Appendix 2

Supplement to: Fei Ma, et al. Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive metastatic breast cancer (PHILA): a randomized, double-blind, multicenter, phase 3 trial

The appendix contains the following items:

1. Original protocol (V1.0)
2. Final protocol (V5.0)
3. Protocol amendments
4. Statistical analysis plan

A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF PYROTINIB MALEATE TABLETS COMBINED WITH TRASTUZUMAB AND DOCETAXEL VS. PLACEBO COMBINED WITH TRASTUZUMAB AND DOCETAXEL IN HER2-POSITIVE RECURRENT/METASTATIC BREAST CANCER

Protocol No.:	HR-BLTN-III-MBC-C
Study Phase:	III
Compound Code:	SHR-1258
Compound Name:	Pyrotinib maleate tablets
Medical Director:	Xiaoyu Zhu
Leading Center of Clinical Study:	Cancer Hospital, Chinese Academy of Medical Sciences
Principal Investigator:	Prof. Binghe Xu
Version No.:	1.0
Version Date:	21 Dec., 2018

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.
No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu 222047, China

VERSION HISTORY/REVISION HISTORY

Document	Version Date	Amendment Rationale and Summary of Changes
Initial Version	21 Dec., 2018	Not applicable

Sponsor's Protocol Signature Page

I have read and confirmed this clinical study protocol (protocol no.: HR-BLTN-III-MBC-C; version no.: 1.0; version date: 21 Dec., 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Xiaoyu Zhu		
Study Director (print)	Study Director (signature)	Signature Date (DD/MM/YYYY)

Statistical Institution's Signature Page

I have read and confirmed this protocol (protocol no.: HR-BLTN-III-MBC-C; version no.: 1.0; version date: 21 Dec., 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Statistical Institution: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Ziqiang Nie		
Statistical Director (print)	Statistical Director (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Protocol Signature Page (Leading Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational drug; and I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial or economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Site: Cancer Hospital, Chinese Academy of Medical Sciences

Binghe Xu		
Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Protocol Signature Page (Participating Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational drug; and I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial or economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Site: _____

Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

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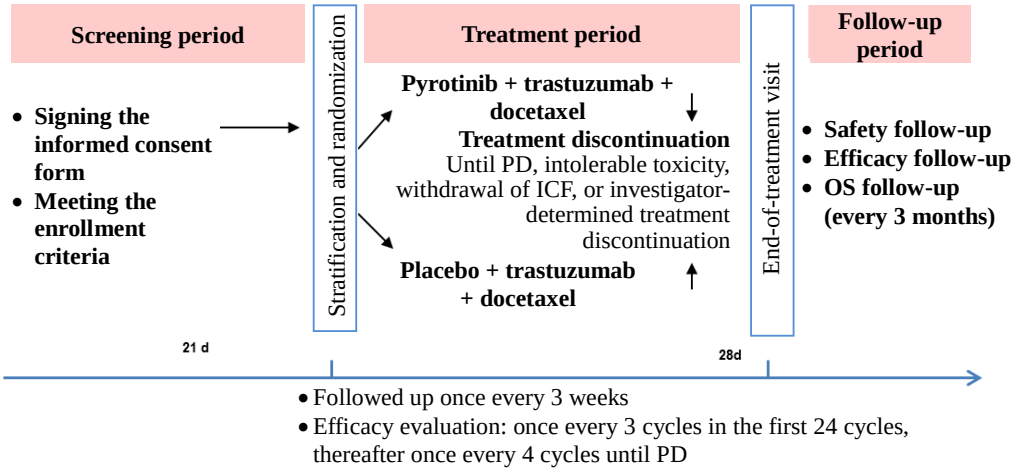
PROTOCOL SYNOPSIS

Study Title	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer
Protocol No.	HR-BLTN-III-MBC-C
Version No.	1.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigator	Prof. Binghe Xu
Participating Study Centers	Approximately 25 study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences
Study Objectives	**Primary objective** • To evaluate the progression-free survival (PFS) of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer **Secondary objectives** • To evaluate the safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer • To compare the efficacy between two groups in overall survival (OS), objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR)
Study Endpoints	**Primary endpoint:** • PFS (investigator-assessed) **Secondary endpoints** • PFS (IRC-assessed) • OS • ORR • DoR • CBR • Safety endpoints: incidence and severity of adverse events (AEs) and serious adverse events (SAEs), according to NCI-CTCAE v4.03; changes in the following parameters from baseline: ECOG PS, vital signs, physical examination, laboratory tests (hematology, urinalysis, routine stool test, and blood biochemistry), 12-lead electrocardiogram (ECG), and echocardiography.

Study Population	Female patients with HER2-positive recurrent/metastatic breast cancer who have not received systematic anti-tumor therapy for their metastatic diseases
Study Design	This is a phase III, randomized, double-blind, placebo-controlled, multicenter clinical study. This study plans to enroll a total of 590 subjects. Eligible subjects will be randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). Randomization is stratified by the following factors: • Prior neoadjuvant/adjuvant therapy: with or without trastuzumab • ER/PR status: positive or negative Subjects will receive study treatment within 48 h after randomization in 21-day cycles until investigator-assessed progressive disease (PD), intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The tumor assessments will be performed by the investigators and independent review committee according to RECIST v1.1. The primary PFS analysis is based on the assessment results by the investigators. For subjects who discontinue the study treatment, the safety visit should occur on D28 ± 7 d after the last administration of study drug, then the subjects should start the survival follow-up period until death or study termination (whichever occurs first). For subjects who discontinue the study treatment due to reasons other than PD or death, scheduled tumor assessments need to be collected until PD, start of a new anti-tumor treatment, or death (whichever occurs first). This study plans to perform 1 safety assessment and 1 interim analysis by Independent Data Monitoring Committee (IDMC). After the data review, the IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study. An overview of the study design is shown below: 

<table>
<tr><td>Study Drugs</td><td>Pyrotinib maleate tablets (hereinafter referred to as "pyrotinib")
Dummy of pyrotinib maleate tablets (hereinafter referred to as "placebo")
Trastuzumab for injection (Herceptin®, hereinafter referred to as "trastuzumab")
Docetaxel injection (Ai Su®, hereinafter referred to as "docetaxel")</td></tr>
<tr><td>Method of Administration</td><td>Subjects will receive study treatment continuously in 21-day cycles until investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation.
The specific methods of administration are as follows:
<u>Pyrotinib/Placebo</u>
Oral administration (PO), 400 mg/day, once a day. Dose modification and delay may be carried out according to the protocol (Section 6.1.6) if an intolerable adverse event occurs during study drug administration. If pyrotinib/placebo is interrupted for more than 1 cycle due to intolerable toxicity, all study treatments of the subjects will be discontinued.
<u>Trastuzumab</u>
Intravenous infusion (IV), 8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose in subsequent cycles. The dose of trastuzumab dose not need to be recalculated except for a change of > 10% in body weight. The drug is given on Day 1 of each cycle (D1) via intravenous injection, once every 3 weeks.
Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. No dose reduction will be allowed. If the subject misses a dose of trastuzumab for one cycle (e.g., the time interval between 2 sequential administrations is 6 weeks or more apart), the re-loading dose of 8 mg/kg will be administered, and the docetaxel will also be administered on the same day. Maintenance trastuzumab doses of 6 mg/kg will be given every 3 weeks.
<u>Docetaxel</u>
IV, at a starting dose of 75 mg/m^2. D1, once every 3 weeks. The dose of docetaxel does not need to be recalculated if the body weight increases/decreases by < 10% from baseline.
Dose modification and delay may be carried out according to the protocol (Section 6.1.6) if an intolerable adverse event occurs during study drug administration. If the administration of docetaxel must be delayed by one or more days, the administration of trastuzumab also needs to be delayed for the same period of time.
<table>
<tr><td rowspan="3">Treatment Group</td><td>Pyrotinib</td><td>400 mg, once daily, consecutive administration</td></tr>
<tr><td>Trastuzumab</td><td>8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles</td></tr>
<tr><td>Docetaxel</td><td>75 mg/m^2, D1</td></tr>
<tr><td rowspan="3">Control Group</td><td>Placebo</td><td>400 mg, once daily, consecutive administration</td></tr>
<tr><td>Trastuzumab</td><td>8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles</td></tr>
<tr><td>Docetaxel</td><td>75 mg/m^2, D1</td></tr>
</table>
</td></tr>
</table>

Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for study entry: *1.* Females aged ≥ 18 and ≤ 75 years old. *2.* Histologically confirmed HER2-positive invasive breast cancer, while meeting the following conditions: • HER2 positive is defined as 3+ by immunohistochemistry (IHC) or an *in situ* hybridization (ISH) result of HER2 gene amplification. A HER2-positive breast cancer confirmed by the pathology department of the participating study center. • Tumor staging: recurrent or metastatic breast cancer; locally recurrent disease must not be amenable to resection with curative intent. *3.* Have at least one measurable lesion according to RECIST v1.1. *4.* ECOG PS: 0-1. *5.* The functional levels of major organs must meet the following requirements (no blood transfusion or treatment with leukogenic and thrombopoietin drugs within 2 weeks prior to screening): • Absolute neutrophil count (ANC) ≥ 1.5×10^9/L; • Platelet count (PLT) ≥ 90×10^9/L; • Hemoglobin (Hb) ≥ 90 g/L; • Total bilirubin (TBIL) ≤ upper limit of normal (ULN); for patients with Gilbert's syndrome, TBIL ≤ 2 × ULN; • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN; for patients with liver metastases, ALT and AST ≤ 5 × ULN; • Alkaline phosphatase ≤ 2.5 × ULN; • Urea/urea nitrogen (BUN) and creatinine (Cr) ≤ 1.5 × ULN; • Left ventricular ejection fraction (LVEF) ≥ 50%; • Fridericia-corrected QT interval (QTcF) < 470 msec. *6.* Participate in the study voluntarily, sign the informed consent form, have good compliance, and willing to cooperate with follow-up visits.
Exclusion Criteria	Subjects meeting any of the following exclusion criteria are not eligible to participate in this study: *1.* Have received any systemic anti-tumor therapy for the recurrent/metastatic diseases, including any anti-EGFR or anti-HER2 agents, systemic chemotherapy, immunotherapy, and more than one prior hormonal regimen, as well as other anti-tumor therapies that shall be excluded as judged by the investigator. *2.* History of anti-HER tyrosine kinase inhibitor (TKI) or macromolecular antibody for breast cancer in any treatment setting, except trastuzumab used in the (neo) adjuvant therapy.

