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Research article

Inetetamab combined with pyrotinib and oral vinorelbine for patients with human epidermal growth factor receptor 2 positive advanced breast cancer: A single-arm phase 2 clinical trial

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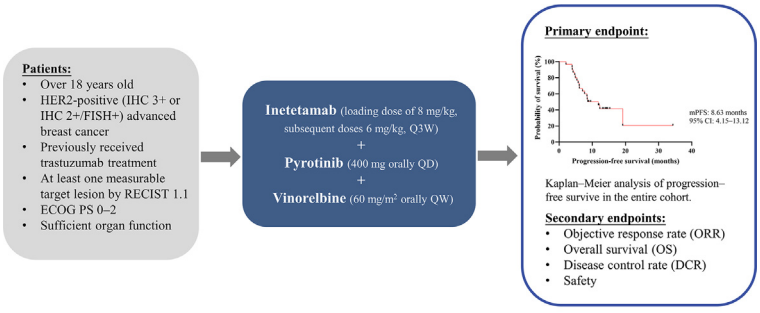
HIGHLIGHTS

- The triplet regimen of inetetamab, pyrotinib, and oral vinorelbine showed outstanding efficacy against human epidermal growth factor receptor 2 positive advanced breast cancers.
- The triplet regimen was well tolerated and did not increase the risk of overlapping toxicities.
- The potential clinicopathological characteristics affecting progression-free survival of patients receiving the triplet regimen were explored.

GRAPHICAL ABSTRACT



CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; FISH: Fluorescence *in situ* hybridization; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; mPFS: Median progression-free survival; QD: Quaque die; QW: Quaque week; RECIST: Response Evaluation Criteria in Solid Tumors.

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ABSTRACT

Background: Human epidermal growth factor receptor 2 (HER2)-targeted agents have significantly improved the outcomes of patients with HER2-positive breast cancer; however, a large proportion of patients still develop resistance to trastuzumab. In this study, we investigated the efficacy and safety of inetetamab, another anti-HER2 antibody, combined with pyrotinib and oral vinorelbine in patients with HER2-positive advanced breast cancer so as to provide new ideas for the treatment.

Methods: In this prospective, single-arm, phase 2 trial, patients with HER2-positive advanced breast cancer with disease progression after trastuzumab were recruited. Patients received a combination of inetetamab (loading dose of 8 mg/kg and subsequent doses of 6 mg/kg intravenously once every 3 weeks), pyrotinib (400 mg orally once daily), and vinorelbine (60 mg/m^2 orally once weekly) until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). The secondary endpoints included objective response rate (ORR), overall survival (OS), disease control rate (DCR), and safety.

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Results: Between February 13, 2022 and December 25, 2022, 30 patients were screened and enrolled in this study. The median age of the patients at enrollment was 54 years, 12 patients (40.0 %) had hormone-receptor-positive disease and 23 patients (76.7 %) had visceral metastasis. The median PFS was 8.63 months (95 % confidence interval [CI] 4.15–13.12 months). The median OS was not reached. The ORR was 53.3 % (16/30) and the DCR was 96.7 % (29/30). The most common Grade III/IV adverse events were leukopenia ($n = 5$, 16.7 %), neutropenia ($n = 4$, 13.3 %), and diarrhea ($n = 3$, 10 %). No treatment-related serious adverse events or deaths occurred.
Conclusions: The combination regimen of inetetamab, pyrotinib, and oral vinorelbine showed encouraging efficacy and favorable safety in patients with HER2-positive advanced breast cancer and could be considered as an alternative treatment option for the patients.
Trial registration: No.NCT05823623; https://www.clinicaltrials.gov/.

