


Inetetamab-Based Regimens for Patients with HER2-Positive Metastatic Breast Cancer: A Real-World Retrospective Study

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Background: Inetetamab is a Chinese-origin recombinant anti-HER2 monoclonal antibody. Herein, we assessed the efficacy and safety of inetetamab-containing regimens in patients with HER2-positive metastatic breast cancer (MBC).

Patients and Methods: We retrospectively reviewed the medical records of patients with HER2-positive MBC who received inetetamab-containing regimens as a salvage treatment in metastatic setting from December 2020 to April 2024. The primary endpoint was progression-free survival (PFS) in the total population (TP). Patients with brain metastases were also included. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), and safety.

Results: At the data cut-off date of June 1, 2024, a total of 90 patients were included in this analysis. Median follow-up duration was 7.2 months (IQR 3.6–13.1). The median PFS was 12.0 months (95% confidence interval [CI] 7.3 to 17.0 months) in the TP. The median PFS in the subgroup with brain metastases reached 10.0 months (95% CI 5.9 to NA months). The ORR was 46.6% (42/90), and the DCR was 92.2% (83/90). The most frequently combined chemotherapy was vinorelbine (83/90, 92.2%). The most frequently concomitant targeted drug was pyrotinib (70/90, 77.8%). The median PFS not reached for first-line, 15.9 months (95% CI 11.9 to NA months) for second-line, and 5.9 months (95% CI 4.4 to 12.2 months) for third-line or later therapy. Cox univariate and multivariate analyses demonstrated that lines of treatment were the only significant predictive factor for PFS (first- and second-line vs third-line or above: 15.9 vs 5.9 months, $p=0.0021$). The toxicity was tolerable. The most frequent grade 3 or 4 treatment-related adverse events were diarrhea (12.2%).

Conclusion: Inetetamab offers a promising option and a manageable safety profile for HER2-positive MBC who pretreated with multiple-line therapies. Meanwhile, inetetamab plus small-molecule TKIs regimens shows good anti-tumor efficacy for MBC with brain metastases, which deserves further validation in a larger group trial.

Keywords: inetetamab, HER2-positive metastatic breast cancer, pretreated, safety

Introduction

According to GLOBOCAN 2020, Breast cancer (BC) is the most common cancer among women in China and abroad.¹ Human epidermal growth factor receptor 2 (HER2)-positive patients account for approximately 15–20% of breast cancers.² HER2-positive BC represented a more aggressive subtype, with higher tumor grade, more recurrence, and poorer prognosis in the absence of systemic therapy.^{3–5} Although huge progresses have been achieved in treating HER2-positive BC, metastatic disease remains incurable. Nearly all the metastatic breast cancer (MBC) patients will suffer from disease progression after first-line treatment with trastuzumab.^{6,7} In the last decades, the development of multiple anti-HER2 agents, including monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and antibody drug conjugates (ADCs),⁸ has significantly improved the survival of patients with HER2-positive BC. However, in China, a huge proportion of patients with HER2-positive MBC have to abandon treatment due to high expenditure on drugs like ADCs which are not included in medical insurance.⁹ Continuous inhibition of the HER2 pathway offers a survival benefit to MBC patients treated with trastuzumab beyond progression.¹⁰ A combination of anti-HER2 antibodies and chemotherapy are still needed through first- and later-line treatment.

Inetetamab (Cipterbin[®])¹¹ is an innovative anti-HER2 monoclonal antibody developed by Shanghai CP Guojian Pharmaceutical Co. in China. Inetetamab is an Fc-engineered anti-HER2 monoclonal antibody, distinct from trastuzumab, with modification at positions 359 and 361 in the CH3 domain. Similar to margetuximab, this engineering enhances its binding to the activating Fcγ receptor CD16A and reduces affinity for the inhibitory receptor CD32B, thereby potentiating antibody-dependent cellular cytotoxicity (ADCC). The products demonstrated a comparable anti-tumor efficacy to that of trastuzumab *in vivo*.¹² Inetetamab possesses distinct mechanistic features that set it apart from trastuzumab and margetuximab. The HOPES study confirmed the significant efficacy and manageable safety of the combination of vinorelbine for HER2-positive MBC.¹³ While clinical trials have established the efficacy of inetetamab, real-world evidence is still in need. For instance, a recent large-scale retrospective study of 329 Chinese patients with HER2-positive MBC demonstrated promising activity and safety of inetetamab in first- and second-line settings.¹⁴ Furthermore, our team's previous multicenter, retrospective, real-world study (ILLUMINE) supports the efficacy of combining inetetamab with pyrotinib.¹⁵ Despite these valuable insights, data on the use of inetetamab in later lines of therapy and in specific subgroups, such as those with brain metastases (BM), remains limited. The current study is aimed to provide real-world evidence by analyzing the data from our center on study of inetetamab-based treatment strategies for patients with HER2-positive MBC.