3. History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (except endocrine therapy) to metastatic diagnosis of < 12 months.
4. Current Grade ≥ 3 peripheral neuropathy as per CTCAE v4.03.
5. Not suitable for systemic chemotherapy as judged by the investigator.
6. Have received endocrine therapy within 7 days prior to randomization.
7. History of other malignant tumors within the past 5 years, except for cured cervical carcinoma *in situ*, skin basal cell carcinoma or squamous cell carcinoma (patients with other malignant tumors that occurred more than 5 years before the date of randomization are allowed to be enrolled only if they have been cured by surgery).
8. Current brain metastases.
9. Subjects with bone or skin as the only target lesion.
10. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin or doxorubicin liposome > 360 mg/m^2
    - Epirubicin > 720 mg/m^2
    - Mitoxantrone > 120 mg/m^2, idarubicin > 90 mg/m^2
    - Others (for example, in case of other anthracyclines or multiple anthracyclines, the cumulative dose > the dose equivalent to 360 mg/m^2 of doxorubicin)
11. Have undergone major surgery or apparent trauma within 4 weeks prior to randomization, or expected to undergo a major surgery during the course of study treatment.
12. With severe cardiovascular disease or discomfort, including but not limited to the following:
    - Medical history of cardiac failure or systolic dysfunction (LVEF < 50%)
    - Angina or arrhythmia that requires treatment or of high risk (such as type 2 second-degree atrioventricular block or third-degree atrioventricular block, ventricular tachycardia)
    - Clinically significant valvular heart disease
    - Transmural myocardial infarction as indicated by ECG
    - Poorly controlled hypertension (systolic pressure > 150 mmHg and/or diastolic pressure > 100 mmHg)
13. With dysphagia, chronic diarrhea, intestinal obstruction, or other factors affecting drug intake and absorption.
14. With known allergies to the components of the study drugs.
15. History of immunodeficiency, including HIV infection or other acquired and congenital immunodeficiencies, or organ transplantation.
16. Presence of third spacing (such as hydrothorax and ascites) that cannot be controlled by drainage or other methods.
17. Pregnant or lactating female subjects, or subjects of childbearing potential who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose.

	18. Presence of severe concurrent disease or other concurrent diseases that may interfere with planned treatment, or any other conditions rendering the subjects unsuitable for participating in this study, such as active hepatitis B and lung infection requiring treatment.
Determination of Sample Size	In this study, PFS is used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to evaluate the efficacy of the drugs and to determine whether to terminate or continue the study. The assumptions for sample size calculation are as follows: • Enrollment duration = 24 months, minimum follow-up = 18 months (overall duration of 42 months) • Randomization in a 1:1 ratio • Overall alpha = 0.025 (one-sided) • The power of test is 80% • Hazard ratio (HR) = 0.76 (median PFS is 12.5 months in the control group and 16.5 months in the treatment group) • An interim analysis will be performed when 50% of PFS events (205 events) are collected to evaluate the efficacy of the drugs, and to decide whether to terminate or continue the study. Based on the above parameters, at least 410 PFS events should be collected according to the log rank test for PFS comparison between two groups and the Lan-DeMets α spending function (EAST 6.4.1) constrained by the O'Brien & Fleming boundaries. Assuming that the PFS dropout rate is 15% for 24 months, approximately 590 subjects should be enrolled.
Data Analysis/Statistical Methods	This study plans to perform 2 IDMC meetings (including 1 safety assessment and 1 interim analysis) and 1 final analysis. One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the blinded safety evaluation. The interim analysis will be carried out when 50% of PFS events (205 events) are collected to evaluate the efficacy of the drugs and to decide whether to terminate or continue the study. The final analysis will be performed when the number of PFS events reaches 410. The time-to-event variables (such as PFS, OS, and DoR) will be analyzed using the Kaplan-Meier (KM) method, the survival functions of the two groups will be estimated, and the survival curves will be plotted. In addition, the Cox regression model will be used to estimate the hazard ratio between the two groups and its 95% confidence interval (95% CI). For binary variables, the Cochran-Mantel-Haenszel (CMH)/Chi-square/Non-parametric test (if applicable) methods can be used to test the inter-group difference and compute its 95% CI. The safety data will be summarized using descriptive statistics.
Interim Analysis	In the study, one interim analysis will be performed for the primary efficacy endpoint. The main objectives of interim analysis include but are not limited to: 1. Early termination of the study due to superiority; 2. Continuation of the study as planned;

The interim analysis will be conducted when 50% of PFS events (205 events) are collected. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:

Time Point	Number of PFS Events	Boundary Z-Value (Corresponding HR)	One-Sided Nominal Significance Level
Interim (1st)	205 (50%)	-2.963 (HR = 0.66)	0.002
Final	410	-1.969 (HR = 0.82)	0.024

Note: HR = Hazard ratio; PFS = Progression-free survival;

The interim analysis will be completed by independent statisticians and their programming team. The results of interim analysis will be reviewed by the Independent Data Monitoring Committee (IDMC), which will recommend whether to continue the study based on the results.

Study Period

Anticipated enrollment of the first subject: Mar. 2019

Anticipated enrollment of the last subject: Mar. 2021

Anticipated study completion: Jul. 2024

SCHEDULE OF ACTIVITIES

Item \ Time	Screening Period		Treatment Period	End-of-Treatment Visit	Follow-up Period		
					Safety	Efficacy[20]	Survival[21]
	D-21 to D-1	D-7 to D-1	D1 in each cycle		28 days after the last dose		
			± 3 d		7 d	± 7 d	± 7 d
Visit	**Screening period**		**CnD1**	**EOT**	**Safety visit**	**Efficacy follow-up**	**Survival follow-up**
Signing of Informed Consent Form[1]	×						
Demographics[2]	×						
Complete Medical History[3]	×						
ECOG PS	×		×	×	×		
Vital Signs[4]	×		×	×	×		
Physical Examination[5]	×		×	×	×		
Hematology[6]		×	×	×	As needed		
Urinalysis[7]		×	Every 4 cycles	×	As needed		
Routine Stool Test[8]		×	Every 4 cycles	×	As needed		
Blood Biochemistry[9]		×	×	×	As needed		
Infectious Disease Screening[10]	×						
Pregnancy Test[11]		×	When necessary	×	As needed		
12-Lead ECG[12]		×	×	×	As needed		
Echocardiography[13]	×		Every 4 cycles	×	As needed		
Tumor Assessment[14]	×		Once every 3 cycles in the first 24 cycles, thereafter once every 4 cycles until PD				
Bone Scan[15]	×		When necessary				
Review of Inclusion and Exclusion Criteria	×						

Item \ Time	Screening Period		Treatment Period	End-of-Treatment Visit	Follow-up Period		
					Safety	Efficacy[20]	Survival[21]
	D-21 to D-1	D-7 to D-1	D1 in each cycle		28 days after the last dose		
			± 3 d		7 d	± 7 d	± 7 d
Randomization	×						
Pyrotinib[16]			Once daily				
Trastuzumab[16]			D1 in each cycle				
Docetaxel[16]			D1 in each cycle				
Subject Diary Card			×	×			
Drug Return			×	×			
Prior/Concomitant Treatment[17]	×						
Adverse Events[18]	×						
Time of PD/Death						×	×
Subsequent Anti-Tumor Treatment[19]				×	×	×	×

Note: The following examinations should be performed according to the time window specified in the Schedule of Activities. In the event of statutory holidays, the examinations may be performed earlier and the reason should be documented. The investigator may add test items or increase the frequency of visits depending on the subjects' clinical conditions.

1. Informed consent form: may not be signed within 21 days prior to randomization, but must be signed prior to any study procedure.
2. Demographics (name initials, gender, ethnicity, marital status, date of birth, height, weight, and body surface area and body mass index calculated accordingly).
3. Complete medical history: including prior medical and treatment history (clinical/histological diagnosis, time of diagnosis, clinical/pathological staging, HER2/ER/PR status; surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy, time of progression, evidence for progression; LVEF before, during, and after administration of trastuzumab must be collected if trastuzumab is used as neoadjuvant/adjuvant therapy; anti-tumor treatments for recurrent/metastatic breast cancer, such as surgery and endocrine therapy), history of smoking and drinking, history of drug allergies (drug name and symptoms), concurrent diseases and concomitant treatments (disease name, name of concomitant medication, dose, and method of administration).
4. Vital signs: including body temperature, blood pressure, respiratory rate, and pulse.

