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Emerging Anti-HER2 Antibody–Drug Conjugates versus Dual HER2-Targeted Antibodies in HER2-Positive Metastatic Breast Cancer Resistant to Tyrosine Kinase Inhibitors

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Abstract

For patients with HER2-positive metastatic breast cancer (MBC) who have experienced tyrosine kinase inhibitor (TKI) failure, treatment options include novel anti-HER2 antibody-drug conjugates (ADCs) and the combination of pertuzumab and trastuzumab (HP) with chemotherapy. Prior investigations by our group demonstrated considerable efficacy of novel anti-HER2 ADCs in this population. However, no direct comparative data exist evaluating novel anti-HER2 ADCs versus HP plus chemotherapy. This study aimed to assess and contrast the efficacy and safety of these two therapeutic approaches in patients after TKI failure. Patients with HER2-positive MBC treated with either novel anti-HER2 ADCs or HP combined with chemotherapy from January 2019 to August 2023, all with prior TKI exposure, were included. The primary endpoint was progression-free survival (PFS), while secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), and safety profiles.

Among 150 eligible patients, 83 received novel anti-HER2 ADCs (36 with trastuzumab deruxtecan [T-Dxd] and 47 with other ADCs), and 67 received HP with chemotherapy. Median PFS was 7.0 months in the ADC group and 8.9 months in the HP+chemotherapy group, with ORRs of 51.8% versus 26.9% and CBRs of 69.9% versus 65.7%, respectively. Subgroup analysis indicated improved PFS with T-Dxd compared to HP plus chemotherapy. The most frequent grade 3–4 adverse events were neutropenia and gastrointestinal toxicity in both cohorts. In HER2-positive MBC patients following TKI failure, both novel anti-HER2 ADCs and HP combined with chemotherapy provide moderate efficacy with manageable toxicity. Novel anti-HER2 ADCs are recommended as the preferred option, while HP plus chemotherapy remains a viable alternative, particularly where ADCs are less accessible.

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

Introduction

Human epidermal growth factor receptor 2 (HER2) acts as both a driver gene and a therapeutic target in breast cancer, with anti-HER2 therapies markedly improving patient outcomes [1, 2]. In HER2-positive MBC, the introduction of the PHILA regimen has led Chinese guidelines to recommend frontline dual blockade using the TKI pyrotinib with trastuzumab and chemotherapy [3]. Phase III trials PHENIX and PHOEBE confirmed pyrotinib's notable efficacy in patients who failed prior trastuzumab therapy [4, 5], resulting in increased TKI usage in this population in China.

Antibody-drug conjugates (ADCs) have become central to second-line and later therapies for HER2-positive MBC. The EMILIA study established T-DM1 as a standard second-line treatment internationally [6], while DESTINY-Breast03 repositioned T-Dxd (trastuzumab deruxtecan, DS8201) as a preferred option, now incorporated into major guidelines worldwide [7]. In China, where T-DM1 access has historically been limited, T-Dxd and HP with chemotherapy represent practical second- and third-line options, although

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accessibility and coverage issues exist. The PFS advantage reported in PHILA supports the frontline use of domestic TKIs in trastuzumab-sensitive or resistant cancers.

For patients progressing after TKI therapy, continuous anti-HER2 strategies remain essential to inhibit HER2-driven pathways [8, 9]. According to the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2023, HP plus chemotherapy may be employed after TKI failure in pertuzumab-naïve patients, although this recommendation is supported by limited evidence [10, 11]. The PHEREXA study examined pertuzumab in trastuzumab-resistant cases but did not show definitive benefit [11]. Our previous work demonstrated that novel anti-HER2 ADCs achieve substantial efficacy in TKI-resistant patients [12]; however, no randomized trials have compared this with HP plus chemotherapy. This study therefore aimed to directly evaluate and contrast the effectiveness and safety of these two regimens in HER2-positive MBC patients after TKI failure.

