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ORIGINAL RESEARCH

Intracranial Efficacy of Pyrotinib and Capecitabine Combination Therapy in HER2-Positive Breast Cancer with Brain Metastases

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Aim: Approximately 50% of patients diagnosed with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (BC) are estimated to develop brain metastases (BMs). This study was aimed to assess the intracranial efficacy and survival benefits of pyrotinib and capecitabine combination therapy in the treatment of BMs in patients with HER2-positive BC.

Methods: A total of 56 HER2-positive BC patients with BMs were treated with 400 mg pyrotinib once daily along with 1000 mg/m^2 capecitabine twice daily for 14 days in 21-day cycles. The patients were allocated into three cohorts: (1) Cohort A composed of patients with newly diagnosed BMs without prior local radiotherapy, (2) Cohort B included patients with stable post-local radiotherapy, and (3) Cohort C composed of patients with progression following local radiotherapy. The primary endpoint was the intracranial objective response rate (CNS-ORR), while secondary endpoints included intracranial disease control rate (CNS-DCR), progression-free survival (PFS), overall survival (OS), safety, as well as QoL.

Results: The observed CNS-ORR CNS-ORR of 72.73% (95% CI 51.85–86.85%) in cohort A, 55% (95% CI 34.21–74.18%) in cohort B, and 42.86% (95% CI 21.38–67.41%) in cohort C. The mPFS was 11 months, 8.4 months, and 5.2 months in cohorts A, B, and C, respectively. Diarrhea, accounting for 23.21% of all the patients, was the most common grade 3/4 adverse event related with treatments (6/22 [27.3%] in cohort A, 4/20 [20.0%] in cohort B, and 3/14 [21.4%] in cohort C). However, there were no deaths related with treatments observed. Importantly, the QoL was efficiently maintained throughout the treatment duration.

Conclusion: Pyrotinib and capecitabine combination therapy proved significant effectiveness as well as tolerability in treating HER2-positive BC with BMs, yielding satisfactory results, especially in radiotherapy-naive population.

Keywords: breast cancer, brain metastases, pyrotinib, capecitabine, HER2, radiotherapy

Introduction

Approximately 20% of breast tumors overexpress human epidermal growth factor receptor 2 (HER2),[1] which is linked to aggressive malignant behavior, poor response to chemotherapy, and higher rates of recurrence and metastasis.[2] Moreover, about 50% of HER2-positive metastatic breast cancer (BC) patients eventually have brain metastases (BMs).[3–5]

In recent years, HER2-targeted therapies such as trastuzumab,[6] pertuzumab,[7] lapatinib,[8] trastuzumab emtansine (T-DM1),[9] and other targeted drugs have significantly improved the survival of metastatic HER2-positive BC patients.[10] However, the incidence of BC BMs has been escalating. The treatments of BC with BMs mainly include stereotactic radiosurgery (SRS), surgical resection, as well as whole-brain radiation therapy (WBRT), but the outcomes are suboptimal.[11] Additionally, chemotherapy, endocrine therapy, and anti-HER2 targeted therapy often yield limited results, which could be attributed to the inadequate ability of drugs in penetrating the blood–brain barrier.[12]

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HER2-targeted agents, such as monoclonal antibodies, tyrosine kinase inhibitors (TKIs), as well as antibody-drug conjugates, have been investigated in BC with BMs. For instance, the CLinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) study demonstrated that the combination of trastuzumab and pertuzumab significantly delayed BM development compared to trastuzumab alone (15 vs 11.9 months) and prolonged overall survival (OS) (34.4 vs 26.3 months).[13] In the EMILIA study,[14] T-DM1 significantly extended OS among patients with BMs (26.8 months) in contrast with the combination of lapatinib and capecitabine (12.9 months). The KAMILLA study[15] also demonstrated that among 126 patients with stable BMs at baseline, T-DM1 treatment reduced metastases in 84 patients. Similarly, the DESTINY-Breast01 study[16] reported an overall response rate (ORR) of 58.3%, progression-free survival (PFS) of 18.1 months, as well as the duration of response of 16.9 months in the BM subgroup. These findings suggest that DS-8201 holds significant therapeutic potential for BC patients with stable BMs.

