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ORIGINAL RESEARCH

# Continuous Anlotinib Combined with Oral Vinorelbine has Shown Anti-Tumor Efficiency in Refractory HER2 Negative Advanced Breast Cancer

Jia-Yi Huang[1,*], Yan Zhang[2,*], Cai-Wen Du[1]

[1]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, Guangdong, 518116, People's Republic of China; [2]Department of Emergency, Shenzhen Longhua District People's Hospital, Shenzhen, Guangdong, 518109, People's Republic of China

*These authors contributed equally to this work

Correspondence: Cai-Wen Du, Email dusumc@aliyun.com



**Purpose:** To explore the efficacy and safety of continuous administration of anlotinib combined with oral vinorelbine in refractory human epidermal growth factor-2 (HER2) negative advanced breast cancer (ABC).

**Patients and Methods:** This retrospective study included 41 HER2 negative ABC patients who received anlotinib (8mg orally per day without interruption) plus oral vinorelbine during November 2019 and February 2023. These patients have received at least two treatments in the past. The efficacy and adverse events (AEs) of these patients need to be evaluated.

**Results:** The median follow-up time for this study was 35.6 months. Among 41 patients with HER2 negative ABC, 16 were HR positive/HER2 negative and 25 were triple negative breast cancer (TNBC). The median progression free survival (PFS) and overall survival (OS) were 6.7 months (95% CI, 4.9–8.5 months) and 28.3 months (95% CI, 10.6–46.0 months). There were no statistical differences in PFS (p=0.200) and OS (p=0.494) between the HR positive/HER2 negative and TNBC subgroups. The objective response rate (ORR), clinical benefit rate (CBR) and disease control rate (DCR) were 22.0%, 61.0% and 82.9%, respectively. Forty patients (97.6%) experienced varying grades of AEs and 31.7% of patients for grades 3–4. The most common grade 3–4 AEs that we observed were neutropenia (17.1%), leukopenia (9.8%) and diarrhea (9.8%).

**Conclusion:** Continuous administration of anlotinib combined with oral vinorelbine demonstrates to be efficacious and well tolerated for refractory HER2 negative ABC.

**Keywords:** anlotinib, anti-angiogenesis therapy, oral vinorelbine, advanced breast cancer

## Introduction

Although the death rate of breast cancer has decreased year by year with the continuous progress of anti-tumor drugs and treatment methods, advanced breast cancer (ABC) is still incurable.[1] Human epidermal growth factor-2 (HER2) negative breast cancer includes hormone receptor (HR) positive/HER2 negative and triple negative breast cancer (TNBC), accounting for 78–85% of all breast cancer patients.[2,3] The combination of cyclin dependent kinase (CDK) 4/6 inhibitor and endocrine therapy is preferred for ABC with HR positive/HER2 negative in the first-line treatment stage. After CDK4/6 inhibitor treatment, the treatment plan for HR positive/HER2 negative ABC includes continuing the combination therapy of CDK4/6 inhibitors and endocrine therapy, or combination of CDK2 inhibitor, or phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of the rapamycin (mTOR) pathway combination treatment, or chemotherapy or T-Dxd (for patients with low HER2 expression), but there is no universally recognized treatment method as the best.[4] Due to the negative expression of ER, PR, and HER2 in TNBC, they are ineffective in endocrine therapy and targeted therapy. Therefore, chemotherapy is the main method for treating TNBC.[5] The efficacy of chemotherapy alone for advanced TNBC is not very satisfactory, new drugs are also actively being explored. In combination of pembrolizumab

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with chemotherapy can significantly prolong the PFS of patients with advanced TNBC with CPS≥10.[6] The PFS of antibody-drug conjugates targeting TROP-2 in advanced TNBC is also longer than that of conventional chemotherapy.[7] However, the treatment of refractory HER2 negative ABC is still very difficult.

Neoangiogenesis is a key factor in the occurrence, development, and metastasis of malignant tumors.[8] Therefore, blocking the neovascularization of malignant tumors can effectively inhibit tumor growth.[9,10] At present, anti-angiogenesis drugs such as bevacizumab and small molecule tyrosine kinase inhibitor (TKI) drugs have shown efficacy in the treatment of ABC.[11–14]

Anlotinib is an oral small molecule multi-target TKI that mainly exerts anti-tumor angiogenesis and inhibition of tumor growth by blocking the activity of kinases such as vascular endothelial growth factor receptor (VEGFR1-3), platelet-derived growth factor receptor (PDGFR α, PDGFR β), fibroblast growth factor receptor (FDGFR1-4), and stem cell growth factor receptor.[15,16] A Phase II clinical study showed that the median PFS of anlotinib alone in the treatment of HER2 negative ABC was 5.22 months.[17] The anti-tumor activity of anlotinib combined with chemotherapy in ABC seems to be superior than anlotinib alone.[18–20]