5. Physical examination: including general condition, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental state; height is only measured at baseline, and weight is measured during each physical examination.
6. Hematology: including absolute counts of WBC, ANC, LC, RBC, Hb, and PLT; for the first 3 cycles of chemotherapy, additional hematology tests should be performed on D8 ± 1 day of each cycle.
7. Urinalysis: including urine protein, urine glucose, and urine occult blood; in case of a urine protein ≥ ++, a 24-h urine protein quantitation should be tested.
8. Routine stool test: including fecal occult blood.
9. Blood biochemistry: including glucose, TP, A/G, ALT, AST, ALP, γ-GT, ALB, TBIL, DBIL, IBIL, TG, CHOL, UA, BUN, Cr, K^+, Na^+, Mg^{2+}, Cl^-, Ca^{2+}, and P; the investigator may perform myocardial zymography as needed based on subjects' conditions.
10. Infectious disease screening: including hepatitis B test (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HIV antibodies, and HCV antibodies.
11. Pregnancy test: Pregnancy must be ruled out in female subjects of childbearing potential by blood HCG test during the screening period; urine pregnancy test may be used subsequently, but a positive urine pregnancy test result must be confirmed by a blood HCG test.
12. 12-Lead ECG: The heart rate, QT, QTc, and P-R interval should be monitored. If QTcF interval increases by > 30 msec from baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG measurements are required (at least 10 min apart).
13. Echocardiography: The results obtained within 21 days prior to randomization (including qualified echocardiography completed before signing the ICF) can be used. If a subject shows symptoms such as precordial pain and palpitations during the study, additional examinations can be carried out.
14. Tumor assessments: Multidetector spiral CT or contrast-enhanced MRI of the brain, chest, and abdomen should be at least performed during the screening period. Multidetector spiral CT or contrast-enhanced MRI of the chest and abdomen should at least be performed at subsequent visits. The investigator may decide to perform brain imaging evaluation depending on subjects' clinical symptoms. The investigator may add other scan sites such as the neck and pelvic cavity in the tumor assessments at baseline or later based on clinical indications. The time window for tumor assessments is ± 7 days. During the screening period, reports issued within 21 days prior to randomization (including qualified tumor assessments completed before signing the ICF) should be used. The tumor assessment schedule during the administration period is determined after the start of treatment and is not changed regardless of dose interruptions due to toxicity. Tumor assessments are continued until investigator-assessed PD. The tumor assessments should be continued whenever possible for those who withdraw from study due to intolerable toxicities until PD, start of a new anti-tumor treatment, or lost to follow-up.
15. Bone scan: A bone scan is required for subjects who have not undergone a bone scan within 21 days prior to randomization. Positive bone lesions should be reviewed by CT/MRI examinations (or X-ray), and metastatic bone lesions should be followed up subsequently as per the tumor assessment schedule with the same imaging method for baseline. During treatment period and follow-up period, the investigator may decide to perform bone scan or CT/MRI of bones depending on subjects' clinical symptoms.
16. Dosing regimen:

- Pyrotinib/placebo: 400 mg orally once a day within 30 min after breakfast in 21-day cycles.
- Trastuzumab: 8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles. Trastuzumab is administered once every 3 weeks. The dose of trastuzumab does not need to be recalculated except for a change of > 10% in body weight.

- Docetaxel (75 mg/m^2, D1, the dose of docetaxel does not need to be recalculated if the body weight increases/decreases by < 10% from baseline) is administered once every 3 weeks.

  Subjects will continue the treatment until PD, intolerable toxicity, withdrawal of ICF, or investigator-determined treatment discontinuation. Refer to Sections 6.1.5 and 6.1.6 for the detailed method of administration and dose modifications.

17. Prior/concomitant treatment: Concomitant medications within 28 days prior to randomization and during the study should be documented. Once the study treatment is permanently discontinued, only concomitant medications or treatments for new or unresolved AEs related to study treatment should be documented. Concomitant medications or treatments for cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has resolved or disappeared, or until 12 months after the last dose.
18. Observation and recording of AEs: AEs should be monitored starting from the signing of the ICF until 28 days after the last study drug administration [cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has resolved or disappeared, or until 12 months after the last dose]. AEs, concomitant medications/treatments, and unscheduled examinations should be documented in detail.
19. Subsequent anti-tumor treatment: Other anti-tumor treatments from the date of discontinuation of study treatment to the end of survival follow-up should be documented. Only anti-tumor treatments should be recorded for the survival follow-up, and concomitant medications for other diseases may not be recorded.
20. Efficacy follow-up: Subjects who discontinue study treatment for reasons other than PD and death should continue to receive efficacy follow-ups based on the tumor assessment schedule specified in the protocol until PD, start of a new anti-tumor treatment, or death (whichever occurs first); The follow-up time, tumor assessment results, and other anti-tumor treatments should be documented.
21. Survival follow-up (collection of OS data): Subjects will continue to receive survival follow-up after completing the end-of-treatment visit. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), starting from the day of completion of the end-of-treatment visit, until death, lost to follow-up, or completion of OS data collection (whichever occurs first). Data from each survival follow-up should be documented and entered into the appropriate eCRF.

ABBREVIATIONS

Abbreviations	Full Name
12-Lead ECG	12-Lead electrocardiogram
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CK	Creatine kinase
CK-MB	Creatine kinase-MB
Cl^-	Blood chlorine
Cr	Creatinine
CRF	Case report form
D	Day
EC	Ethics committee
GCP	Good Clinical Practice
GLU	Blood glucose
GLU-U	Uglu urine glucose
h	Hour
Hb	Hemoglobin
HDL-C	High-density lipoproteincholesterol
IB	Investigator's brochure
K^+	Serum potassium
KET	Urine acetone bodies
kg	Kilogram
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LYMPH	Lymphocyte
mg	Milligram
min	Minimum
mL	Milliliter
mm	Millimeter
Na^+	Plasma sodium
NEUT	Neutrophil
PLT	Blood platelet
PRO	Protein in urine
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical analysis plan
T-BIL	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
UA	Uric acid
UBIL	Urine bilirubin
URBC	Urine red blood cell
WBC	White blood cell count

1. KEY FUNCTIONAL ROLES

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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

2.1.1. Overview of breast cancer and HER2-targeted therapy

Breast cancer is one of the most common malignancies in women and its incidence is increasing year by year. It has been estimated that in 2012, approximately 1.67 million cases of breast cancer were newly diagnosed worldwide. The morbidity and mortality of breast cancer vary worldwide depending on the region. The incidence of breast cancer is higher in developed regions (73.4/100,000) than in less developed regions (31.3/100,000). The mortality of breast cancer is close between developed regions (14.9/100,000) and less developed regions (11.5/100,000)[1]. This is likely because the early screening, diagnosis, and treatment system in developed regions are more complete, and more new drugs are commercially available. In China, the prevalence of breast cancer is about 37.86/100000 and ranks the first among all cancers in women[2], and the onset age of breast cancer in China was younger than that in Western countries.

In the 1980s, scientists discovered that HER2 overexpression is directly related to the aggressive growth and poor prognosis of tumor[3]. About 10%-34% of subjects with invasive breast cancer have overexpression of human epidermal growth factor receptor 2 (HER2, also known as erbB2, neu, and p185HER2) or amplification of HER2 gene[4]. So far, no ligand has been found to bind to the HER2 receptor. The HER2 molecule mainly forms heterodimers with other receptors of the epidermal growth factor receptor (EGFR) family, further activating MAPK, JAK, PI3K, STAT3, and other pathways to promote the occurrence and progression of cancers. Normal epithelial cells have low levels of HER2 expression. The HER2 gene is amplified/overexpressed in over 30% of human cancers, including breast cancer, gastric cancer, and lung cancer. HER2 molecule is an independent factor for the poor prognosis of breast cancer. With the standardization of HER2 amplification testing, targeted therapy for HER2 positive subjects has become a focus of basic and clinical research[5]. At present, several anti-HER2 drugs have been approved worldwide (see Table 1).

Table 1. Existing anti-HER2 drugs on the market

	Drug Name	Company	Marketed in the U.S.	Indication	Marketed in China
Macromolecular Drugs	Trastuzumab -	Roche -	1998 Herceptin	HER2+ breast cancer; metastatic HER2+ gastric cancer and gastroesophageal junction adenocarcinoma	2002 Herceptin
	Pertuzumab -	Roche -	2012 Perjeta	In combination with trastuzumab and docetaxel: for the treatment of advanced HER2+ (metastatic) breast cancer; used as preoperative neoadjuvant therapy for early disease	——
Antibody-Drug Conjugate (ADC)	T-DM1	Roche -	2013 Kadcyla	Monotherapy: for patients with HER2+ metastatic breast cancer who previously have received trastuzumab or taxane, separately or in combination	——
First-Generation Small Molecule Inhibitor	Lapatinib -	GlaxoSmithKline -	2007 Tykerb	In combination with capecitabine: for the treatment of patients with HER2+ metastatic breast cancer who previously have received trastuzumab or taxane, separately or in combination; In combination with letrozole: for the treatment of postmenopausal women with ER+, HER2+ metastatic breast cancer	2013 Tykerb
Second-Generation Small Molecule Inhibitor	Neratinib (HKI-272) -	Puma	2017 Nerlynx	Adjuvant therapy for breast cancer and systemic treatment for advanced disease	——

Approximately 20% to 30% of breast cancer subjects in China have HER2 amplification/ overexpression. About 42.6% (1342/3149) of the subjects were tested positive for HER2 (2+/3+) by immunohistochemistry (IHC) and 46.9% (1477/3149) were tested positive by fluorescence *in situ* hybridization (FISH) [6]. Currently, in China, all HER2-targeted drugs are imported, including trastuzumab and lapatinib. According to the 2016 Expert Consensus on Clinical Diagnosis and Treatment of Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer[7], the National Comprehensive Cancer Network (NCCN) guidelines recommend pertuzumab and trastuzumab combined with taxanes as the preferred first-line regimen for the treatment of HER2-positive advanced breast cancer. However, pertuzumab has not been approved for marketing in China, so chemotherapy based on trastuzumab combined with taxanes is preferably chosen as the first-line treatment for patients with HER2-positive metastatic breast cancer in China.