Materials and Methods

Study population

This investigation included female patients diagnosed with HER2-positive metastatic breast cancer (MBC) who received treatment at the Breast Cancer Ward, Department of Oncology, Chinese People's Liberation Army General Hospital, between January 2019 and August 2023. Eligible participants had complete clinical records and an ECOG performance status of 0–1. HER2 positivity was confirmed by immunohistochemistry (IHC) or FISH (HER2+++), or by evaluating the primary tumor if a metastatic biopsy was unavailable. Patients were required to have at least one measurable extracranial lesion or osteolytic/mixed bone metastases and normal organ function (heart, liver, kidney, lungs) according to RECIST 1.1 criteria. Prior treatment with pyrotinib was considered a failure if discontinued due to disease progression, adverse events, or patient decision. Patients had to have received a minimum of six weeks of either novel anti-HER2 ADC therapy or HP combined with chemotherapy, along with at least one treatment response assessment. Patients were excluded if they had symptomatic brain metastases, other active malignancies, or serious comorbid conditions.

Clinical data, including demographic information, prior therapy history, treatment responses, and adverse events, were obtained from electronic medical records. The final follow-up was conducted on August 1, 2023.

Treatment regimens and dose adjustments

Patients in the novel anti-HER2 ADC cohort received agents such as T-Dxd or other ADCs with similar mechanisms. Standard dosing schedules were followed: T-Dxd 3.6 mg/kg every three weeks; RC48 2.0 mg/kg every 2 weeks; MRG002 2.6 mg/kg every three weeks; ARX788 1.5 mg/kg every three weeks.

In the HP plus chemotherapy group, patients received trastuzumab (loading 8 mg/kg, then 6 mg/kg q3w) and pertuzumab (loading 840 mg, then 420 mg q3w) combined with chemotherapeutic agents, including docetaxel (75 mg/m² q3w), paclitaxel-albumin (260 mg/m² on days 1 and 8 q3w), vinorelbine (25 mg/m² on days 1 and 8 q3w), or gemcitabine (1000 mg/m² on days 1 and 8 q3w). After 6–8 chemotherapy cycles, regimens were modified or discontinued by senior oncologists based on efficacy and tolerability; endocrine therapy was considered according to hormone receptor status.

Endpoints and assessments

The primary endpoint was progression-free survival (PFS), measured from the start of treatment to radiologically confirmed progression or death. Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), and safety. ORR encompassed complete and partial responses, while CBR included responses plus stable disease lasting ≥6 months. Tumor assessments were conducted every two cycles per RECIST 1.1. Adverse events were recorded throughout treatment and graded using CTCAE version 4.0.

Statistical analysis

Continuous variables were analyzed using t-tests or Wilcoxon rank-sum tests, and categorical variables—including ORR and CBR—were compared using χ^2 or Fisher's exact tests. Kaplan-Meier analysis was employed for PFS, with the log-rank test for comparisons. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazards models. Subgroup analyses for PFS were conducted using Cox regression and visualized in forest plots with GraphPad Prism 7.0. Two-sided P values <0.05 were considered statistically significant.

Results and Discussion

Patient characteristics

A total of 150 patients were included, with a median age of 48 years (range 25–89). The novel anti-HER2 ADC group (n=83) received T-Dxd (36 patients, 43.4 percent), MRG002 (24 patients, 28.9 percent), ARX788 (13 patients, 15.7 percent), and RC48 (10 patients, 12.0 percent). In the HP plus chemotherapy group (n=67), 47 patients (70.1 percent) received taxanes, 11 (16.4 percent) received vinorelbine, and 9 (13.4 percent) received gemcitabine.

Overall, baseline characteristics were largely balanced between groups, including rates of liver, lung, and brain metastases. Notably, multiple metastatic sites (≥3) were more frequent in the ADC group compared with the HP plus chemotherapy group (62.7 percent vs 31.3 percent, P < .001). A higher proportion of patients in the ADC cohort had undergone three or more prior lines of anti-HER2 therapy compared to the HP cohort (54.2 percent vs 32.8 percent, P = .008). All patients had previously received trastuzumab and pyrotinib, and prior therapy efficacy was similar, except that pertuzumab exposure was higher in the ADC group (74.7%) **(Table 1)**.