For patients with refractory ABC, chemotherapy is also a very important treatment. Eribulin, carboplatin, intravenous vinorelbine, etc. all play an important role in the treatment of advanced breast cancer.[21–23] However, these intravenous chemotherapy drugs often have serious adverse reactions such as hematological toxicity, require multiple hospitalizations during treatment, and cannot be used for a long time. Oral chemotherapy drugs have the characteristics of convenient use, mild adverse effects (AEs), and long-term oral control of the disease. Vinorelbine is a semi synthetic chemotherapy drug containing vinblastine alkaloids. It inhibits microtubule polymerization, blocks G2-M phase mitosis, and leads to cell death.[24–26] Vinorelbine has two dosage forms, intravenous and oral, with similar therapeutic effects. However, the oral dosage form has the advantages of convenient use, reduced hospitalization, and mild adverse events.[27] Previous studies have reported a median progression free survival (PFS) of 5.5 to 8.4 months for monotherapy oral administration of vinorelbine.[28,29] Meanwhile, the PFS of vinorelbine combined with other drugs is 7.1 to 8.4 months.[30–32]

We retrospectively analyzed the efficacy and safety of patients with refractory HER2 negative ABC who received continuous administration of anlotinib combined with oral vinorelbine in our center from November 2019 to February 2023, to provide reference for clinical use of this dual oral combination treatment scheme. We hope that the results of this study can suggest that continuous anlotinib combined with oral vinorelbine can be an effective, safe and convenient treatment option for patients with refractory HER2 negative ABC.

# Material and Methods

## Study Design

The present retrospective study collected the medical data from 41 heavily pretreated HER2 negative ABC patients who received anti-tumor treatment at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. These patients who received continuous administration of anlotinib combined with oral vinorelbine from November 2019 to February 2023 were enrolled in our study. The research subject of this study is humans, therefore it follows the Helsinki Declaration and has been approved by the National Cancer Hospital & Shenzhen Hospital Institutional and Ethical Committee (Approval Number: 2019–33-2). Due to the retrospective observational nature of this study and the anonymity of the patients, the participants were exempted from signing informed consent forms by the Ethics Committee.

## Patients and Treatment

If patients have received at least 2 cycles of continuous administration of anlotinib (8mg orally per day without interruption) in combination with oral vinorelbine, they will be included in the study (see Figure 1). Termination of treatment is mainly due to the occurrence of disease progression or adverse events that cannot be improved by adjusting drug dosage. These patients also need to meet the following conditions: (1) adult females aged ≥ 18; (2) histopathology confirmed that the primary breast tumor specimen was HER2 negative breast cancer, or the metastatic lesion was HER2 negative; (3) immunohistochemistry (IHC) 0–1+; or IHC 2+ simultaneously satisfying fluorescence in situ hybridization (FISH) without amplification is defined as

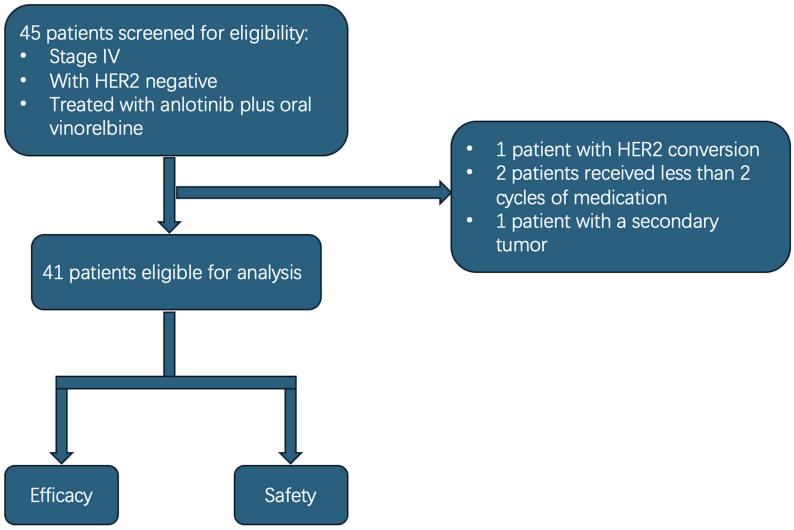


**Figure 1** The flow diagram of screening for patient eligibility.
**Abbreviation**: HER2, human epidermal growth factor receptor 2.

HER2 negative; (4) the scoring status of the Eastern Cancer Collaboration Group (ECOG) was 0–2. The following situations will not be considered for inclusion in this study: (1) merge with other primary malignant tumors; (2) HER2 status was positive or uncertain; (3) the duration of treatment with this combination therapy was less than 2 cycles (42 days).