2.1.2. Main information of pyrotinib

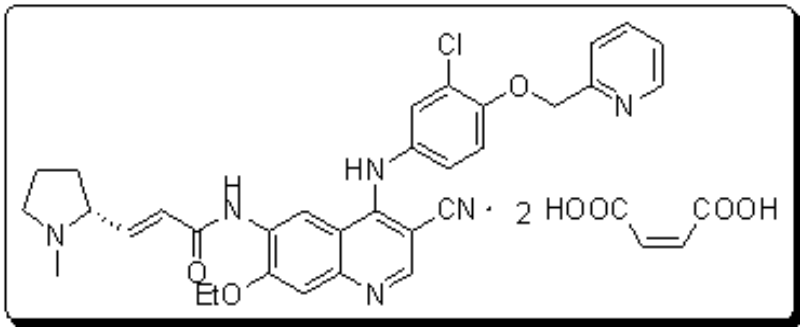
2.1.2.1. Drug name and molecular structure

Generic name: Pyrotinib Maleate Tablets

R&D code: SHR1258

Chemical name (IUPAC): (R,E)-N-(4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino-3-cyano-7-ethoxyquinolin-6-yl)-3-
(1-methylpyrrolidin-2-yl)) acrylamide, maleate (1:2)

CAS No.: 1397922-61-0



Molecular formula: $C_{32}H_{31}ClN_6O_3 \cdot 2C_4H_4O_4$

Molecular weight: 815.22

Dosage form and strength:

This product is a film-coated tablet. A tablet of the 40 mg, 60 mg, 200 mg, 160 mg, and 80 mg strengths contains 55.9 mg, 83.9 mg, 279.6 mg, 223.7 mg, and 111.8 mg of pyrotinib maleate, respectively, equivalent to 40 mg, 60 mg, 200 mg, 160 mg, and 80 mg of pyrotinib, respectively.

2.1.2.2. Pharmacological type and mechanism of action of pyrotinib

Pyrotinib is an irreversible dual-receptor tyrosine kinase inhibitor (TKI) targeting mainly epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). *In vitro* and *in vivo* studies of pyrotinib have been conducted to assess the mechanism of action as well as the effect on tumor growth inhibition and tyrosine phosphorylation. Studies investigating the effects of pyrotinib on several human tumor cell lines were performed in both cell culture and mice xenograft models.

Pyrotinib significantly inhibited EGFR1 and EGFR2/HER2 at the molecular level, with median half-maximal inhibitory concentrations (IC_{50}) of 5.6 nM and 8.1 nM, respectively, which were comparable to the IC_{50} values of the positive control neratinib. It was observed that pyrotinib slightly inhibited the activity of the SRC proto-oncogene non-receptor tyrosine kinase (c-Src), with an IC_{50} of 790.3 nM, which was comparable to that of the positive control. Pyrotinib showed no significant inhibitory effect on the following kinases: KIT proto-oncogene receptor tyrosine kinase (c-Kit), kinase insert domain receptor (KDR), MET proto-oncogene receptor tyrosine kinase (c-Met), and beta platelet-derived growth factor receptor (PDGFRβ), suggesting that pyrotinib is a receptor tyrosine kinase inhibitor that targets mainly EGFR and HER2.

Growth inhibition of pyrotinib on tumor cells was evaluated in HER2 over-expression cell lines, EGFR over-expression cell lines, and HER2 and EGFR low-expression cell lines. The results showed that pyrotinib significantly inhibited the proliferation of HER2 over-expression cell lines, and it also significantly inhibited the proliferation of EGFR over-expression cell lines. As expected, pyrotinib showed no significant inhibitory effect on the proliferation of cells with low HER2 and EGFR expression.

In EGFR-overexpressing A431 cells, pyrotinib significantly inhibited the phosphorylation of EGFR receptor and its downstream signals ERK1/2 and AKT serine/threonine kinase (Akt), with comparable potency to that of neratinib. In HER2-overexpressing BT-474 cells, pyrotinib significantly inhibited the activation of HER2 and its downstream signals ERK1/2 and Akt, with comparable inhibitory potency to that of neratinib. Furthermore, the inhibitory effect of pyrotinib on HER2 was irreversible. In c-Kit-overexpressing Mo7e cells and PDGFRβ-overexpressing NIH-3T3 cells, pyrotinib showed no significant inhibitory effect on the phosphorylation of c-Kit and PDGFR kinases stimulated by SCF-1 and $PDGF_{BB}$, respectively, while the positive control sunitinib significantly inhibited the phosphorylation of these kinases.

The *in vivo* anti-tumor effects of pyrotinib and HKI-272 (neratinib) in cell lines with HER2 overexpression such as BT-474 (human breast cancer), SK-OV-3 (human ovarian cancer), Calu-3 (human non-small cell lung cancer), as well as human epidermoid carcinoma A431 cell line with high expression of EGFR were compared in nude mice xenografts. The results showed that pyrotinib significantly inhibited the growth of HER2-overexpressing tumor models, such as SK-OV-3, Calu-3, and BT-474. The tumor growth inhibition was significant and dose-dependent, and resulted in tumor size shrinkage. The overall efficacy was comparable to or superior to that of neratinib without increased toxicity. When it was administered at an effective dose comparable to the models with high expression of HER2, pyrotinib showed no significant effect on A431 of EGFR overexpression model. The above results suggested that pyrotinib is a small-molecule tyrosine kinase inhibitor that primarily targets HER2.

2.1.2.3. Safety pharmacology

Safety pharmacology studies were conducted to evaluate the effects of pyrotinib on locomotor activity and general behaviors of mice and on the cardiovascular and respiratory systems of anesthetized dogs.

Single dose intragastric administration of pyrotinib was given to mice at the dose levels of 20, 60 and 200 mg/kg. Within 24 hours, there were no changes in appearance, posture and gait, salivation and muscle trembling in each dose group. The mice of all dose groups had normal food and water intake, and no other abnormal reactions. No noticeable changes in locomotor activity were observed in mice. These results suggested that pyrotinib had no effect on the general behavior of the mice and little or no effect on locomotor activity.

Single dose intraduodenal administration of pyrotinib at dose levels of 5, 15 and 50 mg/kg to anesthetized beagle dogs produced no arrhythmia when measured at up to 240 minutes after administration. No change in PR, QRS, and corrected QT interval (QTc) on ECG was observed in the animals of all dose groups during the 240 min observation period after administration, nor in systolic and diastolic blood pressure and mean arterial pressure. The heart rhythm of the anesthetized dog was normal. These results suggested that pyrotinib at doses of 50 mg/kg or lower had no adverse effects on blood pressure, heart rate, heart rhythm, or ECG, nor on respiratory rate or amplitude (measured 240 min after administration) in anesthetized dogs.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for details.

2.1.2.4. Preclinical pharmacokinetic study of pyrotinib

The pharmacokinetics (PK), absorption, distribution, metabolism, and excretion (ADME) of pyrotinib were investigated *in vitro* and in Sprague Dawley (SD) rats and beagle dogs orally and/or intravenously (IV) administered with unlabeled drugs.

Absorption:

SD rats were given pyrotinib orally (gavage) at 1.0, 3.0 and 10 mg/kg, or IV at 3.0 mg/kg. After pyrotinib was administered to the rats orally (gavage), the average time to maximum plasma concentration (T_{max}) was 4.86 h. The elimination half-life ($t_{1/2}$) of pyrotinib was 3.23 h. After intravenous administration of pyrotinib, the average plasma clearance, the volume of distribution (Vd), and the $t_{1/2}$ was 0.21 mL/h/kg, 1.35 mL/kg, and 4.42 h, respectively. After gavage administration to the rats at various doses, the logarithmic values of C_{max} and AUC_{0-t} of pyrotinib were calculated against the logarithmic dose values using linear regression. Within the dose range of 1-10 mg/kg, the increase of the C_{max} was proportional to the increase of the dose of pyrotinib, while the increase of AUC_{0-t} was slightly higher than the increase of the dose.

Pyrotinib was given to beagle dogs orally (gavage) at 0.5, 1.5, and 5 mg/kg or IV at 1.5 mg/kg. Pyrotinib was quickly absorbed in beagle dogs after gavage administration. The average time to maximum plasma concentration was 1.5 h, and the plasma $t_{1/2}$ was 2.45 h for gavage administration. For IV administration, the average plasma clearance, apparent Vd, and plasma $t_{1/2}$ of pyrotinib were 2.57 L/h/kg, 10.7 L/kg, and 2.99 h, respectively. The logarithmic values of C_{max} and AUC_{0-t} against the logarithmic value of pyrotinib oral doses were calculated using linear regression. Within the dose range of 0.5-5.0 mg/kg, the C_{max} of pyrotinib was proportional to the increase of the dose, while the increase of $AUC_{0-\infty}$ was slightly higher than the increase of the dose.

Distribution:

In this study, the plasma protein binding rates of pyrotinib in human, rat, dog, monkey, and mouse plasma proteins at 10, 100, and 4000 ng/mL dose levels were investigated using equilibrium dialysis assay. Pyrotinib showed no species differences in plasma protein binding rate, no significant differences at various concentration levels, and its plasma protein binding rate was not concentration-dependent.

