

# Anlotinib Combined With Chemotherapy and Neoadjuvant Therapy for Hormone Receptor-positive HER-2 Negative Breast Cancer

## Protocol

Lead Organization: Xijing Hospital

PI: Ting Wang

Department: Thyroid, Breast and Vascular Surgery

Tel: 029-84775271

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## Protocol

Project	Anlotinib combined with chemotherapy as neoadjuvant therapy for hormone receptor-positive HER-2 Negative Breast Cancer
Aims	To preliminarily assess the pathological complete response (pCR) rate of neoadjuvant therapy of Anlotinib and chemotherapy in hormone receptor-positive, HER2-negative breast cancer
Design	This is an open-label, single-arm, single-center, exploratory clinical trial designed to investigate the combination of Anlotinib Hydrochloride and Albumin-Bound Paclitaxel in patients with early-stage hormone receptor-positive, HER2-negative breast cancer. Exploratory Factors: Axillary lymph node metastasis status; Ki-67 index.
Sample Size	31
Eligibility Criteria	<p><b>Inclusion Criteria</b></p> <ol style="list-style-type: none"> <li>1. Female patients aged <math>\geq 18</math> and <math>\leq 70</math> years at the time of signing informed consent.</li> <li>2. ECOG performance status of 0 or 1.</li> <li>3. Patients assessed and diagnosed with early-stage, hormone receptor-positive, HER2-negative breast cancer, meeting all of the following criteria: <ul style="list-style-type: none"> <li>➤ Immunohistochemistry (IHC) positive for ER and/or PR (defined as <math>&gt;1\%</math> positive staining);</li> <li>➤ IHC score of 0 or 1+ for HER2, or IHC 2+ with a negative fluorescence in situ hybridization (FISH) result;</li> <li>➤ Tumor Stage IIA, IIB, IIIA, IIIB, or IIIC;</li> <li>➤ Required staging work-up (all assessments valid within 28 days) must include: abdominal CT, bone scan, chest CT, and cranial MRI.</li> </ul> </li> <li>4. No prior anticancer therapy (including but not limited to chemotherapy, radiotherapy, or traditional Chinese medicine) within one month before initiation of study treatment.</li> <li>5. Adequate organ function, meeting the following laboratory parameters within 7 days prior to enrollment (without transfusion or growth factor support within 7 days prior to screening): <ul style="list-style-type: none"> <li>➤ Blood Routine: <ul style="list-style-type: none"> <li>▪ Absolute Neutrophil Count (ANC) <math>\geq 1.5 \times 10^9/L</math></li> <li>▪ Absolute Lymphocyte Count (ALC) <math>\geq 0.5 \times 10^9/L</math></li> <li>▪ Platelets (PLT) <math>\geq 100 \times 10^9/L</math></li> <li>▪ Hemoglobin (Hb) <math>\geq 90</math> g/L</li> <li>▪ White Blood Cell Count (WBC) <math>\geq 3.0 \times 10^9/L</math> and <math>\leq 15 \times 10^9/L</math></li> </ul> </li> </ul> </li> </ol>

- Blood Biochemistry (without transfusion or albumin infusion within 7 days prior to screening):
  - ALT and AST  $\leq 2.5 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  for patients with liver metastases)
  - Alkaline Phosphatase (ALP)  $\leq 2.5 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  for patients with bone metastases)
  - Blood Urea Nitrogen (BUN) and Creatinine (Cr)  $\leq 1.5 \times \text{ULN}$ , and Creatinine Clearance  $\geq 60 \text{ mL/min}$  (calculated by Cockcroft-Gault formula)
- Coagulation Profile:
  - Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT)  $\leq 1.5 \times \text{ULN}$
  - International Normalized Ratio (INR)  $\leq 1.5$  (for patients not receiving anticoagulant therapy)
- Urinalysis:
  - Urine protein  $< 2+$ ; if urine protein  $\geq 2+$ , a 24-hour urine protein quantification must demonstrate protein  $\leq 1 \text{ g}$ .
- Thyroid Function:
  - Thyroid-Stimulating Hormone (TSH)  $\leq \text{ULN}$ ; if abnormal, T3 and T4 levels must be within normal limits for patient eligibility.
- 6. Women of childbearing potential must have a negative serum pregnancy test within 3 days before the first dose. They must agree to use highly effective contraception methods during the study period and for at least 180 days after the last dose of the study drug.
- 7. Voluntarily participate in the study, sign the informed consent form, demonstrate good compliance, and be willing to cooperate with follow-up.