All patients in our study received at least 2 cycles of combination therapy with anlotinib and oral vinorelbine. The administration of anlotinib was 8mg daily without interruption. In case of grade 3–4 adverse events (such as hypertension, proteinuria, hand foot syndrome, etc)., drug intervention may be considered, with delayed administration if necessary. The oral administration of vinorelbine was taken on the 1st and 8th day of each cycle (with 21 days as one cycle). The initial dose was 60mg/m$^2$, and the subsequently cycles adjusted to 80mg/m$^2$. If there was a grade 3–4 adverse time (such as leukopenia or neutropenia, diarrhea, etc)., drug intervention also can be considered, and the dose can be adjusted if necessary (reduce dosage by 20%). Both anlotinib and oral vinorelbine need to be taken continuously until disease progression or intolerable serious adverse events occur.

## Data Collection and Assessment

The basic information and medical data of the patient (age, tumor pathological characteristics, previous treatment, etc.) are obtained through querying the electronic medical record system, and the patient's survival status is obtained through electronic medical record system or telephone follow-up. According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the efficacy can be evaluated as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) includes CR and PR, disease control rate (DCR) includes CR, PR, and SD, and clinical benefit rate (CBR) includes CR, PR, and SD lasting $\geq$ 24 weeks. PFS is defined as the time from the start of using anlotinib in combination with oral vinorelbine until disease progression or death from any cause occurs without disease progression. Overall survival (OS) is defined as the time from the initiation of combined oral therapy to death from any cause. Adverse events (AEs) were classified into 0–5 levels according to the Common Terminology Criteria Adverse Events Version 5.0 (CTCAE v5.0).

## Statistical Analyses

SPSS 26.0 software and GraphPad prism 10 software were used for all statistical analysis. Survival data (PFS and OS) were estimated by Kaplan Meier method, and Cox proportional hazards regression model was used to compare the differences of PFS and OS between HR positive/HER2 negative breast cancer subgroup and TNBC subgroup. Cox


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proportional hazards regression model was also used to perform univariate and multivariate analyses to predict key factors affecting PFS and OS. A p-value<0.05 was defined as statistically significant.

# Results

## Patient Characteristics

The final follow-up date was December 31, 2024, with a median follow-up of 35.6 months (28.5–42.7 months). The baseline characteristics of all 41 patients are shown in Table 1. A total of 41 female patients with HER2 negative ABC were included in this study, including 16 HR positive/HER2 negative breast cancer patients and 25 TNBC patients. The ECOG score of 28 patients (68.3%) was 0–1, while the ECOG score of 13 patients (31.7%) was 2. The histological grade of 16 patients (39.0%) was grade I–II, and 25 patients (61.0%) were grade III. In our study, one patient in the HR positive/HER2 negative subgroup and one patient in the TNBC subgroup had de novo metastatic disease, and the rest patients were recurrent after treatment. Twenty-five patients (61.0%) were diagnosed as stage I–II at the time of initial diagnosis, and 16 patients (39.0%) were diagnosed as stage III–IV. Among them, 23 patients (56.1%) had disease-free

**Table 1** Patient Characteristics at Baseline

| Characteristic | Total N=41, n (%) | HR+/HER2- N=16, n (%) | TNBC N=25, n (%) |
|---|---|---|---|
| Age, years | | | |
| <50 | 24 (58.5) | 11 (68.7) | 13 (52.0) |
| ≥50 | 17 (41.5) | 5 (31.3) | 12 (48.0) |
| Location | | | |
| Left | 20 (48.8) | 8 (50.0) | 12 (48.0) |
| Right | 21 (51.2) | 8 (50.0) | 13 (52.0) |
| ECOG performance status | | | |
| 0–1 | 28 (68.3) | 11 (68.7) | 17 (68.0) |
| 2 | 13 (31.7) | 5 (31.3) | 8 (32.0) |
| Histopathologic grade | | | |
| I–II | 16 (39.0) | 7 (43.7) | 9 (36.0) |
| III | 25 (61.0) | 9 (56.3) | 16 (64.0) |
| TNM stage at diagnosis | | | |
| I–II | 25 (61.0) | 8 (50.0) | 17 (68.0) |
| III–IV | 14 (34.1) | 7 (43.8) | 7 (28.0) |
| IV | 2 (4.9) | 1 (6.3) | 1 (4.0) |
| DFS duration, months | | | |
| ≤24 | 23 (56.1) | 7 (43.7) | 18 (72.0) |
| >24 | 18 (43.9) | 9 (56.3) | 7 (28.0) |
| Lines of treatment, lines | | | |
| 2 | 22 (53.7) | 6 (37.5) | 16 (64.0) |
| ≥3 | 19 (46.3) | 10 (62.5) | 9 (36.0) |
| Type of metastatic site | | | |
| Non-visceral | 11 (26.8) | 2 (12.5) | 9 (36.0) |
| Visceral | 30 (73.2) | 14 (87.5) | 16 (64.0) |
| Number of metastatic sites, n | | | |
| ≤3 | 26 (63.4) | 7 (43.7) | 18 (72.0) |
| >3 | 15 (36.6) | 9 (56.3) | 7 (28.0) |
| Metastatic sites | | | |
| Bone | 23 (56.1) | 11 (68.7) | 12 (48.0) |
| Lung | 24 (58.5) | 10 (62.5) | 14 (56.0) |
| Liver | 19 (46.3) | 14 (87.5) | 5 (20.0) |
| Brain | 12 (29.3) | 7 (43.7) | 5 (20.0) |

