Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2022, Volume2, Issue 2, Page No: 100-110

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Novel Anti-HER2 Antibody–Drug Conjugates Compared With Dual HER2 Blockade after Tyrosine Kinase Inhibitor Failure in Metastatic Breast Cancer

Omar Moore[1], Mei Q. Brown[1]*, Giulia P. Ferrari[1]

[1]Department of Translational Oncology, Faculty of Health and Medical Sciences, University of Tokyo, Tokyo, Japan.

***E-mail** ✉ mbrown@outlook.com

Received: 04 August 2022; **Revised:** 29 October 2022; **Accepted:** 02 November 2022

ABSTRACT

After failure of tyrosine kinase inhibitor (TKI) therapy, treatment options for patients with HER2-positive metastatic breast cancer (MBC) mainly include next-generation anti-HER2 antibody–drug conjugates (ADCs) or dual HER2 blockade with pertuzumab and trastuzumab plus chemotherapy (HP+C). Although our previous work indicated meaningful clinical benefit from novel anti-HER2 ADCs in TKI-refractory disease, comparative evidence between these agents and HP-based chemotherapy is lacking. This study aimed to evaluate and contrast the clinical outcomes and tolerability of these two strategies in patients with prior TKI exposure. We retrospectively reviewed patients with HER2-positive MBC who had received TKIs and were subsequently treated with either novel anti-HER2 ADCs or HP in combination with chemotherapy between January 2019 and August 2023. Progression-free survival (PFS) was the primary outcome. Secondary outcomes included objective response rate (ORR), clinical benefit rate (CBR), and treatment-related adverse events. A total of 150 patients were analyzed, with 83 receiving novel anti-HER2 ADCs and 67 treated with HP plus chemotherapy. Within the ADC cohort, 36 patients were administered trastuzumab deruxtecan (T-DXd), while 47 received other investigational ADCs. Median PFS was 7.0 months in the ADC group and 8.9 months in the HP+C group. The ADC cohort achieved a higher ORR than the HP+C cohort (51.8% vs. 26.9%), whereas CBR was comparable between groups (69.9% vs. 65.7%). Subgroup analysis demonstrated superior PFS in patients treated with T-DXd compared with those receiving HP combined with chemotherapy. Severe (grade 3–4) toxicities were predominantly hematologic and gastrointestinal in both treatment arms. In patients with HER2-positive MBC who progress after TKI therapy, both novel anti-HER2 ADCs and HP combined with chemotherapy provide clinically meaningful disease control with manageable safety profiles. Anti-HER2 ADCs, particularly T-DXd, may represent the preferred therapeutic approach following TKI failure. However, HP combined with chemotherapy remains a reasonable alternative in circumstances where access to ADCs is limited.

Keywords: TKI treatment, HER2-positive breast cancer, Trastuzumab deruxtecan, Antibody–drug conjugates

How to Cite This Article: Moore O, Brown MQ, Ferrari GP. Novel Anti-HER2 Antibody–Drug Conjugates Compared With Dual HER2 Blockade after Tyrosine Kinase Inhibitor Failure in Metastatic Breast Cancer. Asian J Curr Res Clin Cancer. 2022;2(2):100-10. https://doi.org/10.51847/2cXGQcjXj4

Introduction

The recognition of human epidermal growth factor receptor 2 (HER2) as a critical oncogenic driver in breast cancer has enabled the development of multiple HER2-targeted therapies, leading to marked improvements in patient prognosis [1, 2]. In the metastatic setting, treatment strategies for HER2-positive breast cancer have continued to evolve. With the introduction of the PHILA regimen, Chinese clinical guidelines now recommend a first-line approach based on dual HER2 blockade using the small-molecule TKI pyrotinib in combination with trastuzumab and chemotherapy for HER2-positive MBC [3].

Support for this recommendation is largely derived from the phase III PHENIX and PHOEBE trials, both of which demonstrated substantial clinical benefit of pyrotinib in patients whose disease had progressed following

trastuzumab-containing regimens [4, 5]. Consequently, TKIs—particularly pyrotinib—have been increasingly adopted in China for the management of HER2-positive MBC after trastuzumab failure.

Antibody–drug conjugates (ADCs) have also assumed an important role in the treatment of HER2-positive MBC beyond the first-line setting. The EMILIA trial provided robust evidence establishing trastuzumab emtansine (T-DM1) as a standard second-line therapy worldwide [6]. More recently, the DESTINY-Breast03 study fundamentally altered the treatment landscape by demonstrating superior efficacy of the novel anti-HER2 ADC trastuzumab deruxtecan (T-DXd; DS-8201), which has since been incorporated into major domestic and international treatment guidelines [7].

In real-world practice in China, however, access to T-DM1 has historically been limited. As a result, later-line treatment options have predominantly consisted of T-DXd and HP combined with chemotherapy. Despite the clinical promise of ADCs, challenges related to availability, treatment continuity, and insurance reimbursement remain significant. In contrast, the prolonged progression-free survival (PFS) reported in the PHILA study—conducted entirely in an Asian population—has strengthened confidence in TKI-based regimens as frontline therapy in China, leading to preferential use of domestic TKIs in both trastuzumab-sensitive and -resistant disease. For patients who experience disease progression after TKI therapy, continued inhibition of the HER2 signaling pathway remains a key therapeutic principle, consistent with the concept of sustained anti-HER2 treatment [8, 9]. The 2023 Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines recommend HP combined with chemotherapy as a subsequent treatment option for patients who have not previously received pertuzumab following TKI failure. However, this recommendation is supported by relatively limited evidence [10, 11]. The PHEREXA study explored the use of pertuzumab beyond trastuzumab resistance but did not conclusively demonstrate a survival benefit [11].