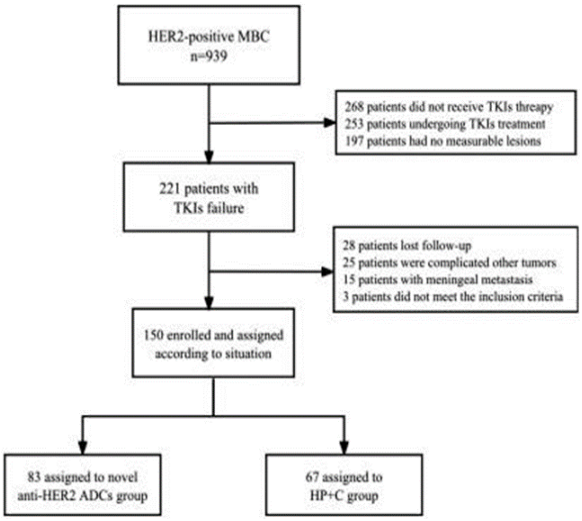

Figure 1. Flowchart depicting the selection of 150 female patients with HER2-positive metastatic breast cancer who received treatment with either novel anti-HER2 ADCs or the HP plus chemotherapy regimen. Abbreviations: HER2= human epidermal growth factor receptor 2; ADCs= antibody-drug conjugates; HP+C= pertuzumab + trastuzumab + chemotherapy; TKI= tyrosine kinase inhibitor.

Table 1. Baseline demographics and clinical profiles of 150 women with HER2-positive metastatic breast cancer receiving either novel anti-HER2 ADCs or HP+C

Characteristic	HP+C Group (N = 67)	ADC Group (N = 83)	P-value
Age at diagnosis (years)			.787
Median (range)	48 (25–72)	48 (25–89)	
Younger than 50	37 (55.2%)	44 (53.0%)	
50 or older	30 (44.8%)	39 (47.0%)	
Hormone receptor expression			.981
Negative	30 (44.8%)	37 (44.6%)	
Positive	37 (55.2%)	46 (55.4%)	
Stage at initial diagnosis			.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%)	
Extent of metastasis			<.001
Fewer than 3 lesions	46 (68.7%)	31 (37.3%)	
Three or more lesions	21 (31.3%)	52 (62.7%)	
Metastatic sites			
Liver involvement	31 (46.3%)	42 (50.6%)	.598
Lung involvement	36 (53.7%)	48 (57.8%)	.615
Brain involvement	22 (32.8%)	20 (24.1%)	.236
Bone involvement	36 (53.7%)	44 (53.0%)	.930
Prior anti-HER2 therapies			
Trastuzumab alone	67 (100%)	83 (100%)	–
Trastuzumab + Pertuzumab	0 (0%)	62 (74.7%)	<.001
Pyrotinib	67 (100%)	83 (100%)	–
Lapatinib	29 (43.3%)	18 (21.7%)	<.001
Lines of previous anti-HER2 treatment			.008
Up to 3 lines	45 (67.2%)	38 (45.8%)	
More than 3 lines	22 (32.8%)	45 (54.2%)	
Observed benefits from previous treatment			
Response to Trastuzumab	50 (74.6%)	63 (75.9%)	.857
Response to TKIs	52 (77.6%)	58 (69.9%)	.287

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

Efficacy

By August 2023, the median duration of follow-up was 6 months, ranging from 2 to 25.6 months. In the cohort receiving novel anti-HER2 ADCs, 24 patients (28.9%) remained on therapy, while 58 patients (69.9%) discontinued treatment due to disease progression, and 1 patient (1.2%) stopped therapy because of interstitial lung disease. Among patients treated with HP plus chemotherapy, only 5 individuals (7.5%) continued treatment, whereas 62 patients (92.5%) discontinued due to disease progression. Complete responses (CR) were not observed in either treatment group. Partial response

(PR) was achieved in 51.8% of patients receiving anti-HER2 ADCs compared to 26.9% in the HP+C group, while stable disease (SD) was observed in 43.4% versus 64.2%, respectively. The overall response rate (ORR) was significantly higher in the anti-HER2 ADC group compared with the HP+C group (51.8 percent vs 26.9 percent, P = .002), whereas the clinical benefit rate (CBR) did not differ significantly between the two groups (69.9 percent vs 65.7 percent, P = .583) **(Table 2)**.