The distribution of pyrotinib in major tissues and plasma of rats was evaluated at 1, 4, and 8 h after oral (gavage) administration of pyrotinib to rats at 3.0 mg/kg. Pyrotinib mainly resided in the lungs, spleen, fat, and gastrointestinal (GI) tract and other tissues. Except in stomach, small intestine, spleen, fat, and lungs, the concentrations of pyrotinib in other tissues were all lower than the that in plasma. The time to maximum concentration of pyrotinib in tissues was the same as that in the plasma (4 h). The concentrations of pyrotinib in most of the tissues were about half of the maximum concentration at 8 h after administration. The concentrations of pyrotinib in brain tissues and cerebrospinal fluid were measurable and were much lower when compared to other tissues.

Metabolism:

The *in vitro* metabolic stability of pyrotinib in the liver microsomes from mice, rats, dogs, monkeys, and humans was determined using liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS). After 60-min incubation, the contents of pyrotinib in the liver microsome incubation systems of mice, rats, dogs, monkeys, and humans were 10.79%, 19.34%, 22.0%, 0.05%, and 2.09% of the initial dose, respectively. Pyrotinib was stable in human liver microsome 450 (CYP450) isoenzymes CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP4A11, with less than 2% degradation of the parent drug. Pyrotinib had no obvious inhibitory effect on cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (IC_{50} > 25 μM) but had a relatively weak inhibitory effect on CYP2C19 (IC_{50} =

18.52 μM). Pyrotinib at final concentrations of 1 μM and 10 μM was incubated with human primary hepatocytes for two days, respectively. The results showed that pyrotinib did not induce CYP1A2 and CYP3A4.

Excretion:

After a single oral dose of pyrotinib at 3.0 mg/kg in SD rats, the potential metabolites in plasma, urine, feces, and bile samples were detected using ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS). Of the seven metabolites detected in the rat plasma, the peak areas of extracted ion chromatograms of individual metabolites in plasma were less than 10% of that of the parent compound. Of the seven metabolites detected in the rat feces, the peak area of the major metabolite was 11.6% of that of the parent compound, while the corresponding results for the remaining 6 metabolites were less than 8.0%. Five metabolites were detected in rat urine and four in rat bile. In terms of the amount and relative ratios of metabolites, no significant gender difference in the *in vivo* metabolism of pyrotinib in rats was observed. The excretion amount of the parent compound in fecal samples within 0-48 h accounted for 17.45 ± 3.37% of the dose administered; the excretion amount of the parent compound in urine samples within 0-48 h accounted for 0.50 ± 0.47% of the dose administered; the excretion of parent compound in bile samples within 0-48 h accounted for 0.16 ± 0.15% of the dose administered; and the excretion in fecal and urine samples in total accounted for 17.95 ± 3.25% of the dose administered. After a single oral dose of [^{14}C]pyrotinib at 3 mg/kg in SD rats, the parent drug and its metabolites were mainly excreted in bile (about 44%) and feces (about 59%), and in a small proportion in urine (less than 1%). No significant difference in the total cumulative excretion in urine and feces was observed between male and female rats.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for details.

2.1.2.5. Clinical studies of pyrotinib

As of 22 Oct., 2018, 12 clinical studies of pyrotinib have been conducted in China: 7 phase I clinical studies, including 4 in healthy subjects, 2 in subjects with HER2-positive metastatic breast cancer (mBC) (BLTN-Ib, BLTN-Ic), and 1 in subjects with advanced gastric cancer (BLTN-Id); a phase I/II clinical study in subjects with mBC (HR-BLTN-I/II-mBC); an ongoing phase II clinical study in subjects with HER2-mutant non-small cell lung cancer (NSCLC) (HR-BLTN-II-NSCLC), and 3 phase III clinical studies in subjects with breast cancer (HR-BLTN-III-MBC-A, HR-BLTN-III-MBC, and HR-BLTN-III-NeoBC). There is currently a phase I clinical study underway in the United States involving subjects with HER2-positive and HER2-mutant solid tumors who develop PD following prior HER2-targeted therapy.

Table 2. Summary of ongoing or completed clinical studies of pyrotinib

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
Phase I Study in Healthy Chinese Subjects					
BLTN-Ia	Healthy males and females Age: 18-45 years	**Primary objective**: To evaluate the tolerability and safety of a single oral dose of pyrotinib in healthy subjects **Secondary objective**: To characterize the PK of pyrotinib in healthy subjects.	**Design**: A phase I, randomized, double-blind, single-dose study to evaluate the safety and to characterize the PK of pyrotinib in healthy male and female subjects. Subjects are randomized to either the pyrotinib group or placebo group. **Dose**: Pyrotinib: 20, 40, 80, 160, 240, 320, or 400 mg, given as a single oral dose within 30 min after breakfast	56/56 46: pyrotinib 10: placebo	Completed
BLTN-Ie (also known as HR-BLTN-FDI/MB)	Healthy males Age: 18-45 years	**Primary objectives**: To determine the food effect on the PK of pyrotinib, to investigate the metabolic pathway, excretion pathway, and excretion level of pyrotinib in the human body, and to further confirm the safety of a single oral dose of 320 mg pyrotinib maleate tablets.	**Design**: A phase I, randomized, open-label, single-dose, two-stage crossover study to determine the food effect on the PK of pyrotinib in healthy male subjects. The study also aims to further investigate the metabolic pathway, excretion pathway, and excretion level after a single oral dose of 320 mg pyrotinib. Further studies on safety evaluation will be conducted. **Dose**: Pyrotinib: single oral dose at 320 mg, administered to subjects under fasting or fed condition (within 30 min after the meal)	12/12	Completed
Mass balance study	Healthy males Age: 18-45 years	**Primary objective:** To evaluate the mass balance and metabolic transformation pathways of [^{14}C]pyrotinib maleate in healthy male Chinese subjects after a single oral dose.	**Design**: A single center, single-dose, non-randomized, and open-label study **Dose**: Administration of 200 mL of a suspension containing 402 mg of pyrotinib (approximately 5.55 MBq radioactivity, 150 μCi) under fasting condition.	4-6/6	Ongoing
BE	Healthy males and females Age: 18-65 years	**Primary objective:** To investigate the human bioavailability and bioequivalence of pyrotinib maleate tablets (160 mg × 2 tablets + 80 mg × 1 tablet) after	**Design:** A single-center, randomized, open-label, single-dose, two-period, crossover bioequivalence study **Dose:** 42 male and female subjects. In Cycle 1, 21 subjects are given oral dose of pyrotinib maleate tablets before the process change (200 mg × 2 tablets)	42/42	Completed

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		the process change using the pyrotinib maleate tablets before the process change (200 mg × 2 tablets) as the reference product. **Secondary objective:** To investigate the safety of pyrotinib maleate tablets in healthy subjects before and after the change of preparation process.	under fed condition, and the other 21 subjects are given oral dose of pyrotinib maleate tablets after the process change (160 mg × 2 tablets + 80 mg × 1 tablet) under fed condition. The subjects cross over to receive Cycle 2 treatment after 8 days.		
Study in Chinese Subjects with HER2-Positive Metastatic Breast Cancer					
BLTN-Ib	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective**: To determine the DLT and MTD of pyrotinib by oral administration once daily at escalating doses in female subjects with advanced HER2-positive metastatic breast cancer. **Secondary objectives**: 1) To evaluate the PK and clinical efficacy of pyrotinib by oral administration, 2) To explore the relationship between HER2 expression status and efficacy	**Design**: A phase I, single-arm, open-label, dose-escalation study to determine the DLT, MTD, and RP2D of pyrotinib by oral administration and to evaluate the PK and clinical efficacy. The study also aims to explore the relationship between HER2 expression status and clinical efficacy at various dose levels. **Dose**: Pyrotinib: multiple ascending doses at 80, 160, 240, 320, 400, or 480 mg, once daily, orally administered within 30 min after breakfast	40/38	Completed
BLTN-Ic	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective**: To determine the MTD and evaluate the safety of pyrotinib combined with capecitabine in female subjects with advanced HER2-positive metastatic breast cancer **Secondary objective**: To evaluate the PK and clinical efficacy of pyrotinib by oral administration.	**Design**: A phase I, single-arm, open-label, dose-escalation study to determine the MTD of pyrotinib combined with capecitabine by oral administration in female subjects with advanced HER2-positive metastatic breast cancer and to evaluate the safety, PK, and clinical efficacy. **Dose**: Pyrotinib: multiple ascending doses at 160, 240, 320, or 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle)	29/29	Completed