Our prior research has indicated meaningful clinical activity of novel anti-HER2 ADCs in patients with TKI-refractory HER2-positive MBC [12]. Nevertheless, to date, no randomized controlled trials have directly compared the efficacy and safety of novel anti-HER2 ADCs with HP combined with chemotherapy in this setting. Therefore, the present study was undertaken to address this evidence gap by evaluating and comparing these two treatment strategies in patients with HER2-positive MBC who failed TKI therapy.

Materials and Methods

Patient population

This retrospective study included patients with HER2-positive metastatic breast cancer treated at the Breast Cancer Ward of the Department of Oncology, Chinese People's Liberation Army General Hospital, between January 2019 and August 2023. Eligible patients met the following inclusion criteria: female sex; complete clinical and treatment records; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; pathologically confirmed HER2-positive MBC, defined by immunohistochemistry or fluorescence in situ hybridization (FISH) showing HER2 3+ expression. For patients in whom metastatic lesions could not be re-biopsied, HER2 status was determined based on the primary tumor specimen.

Additional inclusion requirements included the presence of at least one measurable extracranial lesion or osteolytic or mixed bone metastases, as well as adequate cardiac, hepatic, renal, and pulmonary function in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). For patients previously treated with pyrotinib, treatment failure was defined as discontinuation due to disease progression, patient refusal to continue therapy, or other factors such as treatment-related adverse events. Patients were required to have received treatment with either novel anti-HER2 ADCs or HP combined with chemotherapy for more than six weeks and to have undergone at least one post-treatment efficacy assessment.

Exclusion criteria included the presence of symptomatic brain metastases, concurrent second primary malignancies, or severe comorbid conditions.

Clinical data—including baseline characteristics, prior treatment history, efficacy outcomes, and safety information—were extracted from the institutional electronic medical record system for all eligible patients. The final follow-up date was August 1, 2023.

Treatment administration and dose adjustment

Patients in the ADC cohort were managed exclusively with anti-HER2 antibody–drug conjugates, predominantly trastuzumab deruxtecan (T-DXd) and other agents sharing similar payload-delivery mechanisms. All ADCs were

administered at their recommended clinical doses and intervals: T-DXd at 3.6 mg/kg every 3 weeks; RC48 at 2.0 mg/kg every 2 weeks; MRG002 at 2.6 mg/kg every 3 weeks; and ARX788 at 1.5 mg/kg every 3 weeks.
Patients treated in the HP plus chemotherapy cohort received dual monoclonal antibody blockade consisting of trastuzumab and pertuzumab in combination with cytotoxic agents. Trastuzumab was given as an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks, while pertuzumab was administered at an initial dose of 840 mg followed by 420 mg every 3 weeks. Chemotherapy backbones included docetaxel (75 mg/m² every 3 weeks), albumin-bound paclitaxel (260 mg/m² on days 1 and 8 of each 3-week cycle), vinorelbine (25 mg/m² on days 1 and 8 every 3 weeks), or gemcitabine (1000 mg/m² on days 1 and 8 every 3 weeks). After 6–8 cycles of combination therapy, treatment intensity was reassessed by an experienced oncologist, with chemotherapy dose reduction or discontinuation determined according to clinical response and treatment tolerance. The introduction of endocrine therapy was considered based on hormone receptor status.

Study endpoints and evaluation
The primary outcome measure was progression-free survival (PFS), defined as the duration from initiation of study treatment to radiographic disease progression confirmed by computed tomography or magnetic resonance imaging, or death from any cause. Secondary endpoints comprised objective response rate (ORR), clinical benefit rate (CBR), and safety. ORR was defined as the proportion of patients achieving either complete or partial tumor regression, while CBR included patients with complete response, partial response, or stable disease maintained for at least six months. Tumor response assessments were conducted every two treatment cycles according to RECIST version 1.1. All treatment-related adverse events were continuously monitored and graded using the Common Terminology Criteria for Adverse Events version 4.0.

Statistical methods
Data analysis was performed using SPSS software version 19.0. Continuous variables were compared using either parametric or non-parametric tests, depending on data distribution. Categorical variables, including response rates, were analyzed using chi-square or Fisher's exact tests as appropriate. Progression-free survival was estimated using Kaplan–Meier methodology, and survival differences between groups were evaluated with the log-rank test. Cox proportional hazards regression models were applied to calculate hazard ratios and corresponding 95% confidence intervals. To examine the influence of predefined baseline variables on PFS, subgroup analyses were conducted using multivariable Cox models, with results presented graphically in forest plots generated using GraphPad Prism version 7.0. All analyses were two-tailed, and statistical significance was defined as a P value below 0.05.