Table 2. Efficacy comparison between novel anti-HER2 ADCs and HP+C

Response Type	HP+C (n = 67)	Anti-HER2 ADCs (n = 83)	P-value
Complete response (CR)	0	0	–
Partial response (PR)	18 (26.9%)	43 (51.8%)	
Stable disease (SD)	43 (64.2%)	36 (43.4%)	
SD lasting ≥6 months	26 (38.8%)	17 (20.5%)	
Progressive disease (PD)	6 (9.0%)	4 (4.8%)	
Objective response rate (ORR)	18 (26.9%)	43 (51.8%)	.002
Clinical benefit rate (CBR)	44 (65.7%)	58 (69.9%)	.583

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

The median progression-free survival (PFS) was 7.0 months for patients receiving novel anti-HER2 ADCs and 8.9 months for those in the HP+C group, with no statistically significant difference observed between the two treatments (HR = 0.75; 95 percent CI, 0.53–1.08; P = .126, **(Figure 2)**). Subgroup analyses using forest plots showed consistent PFS outcomes across all examined categories, including age, hormone receptor status, menopausal status, the number of prior anti-HER2 therapy lines, presence of visceral metastases, and prior responses to trastuzumab or tyrosine kinase inhibitors **(Figure 3)**.

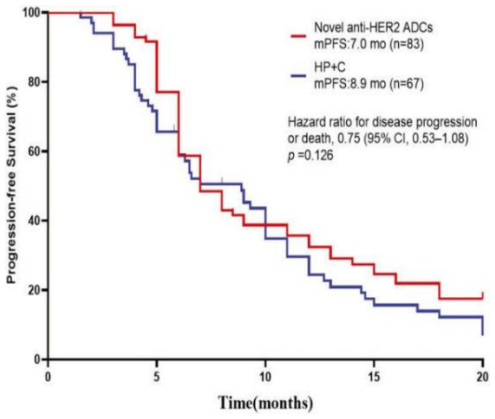

Figure 2. Kaplan-Meier curves depicting progression-free survival (PFS) in patients receiving novel anti-HER2 ADCs versus HP+C. Abbreviations: ADCs= antibody-drug conjugates; CI= confidence interval; HER2= human epidermal growth factor receptor 2; HP+C= pertuzumab + trastuzumab + chemotherapy; mo= months.

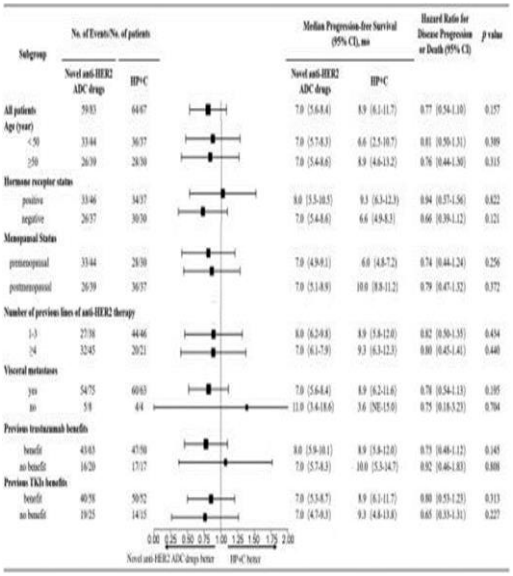

Figure 3. Subgroup analysis of progression-free survival (PFS) across different patient groups. Abbreviations: ADCs= antibody-drug conjugates; CI= confidence interval; HER2= human epidermal growth factor receptor 2; HP+C= pertuzumab + trastuzumab + chemotherapy; mo= months; TKI= tyrosine kinase inhibitor.

