ISRCTN72521486 https://doi.org/10.1186/ISRCTN72521486

Pyrotinib as a novel irreversible tyrosine kinase inhibitor for locally advanced human epidermal growth factor receptor 2-positive breast cancer

Submission date
30/08/2019

Recruitment status
No longer recruiting

Registration date
24/09/2019

Overall study status
Ongoing

Last Edited
23/09/2019

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Breast cancer ranks first in the incidence of female cancers in China. Its incidence is on the rise year by year. Neoadjuvant chemotherapy, also known as preoperative chemotherapy, mainly refers to the preoperative systemic chemotherapy of patients, and then surgical treatment after a certain curative effect. It is currently one of the standard treatment measures for locally advanced breast cancer, which can increase the rate of breast resection or breast-conserving. About a quarter of Chinese breast cancer patients have abnormal HER2 gene, which is considered to be one of the independent factors of poor prognosis of breast cancer. Because HER2 overexpressed breast cancer patients are insensitive to endocrine therapy and standardized therapy, application of anti-HER2 monoclonal antibody trastuzumab in postoperative adjuvant therapy and advanced breast cancer can improve the prognosis of these patients. In clinical practice, trastuzumab combined with chemotherapy can significantly increase the pCR rate and improve the prognosis of patients, which has become the standard model of neoadjuvant therapy for HER2-positive breast cancer.

Pre-clinical trials of pyrotinib, an irreversible inhibitor of small TKI targeting epidermal growth factor receptor (EGFR) and HER2, showed that it had a significant inhibitory effect on HER2-positive breast cancer. Clinical studies have shown that pyrotinib is safe and well-tolerated in patients with advanced breast cancer. In recent years, dual anti-HER2 targeted therapy has become a hot research topic in adjuvant therapy and neoadjuvant therapy for breast cancer. Its efficacy and safety have been verified in clinical trials, and some treatment models have been approved by clinical practice. Therefore, based on preliminary clinical studies, a multi-center, randomized, open-label, parallel-group, controlled phase III clinical trial will be conducted. In this trial, trastuzumab, docetaxel, and carboplatin will be used in combination in the control group to investigate the therapeutic effects of neoadjuvant chemotherapy with pyrotinib, trastuzumab, docetaxel, and carboplatin in combination on locally advanced HER2-positive breast cancer.

Who can participate?

Patients with locally advanced HER2-positive breast cancer.

What does the study involve?
Preoperative neoadjuvant chemotherapy will be conducted in patients with locally advanced HER-2-positive breast cancer. All included patients will receive neoadjuvant chemotherapy with trastuzumab, docetaxel, and carboplatin in combination. Patients in the trial group will also receive pyrotinib administration. There will be six 21-day sessions of chemotherapy. All patients will undergo breast-conserving surgery or mastectomy after neoadjuvant chemotherapy. The primary outcome measure, tpCR rate, will be obtained by evaluating the tumor tissue sections. The secondary outcome measures will be ORR, ECOG performance status score, routine blood test, biochemical indicators, and routine urine test.

What are the possible benefits and risks of participating?
Patients may benefit from participating in this study to alleviate their illness, but there is no guarantee or commitment that patients will benefit from this study. You and other patients participate in and cooperate with the completion of this study, which will be helpful to patients with the same disease in the future. The results may be of great significance for the treatment of more patients and the promotion of medical development in the future. This study was sponsored by investigators and the costs of hospitalization, examination and trial drugs will be borne by patients themselves or by patients' medical insurance. There will be no reward for patients participating in this study. This study does not provide transportation compensation. The drugs used in this study are routine drugs for breast cancer. The possible adverse reactions include varying degrees of diarrhea, hand-foot syndrome, skin rash, abnormal liver function, nausea, vomiting, muscle and joint pain, dyslipidemia, osteoporosis, and other adverse reactions. General tolerance is good. Nevertheless, there may be unpredictable adverse reactions in the study, but the doctor will closely observe the changes in your condition and deal with them in time to ensure your safety. Any changes in the course of the study and any recent and definite adverse reactions will be truthfully reported to you. During this study, if you have serious adverse reactions related to the drug under trial, your doctor will suspend or permanently terminate the drug under study, or reduce your original dosage.