Materials and Methods

Study Design

This was a single-center study, which retrospectively reviewed the medical data of consecutive patients with HER2-positive MBC treated with inetetamab at National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital (Shenzhen, Guangdong, China) between December 2020 and April 2024. This study, involving human subjects, was conducted in accordance with the Helsinki Declaration. This study received approval from the Institutional Review Board and Ethics Committee of the National Cancer Hospital & Shenzhen Hospital (Approval No. YW2024-26-1). Because this study was retrospective and observational in design and all patient data were anonymized, the Ethics Committee waived the requirement for written informed consent.

Patients and Treatment

The inclusion criteria were as follows: female patients, age ≥ 18 years old, histologically confirmed HER2-positive MBC (including hormone receptor positive/negative breast cancer), at least two cycles of inetetamab, and complete medical records. HER2 status was defined as 3+ based on immunohistochemistry (IHC) or 2+ with gene amplification by fluorescence in situ hybridization (FISH) staining of primary or metastatic lesion samples. The exclusion criteria were patients with no measurable or evaluable metastatic lesions defined by the Response Evaluation Criteria in Solid Tumors (RECIST); or those lost to follow-up. The last follow-up was conducted on June 1, 2024.

All eligible patients were treated with inetetamab-based therapy. Inetetamab was administrated at a dose of 6 mg/kg of body weight intravenously per 21 days, with an initial loading dose of 8 mg/kg. Other anti-HER2 targeted agents and chemotherapy were allowed to be used in combination with inetetamab.

End Points

The primary end point was PFS, which was defined as the time gap between date of initiation of first inetetamab-based regimens to the date of documented disease progression or death from any cause or the last follow-up. The secondary end points included the objective response rate (ORR, defined as the percentage of patients who had a confirmed complete response or partial response); disease control rate (DCR, defined as the percentage of patients who had a confirmed complete response or partial response or stable disease for at least 4 weeks); and safety.

Data Collection and Assessment

The baseline characteristics of the patients were collected, including general information (age, sex, ECOG score), tumor characteristics (TNM stage, pathology, hormone receptor and HER2 status, and metastatic site), and treatment information (previous chemotherapy/targeted therapy, radiation, or surgery history, and (neo)adjuvant therapy history).

All patients underwent regular check-ups, including physical examination, laboratory examinations, electrocardiogram, and imaging (computed tomography or positron emission tomography/CT (PET/CT) or contrast-enhanced magnetic resonance imaging). Tumor response was evaluated retrospectively by the treating physician based on routinely collected imaging data and assessed according to RECIST version 1.1. Imaging was performed per routine clinical practice, typically every 2 treatment cycles. Patients with missing or off-schedule imaging assessments were censored at the date of their last available radiographic evaluation. Safety evaluations were conducted every cycle. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The study did not interfere with any physician's decisions and did not change any treatment.

Statistical Analysis

All data were analyzed using R4.2.2 (<http://www.Rproject.org>; The R Foundation, Vienna, Austria) and GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive analysis was utilized to display clinicopathological features. The Kaplan–Meier method was used to estimate PFS. Additionally, Cox univariate models were used to identify the predictive variables for PFS, presented as hazard ratios (HR), and corresponding 95% confidence intervals (CIs). All reported *p* values were two-sided, with *p*<0.05 being regarded as statistically significant.

Results

Patient Clinicopathological Characteristics

Between December 2020 and April 2024, a total of 104 patients treated with inetetamab were recruited. Only 90 patients were eligible for the study, according to inclusion and exclusion criteria (Figure 1). The cutoff date for follow-up was June 1, 2024. The median follow-up time for this study was 7.2 months (range: 3.6 to 38.1 months).