(*Continued*)

**Table 1** (Continued).

| Characteristic | Total N=41, n (%) | HR+/HER2- N=16, n (%) | TNBC N=25, n (%) |
|---|---|---|---|
| Prior target treatment | | | |
| CDK4/6 inhibitors | 9 (22.0) | 9 (56.3) | 0 (0.0) |
| Palbociclib | 7 (17.1) | 7 (43.8) | 0 (0.0) |
| Abemaciclib | 2 (4.9) | 2 (12.5) | 0 (0.0) |
| Anti-VEGFR treatment | 22 (53.7) | 11 (68.7) | 11 (44.0) |
| PD-1 inhibitors | 3 (7.3) | 0 (0.0) | 3 (12.0) |
| Previous chemotherapy | | | |
| Anthracycline | 37 (90.2) | 14 (87.5) | 23 (92.0) |
| Taxane | 39 (95.1) | 14 (87.5) | 25 (100.0) |
| Gemcitabine | 15 (36.6) | 5 (31.3) | 10 (40.0) |
| Platinum | 13 (31.7) | 3 (18.8) | 10 (40.0) |
| Capecitabine | 6 (14.6) | 1 (6.3) | 5 (20.0) |
| Eribulin | 4 (9.8) | 0 (0.0) | 4 (16.0) |

**Abbreviations**: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; ECOG, Eastern Cooperative Oncology Group; TNM stage, the stage of tumor, node and metastasis; DFS, disease free survival; CDK4/6, cyclin-dependent kinase 4/6; VEGFR, vascular endothelial growth factor receptor; +, positive; -, negative.

survival within 2 years, while 18 patients (43.9%) had disease-free survival more than 2 years. Seventy-three point two percent (30/41) of the patients had visceral metastasis, and 63 patients (63.0%) had more than three metastatic sites. Among the 16 patients with HR positive/HER2 negative breast cancer, 9 (56.3%) had received CDK4/6 inhibitors, including 7 cases of palbociclib and 2 cases of abemaciclib. In all 41 patients, 22 patients (38.0%) had received anti vascular endothelial growth factor receptor (VEGFR) treatment. Three patients in the TNBC subgroup had previously received PD-1 inhibitor treatment. More than 90% of the patients had previously received anthracycline and taxane treatment. In addition to anthracyclines and taxanes, chemotherapy drugs previously used in the metastatic setting include gemcitabine (15, 36.6%), platinum (13, 31.7%), capecitabine (6, 14.6%), and eribulin (4, 9.8%).

# Outcomes

## Survival Outcomes

As shown in Figure 2, the median PFS of patients with HER2 negative ABC treated with anlotinib plus vinorelbine was 6.7 months (95% CI, 4.9–8.5 months), and the median OS was 28.3 months (95% CI, 10.6–46.0 months). In the HR positive/HER2 negative breast cancer subgroup, the median PFS was 5.6 months (95% CI, 4.3–6.9 months), and the median OS was

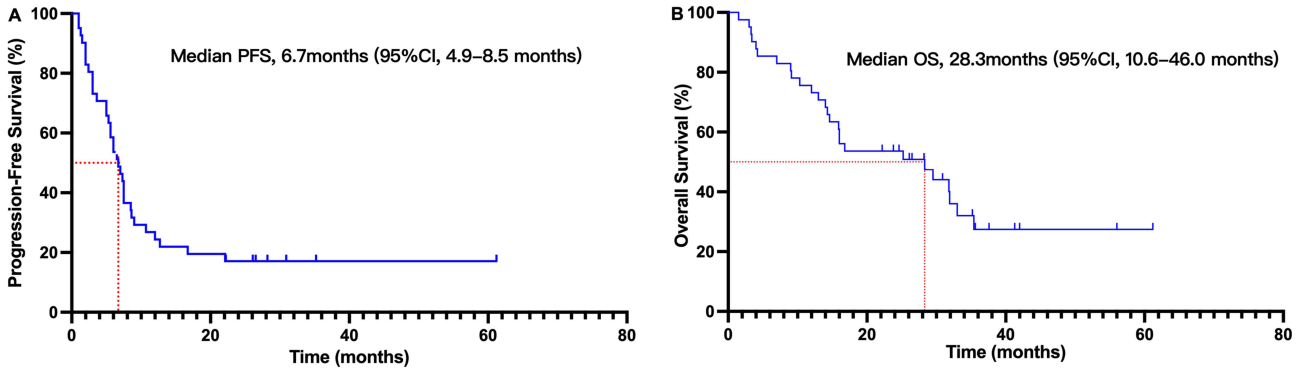


**Figure 2** PFS curve (**A**) and OS curve (**B**) of anlotinib plus oral vinorelbine in the treatment of refractory HER2 negative ABC patients.
**Abbreviations**: PFS, progression- free survival; OS, overall survival; CI, confidence interval; HER2, human epidermal growth factor receptor-2; ABC, advanced breast cancer.