Results and Discussion

Baseline patient characteristics
A total of 150 patients who fulfilled the eligibility criteria were enrolled between January 2019 and August 2023, as illustrated in **Figure 1**. The median age at diagnosis was 48 years, with a range of 25 to 89 years. In the ADC treatment arm (n = 83), patients received the following therapies: trastuzumab deruxtecan in 36 cases (43.4%), MRG002 in 24 cases (28.9%), ARX788 in 13 cases (15.7%), and RC48 in 10 cases (12.0%).
In the HP plus chemotherapy group (n = 67), chemotherapy regimens varied: taxane-based therapy was administered to 47 patients (70.1%), vinorelbine to 11 patients (16.4%), and gemcitabine to 9 patients (13.4%).
Overall demographic and clinical features were comparable between the two cohorts, including the prevalence of visceral and central nervous system metastases. However, patients receiving ADC therapy were more likely to have extensive disease burden, with a significantly greater proportion presenting with three or more metastatic sites compared with the HP plus chemotherapy group (62.7% vs. 31.3%, P < .001). Additionally, prior treatment exposure differed between groups: more than half of the patients in the ADC cohort had undergone at least three previous lines of anti-HER2 therapy, a rate significantly higher than that observed in the HP cohort (54.2% vs. 32.8%, P = .008). All patients had previously been treated with trastuzumab and pyrotinib. Prior therapeutic benefit was broadly similar across groups, although prior exposure to pertuzumab was more frequent in the ADC cohort (74.7%). Baseline characteristics are detailed in **Table 1.**

Table 1. Baseline demographic and clinical characteristics of patients with HER2-positive metastatic breast cancer treated with anti-HER2 ADCs or HP combined with chemotherapy.

Characteristic	Trastuzumab Deruxtecan + Pertuzumab (n = 67)	Novel anti-HER2 Antibody-Drug Conjugates (n = 83)	P-value
Age at diagnosis (years)			0.787
Median (range)	48 (25–72)	48 (25–89)	
< 50 years	37 (55.2%)	44 (53.0%)	
≥ 50 years	30 (44.8%)	39 (47.0%)	
Clinical stage at initial diagnosis			0.225
Stage I	8 (11.9%)	9 (10.8%)	
Stage II	30 (44.8%)	31 (37.3%)	
Stage III	24 (35.8%)	27 (32.5%)	
Stage IV	5 (7.5%)	16 (19.4%)	
Hormone receptor status			0.981
Positive	37 (55.2%)	46 (55.4%)	
Negative	30 (44.8%)	37 (44.6%)	
Number of metastatic sites			<0.001
3 or more	21 (31.3%)	52 (62.7%)	
Fewer than 3	46 (68.7%)	31 (37.3%)	
Sites of metastasis			
Lung	36 (53.7%)	48 (57.8%)	0.615
Liver	31 (46.3%)	42 (50.6%)	0.598
Bone	36 (53.7%)	44 (53.0%)	0.930
Brain	22 (32.8%)	20 (24.1%)	0.236
Prior anti-HER2 treatments			
Trastuzumab + Pertuzumab	0 (0%)	62 (74.7%)	<0.001
Trastuzumab	67 (100.0%)	83 (100.0%)	–
Lapatinib	29 (43.3%)	18 (21.7%)	<0.001
Pyrotinib	67 (100.0%)	83 (100.0%)	–
Clinical benefit from prior therapies			
Benefit from TKI	52 (77.6%)	58 (69.9%)	0.287
Benefit from trastuzumab	50 (74.6%)	63 (75.9%)	0.857
Number of prior lines of anti-HER2 therapy			0.008
> 3 lines	22 (32.8%)	45 (54.2%)	
≤ 3 lines	45 (67.2%)	38 (45.8%)	

Abbreviations: HER2, human epidermal growth factor receptor 2; ADCs, antibody-drug conjugates; TKI, tyrosine kinase inhibitor; HP+C, pertuzumab + trastuzumab + chemotherapy.

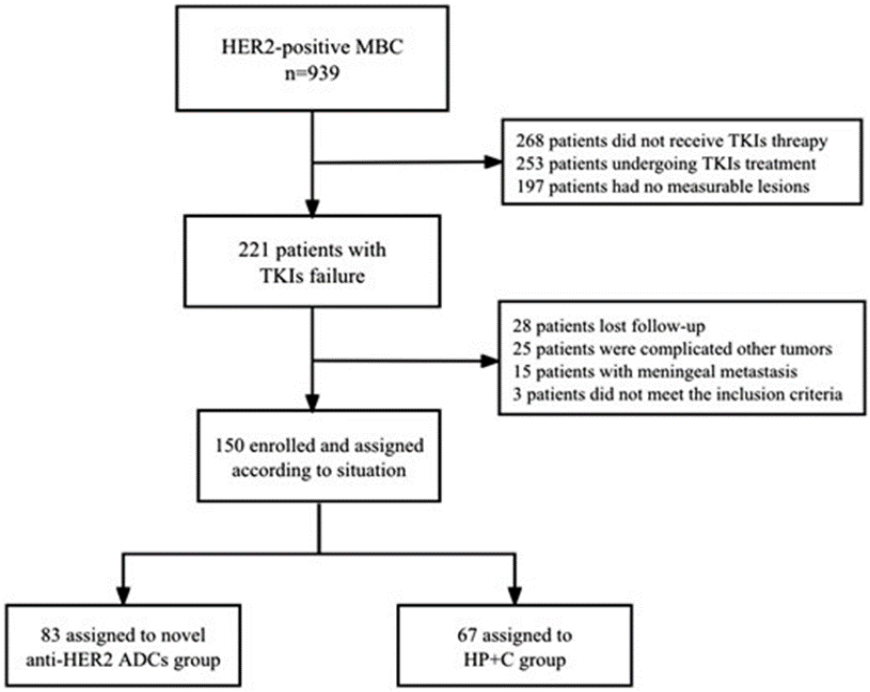


Figure 1. Patient screening and allocation process for 150 individuals diagnosed with metastatic breast cancer with HER2 overexpression who were treated with either anti-HER2 antibody–drug conjugates or a combination regimen consisting of pertuzumab, trastuzumab, and chemotherapy. Abbreviations: HER2, human epidermal growth factor receptor 2; ADCs, antibody–drug conjugates; HP+C, pertuzumab plus trastuzumab with chemotherapy; TKI, tyrosine kinase inhibitor.