#### **Exclusion Criteria**

Patients who meet **any** of the following criteria will be excluded from the study:

1. Tumor-Related Characteristics and Prior Therapy
  - Ki-67 index  $\leq 20\%$ .
  - Prior treatment with anti-angiogenic targeted agents or other therapies targeting VEGFR.
2. Comorbidities and Medical History
  - Any known or suspected autoimmune disease, with the following exceptions:
    - Hypothyroidism managed solely with hormone replacement therapy

	<p>due to autoimmune thyroiditis.</p> <ul style="list-style-type: none"> <li>▪ Stable Type I diabetes mellitus with well-controlled blood glucose.</li> <li>➤ Hypertension that is not adequately controlled with antihypertensive medication (systolic blood pressure &gt;140 mmHg or diastolic blood pressure &gt;90 mmHg).</li> <li>➤ Within 6 months prior to enrollment: myocardial infarction, severe/unstable angina, cardiac insufficiency of NYHA Class 2 or higher, clinically significant supraventricular or ventricular arrhythmia, or symptomatic congestive heart failure.</li> <li>➤ Presence of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic diseases (e.g., diabetes, pulmonary fibrosis, acute pneumonia).</li> <li>➤ History of vaccination with a live attenuated vaccine within 28 days prior to the first dose or anticipated need for such vaccination during the study.</li> <li>➤ Human Immunodeficiency Virus (HIV) infection or known Acquired Immunodeficiency Syndrome (AIDS).</li> <li>➤ Active hepatitis (Hepatitis B, defined as HBV-DNA <math>\geq</math> 500 IU/mL; Hepatitis C, defined as HCV-RNA above the lower limit of detection of the assay) or co-infection with both Hepatitis B and C.</li> <li>➤ Severe infection within 4 weeks before the first dose, including but not limited to bacteremia or severe pneumonia requiring hospitalization; OR active infection of CTCAE Grade <math>\geq</math>2 requiring systemic antibiotic therapy within 2 weeks before the first dose; OR unexplained fever &gt;38.5°C during screening/prior to the first dose (fever judged by the investigator to be due to the tumor may permit enrollment).</li> <li>➤ Evidence of active tuberculosis infection within 1 year prior to initiation of study treatment.</li> <li>➤ Diagnosis of any other malignancy within 5 years prior to study entry, with the exception of adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.</li> <li>➤ Major surgery within 28 days prior to enrollment (tissue biopsy for diagnostic purposes and PICC line placement are permitted).</li> <li>➤ Prior or planned allogeneic bone marrow transplantation or solid organ transplantation.</li> <li>➤ Peripheral neuropathy of Grade <math>\geq</math>2.</li> <li>➤ Presence of clinically significant intestinal obstruction.</li> <li>➤ Arterial or venous thrombotic events within 6 months prior to enrollment, such as cerebrovascular accident (including transient</li> </ul>
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	<p>ischemic attack), deep venous thrombosis (excluding thrombosis related to a prior chemotherapy venous catheter deemed resolved by the investigator), and pulmonary embolism.</p> <ul style="list-style-type: none"> <li>➤ History of hemoptysis with fresh blood (<math>\geq 2.5</math> mL per day at maximum) within 2 months prior to study entry.</li> <li>➤ Clinically significant bleeding symptoms or clear bleeding tendency within 3 months prior to study entry, such as gastrointestinal bleeding, hemorrhagic gastric ulcer, baseline fecal occult blood ++ or higher, or vasculitis.</li> <li>➤ Known hereditary or acquired predisposition to bleeding or thrombosis (e.g., hemophilia, coagulation disorders, thrombocytopenia, hypersplenism).</li> <li>➤ Coagulation dysfunction (INR <math>&gt;1.5</math> or APTT <math>&gt;1.5 \times</math> ULN), bleeding tendency, or requirement for thrombolytic therapy, long-term anticoagulation therapy (e.g., warfarin or heparin), or long-term antiplatelet therapy (aspirin <math>\geq 300</math> mg/day or clopidogrel <math>\geq 75</math> mg/day).</li> </ul> <p>3. Factors Related to Study Treatment</p> <ul style="list-style-type: none"> <li>➤ Treatment with systemic targeted agents or immunostimulants (including but not limited to interferon, interleukin-2, or investigational immunostimulants) within 4 weeks prior to the first dose.</li> <li>➤ Known allergy to the study drug or any of its excipients, or history of severe allergic reaction to other anti-angiogenic targeted agents.</li> </ul> <p>4. Concurrent Clinical Trials</p> <ul style="list-style-type: none"> <li>➤ Participation in another investigational drug trial within 4 weeks prior to enrollment, or the time since the last dose of the previous investigational drug is less than 5 half-lives.</li> </ul> <p>5. Other Considerations</p> <ul style="list-style-type: none"> <li>➤ History of substance abuse, alcohol abuse, or drug addiction.</li> <li>➤ Female patients who are pregnant, lactating, or planning to become pregnant during the study period.</li> <li>➤ Any other condition (e.g., severe concomitant illness, significant laboratory abnormality, or familial/social factors) that, in the investigator's judgment, may compromise the patient's safety, interfere with data/sample collection, or otherwise justify discontinuation from the study.</li> </ul>
Treatment	<p>All enrolled patients received 5 cycles of Anlotinib (12 mg qd, d1-14; q3w) plus 6 cycles of nab-paclitaxel (200 mg/m<sup>2</sup>, q3w), pirarubicin (50 mg/m<sup>2</sup>,</p>