The baseline characteristics of the patients are shown in Table 1. All the patients were female, the median age at diagnosis was 45.0±10.9 years. Fifty-seven patients (63.3%) were aged over 40 years old at diagnosis. Eighty-five patients (94.4%) were invasive ductal cancer. Forty-six patients (51.1%) were estrogen receptor (ER) and/or progesterone receptor (PR) positive. For HER2 status, HER2 3+ by IHC was recorded in 71 patients (78.9%), and HER2 2+ by IHC and amplification by FISH in 19 patients (21.1%). Thirty-five patients (38.9%) had Grades 1–2 histological of tumors, and 35 patients (38.9%) had Grades 3–4 histological of tumors. Twenty-three patients (25.6%) had de novo stage IV disease at their first diagnosis. Forty-five patients (50.0%) had liver/lung metastases and 30 (33.3%) of them had brain metastases at baseline. Of those patients with brain metastases, 22 patients had received local therapies including whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRT) or surgery plus SRT before inetetamab. Most of the patients (67/90, 74.4%) had received anti-HER2 therapy with trastuzumab in metastatic setting. Thirty-nine (43.3%) of them had received pertuzumab, 54 patients (60%) had received TKIs (pyrotinib (42.2%), lapatinib (12.2%), apatinib (4.4%), and neratinib (1.1%)) for their metastatic disease. Four patients were previously treated with TDM-1. One of them was previously treated with trastuzumab deruxtecan (T-DXd). The median lines of treatment were 3 (range 1–8). Twenty-one patients (23.3%) received inetetamab-based regimen as first-line therapy; 36 patients (40.0%) received at least 3 lines of therapy in the metastatic setting.

Treatment Administration

The drugs in combination with inetetamab are presented in Table 2. Most patients were treated with inetetamab combined with chemotherapy and other HER2-targeted therapies. Combined chemotherapeutic agents included vinorelbine (83, 92.2%), nab-paclitaxel (5, 5.6%), pirarubicin (1, 1.1%), and utidelone (1, 1.1%). For the choice of combined anti HER2-targeted treatment, the most common was pyrotinib (70, 77.8%), followed by pertuzumab (8, 8.9%). Four patients received only inetetamab and chemotherapy.

Efficacy

By the end of follow-up, 52 patients had experienced disease progression and 13 patients had died, and 38 patients remained progression-free. The median PFS was 12 months (95% CI 7.3 to 17 months, Figure 2) in total cohort and was

