%)						
Chemotherapy	0	0	52 (100.0)	50 (100.0)	52 (18.8)	50 (18.2)
Endocrine therapy	188 (83.6)	188 (83.9)	42 (80.8)	36 (72.0)	230 (83.0)	224 (81.8)
Targeted therapy	144 (64.0)	139 (62.1)	33 (63.5)	29 (58.0)	177 (63.9)	168 (61.3)
CDK4/6 inhibitor	141 (62.7)	135 (60.3)	28 (53.8)	25 (50.0)	169 (61.0)	160 (58.4)
Immunotherapy	0	0	3 (5.8)	0	3 (1.1)	0
Other targeted therapy	9 (4.0)	14 (6.3)	7 (13.5)	8 (16.0)	16 (5.8)	22 (8.0)
Other	9 (4.0)	9 (4.0)	3 (5.8)	2 (4.0)	12 (4.3)	11 (4.0)

Abbreviations: CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ERBB2, erythroblastic oncogene B; IHC, immunohistochemistry; ISH, in-situ hybridization.

[a] ERBB2 status was evaluated by immunohistochemical analysis at the central laboratory.

[b] Hormone receptor status was evaluated by immunohistochemical analysis at the pathology department of the participating study site. Hormone receptor status is defined as follows: hormone receptor positive for tumors that are either estrogen receptor positive or progesterone receptor positive; hormone receptor negative for tumors that are both estrogen receptor–negative and progesterone receptor–negative.

[c] Patients who had progression that had occurred during or within 6 months after end of neoadjuvant or adjuvant chemotherapy were considered to have had 1 line of previous chemotherapy treatment. Patients who had progression that had occurred within 24 months after receipt of adjuvant endocrine therapy were considered to have had 1 line of previous endocrine therapy.

HR-positive (74.6% vs 40.8%; eTable 5 in Supplement 1) and HR-negative (77.6% vs 42.5%) disease (eTable 6 and eTable 7 in Supplement 1). The median duration of response per blinded independent central review was 15.0 (95% CI, 12.6-17.6) months in the trastuzumab rezetecan group and 6.8 (95% CI, 5.6-7.2) months in the overall population (eTable 4 in Supplement 1). The benefits in duration of response with trastuzumab rezetecan persisted across all subgroups (eTable 4, eTable 5, and eTable 6 in Supplement 1).