	<p>q3w) and cyclophosphamide (500 mg/m<sup>2</sup>, q3w). Upon completion of the NAT, patients received surgery within 2 to 6 weeks. Surgical approach was selected based on the surgeon's clinical judgment and the patient's preference, including breast-conserving surgery, mastectomy or breast reconstruction for affected breast and sentinel lymph node biopsy or lymph node dissection for axillary lymph nodes. Adjuvant therapy (including radiotherapy and endocrine therapy) was administered at the discretion of the physician according to the standard clinical guidelines.</p>
Endpoints	<p>Primary endpoint:</p> <ul style="list-style-type: none"> <li>➤ tpCR rate, defined as the absence of invasive cancer cells in the breast and axillary lymph node (ypT0/Tis, ypN0)</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>➤ ORR, defined as the proportion of patients achieving a best overall CR and PR according to RECIST v1.1.</li> <li>➤ EFS, defined as the time from the initiation of treatment until the first occurrence of any of the following events: disease progression precluding surgical intervention, local or distant recurrence, death from any cause.</li> <li>➤ Safety, the severity grade (according to NCI-CTCAE, v 5.0) and the relationship to study treatment of AEs were assessed by physical examination and laboratory tests before and after every cycle, during follow-up visits, and upon indication by symptoms.</li> </ul> <p>This study also focused on the rates of RCB 0/I, bpCR (ypT0/Tis) and apCR (ypN0).</p>
Statistical Analysis	<p>Unless otherwise specified, this study will summarize the data using appropriate descriptive statistics based on the data type. Specifically, for continuous data, the mean, standard deviation (SD), median, minimum, and maximum will be used. For count data and ordinal data, frequency and percentage will be employed, along with the overall 95% confidence interval.</p>