Antitumor activity

At the time of analysis (August 2023), follow-up duration reached a median of 6 months, ranging from 2.0 to 25.6 months. In the cohort receiving anti-HER2 ADCs, 24 patients (28.9%) continued therapy at data cutoff. Treatment cessation occurred in 58 patients (69.9%) as a result of tumor progression, while one patient (1.2%) discontinued therapy because of interstitial lung disease.

Among patients treated with HP in combination with chemotherapy, only 5 individuals (7.5%) remained on active treatment, whereas 62 patients (92.5%) had terminated therapy due to progressive disease. Complete tumor remission was not documented in either treatment arm. Compared with the HP+C regimen, ADC-based therapy resulted in a higher proportion of partial tumor regressions (51.8% vs. 26.9%). Conversely, disease stabilization was observed more frequently in the HP+C group than in the ADC group (64.2% vs. 43.4%).

Statistical comparison demonstrated a significant advantage in objective response rate for patients receiving novel anti-HER2 ADCs relative to those treated with HP combined with chemotherapy (51.8% vs. 26.9%, P = .002). In contrast, rates of clinical benefit did not differ meaningfully between treatment strategies (69.9% vs. 65.7%, P = .583). A comprehensive comparison of efficacy endpoints is provided in **Table 2.**

Table 2. Comparison of efficacy between novel HP+C and anti-HER2 ADCs.

Response Category	HP + Chemotherapy (n = 67)	Novel anti-HER2 Antibody-Drug Conjugates (n = 83)	P-value
Partial Response (PR)	18 (26.9%)	43 (51.8%)	
Complete Response (CR)	0 (0%)	0 (0%)	
Stable Disease ≥ 6 months	26 (38.8%)	17 (20.5%)	
Stable Disease (SD)	43 (64.2%)	36 (43.4%)	
Objective Response Rate (ORR)	18 (26.9%)	43 (51.8%)	0.002
Progressive Disease (PD)	6 (9.0%)	4 (4.8%)	
Clinical Benefit Rate (CBR)	44 (65.7%)	58 (69.9%)	0.583

Abbreviations: antibody-drug conjugates (ADCs); clinical benefit rate (CBR); complete response (CR); human epidermal growth factor receptor 2 (HER2); pertuzumab + trastuzumab + chemotherapy (HP+C); objective response rate (ORR); progressive disease (PD); partial response (PR); stable disease (SD).

Median progression-free survival was 7.0 months among patients treated with novel anti-HER2 antibody–drug conjugates and 8.9 months in those receiving the HP regimen. The difference in PFS between the two treatment strategies did not reach statistical significance (HR = 0.75; 95% CI, 0.53–1.08; P = .126); **(Figure 2).** Subgroup analyses visualized using forest plots demonstrated consistent PFS outcomes across all evaluated strata, including age, hormone receptor expression, menopausal status, number of prior anti-HER2 treatment lines, presence of visceral metastases, and clinical benefit from prior trastuzumab or TKI therapy **(Figure 3).**

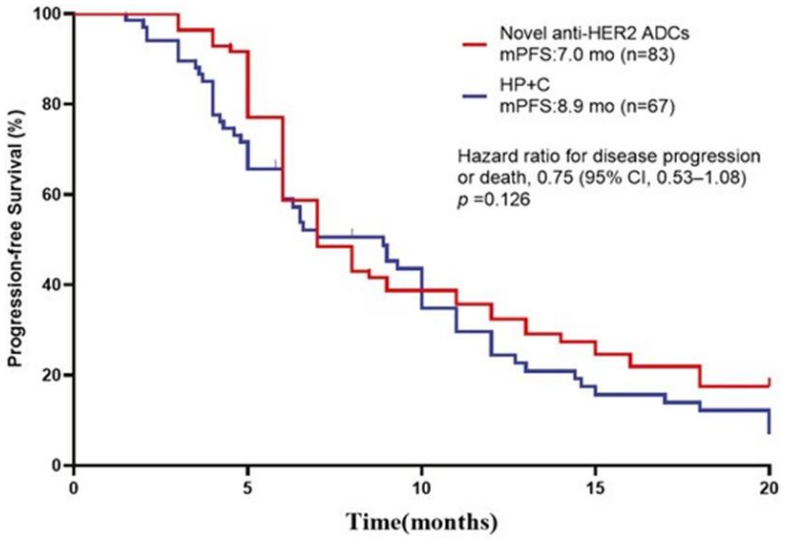
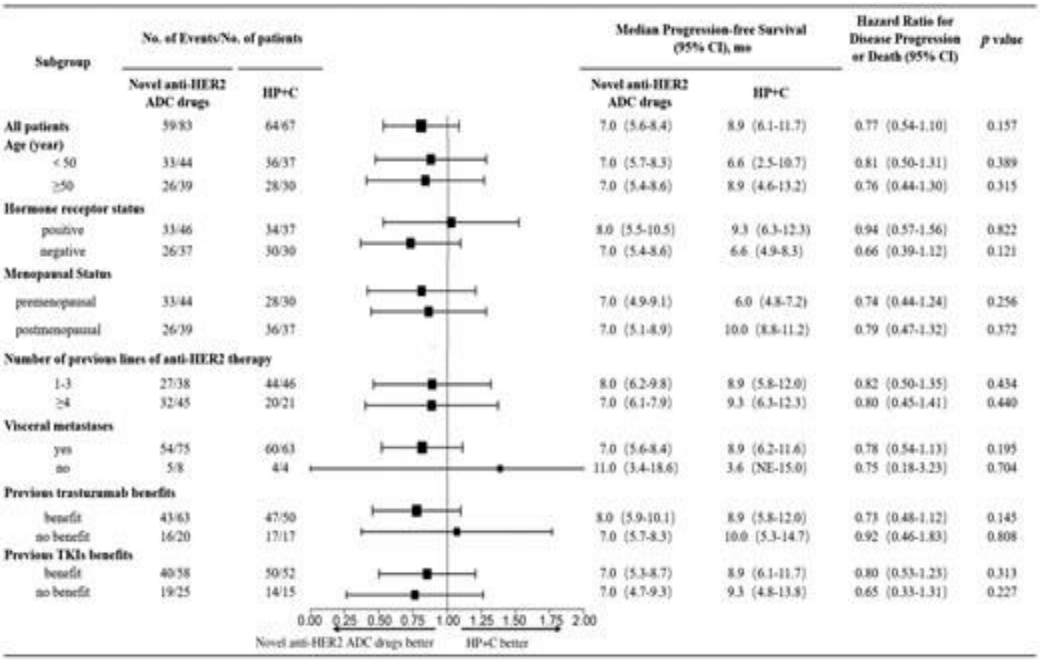