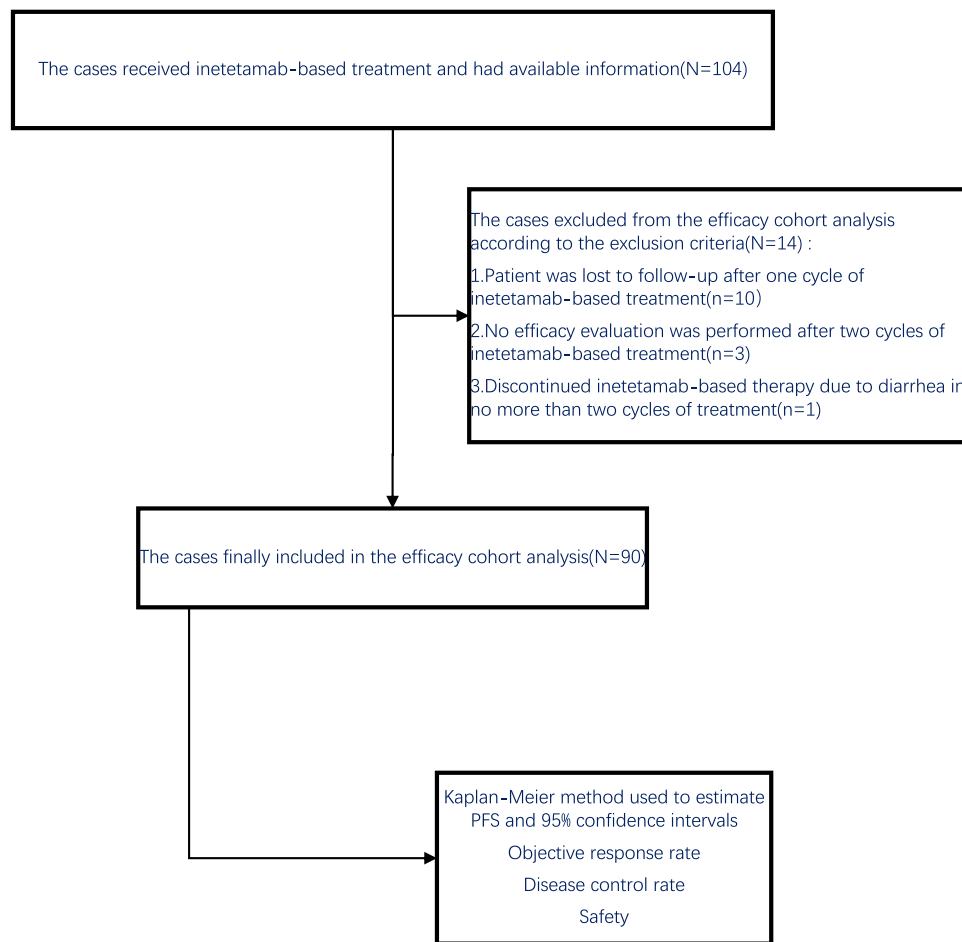


Figure 1 Flow diagram of the analysis.

10 months in the group of brain metastases (95% CI 5.9 to NA months, [Figure 3](#)). There was a statistically difference in PFS (15.9 vs 5.9 months, $p=0.0021$) between the first- and second-line and third-line or above subgroups (seen in [Figure 4A](#)). Patients without liver/lung metastases seemed to obtain a longer PFS than those with liver/lung disease, but the difference was not significant (15.8 vs 7.3 months, $p=0.1$) (seen in [Figure 4B](#)). The PFS was similar (11.9 vs 12 months, $p=0.57$) between the HR-positive and HR-negative subgroups (seen in [Figure 4C](#)).

The evaluations of efficacy are presented in [Table 3](#). CR was achieved in 2 (2.2%) patients, and PR was achieved in 40 (44.4%) patients, and SD was achieved in 41 (45.6%) patients. The ORR and the DCR were 46.6% and 92.2%, respectively. Additionally, 7 (7.8%) patients showed progressive disease at the first assessment. At the time of data cutoff, 52 (57.8%) patients show progression.

Univariate and multivariate analyses were performed to identify predictive factors of PFS for the 90 patients. As shown in [Table 4](#), by means of Cox univariate and multivariate analyses, we found that lines of treatment were the independent prognostic factor for PFS (hazard ratio [HR] 0.4322; 95% CI 0.2495 to 0.7487; $p = 0.00277$; HR 0.3189; 95% CI 0.136 to 0.7477; $p = 0.00857$; respectively).

A total of 30 patients with brain metastases were included. The median PFS in the subgroup with brain metastases reached 10.0 months (95% CI 5.9 to NA months). Twenty-nine patients were treated with inetetamab plus small-molecule TKIs. The median lines of treatment were 2(range 1–4). All patients were treated with trastuzumab before inetetamab. Eighteen patients were treated with TKIs before.

Table 1 The Baseline Characteristics of the Patients

Characteristics	Patients, No (%) N=90
Age, median (range years)	45.0±10.9
Age at diagnosis	
≤40	33 (36.7)
>40	57 (63.3)
Location	
Left	40 (44.4)
Right	47 (52.2)
Bilateral	3 (3.3)
Pathological type	
Invasive ductal cancer	85 (94.4)
Invasive lobular cancer	4 (4.4)
HR status at metastatic setting	
Negative	44 (48.9)
Positive	46 (51.1)
HER2 expression	
IHC3+	71 (78.9)
IHC2+ and FISH+	19 (21.1)
Grade	
1-2	35 (38.9)
3-4	35 (38.9)
NE	20(22.2)
De novo IV stage	
No	67 (74.4)
Yes	23 (25.6)
Brain metastases	
No	60 (66.7)
Yes	30 (33.3)
Brain radiotherapy	
No	68 (75.6)
Yes	22 (24.4)
Liver/Lung metastases	
No	45 (50.0)
Yes	45 (50.0)
Previous trastuzumab treatment:	
Neoadjuvant setting	4(4.4)
Adjuvant setting	27(30.0)
Metastatic setting	67(74.4)
Previous anti-HER2 drugs	
Pyrotinib	38(42.2)
Pertuzumab	39(43.3)
Lapatinib	11(12.2)
Apatinib	4(4.4)
TDMI	4 (4.4)
Neratinib	1(1.1)
Trastuzumab deruxtecan	1(1.1)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence In Situ Hybridization; NE, not estimable; TDMI, Trastuzumab Emtansine.