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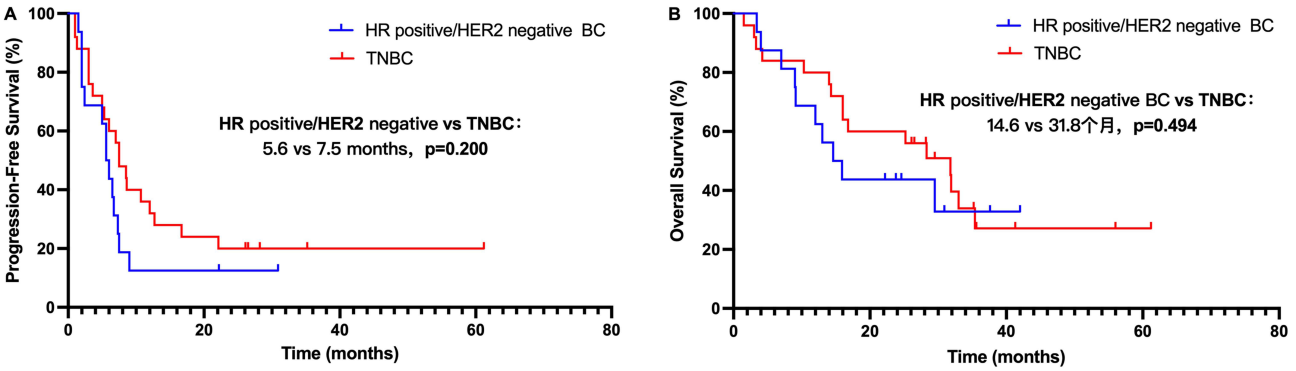


**Figure 3** Survival curve of anlotinib plus oral vinorelbine in the treatment of refractory HER2 negative ABC patients. (**A**) Comparison of PFS curves between HR positive / HER2 negative breast cancer subgroup and TNBC subgroup. (**B**) Comparison of OS curves between HR positive /HER2 negative breast cancer subgroup and TNBC subgroup. p=0.200, the p-value of PFS comparison between HR positive/HER2 negative subgroup and TNBC subgroup is 0.200, indicating no statistical difference between the two subgroups; 5.6 vs 7.5 months, the PFS of HR positive/HER2 negative subgroup and TNBC subgroup were 5.6 months and 7.5 months, respectively; p=0.494, the p-value of OS comparison between HR positive/HER2 negative subgroup and TNBC subgroup is 0.494, indicating no statistical difference between the two subgroups; 14.6 vs 31.8 months, the OS of HR positive/HER2 negative subgroup and TNBC subgroup were 14.6 months and 31.8 months, respectively.

**Abbreviations**: PFS, progression- free survival; OS, overall survival; HR, hormone receptors; HER2, human epidermal growth factor receptor-2; TNBC, triple negative breast cancer; BC, breast cancer; ABC, advanced breast cancer.

14.6 months (95% CI, 8.9–20.3 months). In the TNBC subgroup, the median PFS was 7.5 months (95% CI, 5.1–9.9 months), and the median OS was 31.8 months (95% CI, 23.4–40.1 months). There was no significant difference in PFS (p=0.200) and OS (p=0.494) between HR positive/HER2 negative subgroup and TNBC subgroup (see Figure 3).

## Assessment of Tumor Response

No patient achieved complete remission of tumor lesions in this study. Nine patients achieved PR, 25 patients achieved SD, and 16 patients achieved SD for ≥ 24 weeks. Therefore, the ORR, CBR, and DCR of this study were 22.0% (9/41), 61.0% (25/41), and 82.9% (34/41).

## Cox Univariate Regression Analysis for PFS and OS

As shown in Table 2, univariate analysis showed that patients receiving second-line treatment (p=0.001), patients with 1–3 metastatic sites (p=0.001), patients without visceral metastasis (p=0.009), patients without liver metastasis (p=0.005), patients without bone metastasis (p=0.011) and patients without brain metastasis (p=0.001) had longer PFS.