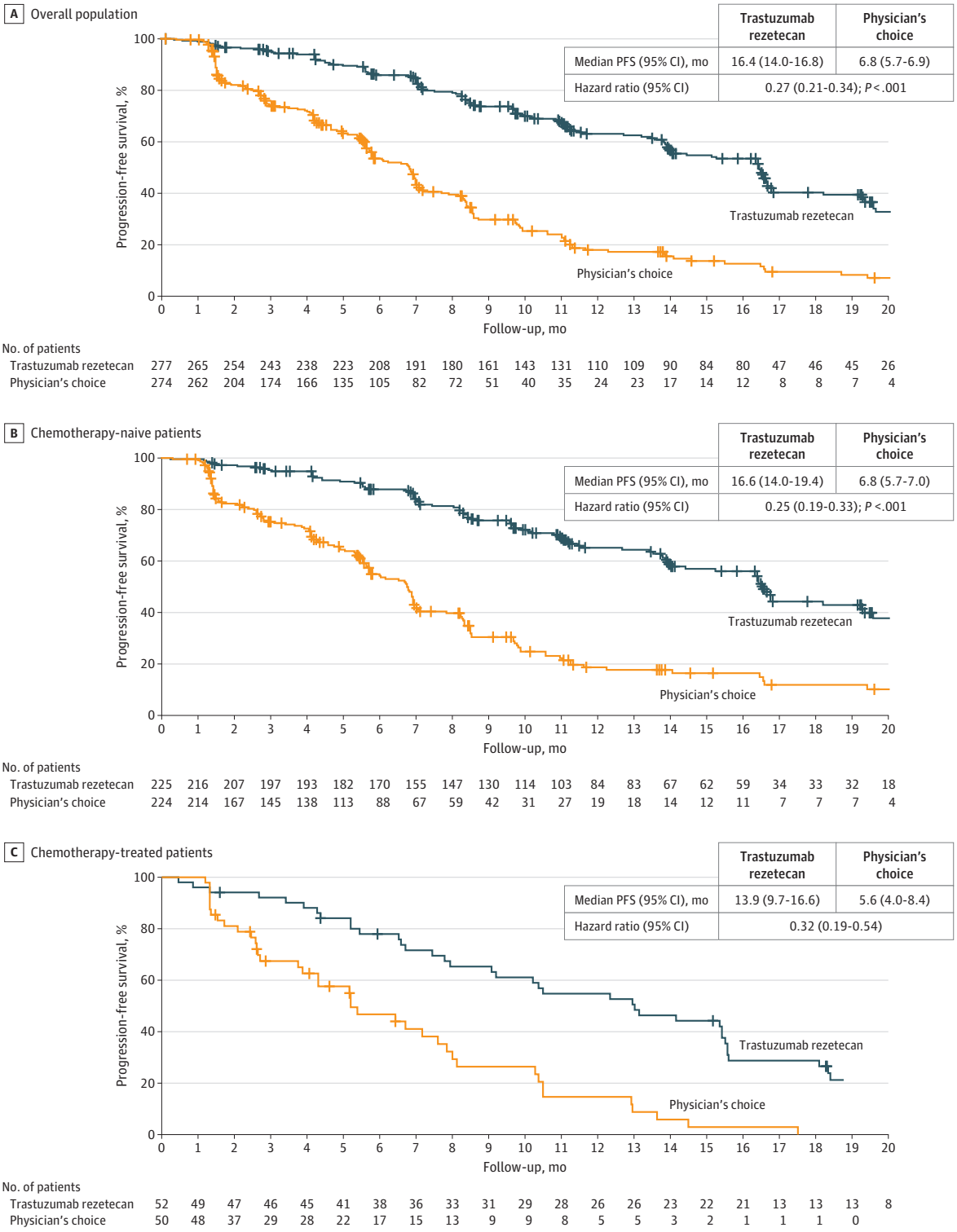
Safety

In total, 276 patients receiving trastuzumab rezetecan and 271 patients receiving physician's choice of chemotherapy were included in the safety analysis. The median duration of treatment was 13.8 (95% CI, 11.9-16.3) months for trastuzumab rezetecan and 5.6 (95% CI, 4.6-6.0) months for physician's choice of chemotherapy. In the trastuzumab rezetecan group, 141 patients (51.1%) required at least 1 dose reduction, predominantly due to adverse events (138/276

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Figure 2. Kaplan-Meier Analysis of Progression-Free Survival (PFS) in the Overall Population and by Receipt of Previous Chemotherapy Treatment