Introduction

Breast cancer is the most common life-threatening malignancy among women in China.[1] Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 20–30 % of breast cancers and has been associated with high invasiveness and poor prognosis.[2–4] Although HER2-targeted agents, represented by trastuzumab, have significantly improved the outcomes of patients with HER2-positive breast cancer, a large proportion of patients still develop resistance to trastuzumab, resulting in disease recurrence and metastasis.[5–7]

A variety of mechanisms can mediate trastuzumab resistance, including epitope masking, truncated HER2 receptors, and the activation of bypass signaling pathways.[8–10] Dual HER2 blockade using HER2-targeted monoclonal antibodies and tyrosine kinase inhibitors (TKIs) is a promising treatment strategy for overcoming these resistance mechanisms. In the HER2CLIMB study, trastuzumab in combination with tucatinib and capecitabine resulted in significantly better progression-free survival (PFS) and overall survival (OS) than trastuzumab combined with capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer, suggesting an encouraging antitumor effect of dual HER2 inhibition via simultaneously blocking the extracellular and intracellular domains of HER2.[11]

Inetetamab is a recombinant humanized anti-HER2 monoclonal antibody that has the same Fab segment as trastuzumab, while modifies Fc segment to endow greater antibody-dependent cell-mediated cytotoxicity (ADCC) than trastuzumab.[12] The efficacy and safety of inetetamab in patients with HER2-positive advanced breast cancer have been demonstrated in a pivotal clinical trial.[13] Pyrotinib is an orally administered, irreversible TKI that targets pan-HER receptors, including HER1, HER2, and HER4.[14] Two multicenter, randomized, controlled, phase III trials have shown that pyrotinib in combination with capecitabine is highly effective and well tolerated for the treatment of patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, leading to the establishment of pyrotinib plus capecitabine as a standard second-line treatment strategy for HER2-positive advanced breast cancer.[15,16] Vinorelbine is a traditional chemotherapeutic drug widely used for the treatment of advanced breast cancer.[17–19] Oral vinorelbine has similar effectiveness, tolerance, and better convenience compared with intravenous vinorelbine in patients with advanced breast cancer.[20–22]

This prospective, single-arm, phase 2 clinical trial was conducted to assess the efficacy and safety of a triplet regimen of inetetamab, pyrotinib, and oral vinorelbine in patients with HER2-positive advanced breast cancer in whom trastuzumab treatment failed so as to provide new ideas for the treatment.

Patients and methods

Study design

This prospective, single-arm, phase 2 clinical trial was designed to assess the efficacy and safety of inetetamab in combination with pyrotinib and oral vinorelbine in patients with HER2-positive advanced breast cancer who experienced disease progression after trastuzumab treatment. This study was conducted at the Department of Oncology of the First Affiliated Hospital of Nanjing Medical University. A summary of the trial profile is shown in Figure 1.

Patient eligibility

Female patients aged 18 years or older with HER2-positive advanced breast cancer who had previously received trastuzumab treatment were recruited for this study, including local recurrence and distant metastasis. Pathological diagnosis of HER2 positive was defined as Immunohistochemistry (IHC) 3+, or IHC 2+ with fluorescence *in situ* hybridization (FISH) testing of amplification. The inclusion criteria were progression during or after the most recent treatment for locally recurrent or metastatic disease or within 12 months after treatment for early-stage disease. Additional eligibility eligible criteria requirements included at least one measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 and sufficient organ function. Patients who had previously received pyrotinib or vinorelbine were eligible. Patients were excluded if they had symptomatic brain metastasis, leptomeningeal disease, gastrointestinal dysfunction, or left ventricular ejection fractions (LVEF) <50 %.

Treatment schedule

All eligible patients received inetetamab (loading dose of 8 mg/kg and subsequent doses of 6 mg/kg intravenously once every 3 weeks), pyrotinib (400 mg orally once daily), and vinorelbine (60 mg/m^2 orally once weekly). The treatment was continued until disease progression or intolerable toxicities were observed.

Disease assessment

At baseline, medical history, contrast-enhanced computed tomography (CT), brain contrast-enhanced magnetic resonance imaging (MRI), electrocardiogram, two-dimensional echocardiography, and laboratory examinations of all enrolled patients were performed. During the treatment period, blood routine and biochemical examinations were performed every 3 weeks. Radiological assessments were conducted every two cycles. For patients with brain metastases at baseline, brain MRI was performed every two cycles. Disease response was assessed using RECIST 1.1. Safety was evaluated based on the incidence and severity of treatment-related adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Study endpoints

The primary endpoint was PFS (defined as the time from the beginning of the study treatment to disease progression or death). The secondary endpoints included objective response rate (ORR, calculated as the percentage of participants whose best response was complete