Table 2 Treatment Administration

Treatment Administration	Patients, No (%) N=90
Lines of inetetamab in metastatic setting	
1	21 (23.3)
2	33 (36.7)
≥3	36 (40.0)
Target regimens with inetetamab	
Pyrotinib	70 (77.8)
Pertuzumab	8 (8.9)
Apatinib	8 (8.9)
No	4 (4.4)
Combined regimens with inetetamab	
Vinorelbine	83 (92.2)
Nab-paclitaxel	5 (5.6)
Pirarubicin	1 (1.1)
Utidelone	1 (1.1)

Safety

The safety assessments of inetetamab-based therapy are summarized in Table 5. The most common adverse events (frequency $\geq 10\%$) were diarrhea (52.2%), vomiting/ nausea (20%), fatigue (20%), and leukopenia (18.9%). Other recorded adverse events included aspartate aminotransferase increase (5.6%), anemia (4.4%), creatinine increase (3.3%), thrombocytopenia (2.2%), peripheral neuritis (2.2%), and hand-foot syndrome (2.2%). The most frequent grade 3 adverse events were diarrhea (12.2%). No grade 4 diarrhea or cardiac-related events were reported. No treatment-related deaths were reported. However, the majority of AEs were unrelated to inetetamab use. Diarrhea, the most common adverse event, is mostly related with the combinations with pyrotinib. The incidence of decline of left ventricle ejection fraction was 2%. No patients stopped inetetamab because of side effects during treatment.

Discussion

In our study, inetetamab-based regimens demonstrated promising efficacy and good safety profile in pretreated HER2 positive MBC. Forty percent of the patients had received more than three prior treatment lines, with the majority previously treated by trastuzumab in the (neo)adjuvant setting. Nevertheless, the median PFS of all 90 patients reached 12 months (95% CI, 7.3–17 months). The result of this study implies that inetetamab-based regimens may exhibit potential antitumor activity in later-line settings.

About 30% of early-stage patients ultimately developed into advanced breast cancer. Advanced breast cancer is still incurable at present, the 5-year survival rate of advanced breast cancer was only 20%, and the median overall survival was 2–3 years.¹⁶ As is well known, anti-HER2 therapy with trastuzumab and chemotherapy significantly reduced the risk of death and disease progression in HER2-positive MBC.^{17,18} The addition of pertuzumab or pyrotinib to trastuzumab and chemotherapy has revolutionized the regimen for first-line therapy for HER2 positive MBC^{19,20} in previous large scale clinical studies. However, most of the enrolled patients are not treated by trastuzumab. Standard second-line therapy of the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) is far from that one could pay due to the high prices not covered by medical insurance in China. Hence, anti-HER2 regimens more suitable for Chinese people is still in unmet need in clinical practice.

Like margetuximab, inetetamab is an Fc-modified anti-HER2 mAb with improved antibody-dependent cell-mediated cytotoxicity (ADCC) effect than trastuzumab.²¹ In the Phase III SOPHIA trial, margetuximab plus chemotherapy could prolong the mPFS over trastuzumab (5.8 vs 4.9 months),²² indicating that the enhancement of ADCC can make advantage of survival. However, the clinical data of inetetamab is mainly based on the HOPES study.¹³ The HOPES study was designed in 2009 in China when trastuzumab was still unreachable due to