For further subgroup evaluation, patients were categorized into three cohorts: 36 patients received T-Dxd, 67 received HP combined with chemotherapy, and 47 received other novel anti-HER2 ADCs. PFS was analyzed across these groups, showing median values of 12.0 months for the T-Dxd group, 8.9 months for the HP+C group, and 7.0 months for the other ADCs group. A statistically significant improvement in PFS was observed for T-Dxd compared with HP+C (HR = 0.59; 95 percent CI, 0.37–0.94; P = .028, **(Figure 4)**).

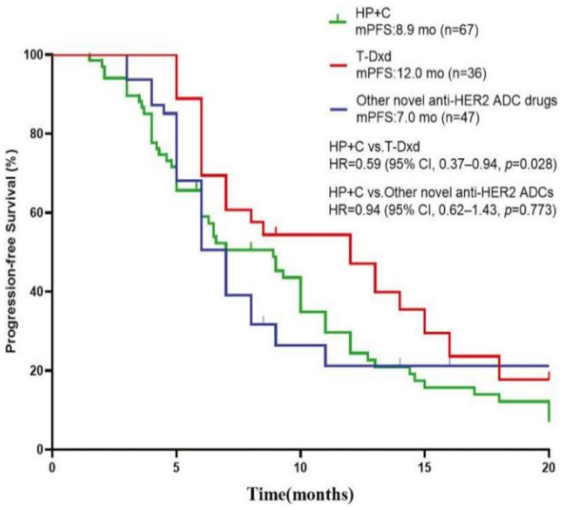

Figure 4. Kaplan-Meier curves comparing progression-free survival (PFS) among patients treated with HP+C, T-Dxd, and other novel anti-HER2 ADCs. Abbreviations: ADCs= antibody-drug conjugates; CI= confidence interval; HER2= human epidermal growth factor receptor 2; HP+C= pertuzumab + trastuzumab + chemotherapy; mo= months.

Safety

The safety profiles of both treatment groups are summarized in **Table 3**. Overall, the novel anti-HER2 ADCs group experienced a higher frequency of grade 3–4 adverse events compared with the HP+C group, particularly nausea and vomiting (both 10.8 percent), leukopenia (9.6 percent), and diarrhea (8.4 percent). Interstitial pneumonia occurred in five patients receiving ADCs, including one grade 4 case that led to study withdrawal. In the HP+C group, the most common grade 3–4 adverse events were nausea (17.9 percent), neutropenia (16.4 percent), and vomiting (14.9 percent). No grade 5 events were reported in either group. All adverse events were either resolved or improved with appropriate supportive care, and no treatment-related deaths occurred. Overall, the safety profile for both regimens was considered manageable.

Table 3. Treatment-emergent adverse events in the two treatment arms (n, %)

Adverse event	HP+C (n = 67)		Novel anti-HER2 antibody-drug conjugates (n = 83)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Leukopenia	27 (40.3)	5 (7.5)	29 (34.9)	8 (9.6)
Neutropenia	23 (34.3)	11 (16.4)	24 (28.9)	7 (8.4)
Anemia	18 (26.9)	5 (7.5)	32 (38.6)	6 (7.2)

Thrombocytopenia	10 (14.9)	3 (4.5)	17 (20.5)	5 (6.0)
Elevated transaminase levels	19 (28.4)	4 (6.0)	16 (19.3)	3 (3.6)
Diarrhea	47 (70.1)	0	18 (21.7)	7 (8.4)
Constipation	15 (22.4)	0	15 (18.1)	1 (1.2)
Nausea	50 (74.6)	12 (17.9)	58 (69.9)	9 (10.8)
Vomiting	29 (43.3)	10 (14.9)	37 (44.6)	9 (10.8)
Fatigue	48 (71.6)	4 (6.0)	50 (60.2)	5 (6.0)
Decreased appetite	28 (41.8)	0	33 (39.8)	0
Peripheral neuropathy	28 (41.8)	3 (4.5)	21 (25.3)	5 (6.0)
Interstitial lung disease	0	0	5 (6.0)	1 (1.2)
LVEF decrease (<50% or ≥15% decline from baseline)	1 (1.5)	0	0	0