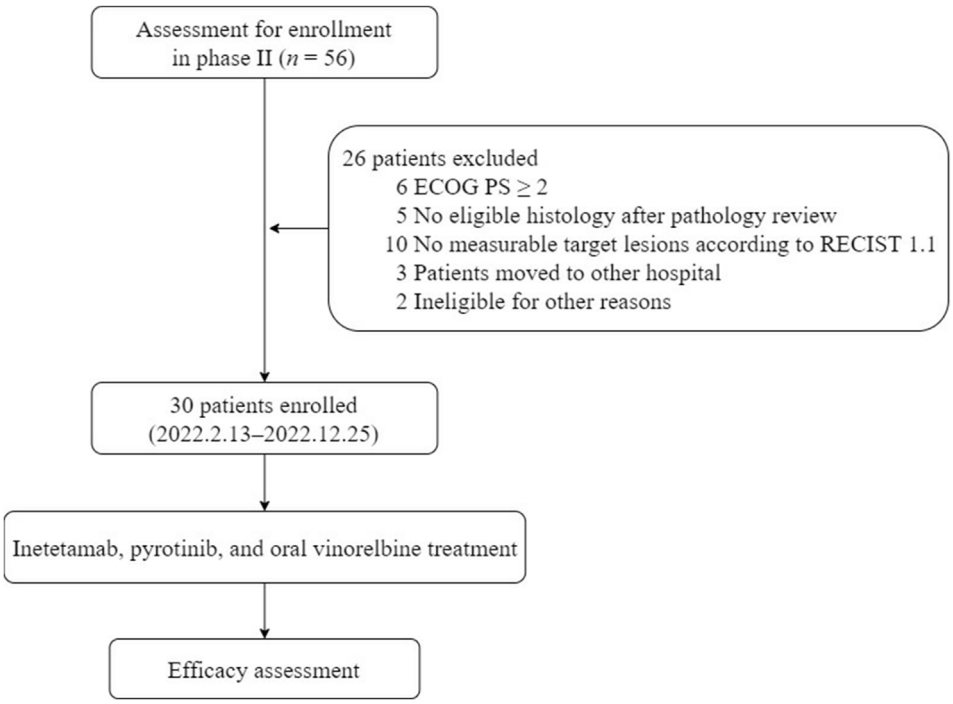

Figure 1. Summary of the trial profile. ECOG PS: Eastern Cooperative Oncology Group performance status; RECIST: Response Evaluation Criteria in Solid Tumors.

response or partial response), OS (defined as the time from the beginning of study treatment to death), disease control rate (DCR, calculated as the percentage of participants whose best response was complete response, partial response, or stable disease lasting for at least 4 weeks) and safety.

Statistical analysis

The sample size was calculated based on the primary endpoint using the Wilcoxon rank-sum test for non-inferiority, referring to HER2CLIMB clinical trial (NCT02614794). 28 patients were required to detect a clinical non-inferiority in PFS between our treatment group and the tucatinib-combination group in HER2CLIMB clinical trial with a significance level of $\alpha = 0.05$ and a power of 80 %. The analysis was conducted using the PASS 2021 statistical software (NCSS, LLC, Kaysville, USA). All analyses were conducted using SPSS 26.0 statistical software (IBM, Shanghai, China) and GraphPad Prism 9 software (GraphPad Software, Boston, USA). Descriptive analysis was performed to represent the clinicopathological characteristics of participants at baseline. The Kaplan–Meier method was used to estimate the median and 95 % confidence intervals (CIs) of PFS for all enrolled patients and subgroups. Univariate and multivariate Cox regression models were utilized to identify factors affecting PFS. All reported P values were two-sided and statistical significance was set at $P < 0.05$.

Results

Participants

30 eligible patients were recruited for this study between February 13, 2022 and December 25, 2022. The median age of all participants at diagnosis was 54 years (range: 26–69 years). Regarding hormone-receptor status, 12 patients (40.0 %) were estrogen receptor (ER)- and/or progesterone receptor (PR)-positive, and 18 patients (60.0 %) were ER- and PR- negative. At baseline, 23 patients (76.7 %) had visceral metastases, 18 (60 %) had lymph node metastases and 8 (26.7 %) had brain metastases. 20 (66.7 %), 13 (43.3 %), and 2 (6.7 %) patients had been previously treated with pertuzumab, TKIs, and trastuzumab emtansine (T-DM1), respectively. The median number of previous treatment lines for patients with advanced disease was one. The baseline clinicopathological features of the participants are shown in Table 1.