Studies have demonstrated that small molecule epidermal growth factor receptor (EGFR)/HER2-specific TKIs could penetrate the blood–brain barrier more effectively. Favorable results have been reported by HER2CLIMB,[17] LANDSCAP[18] and TBCRC-022[19] studies based on the combination of tucatinib, lapatinib, and neratinib. Besides, as an irreversible pan-ErbB receptor TKI, pyrotinib exhibits specificity in targeting EGFR, HER2, as well as HER4.[20] The efficacy of pyrotinib and capecitabine combination therapy against BC has been confirmed by PHENIX study, showing a longer median PFS (mPFS) in the treatment group with statistical significance in contrast with the placebo group (11.1 vs 4.1 months) and a significantly higher ORR (68.6% vs 16.0%).[21] Furthermore, subgroup analysis revealed that among patients with asymptomatic BMs, the mPFS was 6.9 months in contrast with 4.2 months in the respective arms.[22] Therefore, it urgently needs to find a more effective treatment for HER2-positive BC patients with BMs, in this study, we were aimed to analyzed the efficacy and safety of pyrotinib and capecitabine combination therapy in HER2-positive BC patients with BMs.

Methods

Patients

The present study enrolled 56 patients between March 1, 2019, and December 31, 2021. The inclusion criteria of patients included: (1) Patients with histopathologically confirmed HER-2 positive BC, (2) Patients with the presence of ≥1 measurable BM lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1), (3) Patients with no prior treatment with anti-HER2-TKIs, (4) Patients with the age ranging from 18 to 75 years, (5) Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (6) Patients with satisfactory pulmonary and cardiac function, and (7) Patients with the normal organ function.

Study Design

This study was carried out at The Affiliated Yantai Yuhuangding Hospital of Qingdao University, and received approval from the Ethics Committee (Grant Number: 2023–375), adhering to the Declaration of Helsinki. Additionally, all participating patients provided signed informed consent forms. Patients with BMs were divided into the following groups: (1) cohort A composed by patients with new BMs without local radiotherapy, (2) cohort B composed by patients with stable post-local radiotherapy, and (3) cohort C composed by patients with progression after local radiotherapy. All patients received 400 mg pyrotinib once daily as well as 1000 mg/m^2 capecitabine twice daily for 2 weeks in 21-day cycles. Brain MRI was carried out at the baseline, every 6 weeks for 24 weeks, as well as every 9 weeks thereafter. Patients finished the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQC-30) questionnaire at cycles 1, 3, 5, and 7, and every 9 weeks thereafter. Follow-up was achieved every 3 months, and ended on June 30, 2022.

Outcomes and Assessments

The disease was assessed utilizing the response evaluation criteria in solid tumors (RECIST) criteria (version 1.1). Specifically, the intracranial objective response rate (CNS-ORR) referred to the proportion of patients who achieved complete response (CR)/partial response (PR) in intracranial lesions; while the intracranial disease control rate (DCR) was defined as the proportion of patients who achieved CR, PR, or stable disease (SD) in intracranial lesions. PFS pertained to the interval from the point of random assignment to the occurrence of disease progression attributed to any

cause, whichever occurred first. On the other hand, OS denoted the duration from the commencement of treatment until death resulting from any cause. In addition, adverse events (AEs) were assessed using the National Cancer Institute Common Terminology Criteria for AEs version 5.0 (NCI CTCAE v5.0).

Statistical Analysis

SPSS 23.0 software was utilized for the data analysis. Clinical variables were presented with proportions. PFS was analyzed using the Kaplan–Meier method. Inter-group differences were compared utilizing the two-sided Log rank test, with the corresponding 95% confidence intervals (CIs) estimated utilizing the Cox proportional regression model. Reported P-values were two-sided, with a significance level set at 0.05. The linear mixed-effect model was used to analyze changes in quality of life (QoL) over time. Data were presented with mean ± standard deviation (SD). $P < 0.05$ indicated statistically significant.