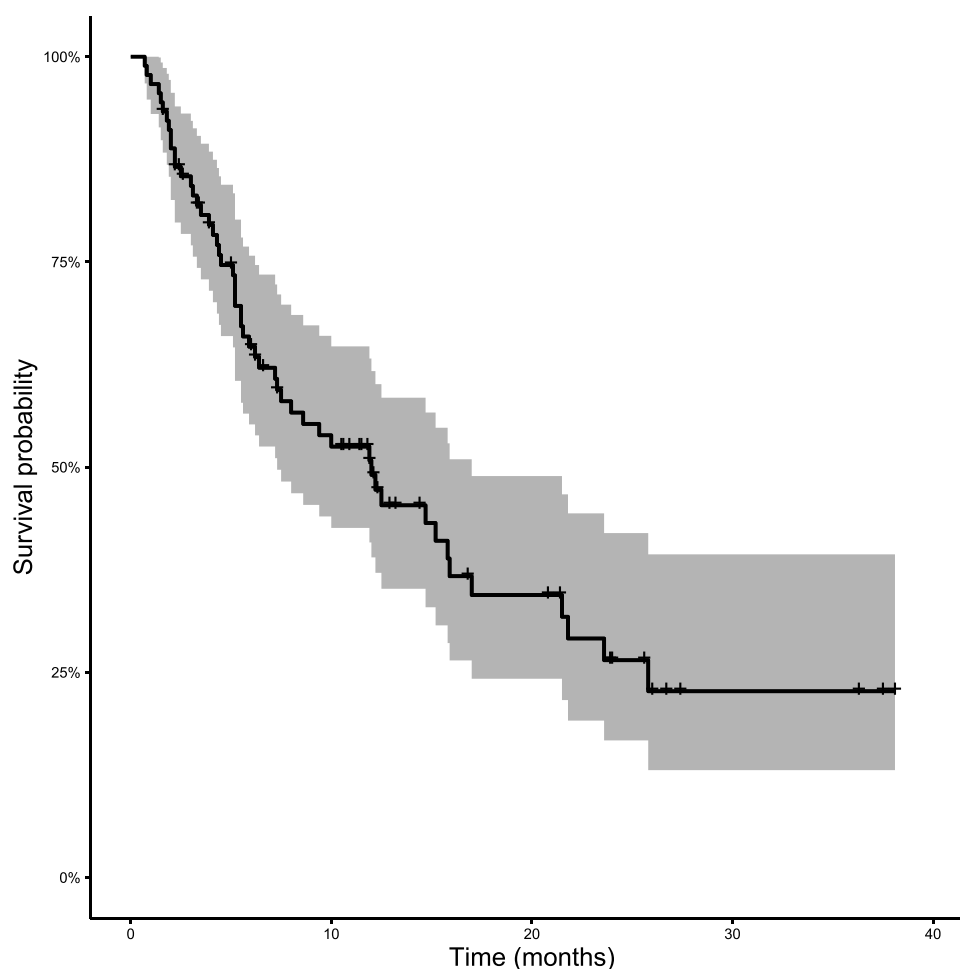


Figure 2 Kaplan-Meier curves of progression-free survival in overall cohort.

expensive cost. In HOPES study, inेतetamab combined with vinorelbine is designed for patients who had not received any anti-HER2-targeted therapy. Our study represented the general population of patients with HER2 positive MBC who were usually pretreated with multiple anti-HER2 agents. What's more, most patients in our study received dual anti-HER2 treatment of inेतetamab in combination with pertuzumab or pyrotinib. While the single-arm, retrospective nature of this study precludes definitive comparative conclusions, the observed mPFS of 12.0 months, is encouraging. These real-world findings generate the hypothesis that inेतetamab-based regimens could offer meaningful clinical benefit in these populations. Future prospective studies are needed to validate these results and define the optimal positioning of inेतetamab within the HER2-positive treatment sequence. In the second-line treatment, mPFS of our study was 15 months, and the third-line or above treatment in our study, the mPFS was 5.9 months, which was similar to that reported in previous study.^{23–25} In addition, we analyzed the predictive factors of PFS, and found that patients who were treated with inेतetamab as a first- and second-line had much longer PFS (treated as first- and second-line vs third-line or above: 15.9 vs 5.9 months, $p=0.0021$). Thus, we propose that the preferred use of inेतetamab in early lines might be more effective.

Brain metastasis is a late event for MBC, which occurs in approximately 50% of patients with HER2+ breast cancer, with a median survival of 7 to 18 months after diagnosis.^{26,27} Radiation and surgery are currently the main local treatment approaches for the brain metastases.²⁸ In recent years, a growing number of TKIs and ADCs produce an antitumor effect on the brain. However, options are limited for the control of breast cancer with brain metastasis patients. In KAMILLA study, trastuzumab emtansine in the 398 patients with baseline BM obtained a mPFS of 5.5 months.²⁹ And in HER2CLIMB study, tucatinib combined with trastuzumab and capecitabine could significantly prolong the mPFS to