Efficacy

All participants were followed up until January 20, 2023. At a median follow-up of 13.1 months, 18 patients had experienced disease progression and 1 patient had died [Supplementary Figure 1]. In the entire cohort, the median PFS was 8.63 months (95 % CI 4.15–13.12 months) [Figure 2A]. As of January 20, 2023, the median OS had not been reached. The ORR was 53.3 % (complete response was seen in 1 patient and partial response was observed in 15 patients) [Table 2]. The DCR was 96.7 % (29 of 30 patients) [Table 2]. Cox univariate and multivariate analyses were used to determine potential factors associated with PFS. Univariate analysis found that patients with a worse ECOG performance status score, brain metastases or previous TKI treatment had significantly shorter PFS (hazard ratio [HR] 3.20, 95 % CI 1.19–8.58, $P = 0.021$; HR 3.10, 95 % CI 1.19–8.03, $P = 0.020$; HR 2.91, 95 % CI 1.12–7.57, $P = 0.028$, respectively) [Table 3]. The multivariate analysis showed that lymph node metastases exerted a significantly adverse impact on PFS (HR 4.27, 95 % CI 1.04–17.53, $P = 0.044$).

We further performed subgroup analyses and found that patients with lymph node metastases had a median PFS of 7.67 months (95 % CI 4.83–10.51 months), whereas the median PFS was not reached in patients without lymph node metastases [Figure 2B].

Safety

The most common adverse events were diarrhea (13, 43.3 %), leukopenia (9, 30.0 %), nausea (6, 20.0 %), neutropenia (5, 16.7 %), and anemia (3, 10.0 %). Other reported adverse events included fatigue (2, 6.7 %), vomiting (2, 6.7 %), alanine aminotransferase increased (1, 3.3 %), creatinine increased (1, 3.3 %), rash (1, 3.3 %) and hair loss (1, 3.3 %). The most frequent Grade III/IV adverse events were leukopenia (5, 16.7 %), neutropenia (4, 13.3 %), and diarrhea (3, 10.0 %). No serious treatment-related adverse events or deaths occurred. Treatment-related adverse events during the study period are summarized in Table 4.

Table 1
Baseline clinicopathological characteristics of patients receiving triplet regimen ($n = 30$).

Characteristics	Value
Age (years), Median (range)	54 (26–69)
ECOG PS	
0	16 (53.3)
1	14 (46.7)
Stage at diagnosis	
I–III	24 (80.0)
IV	6 (20.0)
Hormone-receptor status	
ER and/or PR positive	12 (40.0)
ER and PR negative	18 (60.0)
Metastatic sites	
Lymph node	18 (60.0)
Bone	12 (40.0)
Lung	13 (43.3)
Liver	15 (50.0)
Brain	8 (26.7)
Other	9 (30.0)
Visceral metastases	
No	7 (23.3)
Yes	23 (76.7)
Disease-free survival	
≤2 years	14 (58.3)
>2 years	9 (37.5)
Unknown	1 (4.2)
Previous anti-HER2 treatment	
Trastuzumab	30 (100.0)
Pertuzumab	20 (66.7)
TKI	13 (43.3)
T-DM1	2 (6.7)
Other	2 (6.7)
Previous treatment lines	
0	6 (20.0)
1	13 (43.3)
2	10 (33.3)
≥3	1 (3.3)
Median (range)	1 (0–3)

Data are presented as *n* (%) or median (range). ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; PR: Progesterone receptor; T-DM1: Trastuzumab emtansine; TKI: Tyrosine kinase inhibitor.