Results

Patient Characteristics

In total, 56 patients were included in the study, with a median age of 60.04 years (range: 45–70 years). Among these patients, 58.93% exhibited positive hormonal receptor status for estrogen and/or progesterone, while the remaining 41.07% had negative receptor status. Besides, 71.43% of patients had underwent prior therapies, and all of the patients were administered trastuzumab. Cohort A consisted of 22 patients, cohort B consisted of 20 patients, and cohort C consisted of 14 patients. All patients had measurable intracranial lesions, and 66.07% also had measurable extracranial lesions. Surgical resection was performed for one patient with intracranial metastases, SRT was administered to 21 patients, and WBRT was given to 12 ones. The median number of treatment cycles was 15.7 in cohort A, 8.8 in cohort B, and 6.7 in cohort C. The fundamental clinical characteristics of the patient population is shown in Table 1.

Table 1 Baseline Demographics and Clinical Characteristics of Enrolled Breast Cancer Patients

Variable	Total
Total (n = 56)	56
Age	
< 65	37
≥ 65	19
ECOG	
0	18
1	35
2	3
Hormone receptor	
Estrogen and/or progesterone receptor positive	33
Estrogen and progesterone receptor negative	23
Prior lines of treatment	
0	16
1	28
2	11
≥3	1
Previous anti-HER2 antibody treatment	
Trastuzumab	56
Pertuzumab	10
Inetetamab	3
T-DM1	2
BAT8001	0
No	0

(*Continued*)

Table 1 (Continued).

Variable	Total
Measurable metastatic sites	
Only Intracranial metastasis	19
Intracranial and extracranial metastases	37
BM treatment status at baseline	
Untreated (A)	22
Treated and stable (B)	20
Treated and progressing (C)	14
Prior therapy for BMs	
Surgery	1
SRT	21
WBRT	12
No	22

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, Human Epidermal Growth Factor Receptor 2; BM, brain metastases; SRT, Stereotactic Radiation Therapy; WBRT, whole brain radiotherapy.

Treatment Efficacy

Out of the 56 patients, 4 (7.14%) achieved CR, 29 (51.79%) achieved PR, and 13 (23.21%) were classified as SD. The CNS-ORR was 58.93%, whereas the CNS-DCR was 82.14% (Table 2). In cohort A, the CNS-ORR was 72.73% (95% CI 51.85–86.85%), in cohort B it was 55% (95% CI 34.21–74.18%), and in cohort C it was 42.86% (95% CI 21.38–67.41%). The CNS-DCR was 90.91% (95% CI 72.19–97.47%) in cohort A, 80% (95% CI 58.40–91.93%) in cohort B, and 71.43% (95% CI 45.35–88.28%) in cohort C. As of June 30, 2022, the mPFS duration was 8.4 months (95% CI 8.0–13.9 months), with the mPFS of 11, 8.4, and 5.2 months in the three groups, respectively (Figure 1A–D). 1 (4.5%) of 22 patients in cohort A, 3 (15%) of 20 patients in cohort B and 3 (21.4%) of 14 patients in cohort C came off study due to CNS progression (Table 2). In this study, the median OS has not yet been reached, indicating a noteworthy duration of survival that exceeds the observed period of follow-up.

QoL

QoL assessments were conducted for 56 patients both at baseline and during subsequent follow-up periods. Throughout the treatment period, changes were not significant in the overall QoL score (slope of each follow-up: −0.13, P = 0.953), physical function (0.52, P = 0.363), emotional function score (−0.24, P = 0.835), and cognitive function score (−0.79, P = 0.429) (Figure 2A–D) in cohort A, cohort B, and cohort C patients.

Table 2 Summary of the Pathologic Response

Variable	Total	A	B	C
Total (n = 56)	56	22	20	14
Best overall response				
CR	4	3	1	0
PR	29	13	10	6
SD	16	5	6	5
PD	7	1	3	3
CNS-ORR (%)	58.93	72.73	55.00	42.86
CNS-DCR (%)	82.14	90.91	80.00	71.43

Abbreviations: CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Objective response rate; DCR, Disease control rate.