**Table 2** Cox Univariate Regression Analysis for Progression-Free Survival and Overall Survival

| Variable | Progression-Free Survival | | | Overall Survival | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Age, years (<50 vs ≥50) | 1.936 | 0.951–3.941 | 0.068 | 1.886 | 0.817–4.350 | 0.137 |
| ECOG (0–1 vs 2) | 0.572 | 0.282–1.160 | 0.121 | 0.391 | 0.176–0.865 | **0.021** |
| Histopathologic grade (I–II vs III) | 0.821 | 0.403–1.672 | 0.587 | 0.445 | 0.186–1.065 | 0.069 |
| TNM stage at diagnosis (I–II vs III–IV) | 0.732 | 0.369–1.455 | 0.374 | 0.466 | 0.210–1.036 | 0.061 |
| DFS duration, months (≤24 vs >24) | 1.937 | 0.915–4.097 | 0.084 | 2.493 | 1.000–6.213 | 0.050 |
| Lines of treatment, lines (2 vs ≥3) | 0.274 | 0.132–0.569 | **0.001** | 0.416 | 0.189–0.916 | **0.029** |
| Number of metastatic sites (≤3 vs >3) | 0.214 | 0.099–0.465 | **0.001** | 0.376 | 0.172–0.820 | **0.014** |
| Visceral metastasis (no vs yes) | 0.297 | 0.120–0.735 | **0.009** | 0.738 | 0.295–1.849 | 0.517 |
| Liver metastasis (no vs yes) | 0.356 | 0.174–0.726 | **0.005** | 0.780 | 0.359–1.694 | 0.530 |
| Lung metastasis (no vs yes) | 0.623 | 0.306–1.269 | 0.192 | 0.763 | 0.336–1.729 | 0.516 |
| Bone metastasis (no vs yes) | 0.391 | 0.189–0.808 | **0.011** | 0.492 | 0.218–1.106 | 0.086 |
| Brain metastasis (no vs yes) | 0.225 | 0.101–0.502 | **0.001** | 0.219 | 0.096–0.503 | **0.001** |

**Notes**: Bold values indicate p-values of < 0.05.

**Abbreviations**: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TNM stage, the stage of tumor, node and metastasis; DFS, disease free survival.

**Table 3** Cox Multivariate Regression Analysis for Progression-Free Survival and Overall Survival

| Variable | Progression-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| ECOG (0–1 vs 2) | – | – | – | 0.355 | 0.150–0.844 | **0.019** |
| Lines of treatment, lines (2 vs ≥3) | 0.433 | 0.172–1.094 | 0.077 | 1.010 | 0.372–2.746 | 0.984 |
| Number of metastatic sites (≤3 vs >3) | 0.543 | 0.180–1.641 | 0.279 | 0.804 | 0.304–2.123 | 0.659 |
| Visceral metastasis (no vs yes) | 0.459 | 0.157–1.348 | 0.157 | – | – | – |
| Liver metastasis (no vs yes) | 0.778 | 0.295–2.057 | 0.613 | – | – | – |
| Bone metastasis (no vs yes) | 0.670 | 0.298–1.508 | 0.333 | – | – | – |
| Brain metastasis (no vs yes) | 0.453 | 0.164–1.253 | 0.127 | 0.227 | 0.069–0.743 | **0.014** |

**Notes**: Bold values indicate p-values of < 0.05.
**Abbreviations**: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

In addition, univariate analysis showed that the factors that may have longer OS were ECOG score of 0–1 (p=0.021), received second-line treatment (p=0.029), had 1–3 metastatic sites (p=0.014) and without brain metastasis (p=0.001).

### Cox Multivariate Regression Analysis for PFS and OS

We conducted a multivariate analysis of six factors that may affect PFS in univariate analysis, including the number of treatment lines, number of metastatic sites, visceral metastases, liver metastases, bone metastases, and brain metastases. No statistically significant factors were found in the multivariate analysis. In terms of OS, a multivariate analysis was also conducted on four factors that may affect OS in univariate analysis, including ECOG score, number of treatment lines, number of metastatic sites, and brain metastases. It was found that there was a longer OS in patients with ECOG score of 0–1 (ECOG 0–1 vs ECOG 2, 31.9 vs 14.0 months, HR=0.355, p=0.019) and patients without brain metastases (without vs with brain metastases, 31.9 vs 9.1 months, HR=0.227, p=0.014) (see Table 3 and Figure 4).

## Safety

All patients received at least 2 cycles of anlotinib combined with oral vinorelbine. Table 4 summarizes the AEs at all levels during the treatment. Among the 41 patients included in this study, 40 patients (97.6%) had different degrees of AEs, and the incidence of grade 3–4 AEs was 31.7%. Grade 3–4 AEs mainly included neutropenia (17.1%), leukopenia (9.8%), diarrhea (9.8%), hand-foot syndrome (7.3%), vomiting (4.9%), proteinuria (2.4%), secondary hypertension (2.4%) and thrombocytopenia (2.4%). No death due to adverse events occurred, and no patient completely terminated treatment due to AEs. Four patients suspended oral vinorelbine because of grade 4 neutropenia. Subsequently, oral