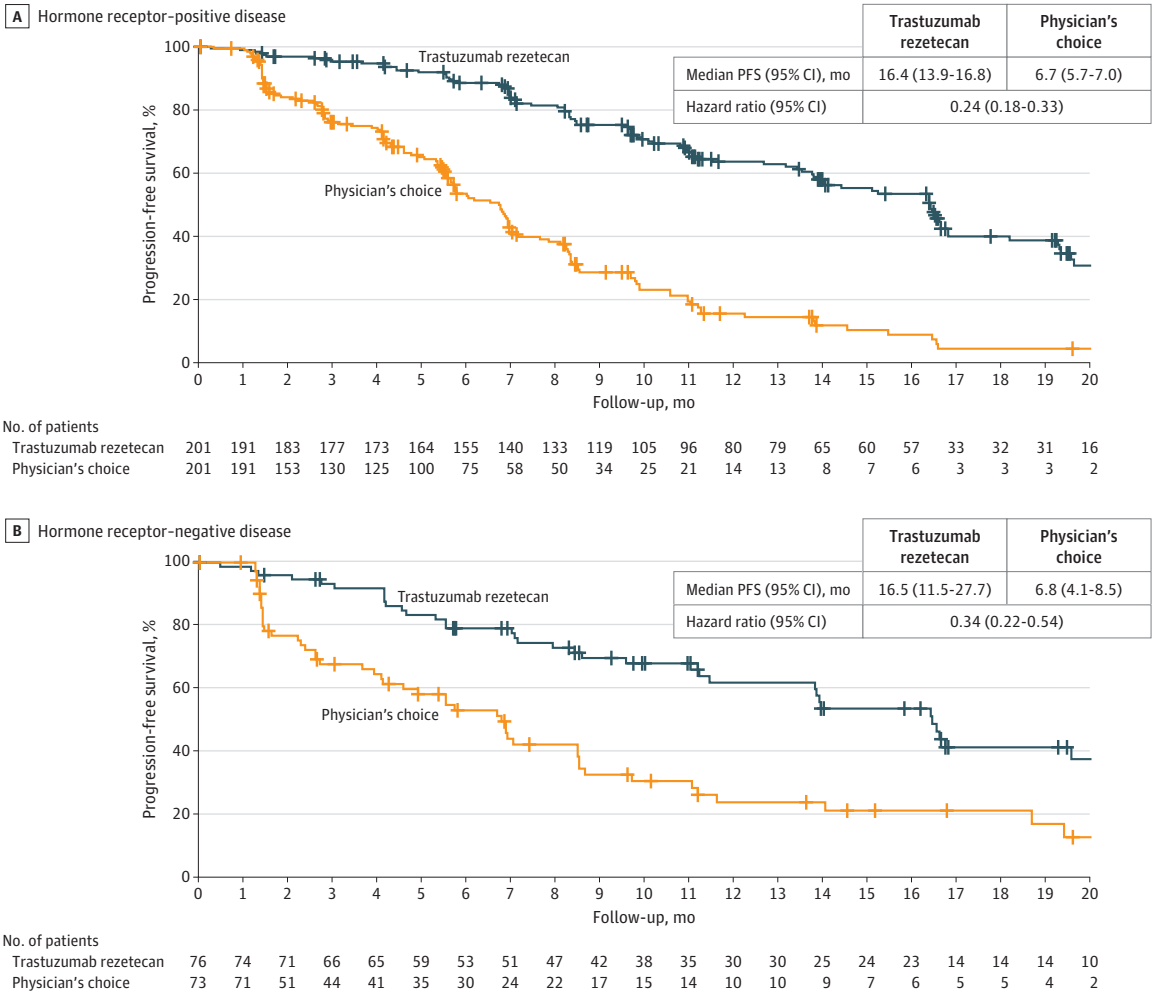


Progression-free survival was determined by blinded independent central review. A, The median (IQR) follow-up was 16.5 (10.8-22.2) months for trastuzumab rezetecan and 14.9 (8.2-20.2) months for physician's choice of chemotherapy. B, The median (IQR) follow-up was 15.0 (10.4-20.9) months for trastuzumab rezetecan and 13.4 (8.1-19.3) months for physician's choice of chemotherapy. C, The median (IQR) follow-up was 22.5 (15.2-25.4) months for trastuzumab rezetecan and 20.4 (10.3-24.6) months for physician's choice of chemotherapy. Plus marks indicate censored patients.

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Figure 3. Kaplan-Meier Analysis of Progression-Free Survival (PFS) by Hormone Receptor Status



A, The median (IQR) follow-up was 16.6 (11.1-22.4) months for trastuzumab rezetecan and 14.3 (8.4-20.0) months for physician's choice of chemotherapy. B, The median follow-up was 16.2 (10.2-22.0) months for trastuzumab rezetecan and 15.7 (8.0-20.9) months for physician's choice of chemotherapy. Plus marks indicate censored patients.

[50.0%]). Specially, 89 patients (32.2%) had 1 dose reduction (to 5.6 mg/kg) and 52 patients (18.8%) had 2 reductions (to a final dose of 4.8 mg/kg; eFigure 6 in Supplement 1).

Treatment-related adverse events of any grade occurred in all patients (eTable 8 in Supplement 1). The most common treatment-related adverse events of any grade were decreased white blood cell count (244 [88.4%] vs 229 [84.5%]), decreased neutrophil count (237 [85.9%] vs 230 [84.9%]), and anemia (256 [92.8%] vs 160 [59.0%]; **Table 2**). Grade 3 or greater treatment-related adverse events were reported in 232 patients (84.1%) receiving trastuzumab rezetecan and 184 (67.9%) receiving chemotherapy; the most frequent were decreased neutrophil count (180 [65.2%] vs 147 [54.2%]), decreased white blood cell count (156 [56.5%] vs 96 [35.4%]), and anemia (118 [42.8%] vs 13 [4.8%]). Serious adverse events related to treatment occurred in 37.7% of patients (104/276) in the trastuzumab rezetecan group and 13.7% of patients (37/271) in the physician's choice of chemotherapy group (eTable 9 in Supplement 1).