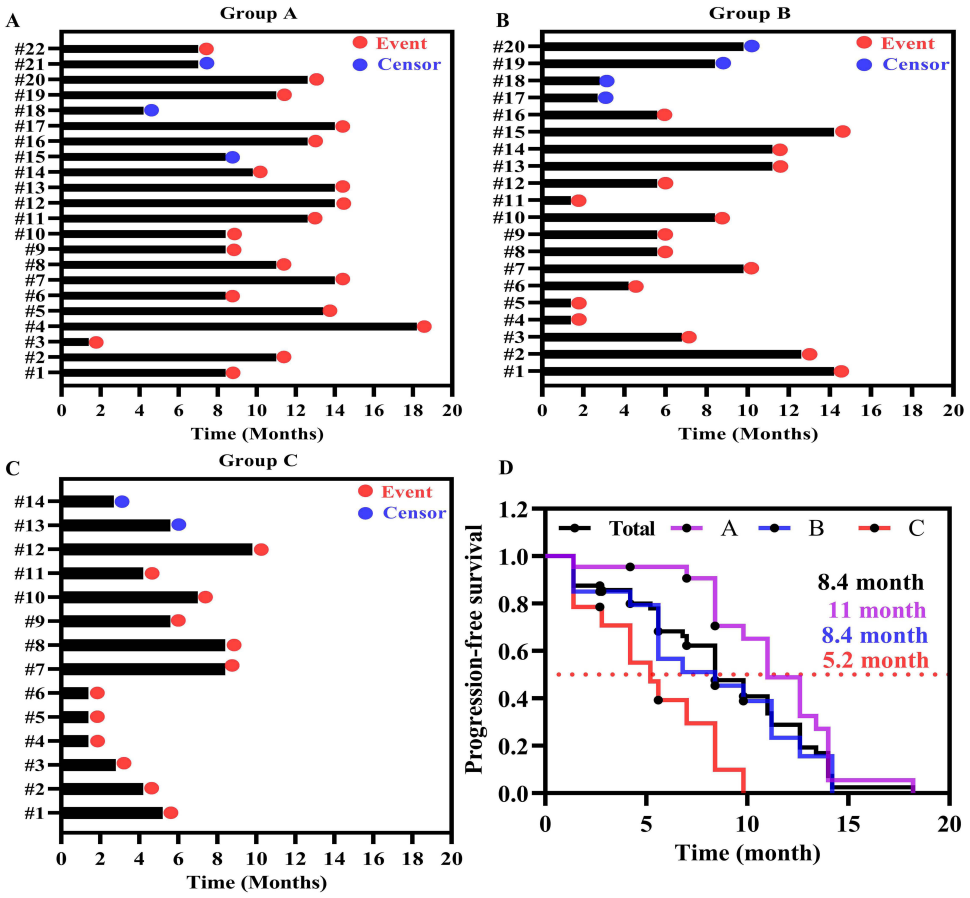

Figure 1 (**A**–**C**) Swimmer-style clinical follow-up plot detailing the clinical course of all enrolled patients in Cohort A–C. (**D**) Kaplan–Meier curves for progression-free survival for patients in Cohort A–C.

Safety

Most AEs reported were of grade 1–2, with diarrhea (13 [23.21%]), reduced white blood cell count (10 [17.8%]), and decreased neutrophil count (10 [17.8%]) being the most common grade 3 or worse treatment-related Aes (Table 3). All AEs were manageable, and deaths related to treatments were not observed. Among the 56 patients, 7 (12.5%) required a reduction in pyrotinib dose from 400 mg to 320 mg (5 [8.9%]) / 240 mg (2 [3.5%]) due to diarrhea. In addition, 7 individuals were excluded from the group due to disease progression.

Discussion

BC BMs are the second most common type of metastasis, following lung cancer, accounting for 15–20% of all BMs.[22] HER2-positive BC is more likely to experience recurrent metastasis after initial treatment compared to other molecular subtypes.[23] While advancements in the treatment of HER2-positive advanced BC have contributed to enhanced patient survival, there has been a concurrent rise in the incidence of BMs has also increased. The primary objective of this study was to examine the effectiveness of pyrotinib and capecitabine combination therapy in individuals diagnosed with HER2-positive BC patients and BMs.

In this study, pyrotinib and capecitabine combination therapy demonstrated a CNS-ORR of 72.73% (95% CI 51.85–86.85%) in cohort A, 55% (95% CI 34.21–74.18%) in cohort B, and 42.86% (95% CI 21.38–67.41%) in cohort C. The mPFS was 11 months, 8.4 months, and 5.2 months in cohorts A, B, and C, respectively. These findings suggest the potential effectiveness of pyrotinib and capecitabine combination therapy in treating HER2-positive BC with BMs, particularly in patients who have not received radiotherapy.