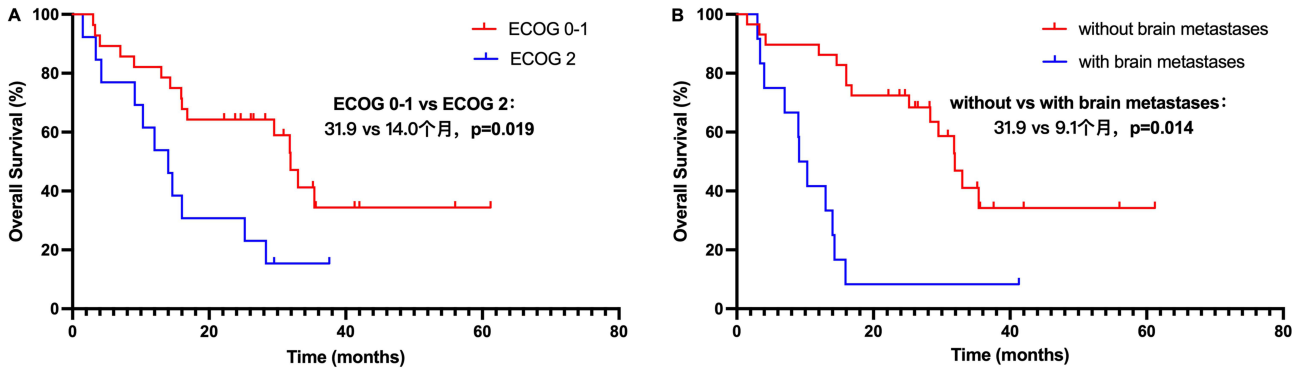


**Figure 4** Survival curve of anlotinib plus oral vinorelbine in the treatment of refractory HER2 negative ABC patients. (**A**) OS curves of patients with ECOG 0–1 and ECOG 2 subgroups; (**B**) OS curves of patients without and with brain metastases subgroups. p=0.019, the p-value of OS comparison between ECOG 0–1 and ECOG 2 subgroups is 0.019, indicating statistical difference between the two subgroups; 31.9 vs 14.0 months, the OS of ECOG 0–1 and ECOG 2 subgroups were 31.9 months and 14.0 months, respectively; p=0.014, the p-value of OS comparison between without and with brain metastases subgroups is 0.014, indicating statistical difference between the two subgroups; 31.9 vs 9.1 months, the OS of without and with brain metastases subgroups were 31.9 months and 9.1 months, respectively.
**Abbreviations**: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor-2; ABC, triple negative breast cancer.


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**Table 4** Treatment-Related Adverse Events

| Adverse Events | All Grade, n (%) | ≥ Grade 3, n (%) |
|---|---|---|
| Leukopenia | 32 (78.0) | 4 (9.8) |
| Neutropenia | 29 (70.7) | 7 (17.1) |
| Vomiting | 23 (56.1) | 2 (4.9) |
| Diarrhea | 22 (53.7) | 4 (9.8) |
| Liver function damage | 22 (53.7) | 0 (0.0) |
| Hand-foot syndrome | 21 (51.2) | 3 (7.3) |
| Proteinuria | 19 (46.3) | 1 (2.4) |
| Hyperlipidemia | 18 (43.9) | 0 (0.0) |
| Secondary hypertension | 17 (41.5) | 1 (2.4) |
| Anemia | 16 (39.0) | 0 (0.0) |
| Thrombocytopenia | 10 (16.0) | 1 (2.4) |
| Oral mucositis | 5 (12.2) | 0 (0.0) |

vinorelbine was adjusted to metronomic chemotherapy (30mg, three times a week). After that, the patients' tolerance was good, and no grade 3–4 neutropenia occurred again.

## Discussion

Despite significant progress in targeted therapy, antibody-drug conjugates, and immunotherapy in recent years, chemotherapy remains one of the most important treatment methods for ABC. Classic cytotoxic drugs such as anthracyclines and taxanes are the most commonly used chemotherapy drugs in the early and late stages of breast cancer. Patients with anthracyclines and taxanes resistant can choose to use vinorelbine, gemcitabine, capecitabine and other chemotherapy drugs alone or in combination.[33] However, there are currently no standard recommended drugs for second-line and above chemotherapy.[34] Oral vinorelbine showed anti-tumor activity in the first-line and second-line or above treatment of advanced breast cancer.[35] Previous studies showed that in the second-line treatment of ABC, the median PFS of vinorelbine combined with capecitabine was 3.4–3.8 months, and the median OS was 11.3 months.[36,37] Therefore, the efficacy of chemotherapy alone (such as oral vinorelbine combined with capecitabine) in the treatment of second-line or above seems unsatisfactory. In the second-line treatment of metastatic TNBC, compared with treatment of physician's choice (TPC), sacituzumab govitecan (SG) significantly prolonged the median PFS (4.8 vs 1.7 months, HR:0.41) and OS (11.8 vs 6.9 months, HR:0.51).[38] Compared with TPC, SG also significantly prolonged PFS (5.5 vs 4.0 months, HR:0.66) in patients with HR positive/HER2 negative advanced breast cancer who had received at least advanced first-line treatment.[39] For ABC patients with low HER2 expression, DESTINY-breast 04 study showed that the efficacy of T-DXd was significantly better than that of TPC (median PFS was 10.1 vs 5.4 months, HR:0.51).[40] These new drugs have brought better curative effect to patients. However, in clinical practice, many patients are unable to receive these treatments due to the high prices of these drugs.