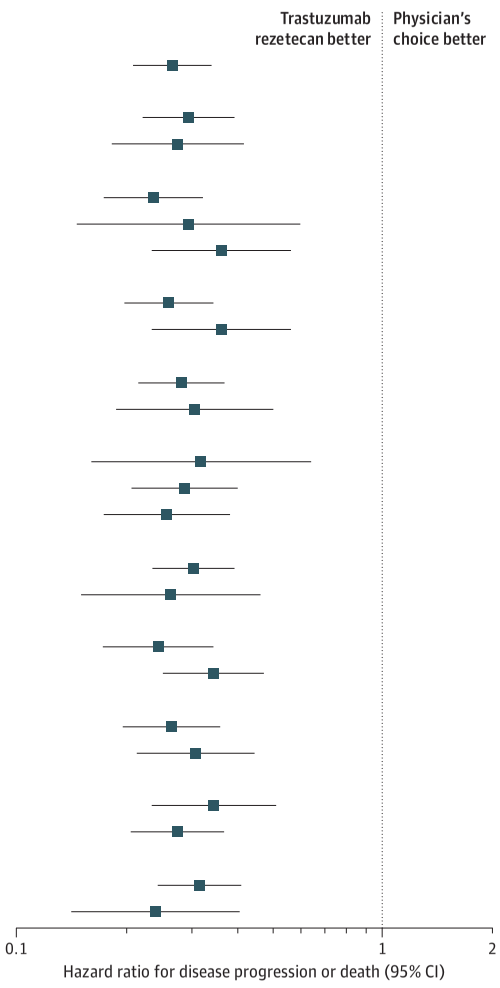
Treatment-related adverse events leading to dose reductions occurred in 50.4% of patients (139/276) in the trastuzumab rezetecan group and 29.2% (79/271) in the physician's choice of chemotherapy group (eTable 10 in Supplement 1); the rates of treatment-related adverse events leading to treatment discontinuation were 8.7% (24/276) and 6.3% (17/271), respectively (eTable 11 in Supplement 1). Three fatal treatment-related adverse events occurred (1.1%) in the trastuzumab rezetecan group (sudden cardiac death [n = 1] and unknown causes [n = 2]) and 2 (0.7%) occurred in the physician's choice of chemotherapy group (obstructive airways disorder [n = 1] and cardiac failure [n = 1]).

Among patients in the trastuzumab rezetecan group, the incidences of any grade and grade 3 or greater decreased neutrophil count were 46.3% and 35.2%, respectively, for those

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Figure 4. Dot-and-Whisker Plot of Subgroup Analysis of Progression-Free Survival in Overall Population