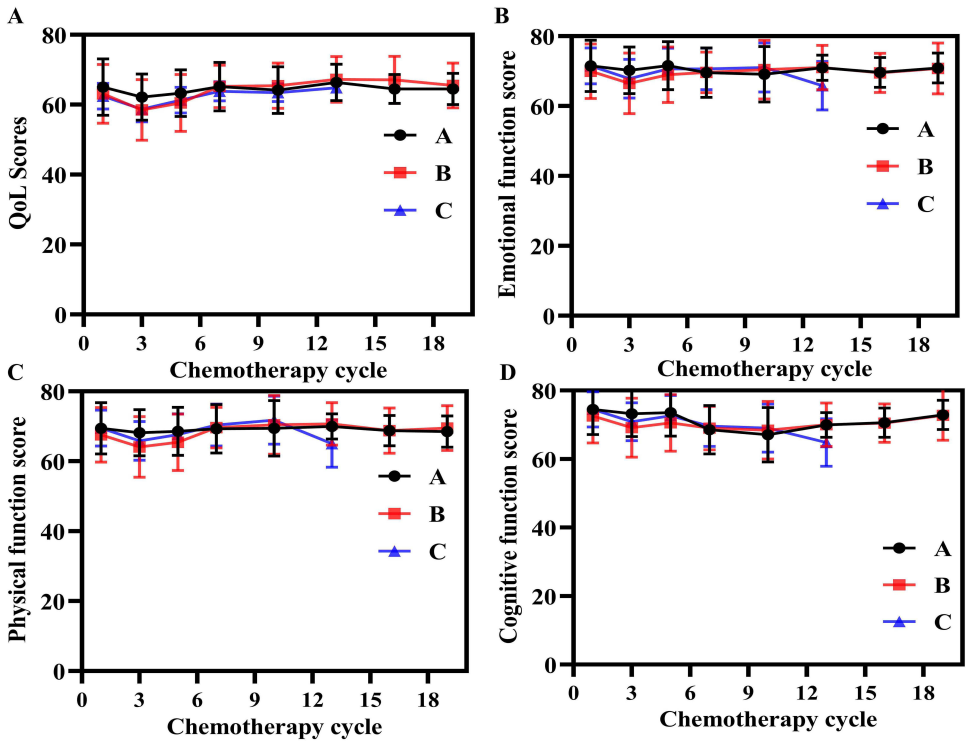

Figure 2 Overall QoL score (**A**), physical function score (**B**), emotional function score (**C**), and cognitive function score (**D**) of patients in Cohort A–C during treatment period.

Due to the limited ability of chemotherapy drugs to penetrate the blood–brain barrier, most treatment regimens have limited effectiveness against intracranial metastatic lesions compared to extracranial lesions, resulting in a limited ORR for the former. Patients presenting with BMs were often removed from participation in clinical trials evaluating new pharmaceutical agents, and some studies restrict the enrollment of such patients. To date, only one large phase III randomized investigation, termed HER2CLIMB, has encompassed individuals affected by active HER2-positive BMs. In

Table 3 Treatment- Related Adverse Events (TRAEs)

Adverse Event	Cohort A (n=22)		Cohort B (n=20)		Cohort C (n=14)		Total (n=56)	
	Grade 3–4	All Grade	Grade 3–4	All Grade	Grade 3–4	All Grade	Grade 3–4	All Grade
Diarrhea	6	21	4	18	3	14	13	53
Hand-foot syndrome	2	14	2	10	1	8	5	32
Anaemia	1	13	2	12	1	8	4	33
Decreased WBC count	4	9	3	8	3	6	10	23
Decreased neutrophil count	4	8	3	8	3	5	10	21
Vomiting	0	10	0	9	1	8	1	27
Nausea	0	10	0	10	0	9	0	29
Decreased appetite	0	6	0	6	0	4	0	16
ALT/AST increased	0	8	0	6	0	4	0	18
TBIL increased	0	9	0	9	0	6	0	24
Asthenia	0	4	0	4	0	4	0	12
Rash	0	1	0	0	0	1	0	2
Weight loss	0	5	0	5	0	3	0	13
Hypokalemia	3	6	2	9	2	7	7	22