Anti angiogenic drugs (such as bevacizumab, sorafenib, sunitinib, apatinib, etc.) combined with chemotherapy have been studied in the field of ABC and have shown efficacy.[11–13,41,42] Anlotinib is a novel small molecule tyrosine kinase inhibitor against angiogenesis, which can inhibit tumor growth by blocking multiple targets.[15,16] The median PFS of second-line treatment of HER2 negative metastatic breast cancer with anlotinib alone was 5.22 months, and the ORR was 15.38%.[17] A phase II single-arm clinical study in our center showed that the median PFS and median OS of anlotinib combined with chemotherapy in the treatment of advanced TNBC were 8.8 months (95% CI:6.5–11.1 months) and 19.0 months (95% CI:12.1–25.9 months), respectively.[20] This study included some patients treated as the first line. In addition, the results of a randomized controlled clinical study of anlotinib combined with eribulin versus eribulin monotherapy in the treatment of HER2 negative advanced breast cancer showed that the median PFS of the anlotinib combined with eribulin group was longer than that of the eribulin monotherapy group (5.1 vs 3.5 months, HR:0.56).[18] There are also some real-world retrospective studies that show that anlotinib combined with chemotherapy has certain curative effect and can bring benefits to patients' disease control.[19,43,44] Anlotinib combined with PD-L1 inhibitor (TQB245) in the treatment of advanced TNBC also showed good anti-tumor activity in a phase IB clinical studies.[45]

Our retrospective real-world study explored the efficacy and safety of continuous administration of anlotinib combined with oral vinorelbine in the treatment of refractory HER2 negative ABC. In this study, the median PFS and OS of 41 patients were 6.7 months (95% CI, 4.9–8.5 months) and 25.2 months (95% CI, 10.9–39.5 months), respectively. In addition, the ORR, CBR and DCR of this retrospective study were 22.0% (9/41), 61.0% (25/41) and 82.9% (34/41), respectively. Therefore, the results of this study show that anlotinib combined with oral vinorelbine showed efficacy on refractory HER2 negative ABC. It is not inferior to the previous efficacy of other drugs in refractory HER2 negative ABC. The advantage of our research is that both drugs are oral preparations that can be prescribed in outpatient clinics and taken orally at home, making treatment convenient, reducing costs, and saving medical resources.

In terms of safety, the AEs observed in this study were similar to previous reports, and no new AEs were found. Most of the AEs were grade 1–2, and the incidence of grade 3–4 AEs was low, and most of the AEs could be alleviated by adjusting the treatment mode or drug intervention. In our study, the most common grade 3–4 AEs were neutropenia, leukopenia and diarrhea. We found that compared with other previous studies, the incidence of grade 3–4 hand-foot syndrome (7.3%), secondary hypertension (2.4%) and proteinuria (2.4%) in our study was lower in our study, which may be due to the use of low-dose (8mg/day) anlotinib. There was no death due to AEs in all patients. Four patients suspended oral vinorelbine due to grade 4. After adjusting the oral vinorelbine to the metronomic chemotherapy (30mg, oral three times a week), the tolerance was good, and grade 3–4 neutropenia did not occur again. This indicates that the AEs of metronomic chemotherapy with vinorelbine seem to be lighter than conventional chemotherapy, which can be used as a treatment option for some patients with poor tolerance.

It is evident that our study has inherent limitations, including retrospective study design, small sample size, lack of randomized control group, and other unavoidable confounding factors. Another limitation is that some enrolled patients did not receive standard treatment in the past, such as 7 HR positive/HER2 negative patients who did not receive CDK4/6 inhibitor treatment in the first-line setting, and only 3 TNBC patients who received PD-1 inhibitor treatment before. All of these may bring some bias to the research results. A larger randomized controlled trial is needed to confirm the efficacy and safety of anlotinib combined with oral vinorelbine. However, anyhow, anlotinib combined with oral vinorelbine showed certain efficacy and good safety for refractory HER2 negative ABC, providing a treatment option for such patients.

## Conclusion

This study shows that anlotinib combined with oral vinorelbine has potential therapeutic feasibility for HER2 negative ABC, and the regimen based on continuous low-dose anlotinib has slight toxicity and good tolerance.

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## Disclosure

The authors report no conflicts of interest in this work.

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