Discussion

To our knowledge, this is the first prospective study investigating the efficacy and safety of dual HER2-targeted therapy with Fc-modified monoclonal antibody and TKI in patients with HER2-positive advanced breast cancer. In this study, all enrolled patients had been exposed to trastuzumab therapy; additionally, 66.7 % of patients had received treatment with pertuzumab, 43.3 % had received TKI treatment and 6.7 % had been treated with T-DM1, indicating that these were refractory breast cancers resistant to multiple HER2-targeted agents. For heavily pretreated patients with HER2-positive advanced breast cancer, the triplet regimen of inetetamab, pyrotinib, and oral vinorelbine still showed outstanding efficacy. The median PFS was 8.63 months (95 % CI 4.15–13.12 months), the ORR was 53.3 % and the DCR was 96.7 %. Further, the triplet regimen was well tolerated. The overall incidence and severity of treatment-related adverse events were comparable to those reported in previous studies, and no new treatment-related adverse events were reported. Most treatment-related adverse events were Grade I/II and could be easily managed. The main Grade III/IV adverse events were hematological toxicities and diarrhea, which were controllable after supportive treatment.

The advent of HER2-targeted agents has significantly improved the prognosis of patients with HER2-positive advanced breast cancer.[5,6] Based on the results of randomized controlled trials CLEOPATRA and PUFFIN, international and domestic guidelines consistently recommend the combination of pertuzumab, trastuzumab, and taxane as the standard first-line treatment strategy for HER2-positive advanced breast cancer.[23–25] However, for HER2-positive advanced breast cancer with progression after previous trastuzumab treatment, there are significant differences in recommendations between China and Western countries. In European and American countries, T-DM1 has been the standard second-line treatment strategy for patients with HER2-positive advanced breast cancer since EMILIA study was published in New England Journal of Medicine (NEJM) in 2012.[26,27] Almost a decade later, the results of DESTINY-BREAST 03 study were announced at the European Society for Medical Oncology (ESMO) annual meeting in 2021. This study showed that, compared with T-DM1, trastuzumab deruxtecan (T-DXd) significantly reduced the risk of progression or death by 72 % (HR 0.28, 95 % CI 0.22%–0.37%) in HER2-positive advanced breast cancer patients who progressed after previous trastuzumab treatment.[28–30] Based on this, T-DXd has become the new second-line standard anti-HER2 therapy in European and American countries. T-DXd has already been approved for the treatment of patients with HER2-positive advanced breast cancer in China; however, the exorbitant price limits its extensive clinical application. Therefore, T-DM1 or pyrotinib plus capecitabine remains the preferred second-line treatment strategy for Chinese patients with HER2-positive advanced breast cancer.[15,16,26,27,31]

Unfortunately, a considerable number of patients exhibit primary or secondary resistance to treatment with T-DM1 or pyrotinib and experience disease progression shortly after the initiation of treatment. Additionally, approximately 40 % of Asian patients receiving T-DM1 treatment experience Grade III or greater thrombocytopenia,[26,27,31] and the incidences of Grade III/IV diarrhea and hand-foot syndrome after combined therapy with pyrotinib and capecitabine were 30.6 % and 16.4 %, respectively.[15,16] Some patients pause or even terminate treatment because of severe adverse reactions. Therefore, for patients with HER2-positive advanced breast cancer previously treated with trastuzumab, more effective and tolerable treatment strategies are needed to increase survival and improve quality of life.

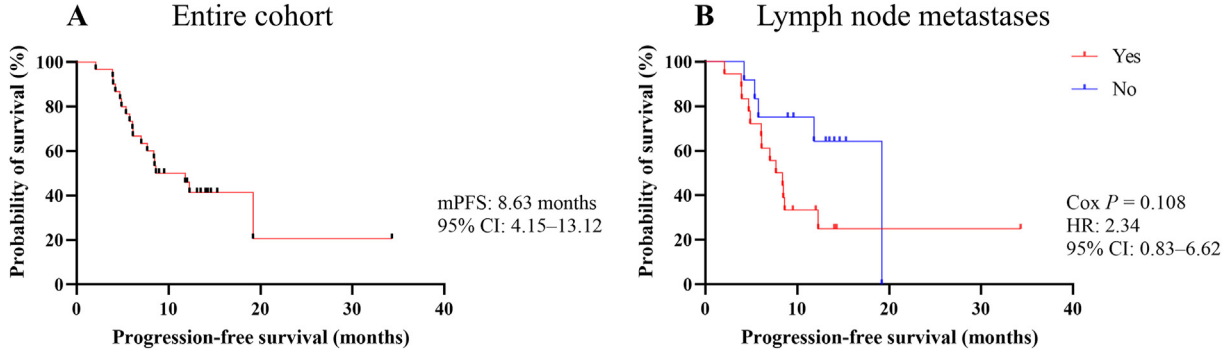

Figure 2. Kaplan–Meier analysis of progression-free survival (PFS) in (A) the entire cohort and (B) patients with and without lymph node metastases. CI: Confidence interval; mPFS: Median progression-free survival.