Figure 2. Kaplan–Meier curves illustrating progression-free survival among patients receiving novel anti-HER2 antibody–drug conjugates compared with those treated with pertuzumab and trastuzumab in combination with chemotherapy.

Abbreviations: antibody-drug conjugates (ADCs); confidence interval (CI); pertuzumab + trastuzumab + chemotherapy (HP+C); human epidermal growth factor receptor 2 (HER2); month (mo).



Subgroup	No. of Events/No. of patients		Median Progression-free Survival (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)	p value
	Novel anti-HER2 ADC drugs	HP+C	Novel anti-HER2 ADC drugs	HP+C		
All patients	59/83	64/67	7.0 (5.6-8.4)	8.9 (6.1-11.7)	0.77 (0.54-1.10)	0.157
Age (year)						
< 50	33/44	36/37	7.0 (5.7-8.3)	6.6 (2.5-10.7)	0.81 (0.50-1.31)	0.389
≥50	26/39	28/30	7.0 (5.4-8.6)	8.9 (4.6-13.2)	0.76 (0.44-1.30)	0.315
Hormone receptor status						
positive	33/46	34/37	8.0 (5.5-10.5)	9.3 (6.3-12.3)	0.94 (0.57-1.56)	0.822
negative	26/37	30/30	7.0 (5.4-8.6)	6.6 (4.9-8.3)	0.66 (0.39-1.12)	0.121
Menopausal Status						
premenopausal	33/44	28/30	7.0 (4.9-9.1)	6.0 (4.8-7.2)	0.74 (0.44-1.24)	0.256
postmenopausal	26/39	36/37	7.0 (5.1-8.9)	10.0 (8.8-11.2)	0.79 (0.47-1.32)	0.372
Number of previous lines of anti-HER2 therapy						
1-3	27/38	44/46	8.0 (6.2-9.8)	8.9 (5.8-12.0)	0.82 (0.50-1.35)	0.434
≥4	32/45	20/21	7.0 (6.1-7.9)	9.3 (6.3-12.3)	0.80 (0.45-1.41)	0.440
Visceral metastases						
yes	54/75	60/63	7.0 (5.6-8.4)	8.9 (6.2-11.6)	0.78 (0.54-1.13)	0.195
no	5/8	4/4	11.0 (3.4-18.6)	3.6 (NE-15.0)	0.75 (0.18-3.23)	0.704
Previous trastuzumab benefits						
benefit	43/63	47/50	8.0 (5.9-10.1)	8.9 (5.8-12.0)	0.73 (0.48-1.12)	0.145
no benefit	16/20	17/17	7.0 (5.7-8.3)	10.0 (5.3-14.7)	0.92 (0.46-1.83)	0.808
Previous TKIs benefits						
benefit	40/58	50/52	7.0 (5.3-8.7)	8.9 (6.1-11.7)	0.80 (0.53-1.23)	0.313
no benefit	19/25	14/15	7.0 (4.7-9.3)	9.3 (4.8-13.8)	0.65 (0.33-1.31)	0.227

Figure 3. Presents a subgroup evaluation of progression-free survival (PFS).

Abbreviations: month (mo); tyrosine kinase inhibitor (TKI); confidence interval (CI); pertuzumab + trastuzumab + chemotherapy (HP+C); human epidermal growth factor receptor 2 (HER2); antibody-drug conjugates (ADCs).

Further subgroup evaluations stratified participants into three cohorts: 47 individuals treated with other novel anti-HER2 antibody-drug conjugates, 67 individuals receiving HP plus chemotherapy, and 36 individuals on T-DXd. A survival comparison was conducted among these cohorts. Median progression-free survival reached 7.0 months for the other novel anti-HER2 ADCs cohort, 8.9 months for the HP plus chemotherapy cohort, and 12.0 months for the T-DXd cohort. A statistically significant distinction emerged when comparing the T-DXd cohort to the HP plus chemotherapy cohort (HR = 0.59, 95% CI 0.37–0.94, P = .028); **(Figure 4).**