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
HR-BLTN-I/II mBC	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective**: To compare the safety and efficacy of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer. **Secondary objective**: To determine the PFS, TTP, and DoR of pyrotinib combined with capecitabine	**Design**: A phase I/II, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose**: Pyrotinib: 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle) Lapatinib: 1250 mg, in combination with capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)	128/128	Enrollment completed, final report completed (data cutoff date: 15 Mar., 2017)
HR-BLTN-III-MBC-A	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-75 years	**Primary objective**: To evaluate the superiority of pyrotinib combined with capecitabine vs. placebo combined with capecitabine in the treatment of HER2-positive metastatic breast cancer in terms of progression-free survival (PFS). **Secondary objectives** 1. To compare the objective response rate (ORR), duration of response (DoR), disease control rate (DCR), clinical benefit rate (CBR), and overall survival (OS) between the pyrotinib combined with capecitabine group and the placebo combined with capecitabine group. 2. To compare the safety of pyrotinib combined with capecitabine vs. placebo combined with capecitabine in	**Design**: A phase III, randomized, double-blind, placebo-controlled, multicenter study comparing pyrotinib combined with capecitabine vs. placebo combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose**: Pyrotinib/placebo: 400 mg, once daily continuously, orally administered within 30 min after breakfast (in 21-day cycles) Capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)	350/279	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		the treatment of HER2-positive metastatic breast cancer.			
HR-BLTN-III-MBC	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective**: To confirm that the PFS of pyrotinib combined with capecitabine is superior to that of lapatinib combined with capecitabine in treatment of HER2-positive metastatic breast cancer. **Secondary objectives** • To compare the overall survival (OS), objective response rate (ORR), time to progression (TTP), duration of response (DoR), and clinical benefit rate of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer • To compare the safety of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer.	**Design**: A phase III, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose**: Pyrotinib: 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle) Lapatinib: 1250 mg, in combination with capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)	240/258*	Ongoing
HR-BLTN-III-NeoBC	Female patients with early or locally advanced HER2-positive breast cancer Age: 18-75 years	**Primary objective:** To compare the efficacy of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer in terms of tpCR (ypT0/is, ypN0)	**Design**: A phase III, randomized, double-blind, placebo-controlled, multicenter study of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer **Dose**: Pyrotinib/placebo is to be administered at 400 mg orally once daily within 30 min after breakfast from Cycle 1 Day 1 to Cycle 4 Day 21.	294/27*	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		pathologically evaluated by the Independent Review Committee (IRC). **<u>Secondary objectives</u>** • To compare the efficacy of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer in terms of the following endpoints: • tpCR assessed by the pathologist of participating study center • Event-free survival (EFS) • Disease-free survival (DFS) • Distant disease-free survival (DDFS) • Objective response rate (ORR) evaluated per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Safety objective To compare the safety and tolerability of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer.	All subjects will receive docetaxel and trastuzumab by intravenous injection (IV) on Day 1 of each 21-day cycle, for a total of 4 cycles (Cycles 1-4): Trastuzumab is to be administered at 8 mg/kg loading dose in Cycle 1 and at 6 mg/kg in Cycles 2-4. Docetaxel is to be administered at 100 mg/m^2 in Cycles 1-4. Granulocyte colony stimulating factor (G-CSF) must be administered prophylactically to reduce the risk of drug-induced hematologic toxicity. After surgery, subjects will receive the FEC chemotherapy regimen (500 mg/m^2 5-fluorouracil [5-FU], 100 mg/m^2 epirubicin, and 500 mg/m^2 cyclophosphamide) by intravenous infusion (IV), with 3 weeks as a cycle, for 3 cycles (Cycles 5-7). The FEC chemotherapy preparation will be administered on Day 1 of each prescribed cycle.		

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
Phase I Study in Chinese Subjects with Advanced Gastric Cancer					
BLTN-Id	Male and female patients with advanced HER2-positive gastric cancer Age: 18-70 years	**Primary objectives**: To determine the MTD and safety of pyrotinib maleate tablets in monotherapy and in combination with docetaxel in patients with advanced HER2-positive gastric cancer; and to determine the RP2D of pyrotinib maleate tablets in monotherapy and in combination with docetaxel **Secondary objective**: To evaluate the PK and clinical efficacy of pyrotinib by oral administration.	**Design**: A phase I, single-arm, open-label, dose-escalation study to determine the MTD (monotherapy or combination therapy), safety, RP2D, and PK of pyrotinib in monotherapy or in combination with docetaxel in patients with HER2-positive gastric cancer and to observe the clinical efficacy **Dose**: **Part 1**: Pyrotinib monotherapy, at a dose of 240, 320, 400, or 480 mg/day, continuously orally administered within 30 min after breakfast (in 21-day cycles) **Part 2**: Pyrotinib, at multiple ascending doses of 240, 320, 400, or 480 mg/day, once daily continuously, orally administered within 30 min after breakfast, in monotherapy or in combination with docetaxel 60 mg/m^2 IV (on Day 1 of each 21-day cycle)	70/26	Ongoing
Phase II Study in Chinese Subjects with Advanced Non-Small Cell Lung Cancer					
HR-BLTN-II-NSCLC	Male and female patients with HER2-mutant advanced non-small cell lung adenocarcinoma Age: 18-75 years	To evaluate efficacy and safety of pyrotinib maleate tablets in patients with HER2-mutated advanced non-small cell lung adenocarcinoma.	**Design**: A phase II, multicenter, open-label, single-arm study to evaluate the efficacy and safety of pyrotinib in subjects with HER2-mutant advanced non-small cell lung adenocarcinoma who have been treated with at least one platinum-based chemotherapy **Dose**: Pyrotinib 400 mg, once daily continuously, orally administered within 30 min after breakfast	55/55*	Ongoing
Phase I Clinical Study in the United States: involving subjects with HER2-positive solid tumors who develop PD following prior HER2-targeted therapy					
SHRUS 1001	Patients with HER2-positive solid tumors and patients with HER2-mutant NSCLC who develop PD following prior	**Primary objectives**: **Part 1**: To evaluate the safety and tolerability of pyrotinib in patients with HER2-positive advanced solid tumors and to determine the MTD of pyrotinib. **Part 2**: To estimate the ORR in	A phase I, open-label, dose-escalation study containing two parts to evaluate the safety, tolerability, and PK of pyrotinib in patients with HER2-positive solid tumors who develop PD following prior HER2-targeted therapy	Part 1: 15-30/9 Part 2: 40/30*	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
	HER2-targeted therapy	patients with HER2-positive metastatic breast cancer or HER2-mutant NSCLC treated at the MTD or RP2D. **Secondary objectives**: **Part 1**: To preliminarily obtain information on anti-tumor activity and PK. **Part 2**: To confirm the MTD from Part 1 of the study and determine the RP2D, so as to obtain safety and evaluate additional efficacy parameters, including clinical benefit rate: complete response + partial response + stable disease for ≥ 6 months (for metastatic breast cancer) or for ≥ 6 months (for HER2-mutant NSCLC), duration of response with pyrotinib, and TTP.	**Dose**: **Part 1**: Pyrotinib: at ascending doses of 320, 400, 480, 560, and 640 mg, once daily, orally administered 30 min after a meal. **Part 2**: During the study expansion stage, 2 independent groups (at least 20 subjects in each group) are investigated to assess the safety and preliminary efficacy of pyrotinib: Group A includes patients with HER2-positive metastatic breast cancer and Group B includes patients with HER2-mutant NSCLC. Subjects in each group are randomized and treated at 2 selected dose levels based on the preliminary safety, PK, and clinical activity observed in Part 1 to determine the most appropriate RP2D.		

Abbreviations: BID, bis in die; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase II dose; TTP, time to progression; yrs, years.
* As of 22 Oct., 2018

2.1.2.5.1. Clinical safety

The most common adverse events (AEs) are similar across all clinical studies. Gastrointestinal disorders, skin reactions, and subcutaneous reactions are the common AEs reported in clinical studies to date. Most notable AEs are diarrhea, nausea, vomiting, and palmar-plantar erythrodysaesthesia syndrome.

Gastrointestinal disorders

AEs involving gastrointestinal disorders, including diarrhea, nausea, vomiting, and mouth ulceration, are frequently reported in the studies. Diarrhea is the most common AE across studies and the most common Grade ≥ 3 AE. The incidence, severity, and duration of diarrhea, and the frequency in individual subjects are generally dose-dependent. In the BLTN-Ib study, the incidence of diarrhea was 87.5% (7/8 subjects) in the pyrotinib 400 mg group, and the incidence of Grade 3 diarrhea was 25.0% (2/8 subjects). In the HR-BLTN-I/II mBC study, the incidence of diarrhea was 96.9% (63/65 subjects) in the pyrotinib (400 mg QD) combined with capecitabine (1000 mg/m^2 BID) group, and the incidence of Grade 3 diarrhea was 15.4% (10/65 subjects).

AEs related to hematology and blood biochemistry tests

The AEs related to hematology and blood biochemistry tests showed that the most common AEs included: white blood cell count decreased, neutrophil count decreased, hemoglobin decreased, aspartate aminotransferase increased, alanine aminotransferase increased, and blood bilirubin increased. Grade ≥ 3 AEs of laboratory abnormalities reported in the studies mainly include: aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, hemoglobin decreased, white blood cell count decreased, glutamyltransferase increased, blood triglycerides increased, neutrophil count decreased, and hypokalemia.

Skin and subcutaneous tissue AEs

Palmar-plantar erythrodysaesthesia syndrome is the most common skin-related AE. In the study of pyrotinib monotherapy (BLTN-Ib), palmar-plantar erythrodysaesthesia syndrome was observed in 3 (3/38) subjects, and no Grade 3 palmar-plantar erythrodysaesthesia syndrome occurred. However, the incidence and severity of palmar-plantar erythrodysaesthesia syndrome were apparently increased in the combination therapy of pyrotinib and capecitabine. Grade ≥ 3 PPE was reported in 16 subjects (24.6%) who received pyrotinib combined with capecitabine in the HR-BLTN-I/II mBC study.

Cardiac adverse events

Although animal toxicology studies up to now have not suggested any significant effect of pyrotinib on cardiac function, careful monitoring for possible cardiotoxicity is required in clinical studies.

In the HR-BLTN-I/II mBC study, 8 subjects (12.3%) in the pyrotinib group experienced asymptomatic Grade 2 LVEF decreased (decrease by ≥ 10% and < 20% relative to baseline); but all subjects had LVEF above 50%. In addition, 11 subjects (16.9%) had a maximum QTcF interval of ≥ 480 msec or an increase by ≥ 60 msec from baseline, and 5 subjects (7.7%) had an absolute maximum QTcF interval of ≥ 480 msec. None of these subjects showed symptoms related to malignant arrhythmia and syncope, etc. QT interval prolongation may be partially related to the use of drugs that prolong QT interval and hypocalcemia during the treatment period.

One SAE of arrhythmia was considered possibly related to the study treatment (BLTN-Id study). One AE of sinus tachycardia leading to the subject's withdrawal from study was reported (HR-BLTN-III mBC study).