this study, the efficacy of tucatinib, in conjunction with trastuzumab and capecitabine, was compared to a placebo among participants diagnosed with HER2-positive metastatic BC who had previously undergone treatment with trastuzumab, T-DM1, as well as pertuzumab. The results clearly exhibited an obvious improvement in PFS among patients with BMs, demonstrating a CNS-ORR of 47.3%.[17] In January 2022, a phase II clinical study called PERMEATE proved that pyrotinib and capecitabine combination therapy effectively controlled both intracranial and extracranial lesions in HER2-positive BC patients, achieving a CNS-ORR of 74.6%, particularly in patients who had not undergone local radiotherapy to the brain.[24] However, further validation of these results is required through multicenter clinical trials involving large sample sizes.

WBRT and SRT are commonly used treatment strategies for BMs. Local radiotherapy has a rapid and long-lasting effect on BMs. However, radiotherapy can cause irreversible damage to the brain and lead to various adverse reactions. Additionally, the lack of effective maintenance drugs further affects treatment outcomes.[25] In populations that have not received prior radiotherapy, both our study (cohort A) and the PERMEATE study (also cohort A)[24] demonstrated that pyrotinib and capecitabine combination therapy provided a distinct survival advantage compared to the use of lapatinib with capecitabine, as observed in the LANDSCAPE study).[18] This was particularly evident in the significant difference in mPFS rates (11.0 months vs 5.5 months). In contrast to the PERMEATE study, our current research introduced a novel subgroup (cohort B) consisting of patients who had SD after radiotherapy. The results showed that the mPFS was longer in cohort B with statistical significance in contrast with cohort C (8.4 months vs 5.2 months). This suggested that pyrotinib and capecitabine combination therapy could be a potentially effective alternative for individuals with HER2-positive BC and BMs who maintain disease stability following radiotherapy.

In our study, we observed an overall CNS-ORR of 58.93% and a mPFS duration of 8.4 months. Despite these results, pyrotinib still demonstrated better clinical benefit compared to the HER2CLIMB study.[26] Specifically, the CNS-ORR in cohort A was similar to that reported in the PHENIX study (11 months vs 10.9 months). Importantly, individuals in cohorts B and C, who had received more lines of treatment, showed higher resistance and consequently lower response rates compared to those in cohort A.

Previous research has shown that chemotherapy can lead to cognitive changes in 15–50% of cancer patients, particularly affecting attention, learning, and processing speed.[27,28] Patients with BMs often experience a decline in neurocognitive function, which negatively impacts their QoL. The combination of chemotherapy agents and TKIs has shown potential in reversing or improving cognitive function in BC patients. For example, the TUXEDO-1 study demonstrated that trastuzumab-deruxtecan therapy could preserve QoL and neurocognitive functions in HER2-positive BC patients with active BMs.[29] Additionally, the Phase III NALA trial[30] suggested that the combination of neratinib and capecitabine could maintain health-related QoL. Consistent with these findings, our results also provided evidence that pyrotinib and capecitabine combination therapy preserved patients' QoL, cognition, and daily activities throughout the treatment course. This supports the use of this regimen alongside appropriate management strategies.

AEs in our study were consistent with previous reports,[24,31] with diarrhea being the most common AE (94.64%) and grade ≥ 3 AEs occurring in 23.21% of patients. However, diarrhea was reversible with dose modification and antidiarrheic therapy, and did not lead to treatment discontinuation. Other grade 3 or above AEs were also manageable.

Conclusions

In conclusion, pyrotinib and capecitabine combination therapy demonstrated efficacy in HER2-positive BC patients with BMs, particularly in those who had not received prior radiotherapy. No new safety concerns were identified, and QoL and cognitive function were maintained throughout the treatment period. In addition, the AEs were manageable. However, randomized controlled study with larger sample sizes is warranted in further phase III clinical trial.

Data Sharing Statement

All data included in this study are available upon request by contact with the corresponding author.

Ethics Approval

This study was reviewed and approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University (No. 2023-375).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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