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

The advent of new therapeutic agents has expanded options for later-line management of HER2-positive metastatic breast cancer (MBC). Identifying the optimal treatment strategy is particularly critical for patients who have experienced failure with tyrosine kinase inhibitors (TKIs). This study represents the first real-world analysis comparing novel anti-HER2 antibody–drug conjugates (ADCs) with trastuzumab plus pertuzumab (HP) combined with chemotherapy in patients after TKI failure. Our findings revealed a notable difference in overall response rate (ORR) between the novel anti-HER2 ADCs and the HP plus chemotherapy group, whereas median progression-free survival (PFS) and clinical benefit rate (CBR) did not differ significantly between the two cohorts. Subgroup analyses further demonstrated that PFS remained comparable across age groups, hormone receptor status, menopausal status, number of prior anti-HER2 therapy lines, presence of visceral metastases, benefit from prior trastuzumab therapy, and prior TKI efficacy. Safety profiles were acceptable in both groups, with no unexpected toxicities or treatment-related deaths observed.

In this cohort, median PFS was 7.0 months for the novel anti-HER2 ADCs group and 8.9 months for the HP plus chemotherapy group (P = .126). In contrast, randomized controlled trials (RCTs) of T-Dxd have reported median PFS ranging from 16.4 to 25.1 months, with ORRs between 60.9% and 79.7% [7, 13]. The lower median PFS observed in our study likely reflects two main factors. First, RCTs typically enroll highly selected patient populations, whereas real-world patients often present with more comorbidities and higher tumor burden, which can reduce observed treatment efficacy [14, 15]. For example, 89 percent of patients in our novel anti-HER2 ADCs group had visceral metastases, compared with 70% in the DESTINY-Breast03 trial. Baseline disease characteristics and prior treatment history may also contribute to efficacy differences [16, 17]. Second, only 40% of patients in the novel anti-HER2 ADCs cohort received T-Dxd; the remaining patients were treated with other novel anti-HER2 ADCs, many of which are still under clinical investigation with unclear efficacy. To account for this, we subdivided the novel anti-HER2 ADCs cohort into a T-Dxd group and an "other ADCs" group and compared each to the HP plus chemotherapy group. The analysis showed statistically significant differences between the T-Dxd group and the HP plus chemotherapy group, which may partly reflect the limited sample size and absence of interaction analysis.

The combination of trastuzumab and pertuzumab with chemotherapy is established as the standard first-line therapy for HER2-positive metastatic breast cancer (MBC). In the CLEOPATRA trial, this regimen extended median progression-free survival (PFS) from 12.4 to 18.7 months and achieved a median overall survival (OS) of 57.1 months [18, 19], while the PUFFIN study confirmed comparable benefits in a Chinese cohort [20]. However, since pertuzumab only became available in China in 2019, many patients initially receive trastuzumab plus chemotherapy, leaving limited data on the use of the dual antibody combination in later lines of therapy [10]. The PHEREXA trial, which investigated pertuzumab after prior trastuzumab failure, did not show a survival advantage [11]. Additionally, it is well-established that the efficacy of anti-HER2 therapies generally diminishes

as treatment lines progress [21, 22]. In the present study, median PFS for patients receiving HP plus chemotherapy was 8.9 months, notably shorter than first-line outcomes from CLEOPATRA and PUFFIN [19, 20], yet similar to the PFS observed in the novel anti-HER2 ADC cohort. From a practical perspective, drug accessibility and reimbursement policies in China make HP plus chemotherapy a common choice for many patients.

Subgroup analyses indicated that previous response to trastuzumab or TKIs did not significantly affect outcomes, with PFS remaining comparable between the novel anti-HER2 ADCs and HP plus chemotherapy groups. Prior reports in TKI-resistant populations showed that trastuzumab alone achieved a median PFS of only 3.4 months [22]. The observed benefit in the HP group may be explained by complementary mechanisms of action: trastuzumab inhibits ligand-independent HER2-HER3 signaling [23], whereas pertuzumab blocks ligand-dependent HER2-HER3 signaling [24]; their combination achieves broader suppression of HER2-mediated pathways [25]. These findings support the notion that dual-target therapy combined with chemotherapy can achieve superior PFS compared to single-target approaches [22]. Efforts are ongoing to identify patient populations most likely to benefit from this combination through translational research.