All patients	No. of patients	No. of events/No. of patients		Median PFS (95% CI), mo		Hazard ratio for disease progression or death (95% CI)
		Trastuzumab rezetecan	Physician's choice of chemotherapy	Trastuzumab rezetecan	Physician's choice of chemotherapy	
All patients	551	130/277	185/274	16.4 (14.0-16.8)	6.8 (5.7-6.9)	0.27 (0.21-0.34)
ERBB2 expression						
IHC 1+	360	84/181	121/179	16.6 (14.0-19.3)	6.0 (5.5-6.9)	0.30 (0.22-0.39)
IHC 2+/ISH-	191	46/96	64/95	14.0 (11.2-16.7)	6.9 (5.7-8.3)	0.28 (0.18-0.42)
HR status and prior CDK4/6 inhibitor						
HR+ with prior CDK4/6 inhibitor	321	80/161	110/160	15.2 (13.4-16.5)	6.0 (5.5-6.9)	0.24 (0.17-0.32)
HR+ without prior CDK4/6 inhibitor	81	13/40	24/41	22.2 (16.7-NR)	7.9 (5.6-12.3)	0.30 (0.15-0.60)
HR-	149	37/76	51/73	16.5 (11.5-27.7)	6.8 (4.1-8.5)	0.36 (0.23-0.56)
Hormone receptor status						
Positive	402	93/201	134/201	16.4 (13.9-16.8)	6.7 (5.7-7.0)	0.26 (0.20-0.35)
Negative	149	37/76	51/73	16.5 (11.5-27.7)	6.8 (4.1-8.5)	0.36 (0.23-0.56)
Lines of previous chemotherapy						
0	449	91/225	146/224	16.6 (14.0-19.4)	6.8 (5.7-7.0)	0.28 (0.22-0.37)
1	102	39/52	39/50	13.9 (9.7-16.6)	5.6 (4.0-8.4)	0.31 (0.19-0.50)
Lines of previous therapy						
0	73	14/37	23/36	27.7 (13.9-NR)	8.5 (4.6-11.6)	0.32 (0.16-0.64)
1	289	62/147	92/142	16.8 (14.0-19.6)	6.2 (5.6-7.1)	0.29 (0.21-0.40)
≥2	189	54/93	70/96	13.9 (10.9-16.4)	6.7 (4.9-6.9)	0.26 (0.17-0.38)
Age, y						
<65	447	107/223	152/224	16.4 (13.9-16.7)	6.8 (5.7-6.9)	0.31 (0.24-0.39)
≥65	104	23/54	33/50	16.6 (13.2-NR)	6.7 (4.1-8.5)	0.26 (0.15-0.46)
ECOG performance status						
0	269	62/137	88/132	16.6 (14.0-19.4)	6.9 (5.6-7.2)	0.24 (0.17-0.35)
1	282	68/140	97/142	15.1 (11.5-16.6)	6.0 (5.4-7.7)	0.35 (0.25-0.47)
Liver metastases						
Yes	299	81/149	107/150	13.9 (11.5-16.5)	5.7 (4.6-6.8)	0.27 (0.20-0.36)
No	252	49/128	78/124	16.8 (16.4-NR)	7.0 (6.0-8.5)	0.31 (0.21-0.45)
Lung metastases						
Yes	200	48/98	67/102	13.9 (10.9-19.6)	7.0 (5.3-8.5)	0.35 (0.23-0.51)
No	351	82/179	118/172	16.5 (14.0-16.8)	6.0 (5.6-6.9)	0.28 (0.21-0.37)
Visceral disease						
Yes	429	106/211	148/218	14.0 (12.7-16.6)	6.8 (5.6-7.0)	0.32 (0.24-0.41)
No	122	24/66	37/56	19.3 (16.4-NR)	6.7 (5.6-8.3)	0.24 (0.14-0.41)



CDK indicates cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ERBB2, erythroblastic oncogene B; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NR, not reached; PFS, progression-free survival.

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Table 2. Treatment-Related Adverse Events[a]

	No. (%)			
	Trastuzumab rezetecan (n = 276)		Physician's choice of chemotherapy (n = 271)	
Adverse event	Grade ≥3	Any grade	Grade ≥3	Any grade
Neutrophil count decreased	180 (65.2)	237 (85.9)	147 (54.2)	230 (84.9)
White blood cell count decreased	156 (56.5)	244 (88.4)	96 (35.4)	229 (84.5)
Anemia	118 (42.8)	256 (92.8)	13 (4.8)	160 (59.0)
Platelet count decreased	99 (35.9)	214 (77.5)	5 (1.8)	75 (27.7)
Lymphocyte count decreased	31 (11.2)	60 (21.7)	12 (4.4)	46 (17.0)
Febrile neutropenia	27 (9.8)	27 (9.8)	1 (0.4)	1 (0.4)
Hypokalemia	21 (7.6)	70 (25.4)	7 (2.6)	36 (13.3)
Malaise	13 (4.7)	64 (23.2)	1 (0.4)	36 (13.3)
Hypertriglyceridemia	7 (2.5)	91 (33.0)	10 (3.7)	61 (22.5)
Gamma-glutamyltransferase increased	7 (2.5)	70 (25.4)	10 (3.7)	65 (24.0)
Vomiting	7 (2.5)	113 (40.9)	0	24 (8.9)
Electrocardiogram QT prolonged	6 (2.2)	26 (9.4)	2 (0.7)	13 (4.8)
Pneumonia	5 (1.8)	21 (7.6)	2 (0.7)	9 (3.3)
Fatigue	5 (1.8)	64 (23.2)	1 (0.4)	24 (8.9)
Nausea	5 (1.8)	173 (62.7)	0	51 (18.8)
Alanine aminotransferase increased	4 (1.4)	162 (58.7)	8 (3.0)	149 (55.0)
Decreased appetite	4 (1.4)	138 (50.0)	2 (0.7)	43 (15.9)
Diarrhea	4 (1.4)	77 (27.9)	0	13 (4.8)
Stomatitis	3 (1.1)	33 (12.0)	4 (1.5)	8 (3.0)
Asthenia	3 (1.1)	46 (16.7)	4 (1.5)	21 (7.7)
Hyponatremia	3 (1.1)	52 (18.8)	2 (0.7)	29 (10.7)
Weight decreased	3 (1.1)	131 (47.5)	1 (0.4)	42 (15.5)
Dizziness	3 (1.1)	39 (14.1)	1 (0.4)	16 (5.9)
Hypocalcemia	3 (1.1)	40 (14.5)	0	19 (7.0)
Interstitial lung disease	3 (1.1)	7 (2.5)	0	0
Gastroenteritis	3 (1.1)	4 (1.4)	0	0
Aspartate aminotransferase increased	2 (0.7)	170 (61.6)	13 (4.8)	160 (59.0)
Hypoesthesia	0	12 (4.3)	7 (2.6)	66 (24.4)
Palmar-plantar erythrodysesthesia syndrome	0	2 (0.7)	4 (1.5)	14 (5.2)
Neuropathy peripheral	0	0	3 (1.1)	28 (10.3)