Where is the study run from?
1. The First Hospital of China Medical University
2. Shengjing Hospital of China Medical University
3. The Fourth Affiliated Hospital of China Medical University
4. Liaoning Cancer Hospital/Institute
5. Affiliated Zhongshan Hospital of Dalian University
6. The Second Hospital of Dalian Medical University, China

When is the study starting and how long is it expected to run for?
October 2019 to March 2027

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Feng Jin, jinfeng66cn@hotmail.com

Contact information

Type(s)
Public

Contact name
Dr Feng Jin

ORCID ID
https://orcid.org/0000-0002-0325-5362

Contact details
No. 155 Nanjing North Street
Heping District
Shenyang
China
110001
+86-13998890665
jinfeng66cn@hotmail.com

Type(s)
Public

Contact name
Dr Fan Yao

ORCID ID
https://orcid.org/0000-0001-8689-0291

Contact details
No.155 Nanjingbei Street
Heping District
Shenyang
China
110001
+86-13998373748
yaofancmu@sina.com

Additional identifiers

Protocol serial number
1.0

Study information

Scientific Title
Neoadjuvant chemotherapy with pyrotinib, trastuzumab, docetaxel, and carboplatin in combination for locally advanced human epidermal growth factor receptor 2-positive breast cancer: a multicenter, randomized, open-label, parallel-group controlled phase III trial

Study objectives
Neoadjuvant therapy is one of the standard treatments for locally advanced breast cancer. Preoperative neoadjuvant therapy can reduce the size of tumors and make them more conducive to surgical excision. This effectively increases breast conservation rate and improves surgical effect. The pathologic complete response (pCR) of neoadjuvant therapy is correlated

with disease-free survival (DFS) and overall survival (OS) of early breast cancer. HER2 overexpressed breast cancer patients are not sensitive to endocrine therapy and standardized therapy. Application of anti-HER2 monoclonal antibody trastuzumab in post-operative adjuvant therapy and advanced breast cancer can improve the outcome of these patients. In clinical practice, trastuzumab combined with chemotherapy can significantly increase the pCR rate and improve the prognosis of patients. This has become the standard mode of neoadjuvant therapy for HER2-positive breast cancer.
Pyrotinib is an irreversible small-molecule tyrosine kinase inhibitor (TKI) targeting epidermal growth factor receptor (EGFR) and HER2, which was independently developed by Jiangsu Hengrui Pharmaceutical Co., Ltd., China. Pre-clinical animal experiments showed that pyrotinib has a significant inhibitory effect on HER2-positive breast cancer. Compared with macromolecule HER2-targeting trastuzumab, pyrotinib, a small-molecule inhibitor, acts differently and it also targets EGFR. This may have therapeutic effects on patients for whom trastuzumab is not effective. Compared with lapatinib, a small-molecule inhibitor targeting EGFP and HER2, pyrotinib is irreversible and can produce a better therapeutic effect at a low blood concentration. According to the clinical studies that have been completed or are underway, pyrotinib is safe and well tolerated in patients with advanced breast cancer. Although similar to other EGFR/HER2 targeted drugs, adverse reactions such as diarrhea and rash in patients treated with pyrotinib are mostly mild to moderate, predictable and clinically controllable. In recent years, the double-blockade anti-HER2 treatment of dual-targeted drugs has become a research hotspot for adjuvant therapy and neoadjuvant therapy of breast cancer. Its efficacy and safety have been verified in clinical trials, and some treatment modes have been clinically approved. There are still a large number of studies investigating the therapeutic effects of neoadjuvant therapy with TKI targeting drugs (such as lapatinib and neratinib) and other molecular targeted drugs in combination with chemotherapy on breast cancer.
Therefore, it is hypothesized that compared with conventional adjuvant chemotherapy with trastuzumab, docetaxel and carboplatin in combination, neoadjuvant chemotherapy with pyrotinib (pyrotinib maleate tablets), trastuzumab, docetaxel, and carboplatin in combination produces better therapeutic effects on locally advanced human epidermal growth factor receptor 2-positive breast cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/05/2019, Medical Ethics Committee of the First Hospital of China Medical University (No. 155 Nanjing North Street, Heping District, Shenyang, 110001, China; +86-24-83282837), ref: kelunshen(2019)149