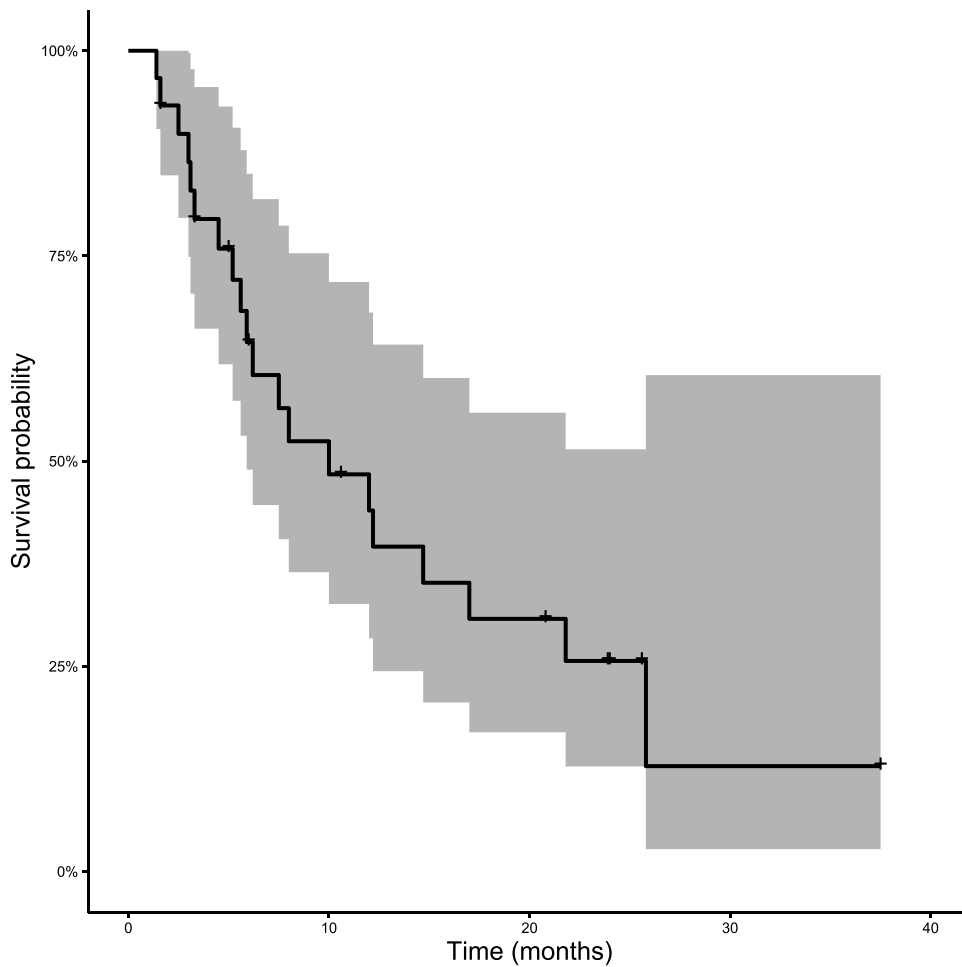


Figure 3 Kaplan-Meier curves of progression-free survival in brain metastases.

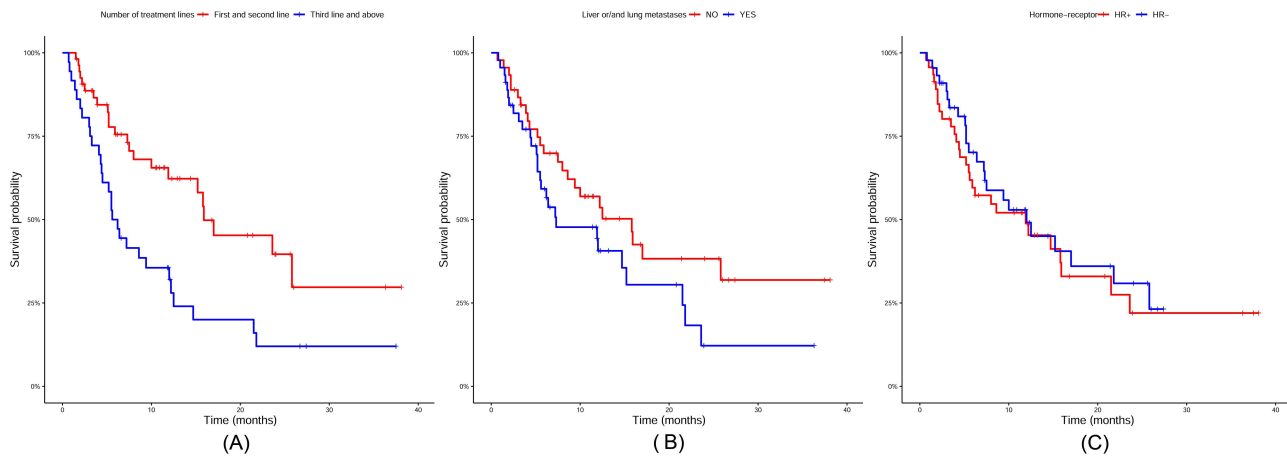


Figure 4 Kaplan-Meier curves of progression-free survival for patients. **(A)** Patients stratified by treatment lines; **(B)** Patients with liver/lung metastases or not; **(C)** Patients stratified by hormone-receptor status.