[a] Grade ≥3 treatment-related adverse events occurring in >1% of patients in either group are listed. Events are shown in descending order of frequency in the trastuzumab rezetecan group.

receiving exploratory and nonrandomized primary prophylaxis to hematological toxicity in the first treatment cycle (n = 162) compared with 92.1% and 65.8%, respectively, among patients not receiving prophylaxis (n = 114) (eTable 12 in Supplement 1). Initiating prophylaxis more than 72 hours after the first dose (n = 104) demonstrated rates of 41.3% for any grade decreased neutrophil count and 26.0% for grade 3 or higher decreased neutrophil count. Additional data from the first 4 treatment cycles showed that the cumulative incidence of any grade and grade 3 or higher events in those who did not receive prophylaxis were 96.5% and 78.1%, respectively, vs 65.4% and 45.1%, respectively, among those who did undergo prophylaxis (eTable 13 in Supplement 1).

Interstitial lung disease occurred in 7 patients (2.5%) in the trastuzumab rezetecan group (grade 1 in 1 patient, grade 2 in 3 patients, grade 3 in 2 patients, and grade 4 in 1 patient). The median (IQR) time to the onset of any-grade interstitial lung disease was 316.0 (179.0-410.0) days (eTable 14 in Supplement 1). The exposure-adjusted incidence rate of interstitial lung disease was 2.5% per patient-year.

Discussion

This pivotal phase 3 trial demonstrates trastuzumab rezetecan as an effective new treatment option compared with the physician's choice of chemotherapy for patients with ERBB2-low metastatic breast cancer who have received no more than 1 prior line of chemotherapy treatment in the metastatic setting. The dual primary end point showed statistically significant improvements in progression-free survival in both chemotherapy-naive and overall patients. There were no new safety signals identified.

Trastuzumab rezetecan also demonstrated improvements in progression-free survival over chemotherapy both in the chemotherapy-treated population and in chemotherapy-naive

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patients with HR-positive disease. Although the control group reflected standard care during trial design, emerging data with trastuzumab deruxtecan in DESTINY-Breast04 (median of 9.9 months of progression-free survival) and DESTINY-Breast06 (median of 13.2 months of progression-free survival) have redefined therapeutic expectations.[6,8] In this study, HR-positive patients had either exhausted standard endocrine-based regimens (including 79.9% who received CDK4/6 inhibitors, 89.1% with aromatase inhibitors, and 54.7% with fulvestrant) or were deemed unsuitable for further endocrine therapy, with primary endocrine resistance rates of 40.0%. Importantly, access to newer targeted agents such as PI3K/AKT/mTOR inhibitors was limited until 2025 in China. Cross-trial comparisons should be interpreted cautiously due to differing study patient demographics, enrollment criteria, and tumor assessment methods. Future head-to-head comparison between trastuzumab rezetecan and trastuzumab deruxtecan is warranted to provide critical insights into this rapidly evolving therapeutic landscape.