Primary study design
Interventional

Study design
Multicenter randomized open-label parallel-group controlled phase III trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Breast cancer

Interventions
It will be performed in the First Hospital of China Medical University, Shengjing Hospital of China Medical University, The Fourth Affiliated Hospital of China Medical University, Liaoning Cancer Hospital/Institute, Affiliated Zhongshan Hospital of Dalian University, The Second Hospital of Dalian Medical University, China. A total of 532 HER2-positive breast cancer will be included in this study. Eligible subjects will be allocated to a trial group and a control group at a 1:1 ratio using the stratified block randomization.
In the trial and control group group, treatment with pyrotinib, trastuzumab, docetaxel, and carboplatin in combination and treatment with trastuzumab, docetaxel, and carboplatin in combination will be performed separately in each 21-day session of treatment. After six treatment sessions, subjects with surgical indications may undergo breast-conserving surgery or mastectomy according to applicable routine clinical practice. The primary outcome measure of this study is total pathologic complete response (tpCR). Secondary outcome measures are objective response rate (ORR), Eastern Cooperative Oncology Group (ECOG) performance status score, routine blood test, blood biochemical indicators, and routine urine test.

Both study and control groups will receive treatment with trastuzumab, docetaxel, and carboplatin in combination.
(1)Trastuzumab (Herceptin®, imported drug registration certificate No. S20110007, Shanghai Roche Pharmaceutical Co., Ltd.) will be intravenously administered on the 1st day of each treatment session. There will be four 21-day sessions of treatment (1-4 sessions of treatment). The subjects will receive 8 mg/kg trastuzumab in the first session and 6 mg/kg trastuzumab in the second to fourth sessions.
(2)Docetaxel (Aventis Pharma, license No. H20140944) will be intravenously administered once every 3 weeks at a dose of 75 mg/m2. There will be six 21-day sessions of treatment (1-6 sessions). Docetaxel will be intravenously administered on the 1st day of each session after the observation period of trastuzumab infusion.
(3)Carboplatin: Carboplatin dose (mg) = AUC (mg/mL/min) x creatinine clearance rate (mL/min) + 25], where AUC = 5.Creatinine clearance rate =[140-age (year)] x body weight (kg) x 1.23/serum creatinine (mol/L) x 0.85.
Control group: From the 1st day of the first session to the 21st day of the sixth session, 400 mg was administered once a day, 30 minutes after breakfast.
Trial group: Pyrotinib maleate tablets (national drug approval number H20180012, Jiangsu Hengrui Pharmaceutical Co., Ltd., China): From the 1st day of the first session to the 21st day of the sixth session, pyrotinib maleate tablets will be administered orally, 400 mg once a day, within 30 minutes after breakfast.
After 6 sessions of neoadjuvant therapy, subjects with surgical indications may undergo breast-conserving surgery or mastectomy according to applicable routine clinical practice.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Trastuzumab, docetaxel, carboplatin, pyrotinib maleate

Primary outcome(s)
Total pathologic complete response (tpCR) rate. Hematoxylin-eosin staining will be performed to observe the presence of residual invasive carcinoma in the surgical sections. If there is no

residual invasive carcinoma (ypT0/isypN0), it will be regarded as total pathologic complete response.
tpCR rate is the percentage of total number of patients having total pathologic complete response among total number of patients.

Key secondary outcome(s)
1. Objective response rate (ORR): It is defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) during receiving neoadjuvant therapy. ORR will be assessed according to RECIST v1.1 guideline.
2. Eastern Cooperative Oncology Group (ECOG) performance status score: It is a 5-point measure indicating a subject's general health status and treatment tolerance. Higher points indicate poor performance status. ECOG performance status will be evaluated on the 1st day of each treatment session and before surgery.
3. Routine blood test: Hemoglobin level, red blood cell, platelet count, white blood cell, and neutrophil counts will be determined before administration on the 1st day of each treatment session (or within 3 days before administration) and before surgery.
4. Biochemical indicators: blood levels of sodium, potassium, chlorine, calcium, magnesium, cholesterol, triglyceride, glucose, urea nitrogen or urea, creatinine, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, total bilirubin, and direct bilirubin will be measured before administration on the 1st day of each treatment session (or within 3 days before administration) and before surgery.
5. Routine urine test: Protein, glucose, and blood in urine will be measured before surgery. If the urine protein is tested positive (two or more ++), a 24-hour urine protein test will be performed.