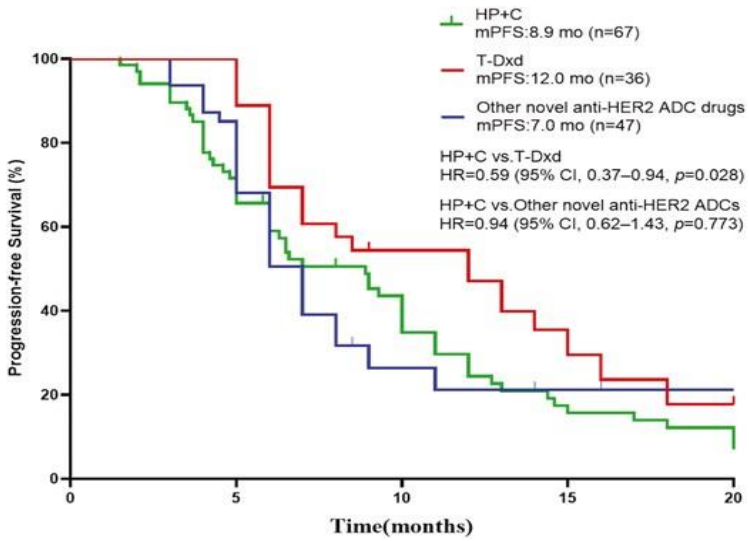


Figure 4. Kaplan–Meier survival curves depicting progression-free survival among patients treated with pertuzumab plus trastuzumab and chemotherapy, trastuzumab deruxtecan, or other newly developed anti-HER2 antibody–drug conjugates.

Abbreviations: HP+C, pertuzumab with trastuzumab and chemotherapy; HER2, human epidermal growth factor receptor 2; ADCs, antibody–drug conjugates; CI, confidence interval; mo, months.

Safety profile

Treatment-emergent adverse events observed in both treatment cohorts are summarized in **Table 3**. Overall, patients receiving novel anti-HER2 antibody–drug conjugates demonstrated a greater incidence of severe toxicities (grade 3–4) than those treated with HP combined with chemotherapy. In the ADC-treated population, the most frequently reported high-grade events included gastrointestinal disturbances and hematologic abnormalities, specifically nausea (10.8%), vomiting (10.8%), leukopenia (9.6%), and diarrhea (8.4%). Interstitial lung disease occurred in five patients receiving ADC therapy; one case reached grade 4 severity and necessitated permanent discontinuation of treatment.

In contrast, the HP combined with chemotherapy cohort most commonly experienced grade 3–4 toxicities related to nausea (17.9%), neutropenia (16.4%), and vomiting (14.9%). No fatal (grade 5) adverse events were reported in either group. All adverse reactions improved or resolved following appropriate supportive interventions, and no treatment-related deaths occurred. Taken together, the toxicity profiles of both treatment approaches were considered clinically controllable.

Table 3. Summary of treatment-associated adverse events in both study groups (n, %).

Adverse Event	**HP + Chemotherapy (n = 67)**		**Novel anti-HER2 Antibody-Drug Conjugates (n = 83)**	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Neutropenia	23 (34.3%)	11 (16.4%)	24 (28.9%)	7 (8.4%)
Leukopenia	27 (40.3%)	5 (7.5%)	29 (34.9%)	8 (9.6%)
Thrombocytopenia	10 (14.9%)	3 (4.5%)	17 (20.5%)	5 (6.0%)
Anemia	18 (26.9%)	5 (7.5%)	32 (38.6%)	6 (7.2%)
Elevated liver enzymes	19 (28.4%)	4 (6.0%)	16 (19.3%)	3 (3.6%)
Diarrhea	47 (70.1%)	0	18 (21.7%)	7 (8.4%)

Nausea	50 (74.6%)	12 (17.9%)	58 (69.9%)	9 (10.8%)
Constipation	15 (22.4%)	0	15 (18.1%)	1 (1.2%)
Fatigue	48 (71.6%)	4 (6.0%)	50 (60.2%)	5 (6.0%)
Vomiting	29 (43.3%)	10 (14.9%)	37 (44.6%)	9 (10.8%)
Peripheral neuropathy	28 (41.8%)	3 (4.5%)	21 (25.3%)	5 (6.0%)
Decreased appetite	28 (41.8%)	0	33 (39.8%)	0
Interstitial lung disease	0	0	5 (6.0%)	1 (1.2%)
Reduced left ventricular ejection fraction (<50% or ≥15% decline from baseline)	1 (1.5%)	0	0	0

Abbreviations: HER2, human epidermal growth factor receptor 2; ADCs, antibody-drug conjugates; LVEF, left ventricular ejection fraction; HP+C, pertuzumab + trastuzumab + chemotherapy.

Advances in systemic therapy have expanded later-line treatment options for patients with HER2-positive metastatic breast cancer (MBC). Among individuals who experience disease progression after tyrosine kinase inhibitor (TKI) therapy, identifying an effective subsequent strategy is critical for long-term disease control. To our knowledge, this study represents the first real-world analysis directly comparing novel anti-HER2 antibody–drug conjugates (ADCs) with pertuzumab plus trastuzumab combined with chemotherapy (HP+C) in patients following TKI failure.

The findings demonstrated a clear difference in objective response rate (ORR) favoring novel anti-HER2 ADCs, whereas no statistically significant differences were observed between treatment groups with respect to median progression-free survival (PFS) or clinical benefit rate (CBR). Furthermore, subgroup analyses revealed consistent PFS outcomes across all examined patient characteristics, including age, hormone receptor expression, menopausal status, prior lines of anti-HER2 therapy, visceral involvement, and clinical benefit derived from previous trastuzumab or TKI exposure. From a safety perspective, both regimens exhibited manageable toxicity profiles, with no unexpected adverse events or treatment-related mortality.