2.1.2.5.2. Clinical efficacy

BLTN-Ib study that has been completed is a phase I, single-center, single-arm, open-label, dose-escalation study of pyrotinib in the treatment of HER2-positive metastatic breast cancer. Efficacy data as of 31 Dec., 2015: The best overall response rates (ORR) at doses of 80, 160, 240, 360, and 400 mg were 0, 50%, 25%, 55.6%, and 87.5%, respectively. The median progression-free survivals (PFS) were 23.7, 31.7, 14.6, 31.9, and 59.7 weeks, respectively.

BLTN-Ic study that has been completed is a phase I, single-arm, open-label, dose-escalation study of pyrotinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer. Among the 28 subjects, 0, 22 (78.6%), 5 (17.9%), and 0 subjects had a best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively; 1 subject (3.6%) did not complete the first efficacy evaluation due to withdrawal of informed consent. The efficacy mentioned above has been confirmed after at least 4 weeks. The overall ORR was 78.6%, with a 95% CI of (59.0%, 91.7%). The ORRs were 66.7%, 66.7%, 72.7%, and 90.9% at pyrotinib doses of 160 mg, 240 mg, 320 mg, and 400 mg, respectively, suggesting a certain dose dependence. The median PFS was 22.1 months, with a 95% CI of (9.0 months, 26.2 months).

HR-BLTN-I/II mBC study is a phase I/II, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer. Among the subjects included in the FAS, in the pyrotinib group and in the lapatinib group, 3 subjects (4.6% of the same group) and 1 subject (1.6% of the same group) achieved a 12-cycle BOR of CR, respectively; 48 subjects (73.8% of the same group) and 35 subjects (55.6% of the same group) achieved PR, respectively; 14 subjects (21.5% of the same group) and 22 subjects (34.9% of the same group) achieved SD, respectively. In addition, 5 subjects (7.9% of the same group) in the lapatinib group and 0 in the pyrotinib group had a BOR of PD. The results showed that the 12-cycle ORRs in the pyrotinib and lapatinib groups were 78.5% (95% CI: 68.5%, 88.5%) and 57.1% (95% CI: 44.9%, 69.4%), respectively. Using CMH chi-squared test with the stratification factor "with/without previous treatment with macromolecular anti-HER2 antibody" being corrected, the ORR was improved by 21.3% (95% CI: 4.0%, 38.7%) in the pyrotinib group compared to the lapatinib group with statistically significant difference, $P = 0.01$.

2.1.2.5.3. Clinical pharmacokinetics

In BLTN-Ia study, the PK analysis showed that the $t_{1/2}$ (mean) was 15.0, 20.9, 18.4, 18.1, and 18.8 h after a single oral dose of pyrotinib at 80, 160, 240, 320, and 400 mg, respectively. The median time to maximum plasma concentration of pyrotinib (T_{max}) ranged within 4-5.5 h. Within the dose range of 80-400 mg, the AUC and C_{max} of pyrotinib increased with increasing dose; C_{max} increased proportionally with the increasing dose ($\beta = 1.0349$), and AUC_{0-t} was roughly proportional to the increase in dose ($\beta = 1.2$). No significant change in Cl/F was observed in all dose groups, suggesting a linear PK profile for pyrotinib within the dose range of 80-400 mg.

The results of the BLTN-Ie study showed that compared with administration in fasted condition, the bioavailability of pyrotinib increased after administration in post-prandial condition, with an increase in AUC by 43.31% and an increase in C_{max} by 78.89%. However, the time to C_{max} or elimination half-life ($t_{1/2}$) was not altered in general. These results suggested that it would be more rational to administer pyrotinib after meals, which supports the method of administration adopted in the phase I study.

In BLTN-Ib study, the PK analysis showed median T_{max} of 3.00-5.00 h, geometric mean $t_{1/2}$ of 9.43-16.5 h, and geometric mean C_{max} of 38.8, 80.8, 98.7, 143, and 147 ng/mL on Day 1 after oral pyrotinib doses at 80, 160, 240, 320, and 400 mg, respectively, in Chinese subjects with breast cancer. On the 8th day of continuous administration, the plasma concentrations reached a steady state. At steady state, the median T_{max} was 2.00-4.00 h, and the geometric mean $t_{1/2}$ was 11.4-15.9 h. At steady state (Day 28) after continuous administration of pyrotinib at 80-400 mg once daily, the geometric mean accumulation ratios R (in terms of AUC_{0-24h}) were 1.32, 1.35,

1.57, 1.35, and 1.22, respectively, suggesting that continuous administration did not produce significant dose-dependent accumulation. The geometric mean C_{max} was 43.0, 102, 156, 175, and 170 ng/mL, respectively, and the geometric mean AUC_{0-24h} was 549, 1260, 2080, 2660, and 2270 h·ng/mL, respectively. The increase of C_{max} was roughly proportional to the increase of dose ($\beta = 0.8092$), and the increase of AUC_{0-24h} was roughly proportional to the increase of dose ($\beta = 0.9066$), suggesting that PK parameters of pyrotinib in steady state basically conformed to the linear kinetic characteristics.

In BLTN-Ic study, the PK showed that after pyrotinib maleate was administered at doses of 160-400 mg once a day in combination with capecitabine, the time to maximum concentration (T_{max}) and the elimination half-life ($t_{1/2z}$) on Day 14 were nearly equal to that on Day 1, with no significant changes occurring due to continuous administration. T_{max} and $t_{1/2z}$ did not change significantly with the increasing dose of pyrotnib. On Day 14, the geometric mean of accumulation ratio R (in terms of AUC) was approximately 1, suggesting no obvious accumulation with continuous administration. The $AUC_{0-24\,h}$ and C_{max} of pyrotinib increased with dose in an almost dose-proportional manner ($\beta = 1.0088$ and 0.8177, respectively) over the dose range of 160-400 mg, indicating that pyrotinib had basically linear PK when used in combination with capecitabine. The pharmacokinetics of capecitabine and 5-fluorouracil after combined administration showed that capecitabine was rapidly absorbed and converted to active metabolite, 5-fluorouracil, after administered at 2000 mg/m^2/day, twice daily. Most subjects had concentrations below quantitation limit at 8 h after administration. There were no significant differences in primary PK parameters (AUC_{0-24h} and C_{max}) of capecitabine and its metabolite 5-fluorouracil between the each dose groups.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for the safety, efficacy, and pharmacokinetic data from clinical studies of pyrotinib in detail.

2.2. Scientific Rationale

2.2.1. Study rationale

The incidence of breast cancer is the highest among all cancers diagnosed in Chinese women and is on the rise. In addition, breast cancer is a common malignancy that hazards to women. Positive HER2 status is an independent factor with poor prognosis in breast cancer. Approximately 20% to 30% of breast cancer patients in China have HER2 amplification/overexpression. Targeted therapy should be used as soon as possible for HER2-positive recurrent and metastatic breast cancer, and earlier use may bring the greater benefit[8, 9].

Pyrotinib is a novel small molecule irreversible inhibitor of tyrosine kinases EGFR and HER2 independently developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd./Shanghai Hengrui Pharmaceutical Co., Ltd. Preclinical *in vivo* studies showed that pyrotinib could significantly inhibit HER2-positive breast cancer. Pyrotinib is an irreversible small molecule inhibitor with dual targets (EGFR and HER2), and has different sites of action and additional EGFR target compared with trastuzumab, a macromolecule antibody directed at the HER2 receptor.

Small molecule inhibitor of HER2 and trastuzumab block different HER2 target regions and have some non-overlapping mechanisms of action[10]. A phase II clinical study of lapatinib combined with trastuzumab and paclitaxel in treatment naive patients with advanced breast cancer showed ORRs of 79%, 71%, and 70% in the lapatinib (1000 mg/d) + paclitaxel (80 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week), lapatinib (1000 mg/d) + paclitaxel (70 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week), and lapatinib (750 mg/d) + paclitaxel (80 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week) groups, respectively. The results showed a certain efficacy of dual-targeted drugs (trastuzumab + lapatinib) combined with first-line therapy in the treatment of HER2-positive advanced breast cancer[11]. In addition, in the NSABP FB-8 study of neratinib, paclitaxel (80 mg/m^2, on D1, D8, and D15, in 28-day cycles), trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg once a week), and neratinib (by oral administration, at 120, 160, or 240 mg, once daily) were administered. The study results of the three-agent combination: overall ORR: 38%; CBR: 52%; median time to progression (mTTP): 3.7 m. The study results showed a certain efficacy of the combination of dual-targeted drugs (neratinib and trastuzumab) in patients with advanced breast cancer previously treated with trastuzumab, lapatinib, T-DM1, taxanes, and multiple lines of chemotherapy[12]. In conclusion, small molecule targeted inhibitor of HER2 combined with monoclonal antibody trastuzumab showed good efficacy in patients with HER2-positive advanced breast cancer. The efficacy and safety need to be further explored in future studies.

The current clinical study results showed that pyrotinib is well tolerated, and has significant anti-tumor efficacy both as a single agent and in combination with docetaxel or capecitabine in patients with HER2-positive and HER2-mutant advanced solid tumors. This study intends to further explore the efficacy and safety of pyrotinib combined with trastuzumab and docetaxel in patients with advanced HER2-positive breast cancer.