Table 2
Clinical efficacy of patients receiving triplet regimen ($n = 30$).

Endpoints	Value
PFS in months, median (95 % CI)	
Total cohort	8.63 (4.15–13.12)
First- or second-line	12.27 (6.63–17.91)
Third-line or later	7.67 (3.85–11.48)
Disease response, *n* (%)	
CR	1 (3.3)
PR	15 (50.0)
SD	14 (46.7)
PD	0 (0.0)
ORR, %	53.3
DCR, %	96.7

CI: Confidence interval; CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; PD: Progression disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

Table 3
Univariate and multivariate analyses of factors predicting progression-free survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age at diagnosis						
≤60 years *vs.* >60 years	1.36	0.44–4.26	0.595			
ECOG PS						
0 *vs.* 1	3.20	1.19–8.58	0.021	1.42	0.21–9.47	0.720
Stage at diagnosis						
I–III *vs.* IV	1.25	0.41–3.83	0.702			
Hormone-receptor status						
Positive *vs.* negative	1.53	0.59–3.98	0.383			
Lymph metastases						
Yes *vs.* no	2.34	0.83–6.62	0.108	4.27	1.04–17.53	0.044
Visceral metastases						
Yes *vs.* no	1.14	0.37–3.50	0.824			
Liver metastases						
Yes *vs.* no	1.27	0.49–3.29	0.628			
Lung metastases						
Yes *vs.* no	1.43	0.57–3.62	0.448			
Brain metastases						
Yes *vs.* no	3.10	1.19–8.03	0.020	2.15	0.52–8.89	0.289
Bone metastases						
Yes *vs.* no	1.46	0.58–3.69	0.423			
Disease-free survival						
≤2 years *vs.* >2 years	0.73	0.24–2.23	0.580			
Previous anti-HER2 treatment						
Pertuzumab (yes *vs.* no)	0.50	0.19–1.33	0.165	0.84	0.25–2.80	0.771
TKI (yes *vs.* no)	2.91	1.12–7.57	0.028	2.49	0.29–21.44	0.408
Previous treatment lines						
≤1 *vs.* >1	2.13	0.82–5.54	0.122	0.96	0.21–4.30	0.956

CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; HR: Hazard ratio; TKI: Tyrosine kinase inhibitor.

It is well known that the robust antitumor effects of HER2-targeted monoclonal antibodies derive not only from direct blocking of HER2 signaling pathway but also from the antitumor immune response through ADCC.[8] Moreover, since the latter is accompanied by immune modulation in the tumor microenvironment, it can provide long-term survival benefits to patients.[32] For monoclonal antibodies targeting HER2, more powerful ADCC effect usually implies a more robust antitumor effect. Inetetamab is a recombinant, humanized anti-HER2 monoclonal antibody. It contains the same Fab segment as trastuzumab and can inhibit the proliferation of HER2-overexpressing breast cancer cells by blocking HER2 signaling pathway. On the other hand, the modification of its Fc segment makes it more capable of binding innate immune cells and inducing ADCC to kill tumor cells.[12] In vitro studies have shown that the ADCC effect of inetetamab is approximately 11.1 % greater than that of trastuzumab.

Table 4
Treatment-related adverse events.