Furthermore, the efficacy was observed in HR-negative ERBB2-low disease, an aggressive, difficult-to-treat subtype that has historically lacked effective targeted options.[22] In the current study's prespecified exploratory cohort, median progression-free survival was longer with trastuzumab rezetecan than chemotherapy, even among chemotherapy-naive patients (16.8 vs 6.8 months; hazard ratio, 0.31). In addition, 71.8% of HR-negative patients had PD-L1 combined positive score less than 1 or an unknown score and achieved median progression-free survival of 14.0 vs 7.1 months. Among the 28.2% with PD-L1 combined positive score of 1 or greater, the median progression-survival was 16.6 vs 6.7 months. These data suggest that trastuzumab rezetecan can provide durable disease control for this population, addressing a critical unmet need. Although pembrolizumab plus chemotherapy is now a standard first-line option for PD-L1–positive metastatic triple-negative breast cancer[16] and recent phase 3 trials have expanded alternatives (sacituzumab govitecan in ASCENT-03: median progression-free survival, 9.7 vs 6.9 months; hazard ratio, 0.62; datopotamab-deruxtecan in TROPION-Breast02: median progression-free survival, 10.8 vs 5.6 months; hazard ratio, 0.57),[14,15] none of these therapies are currently accessible in China. Moreover, cross-trial comparisons are inherently limited by differences in patient populations, enrollment criteria, and control group regimens. These developments materially alter the therapeutic landscape in which the current study's results must be interpreted, thereby possibly limiting the contextual application of the findings. Future studies are needed to define optimal integration strategies, including the ongoing randomized phase 3 trial (NCT07111832) evaluating trastuzumab rezetecan combined with adebrelimab (a PD-L1 inhibitor) as first-line treatment for ERBB2-negative, HR-negative, and PD-L1–positive breast cancer.

The low incidence of interstitial lung disease in the trastuzumab rezetecan group was encouraging, at only 2.5% (n = 7), with no grade 5 adverse events reported. The exposure-adjusted incidence rate of interstitial lung disease was 2.5% per patient-year. Given the currently limited follow-up duration, the interstitial lung disease rate with longer follow-up will be monitored in the future. This safety profile may be attributed to its novel payload design. Specifically, the introduction of a chiral cyclopropyl modification at the α-carbonyl position of the exatecan derivative (payload) enhances plasma stability while preserving potent topoisomerase I inhibition.[18] This structural optimization reduces systemic exposure to the free payload, thereby potentially mitigating off-target toxicity in pulmonary tissue—a known risk with other ERBB2-targeted ADCs.[23] Regarding other safety signals of concern for ERBB2-targeted ADCs, the incidence of cardiac events was aligned with the known profile of ERBB2-targeted therapies.[6,8,20,24]

At the 6.4-mg/kg dose, trastuzumab rezetecan demonstrated a higher incidence of hematologic adverse events, including grade 3 or higher decreased neutrophil count, decreased white blood cell count, and anemia. Dose reductions due to adverse events were required in 50% of patients, reflecting the need for proactive monitoring and management. Although primary prophylaxis was implemented in an exploratory and nonrandomized manner, protocol-permitted primary prophylaxis was associated with a lower observed incidence and severity of decreased neutrophil count.

Treatment-related fatal events occurred with comparable frequency between the trastuzumab rezetecan and physician's choice of chemotherapy groups. Two patients died due to unknown reason in the trastuzumab rezetecan group. One patient developed persistent dyspnea and chest discomfort from cycle 1 but declined further assessment. After 4 cycles with stable disease, death occurred post discontinuation. The other patient experienced grade 4 leukopenia with elevated C-reactive protein after initial dosing. Despite a single dose of short-acting granulocyte-colony stimulating factor, the patient discontinued follow-up care and later died at home.

Limitations

This study has limitations. First, the overall survival data remained immature, which constrains robust conclusions; follow-up is ongoing. Second, caution is warranted in cross-trial comparisons due to inherent variations in patient demographics, enrollment criteria, and tumor assessment methods. Third, this trial was limited to patients in China. Future multinational, randomized clinical studies are warranted to further validate and confirm the generalizability in global patient populations. Fourth, the hazard ratio of 0.25 indicates a marked improvement over chemotherapy, but the heterogeneity in control group regimens and evolving treatment standards necessitate further validation in contemporary comparator trials.