Regarding safety, both treatment strategies primarily caused hematologic and gastrointestinal adverse events, consistent with prior studies [7, 20]. Grade 3–4 toxicities occurred more frequently in the novel anti-HER2 ADC group, exceeding rates reported in DESTINY-Breast03 [7], likely reflecting cumulative effects of tumor burden, prior therapy, and treatment intensity. Interstitial lung disease occurred in five ADC-treated patients, including one grade 4 event, which resolved with drug discontinuation and supportive care, highlighting the importance of close monitoring [26]. In the HP plus chemotherapy cohort, hematologic and hepatic adverse events were mainly attributed to chemotherapy, and no clinically significant cardiotoxicity was observed [20].

This study has limitations, including its retrospective design, small sample size, potential selection bias, and lack of randomization, which may confound the interpretation of outcomes. Nevertheless, it provides meaningful insights into real-world treatment options for patients with HER2-positive MBC following TKI failure.

Conclusion

In patients with HER2-positive MBC who progressed after TKI therapy, both novel anti-HER2 ADCs and dual anti-HER2 antibody plus chemotherapy demonstrated moderate efficacy with manageable toxicity. While novel anti-HER2 ADCs should be considered the preferred option, dual antibody therapy with chemotherapy remains a viable alternative for patients with restricted access to ADCs.

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Conflict of Interest: None

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Ethics Statement: The study complies with all regulations. Data were collected from the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) database. This study was reviewed and approved by the Ethics board of The Affiliated Hospital of Qingdao University, with the approval number: QYFYKYLL 221311920. All patients or their proxies provided informed consent to participate in the study.

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):707-712.
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):4285-4289. 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. 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):13-13. 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, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(3):351-360. 10.1016/s1470-2045(20)30702-6
6. Verma S, Miles D, Gianni L, et al. ; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-1791. 10.1056/NEJMoa1209124
7. Cortés J, Kim SB, Chung WP, et al. ; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022;386(12):1143-1154. 10.1056/NEJMoa2115022
8. Mohd Sharial MSN, Crown J, Hennessy BT.. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast cancer. Ann Oncol. 2012;23(12):3007-3016. 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. 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):3169-3179. 10.1111/cas.15474
11. Urruticoechea A, Rizwanullah M, Im SA, et al. Randomized phase III trial of trastuzumab plus capecitabine with or without pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who experienced disease progression during or after trastuzumab-based therapy. J Clin Oncol. 2017;35(26):3030-3038. 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-e866. 10.1093/oncolo/oyad127
13. Modi S, Saura C, Yamashita T, et al. ; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-621. 10.1056/NEJMoa1914510
14. Penberthy L, Rivera DR, Ward K.. The contribution of cancer surveillance toward real world evidence in oncology. Semin Radiat Oncol. 2019;29(4):318-322. 10.1016/j.semradonc.2019.05.004
15. Ethier JL, Desautels D, Robinson A, et al. Practice patterns and outcomes of novel targeted agents for the treatment of ERBB2-positive metastatic breast cancer. JAMA Oncol. 2021;7(9):e212140. 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):1651-1654. 10.1200/JCO.19.02035
17. Green AK, Curry M, Trivedi N, Bach PB, Mailankody S.. Assessment of outcomes associated with the use of newly approved oncology drugs in medicare beneficiaries. JAMA Netw Open. 2021;4(2):e210030. 10.1001/jamanetworkopen.2021.0030
18. Baselga J, Cortés J, Kim SB, et al. ; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109-119. 10.1056/NEJMoa1113216
19. Swain SM, Miles D, Kim S-B, et al. ; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(4):519-530. 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):689-697. 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):103-103. 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 targeted 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 effectively inhibited by the PI3K inhibitor GDC-0941. Cancer Cell. 2009;15(5):429-440. 10.1016/j.ccr.2009.03.020
24. Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell. 2004;5(4):317-328. 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):2343-2346. 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. 10.1016/j.esmoop.2022.100554