Adverse events	Any grade, *n* (%)	Grade ≥ III, *n* (%)
Diarrhea	13 (43.3)	3 (10.0)
Leukopenia	9 (30.0)	5 (16.7)
Neutropenia	5 (16.7)	4 (13.3)
Nausea	6 (20.0)	0 (0.0)
Anemia	3 (10.0)	0 (0.0)
Fatigue	2 (6.7)	1 (3.3)
Vomiting	2 (6.7)	0 (0.0)
Alanine aminotransferase increase	1 (3.3)	0 (0.0)
Creatinine increase	1 (3.3)	0 (0.0)
Rash	1 (3.3)	0 (0.0)
Hair loss	1 (3.3)	0 (0.0)

HOPES study evaluated the efficacy and safety of inetetamab combined with vinorelbine in patients with HER2-positive metastatic breast cancer who had not previously been treated with HER2-targeted therapy.[13] A total of 315 patients were enrolled and randomly assigned to receive either inetetamab or placebo in combination with intravenous vinorelbine. Inetetamab plus vinorelbine significantly improved the median PFS by 76 % compared with placebo plus vinorelbine (39.1 *vs.* 14.0 weeks; HR 0.24, 95 % CI 0.16–0.36, $P < 0.0001$). The ORR was 46.7 % and the DCR was 79.7 % in the inetetamab group. Further subgroup analysis showed that inetetamab combined with vinorelbine exhibited remarkable efficacy in patients who had not received any treatment for metastatic disease, with a median PFS of 11.1 months and an ORR of 61.5 %,[33] which were comparable to the first-line efficacy data for trastuzumab plus a taxane.

Margetuximab is another Fc-engineered anti-HER2 monoclonal antibody. In SOPHIA study, patients with HER2-positive advanced breast cancer were treated with either margetuximab or trastuzumab plus chemotherapy.[34,35] All patients had previously received trastuzumab and pertuzumab treatment, nearly 90 % had been treated with T-DM1 and approximately 15 % had received TKI therapy. The median PFS of margetuximab combined with chemotherapy was 5.8 months (95 % CI 5.5–7.0 months) and the ORR was 22 % (95 % CI 17–27 %). Compared with margetuximab plus chemotherapy, our triplet regimen showed superior efficacy, indicating the synergistic antitumor activity of dual HER2 inhibition with monoclonal antibodies and TKIs.

Our study also explored the potential clinicopathological characteristics affecting PFS in patients receiving the triplet regimen. Cox multivariate analysis revealed that lymph node metastasis was a significant adverse prognostic factor for PFS. The median PFS was 7.67 months (95 % CI 4.83–10.51 months) in patients with lymph node metastases and not reached in patients without lymph node metastases, indicating that patients without lymph node metastases might benefit more from this combination therapy. Nevertheless, due to the limited number of enrolled patients, this finding should be interpreted with caution and further verified by expanding the sample size in subsequent trials.

This study had some limitations. This preliminary investigation was conducted in a small Chinese population at our center, which lacks sufficient power to confirm the efficacy and safety of this triplet regimen for HER2-positive advanced breast cancer patients previously exposed to multiple HER2-targeted agents. Further, this was a single-arm trial without a control group. The efficacy and safety differences between this triplet regimen and current clinical regimens were not directly compared. Although our triplet regimen showed remarkable efficacy and favorable safety in patients with HER2-positive advanced breast cancer, large-scale randomized controlled studies are required to confirm the efficacy and safety of this combination therapy.

In conclusion, the triplet regimen of inetetamab, pyrotinib, and oral vinorelbine showed encouraging efficacy and safety in patients with HER2-positive advanced breast cancer after disease progression with

trastuzumab treatment and could be considered as an alternative treatment option for the patients. Further validation in randomized controlled trials is required.

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Authors contribution

All authors contributed to the conception and design of this study. Patient follow-up, data collection, and analysis were performed by Jin et al. The radiological evaluation was performed by Siqi Wang. Pathological detection and assessment were performed by Xu et al. Chunxiao Sun, Xueqi Yan, Fan Yang, and Yan Liang recruited and treated the patients. Nan Jin, Siqi Wang, Yi Xu, Chunxiao Sun, Xueqi Yan, Fan Yang, Yan Liang, Weiwei Chen, and Xiang Huang wrote and edited the manuscript. Xiang Huang performed project administration and supervision. All the authors have approved the final manuscript for submission.

Ethics statement

All procedures involving human participants were conducted in accordance with the 1964 *Declaration of Helsinki* and its amendments. This study was registered retrospectively at ClinicalTrials.gov. This study was approved by the institutional ethics committee (No. 2022-SR-494). All the patients provided written informed consent to participate in this study.

Data availability statement

The data supporting this study are available on request from the corresponding author.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.10.004.

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