9.9 months in BM patients.³⁰ In the BM subgroup in our study, the mPFS was 10 months. While direct comparisons are not feasible, the promising PFS and notable activity in patients with brain metastases observed in our study generate the hypothesis that this inetetamab-based therapy could be a valuable treatment option in these clinical contexts. The

Table 3 Evaluation of Efficacy

End Points	Patients N=90
Progress—No. (%)	
Yes	52 (57.8)
No	38 (42.4)
Best overall response—No. (%)	
Complete response	2 (2.2)
Partial response	40 (44.4)
Stable disease	41 (45.6)
Progressive	7 (7.8)
ORR—No. (%)	44 (46.6)
DCR—No. (%)	83 (92.2)

Abbreviations: ORR, objective response rate; DCR, disease control rate.

Table 4 Univariate and Multivariate Analyses

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis (≤ 40 vs > 40)	0.9567	0.5456–1.678	0.877			
HER2 status (3+ vs 2+fish+)	1.263	0.6725–2.371	0.468			
Hormone-receptor status (HR+ vs HR-)	0.8538	0.4947–1.474	0.57			
Previous anti-HER2 antibody treatment in metastatic setting	1.678	0.8168–3.445	0.159			
Previous anti-HER2 TKIs treatment	1.517	0.8573–2.683	0.152			
Brain metastases (yes vs no)	1.118	0.6381–1.96	0.696			
Liver or/and lung metastases (yes vs no)	1.575	0.9075–2.733	0.106			
Number of previous treatment lines (≤ 2 vs > 2)	0.4322	0.2495–0.7487	0.00277	0.3189	0.136–0.7477	0.00857

Abbreviations: HR, hazard ratio; CI, confidence interval; TKIs, tyrosine kinase inhibitors.

Table 5 Safety Assessment

Safety Assessment	All Grade n (%)	Grade3/4 n (%)
Diarrhea	47 (52.2)	11 (12.2)
Fatigue	18 (20.0)	1 (1.1)
Nausea/Vomiting	18 (20.0)	3 (3.3)
Leukopenia	17 (18.9)	5 (5.6)
Aminotransferase increase	5 (5.6)	0
Anemia	4 (4.4)	1 (1.1)
Creatinine increase	3 (3.3)	0
Thrombocytopenia	2 (2.2)	0
Hand-foot syndrome	2 (2.2)	0
Peripheral neuritis	2 (2.2)	0

favorable outcomes observed in our study can likely be attributed to the predominant use of inetetamab combined with pyrotinib. Pyrotinib-based combination therapy was efficient to treat HER2 positive brain metastasis.^{31–33} The mPFS observed in patients with BM in this study was consistent with the findings of the ILLUMINE trial.¹⁵ The novel combination of inetetamab of pyrotinib might be an alternative regimen for this group of patients.

In terms of toxicity, incidences of AEs in this study were similar to previous reports and no new AEs were found. The majority of AEs were Grades 1–2, and the Grades 3–4 AEs were due to the combination agents, including diarrhea, leukopenia. Hence, inestetamab and trastuzumab are equivalently safe, and well tolerated, making it a candidate option besides trastuzumab.

Conclusion

Our study indicates that inestetamab-based regimens are effective for HER2 positive MBC with acceptable toxicity, providing a treatment option for such patients. However, this study has several limitations. Firstly, it is a single-center retrospective study, which makes it vulnerable to selection bias as patient inclusion depends on available records and clinical decisions. Secondly, the sample size is small, potentially reducing the statistical power. Thirdly, the median follow-up time is short, the first-line treatment was not reached, and no benefits of OS were observed. In the future, it needs to be confirmed the efficacy through large-scale prospective randomized controlled clinical studies, which would help to address these limitations and provide more conclusive evidence for clinical practice.

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Disclosure

The authors report no conflicts of interest in this work.

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