In the present cohort, median PFS reached 7.0 months in the ADC-treated population and 8.9 months in patients receiving HP combined with chemotherapy (P = .126). These outcomes contrast with those reported in randomized controlled trials evaluating trastuzumab deruxtecan (T-DXd), in which median PFS ranged from 16.4 to 25.1 months and ORR from 60.9% to 79.7% [7, 13]. The reduced efficacy observed in our real-world population can likely be attributed to multiple factors. First, clinical trials typically enroll highly selected patients, whereas real-world cohorts often include individuals with greater comorbidity burden and more advanced disease, leading to diminished treatment responses compared with controlled trial settings [14, 15]. Notably, 89% of patients in the ADC group in this study had visceral metastases, substantially exceeding the approximately 70% reported in the DESTINY-Breast03 trial. Differences in baseline disease characteristics, treatment history, and prior therapeutic exposure may also contribute to the observed discrepancies in efficacy [16, 17].

Second, T-DXd constituted only approximately 40% of treatments within the novel anti-HER2 ADC cohort. Although other ADCs share similar mechanisms of action, several remain under clinical investigation, and their therapeutic benefit has not yet been fully established. For this reason, we further stratified patients into T-DXd and non–T-DXd ADC subgroups and compared both with the HP+C cohort. This analysis revealed a statistically significant difference between the T-DXd and HP+C groups, a finding that should be interpreted cautiously given the limited sample size and the absence of interaction testing.

The HP combined with chemotherapy regimen is currently established as a standard first-line therapy for HER2-positive metastatic breast cancer. The CLEOPATRA trial demonstrated that HP plus chemotherapy significantly prolonged median PFS from 12.4 to 18.7 months and achieved a median overall survival of 57.1 months [18, 19]. These benefits were subsequently validated in a Chinese population in the PUFFIN study [20]. However, pertuzumab only became available in China in 2019, and as a result, many patients previously received trastuzumab plus chemotherapy alone in the first-line setting. Consequently, evidence supporting the use of HP combined with chemotherapy in later treatment lines remains limited [10]. The PHEREXA trial, the only phase III randomized study evaluating pertuzumab after trastuzumab failure, did not demonstrate a clear survival advantage [11].

It is well established that treatment efficacy generally declines with increasing lines of therapy [21, 22]. Consistent with this concept, the median PFS of 8.9 months observed in the HP+C cohort in this study was markedly shorter than outcomes reported in first-line trials such as CLEOPATRA and PUFFIN [19, 20]. Nevertheless, PFS was

comparable to that achieved with novel anti-HER2 ADCs in the present analysis. Given considerations related to drug accessibility and reimbursement policies in China, HP combined with chemotherapy remains a practical and frequently utilized option for many patients.

Further subgroup analyses indicated that prior benefit from trastuzumab or TKI therapy did not significantly influence comparative PFS outcomes between treatment strategies. Previous research has reported a median PFS of only 3.4 months with trastuzumab monotherapy following TKI failure [22]. The improved PFS observed in the HP combined with chemotherapy cohort in our study may reflect the added contribution of pertuzumab. Mechanistically, trastuzumab inhibits ligand-independent HER2–HER3 signaling [23], while pertuzumab blocks ligand-dependent HER2–HER3 dimerization [24]. The complementary actions of these agents enable more comprehensive suppression of HER2 signaling pathways [25]. Based on these findings, HP combined with chemotherapy appears to provide superior disease control compared with single-agent HER2 blockade [22]. Ongoing translational research is being conducted to identify patient populations most likely to benefit from this regimen.

Safety analyses further contextualized the clinical utility of the HP combined with chemotherapy approach. The adverse event profiles in both groups were dominated by hematologic and gastrointestinal toxicities, consistent with previous reports [7, 20]. However, the incidence of grade 3–4 adverse events was higher in the ADC cohort than in the HP+C cohort, even exceeding rates reported in the DESTINY-Breast03 study [7]. This observation may reflect the combined influence of higher tumor burden, cumulative prior therapies, and treatment intensity. Interstitial lung disease occurred in five patients receiving ADCs, a known risk associated with this drug class [26]. One case reached grade 4 severity but resolved following treatment discontinuation and supportive care. Such toxicities may limit broader acceptance of ADCs and highlight the need for improved monitoring, early diagnosis, and optimized management strategies [26]. In contrast, hematologic toxicity and liver function abnormalities observed in the HP combined with chemotherapy group were primarily attributed to cytotoxic agents [20]. Importantly, no patients developed clinically significant cardiotoxicity during treatment.

Several limitations should be acknowledged, including the retrospective design, limited sample size, potential selection bias, and lack of randomization. Additionally, the observational nature of the study restricts the ability to fully adjust for confounding variables. Despite these constraints, the findings provide valuable real-world evidence to inform treatment decision-making for HER2-positive metastatic breast cancer after TKI failure.