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Female breast cancer patients at the age of ≥ 18 years and ≤ 65 years who received first treatment
2. ECOG (Eastern Cooperative Oncology Group) score of 0 or 1
3. Histologically confirmed invasive breast cancer with a primary tumor diameter of more than 2 cm; TNM staging T2-3, N2 or N3, M0
4. Pathologically confirmed HER2-positive breast cancer, which is defined as the immunohistochemistry score of > 10% immunoreactive cells being 3+ or in situ hybridization results showing HER2 gene amplification
5. Known state of hormone receptors and progesterone receptor is known
6. The functional level of the main organs must meet the following requirements (no blood transfusion and no use of leukocytes- and platelets-raising drugs in 2 weeks before screening): absolute neutrophil count (ANC) ≥ 1.5 × 109/L, platelet (PLT) count ≥ 90 × 109/L, hemoglobin (Hb) ≥ 90 g/L, total bilirubin (TBIL) ≤ upper limits of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN, alkaline phosphatase ≤ 2.5 x ULN, blood urea nitrate (BUN) and creatinine (Cr) < 1.5 × ULN, left ventricular ejection fractions (LVEF) > 55%, corrected QT interval by Fredericia (QTcF) < 470 ms
7. For women who are not menopausal or who have not undergone surgical sterilization, they agree to stay abstinent or use effective contraceptive methods during the whole treatment

period and for at least 7 months after the last administration during the study period
8. Volunteer to participate in the study; provision of written informed consent; good compliance and willing to cooperate during the follow-up

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Female

Key exclusion criteria
1. Stage IV (metastatic) breast cancer
2. Patients who had received antineoplastic therapy or radiotherapy for any malignant tumors, but excluding cured cervical cancer in situ, basal cell carcinoma or squamous cell carcinoma
3. Patients who are receiving anti-cancer therapy in other clinical trials, including endocrine therapy, bisphosphonate therapy or immunotherapy
4. Those who had undergone major breast cancer-free operations within 4 weeks before randomization or who had not yet fully recovered from such surgeries
5. Severe cardiac diseases or discomforts
6. Inability to swallow, intestinal obstruction or other factors affecting drug use and absorption
7. Anyone with known history of allergy to the components of study drugs; history of immunodeficiency, or other acquired or congenital immunodeficiency disorders, or history of organ transplantation
8. Female patients during pregnancy and lactation, those with fertility and providing positive baseline pregnancy test results, or those of childbearing age who are unwilling to take effective contraceptive measures throughout the trial
9. Patients with severe concomitant diseases or other complications that interfere with planned treatment or in any other case considered unsuitable by the researchers to participate in the study

Date of first enrolment
08/10/2019

Date of final enrolment
31/03/2021

Locations

Countries of recruitment
China

Study participating centre
The First Hospital of China Medical University
No. 155 Nanjing North Street
Heping District
Shenyang
China
110001

Study participating centre
Shengjing Hospital of China Medical University
No. 39 Huaxiang Road
Tiexi District
Shenyang
China
110022

Study participating centre
The Fourth Affiliated Hospital of China Medical University
No.4 Chongshan Road
Huanggu District
Shenyang
China
110032

Study participating centre
Liaoning Cancer Hospital/Institute
No.44 Xiaoheyan Road
Dadong District
Shenyang
China
110042

Study participating centre
Affiliated Zhongshan Hospital of Dalian University
No.6 Jiefang Road
Zhongshan District
Dalian
China
116001

Study participating centre
The Second Hospital of Dalian Medical University
No.467 Zhongshan Road
Shahekou District
Dalian
China
116001

Sponsor information

Organisation
The First Hospital of China Medical University

ROR
https://ror.org/04wjghj95

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices), will be available immediately following publication, with no end date. Anonymized trial data will be available indefinitely at www.figshare.com.

IPD sharing plan summary
Available on request