Conclusions

Trastuzumab rezetecan significantly improved progression-free survival vs physician's choice of chemotherapy in ERBB2-low advanced breast cancer in patients who had received no more than 1 line of chemotherapy treatment for metastatic disease. Hematologic toxicity occurred more frequently with trastuzumab rezetecan and often required dose modification, but it was generally manageable with proactive management strategies. Interstitial lung disease maintained a low incidence profile.

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Author Affiliations: Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (Fan); Breast Surgery Department, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China (Y. Liu); Department of Breast Surgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China (Yongsheng Wang); Department of Breast Medicine, Hunan Cancer Hospital & The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China (Q. Ouyang); Ward One of the Department of Breast Medicine, Harbin Medical University Cancer Hospital, Harbin, China (Q. Zhang); Tumor Center Oncology Department, The First Hospital of Jilin University, Changchun, China (J. Cui); Department of Breast Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (J. Li); Breast Center, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China (Ding); Breast Center, Hubei Cancer Hospital, Wuhan, China (Wu); Internal Medicine of Breast Tumors, Zhejiang Cancer Hospital, Hangzhou, China (X. Wang); Breast Medical Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China (Tong); Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China (Zeng); Department of Breast Diseases, Weifang People's Hospital, Weifang, China; (W. Wang); Breast Department, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China (Yan); Fifth Department of Breast Surgery, Nanchang People's Hospital, Nanchang, China (Yili Wang); Breast Cancer Center, Chongqing University Cancer Hospital, Chongqing, China (X. Liu); Breast Oncology Department, Shengjing Hospital of China Medical University, Shenyang, China (K. Li); Department of Breast Surgery, Jiangxi Cancer Hospital, Nanchang, China (Sun); Department of Oncology, General Hospital of Ningxia Medical University, Yinchuan, China (Yuan); Department of Thyroid, Breast and Vascular Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China (T. Wang); Breast, Bone and Soft Tissue Oncology Department, Guangxi Medical University Cancer Hospital & Guangxi Cancer Institute, Guangxi Cancer Hospital & Medical University Oncology School & Cancer Center, Nanning, China (Xie); Breast Oncology Department, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Yao); Department of Medical Oncology, Anhui Provincial Cancer Hospital, Hefei, China (Zhou); Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, China (Hou); Breast Surgery Ward, The First Affiliated Hospital of Xiamen University, Xiamen, China (Z. Ouyang); Biometrics Department, Jiangsu Hengrui Pharmaceuticals Co, Ltd, Shanghai, China (Y. Li); Clinical Development-Oncology, Jiangsu Hengrui Pharmaceuticals Co, Ltd, Shanghai, China (S. Cui, X. Zhang, Zhu); Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Innovative Drug Research and Translational Study for Breast Cancer and State Key Laboratory of Advanced Medical Materials and Devices, Beijing, China (Xu).

Author Contributions: Drs Xu and Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Fan, Zeng, S. Cui, X. Zhang, Zhu, Xu.
Acquisition, analysis, or interpretation of data: Fan, Y. Liu, Yongsheng Wang, Q. Ouyang, Q. Zhang, J. Cui, J. Li, Ding, Wu, X. Wang, Tong, W. Wang, Yan, Yili Wang, X. Liu, K. Li, Sun, Yuan, T. Wang, Xie, Yao, Zhou, Hou, Z. Ouyang, Y. Li, Zhu, Xu.
Drafting of the manuscript: Fan, Zhu, Xu.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Fan, Y. Li.
Administrative, technical, or material support: Fan, Y. Liu, Yongsheng Wang, Q. Ouyang, Q. Zhang, J. Li, Ding, Wu, X. Wang, Tong, Zeng, W. Wang, Yili Wang, X. Liu, K. Li, Sun, Yuan, T. Wang, Xie, Yao, Zhou, Z. Ouyang, Y. Li, S. Cui, X. Zhang, Zhu, Xu.
Supervision: Y. Liu, Yongsheng Wang, Q. Ouyang, Q. Zhang, J. Cui, J. Li, Ding, Wu, X. Wang, Tong, W. Wang, Yili Wang, X. Liu, K. Li, Sun, Yuan, T. Wang, Xie, Yao, Zhou, Z. Ouyang, Y. Li, S. Cui, X. Zhang, Zhu, Xu.

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