Conclusion

In patients with HER2-positive metastatic breast cancer who experience progression following TKI therapy, both novel anti-HER2 antibody–drug conjugates and dual HER2 antibody therapy combined with chemotherapy demonstrate moderate antitumor activity and acceptable safety. Novel anti-HER2 ADCs remain the preferred therapeutic option after TKI failure. However, based on the results of this study, HP combined with chemotherapy represents a reasonable alternative, particularly for patients with limited access to ADC-based therapies.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Slamon D, Godolphin W, Jones L, et al. Studies of the HER-2/ neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-12
2. Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. Proc Natl Acad Sci USA. 1992;89(10):4285-9. doi:10.1073/pnas.89.10.4285
3. Ma F, Yan M, Li W, et al; PHILA Investigators. Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first line treatment in patients with HER2 positive metastatic breast cancer (PHILA): randomised, double blind, multicentre, phase 3 trial. BMJ. 2023;383(26):e076065. doi:10.1136/bmj-2023-

076065
4. Yan M, Bian L, Hu X, et al. Pyrotinib plus capecitabine for human epidermal factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes (PHENIX): a randomized, double-blind, placebo-controlled phase 3 study. Transl Breast Cancer Res. 2020;1(1):13. doi:10.21037/tbcr-20-25
5. Xu B, Yan M, Ma F, et al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, ran-domised, controlled, phase 3 trial. Lancet Oncol. 2021;22(3):351-60. doi:10.1016/s1470-2045(20)30702-6
6. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Tras-tuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91. doi:10.1056/NEJMoa1209124
7. Cortés J, Kim SB, Chung WP, et al; DESTINY-Breast03 Trial Inves-tigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022;386(12):1143-54. doi:10.1056/NEJMoa2115022
8. Mohd Sharial MSN, Crown J, Hennessy BT. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast can-cer. Ann Oncol. 2012;23(12):3007-16. doi:10.1093/annonc/mds200
9. Bian L, Li F, Jiang Z. Thoughts on therapy strategy in the era of "after anti-HER2 TKI" in CSCO BC Guidelines 2022. Transl Breast Cancer Res. 2022;3(3):26. doi:10.21037/tbcr-22-32
10. Yamamoto Y, Iwata H, Taira N, et al. Pertuzumab retreatment for HER2-positive advanced breast cancer: a randomized, open-label phase III study (PRECIOUS). Cancer Sci. 2022;113(9):3169-79. doi:10.1111/cas.15474
11. Urruticoechea A, Rizwanullah M, Im SA, et al. Randomized phase III trial of trastuzumab plus capecitabine with or with-out pertuzumab in patients with human epidermal growth fac-tor receptor 2-positive metastatic breast cancer who experienced disease progression during or after trastuzumab-based therapy. J Clin Oncol. 2017;35(26):3030-3038. doi:10.1200/JCO.2016.70.6267
12. Ji C, Li F, Yuan Y, et al. Novel anti-HER2 antibody-drug conjugates versus T-DM1 for HER2-positive metastatic breast cancer after tyrosine kinase inhibitors treatment. Oncologist. 2023;28(10):e859-e66. doi:10.1093/oncolo/oyad127
13. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investiga-tors. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-21. doi:10.1056/NEJMoa1914510
14. Penberthy L, Rivera DR, Ward K. The contribution of cancer sur-veillance toward real world evidence in oncology. Semin Radiat Oncol. 2019;29(4):318-22. doi:10.1016/j.semradonc.2019.05.004
15. Ethier JL, Desautels D, Robinson A, et al. Practice patterns and out-comes of novel targeted agents for the treatment of ERBB2-positive metastatic breast cancer. JAMA Oncol. 2021;7(9):e212140. doi:10.1001/jamaoncol.2021.2140
16. Templeton AJ, Booth CM, Tannock IF. Informing patients about expected outcomes: the efficacy-effectiveness gap. J Clin Oncol. 2020;38(15):1651-4. doi:10.1200/JCO.19.02035
17. Green AK, Curry M, Trivedi N, Bach PB, Mailankody S. Assess-ment of outcomes associated with the use of newly approved oncology drugs in medicare beneficiaries. JAMA Netw Open. 2021;4(2):e210030. doi:10.1001/jamanetworkopen.2021.0030
18. Baselga J, Cortés J, Kim SB, et al; CLEOPATRA Study Group. Per-tuzumab plus trastuzumab plus docetaxel for metastatic breast can-cer. N Engl J Med. 2012;366(2):109-19. doi:10.1056/NEJMoa1113216
19. Swain SM, Miles D, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive met-astatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lan-cet Oncol. 2020;21(4):519-30. doi:10.1016/S1470-2045(19)30863-0
20. Xu B, Li W, Zhang Q, et al. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (PUFFIN): a phase III, randomized, double-blind, placebo-controlled study. Breast Cancer Res Treat. 2020;182(3):689-97. doi:10.1007/s10549-020-05728-w
21. Li F, Xu F, Li J, et al. Pyrotinib versus trastuzumab emtansine for HER2-positive metastatic breast cancer after previous trastuzumab and lapatinib treatment: a real-world study. Ann Transl Med. 2020;9(2):103. doi:10.21037/atm-20-4054
22. Bian L, Jiang ZF, Wang T, et al. Efficacy and prognostic analysis of retreatment with trastuzumab-based

therapy after multi-line tar-geted therapy resistance in HER2-positive metastatic breast cancer. Zhonghua Yi Xue Za Zhi. 2013;93(1):48-52.

23. Junttila TT, Akita RW, Parsons K, et al. Ligand-independent HER2/ HER3/PI3K complex is disrupted by trastuzumab and is effec-tively inhibited by the PI3K inhibitor GDC-0941. Cancer Cell. 2009;15(5):429-40. doi:10.1016/j.ccr.2009.03.020
24. Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB sig-naling from the structure of the ErbB2-pertuzumab complex. Cancer Cell. 2004;5(4):317-28. doi:10.1016/s1535-6108(04)00083-2
25. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res. 2004;64(7):2343-6. doi:10.1158/0008-5472.can-03-3856
26. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open. 2022;7(4):100554. doi:10.1016/j.esmoop.2022.100554