2.2.2. Rationale for the dose of docetaxel and trastuzumab

Docetaxel (100 mg/m^2 for every 3 weeks) combined with trastuzumab showed a positive benefit-risk ratio compared with docetaxel monotherapy in the treatment of HER2-overexpressing metastatic breast cancer[13]. That is, adding anti-HER2 targeted therapy on the basis of chemotherapy can provide clinical benefit to subjects. Studies have shown a significantly higher

incidence of febrile neutropenia in Asian subjects than in other populations with docetaxel 75 mg/m^2. This result is consistent with the overall observation of tolerability of taxane in such a population[14, 15]. However, lapatinib (1000 mg/day)[16] (small molecule tyrosine kinase inhibitor of HER2) and neratinib (240 mg/day)[17] combined with trastuzumab at standard dose and paclitaxel (80 mg/m^2, once a week) may result in a higher incidence of Grade 3 diarrhea. Considering the subjects' tolerance, efficacy, race, and other factors, the dose of docetaxel in this study is set at 75 mg/m^2.

In this study, following one of the recommended dosing regimens in the instruction for use, trastuzumab will be administered once every 3 weeks, with an initial loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary objective

- To evaluate the progression-free survival (PFS) of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer

3.1.2. Secondary objectives

- To evaluate the safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer
- To compare the efficacy between two groups in overall survival (OS), objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR).

3.2. Study Endpoints

3.2.1. Primary endpoint:

- PFS (investigator-assessed)

3.2.2. Secondary endpoints

- PFS (IRC-assessed)
- OS
- ORR

- DoR
- CBR
- Safety endpoints: incidence and severity of adverse events (AEs) and serious adverse events (SAEs), according to NCI-CTCAE v4.03; changes in the following parameters from baseline: ECOG PS, vital signs, physical examination, laboratory tests (hematology, urinalysis, routine stool test, and blood biochemistry), ECG, and echocardiography.

4. STUDY DESIGN

4.1. Overview of Study Design

This is a phase III, randomized, double-blind, placebo-controlled, multicenter study.

This study plans to enroll a total of 590 subjects. Eligible subjects will be randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). Randomization is stratified by the following factors:

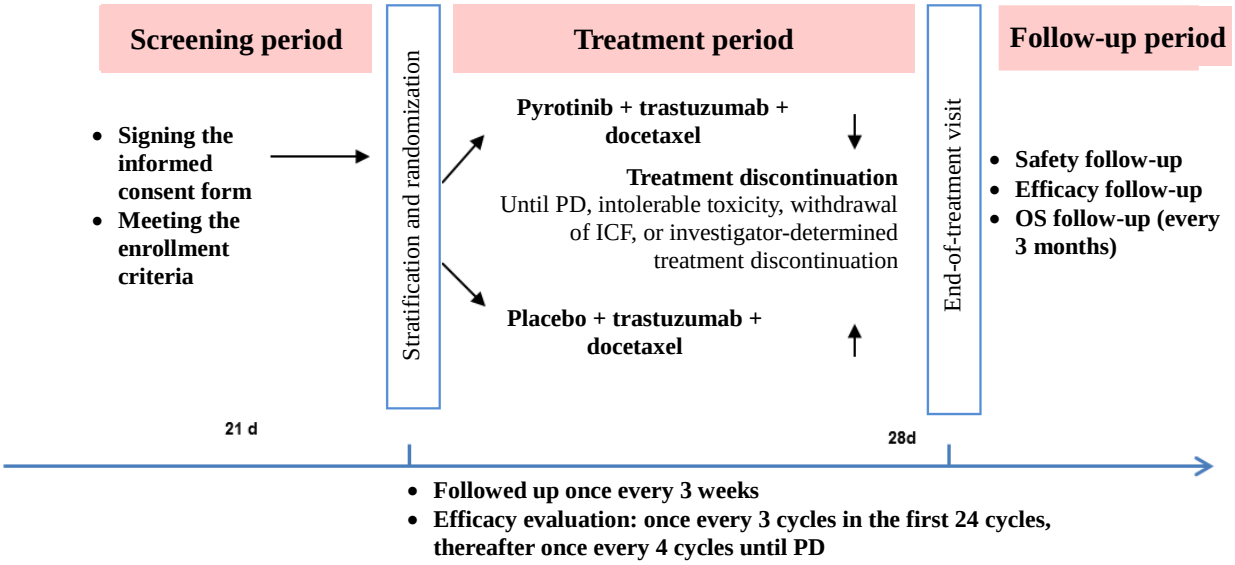
- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

Subjects will receive study treatment within 48 h after randomization in 21-day cycles until investigator-assessed progressive disease (PD), intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The tumor assessments will be performed by the investigators and independent review committee according to RECIST v1.1. The primary PFS analysis is based on the assessment results by the investigators.

For subjects who discontinue the study treatment, the safety visit should occur on D28 ± 7 d after the last administration of study drug, then the subject should start the survival follow-up period until death or study termination (whichever occurs first). For subjects who discontinue the study treatment due to reasons other than PD or death, scheduled tumor assessments need to be collected until PD, start of a new anti-tumor treatment, or death (whichever occurs first).

This study plans to perform 1 safety assessment and 1 interim analysis by Independent Data Monitoring Committee (IDMC). After the data review, the IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study.

An overview of the study design is shown below:



4.2. Methods to Reduce Bias

4.2.1. Enrollment/randomization/blinding

This is a randomized, double-blind clinical study. The sponsor's randomization specialist uses SAS (version 9.4 or higher) to simulate the generation of the randomization table and drug number list, which are kept by the randomization specialist. The generation process is reproducible. The subjects, investigators, and all medical personnel participating in the study or clinical evaluation as well as the sponsor's research team are blinded to the subject's medication assignment.

The subjects are randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). The study centers screen for subjects who meet all the inclusion criteria and do not meet any exclusion criteria. The personnel with relevant authority log in to the Interactive Web Response System (IWRS) for stratified randomization. The stratification factors include: 1) prior neoadjuvant/adjuvant therapy: with or without trastuzumab; 2) ER/PR status: positive or negative. The screening information is entered into the system. Randomization number and drug number are obtained. The subjects must start the assigned study medication within 48 h after randomization.

4.2.2. Unblinding

When the principal investigator of a study center (or the drug regulatory authority (such as the National Center for Drug Evaluation)) believes it necessary to know the group assignment for the safety of the subject, the principal investigator of the study center applies for emergency unblinding in the IWRS and contacts the sponsor's research team. The project manager or CRA contacts the randomization specialist. The randomization specialist logs in the IWRS to confirm the application for emergency unblinding and executes unblinding, and informs the project manager or CRA of the completion of unblinding. The investigator logs in the IWRS to obtain the grouping information of the subject. If the IWRS cannot be used when applying for emergency unblinding, the principal investigator of the study center fills out a notice of emergency unblinding and mail it to the sponsor's research team. The project manager or CRA forwards it to the randomization specialist. The randomization specialist provides a Blind Code Handover Sheet of the corresponding subject by email.

The clinical care for the subject should remain unchanged regardless of the blinded treatment assignment.

Unblinding by the Independent Data Monitoring Committee (IDMC) during the safety monitoring should be performed by an independent statistician and the integrity of the study should be guaranteed.

The subjects, study center personnel, sponsor's MA, CRA, project manager, and project statisticians participating in the study are kept blinded. Upon deterministic analysis of the primary efficacy endpoint, after review under blinding, the database will be locked. The statistician will apply to the randomization specialist for unblinding, i.e., inform the statistician of the corresponding group of each subject's number for statistical analysis of all data.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

The enrollment of eligible subjects is critical to ensure the outcome of the study. Subjects must meet the following inclusion criteria to be allowed to participate in this study. Any medical or non-medical conditions of a subject are considered for his/her eligibility.

Before the subject's enrollment in the study, the investigator should review, confirm, and document whether the subject is suitable for participating in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for study entry:

1. Females aged ≥ 18 and ≤ 75 years old.
2. Histologically confirmed HER2-positive invasive breast cancer, while meeting the following conditions:
   - HER2 positive is defined as 3+ by immunohistochemistry (IHC) or an *in situ* hybridization (ISH) result of HER2 gene amplification. A HER2-positive breast cancer confirmed by the pathology department of the participating study center.
   - Tumor staging: recurrent or metastatic breast cancer; locally recurrent disease must not be amenable to resection with curative intent.
3. Have at least one measurable lesion according to RECIST v1.1.
4. ECOG PS: 0-1.
5. The functional levels of major organs must meet the following requirements (no blood transfusion or treatment with leukogenic and thrombopoietin drugs within 2 weeks prior to screening):
   - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L;
   - Platelet count (PLT) ≥ 90×10^9/L;
   - Hemoglobin (Hb) ≥ 90 g/L;
   - Total bilirubin (TBIL) ≤ upper limit of normal (ULN); for patients with Gilbert's syndrome, TBIL ≤ 2 × ULN;
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN; for patients with liver metastases, ALT and AST ≤ 5 × ULN;
   - Alkaline phosphatase ≤ 2.5 × ULN;
   - Urea/urea nitrogen (BUN) and creatinine (Cr) ≤ 1.5 × ULN;
   - Left ventricular ejection fraction (LVEF) ≥ 50%;
   - Fridericia-corrected QT interval (QTcF) < 470 msec.
6. Participate in the study voluntarily, sign the informed consent form, have good compliance, and willing to cooperate with follow-up visits.

5.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to participate in this study:

1. Have received any systemic anti-tumor therapy for the recurrent/metastatic diseases, including any anti-EGFR or anti-HER2 agents, systemic chemotherapy, immunotherapy, and more than one prior hormonal regimen, as well as other anti-tumor therapies that shall be excluded as judged by the investigator.
2. History of anti-HER tyrosine kinase inhibitor (TKI) or macromolecular antibody for breast cancer in any treatment setting, except trastuzumab used in the (neo) adjuvant therapy.
3. History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (except endocrine therapy) to metastatic diagnosis of < 12 months.
4. Current Grade ≥ 3 peripheral neuropathy as per CTCAE v4.03.
5. Not suitable for systemic chemotherapy as judged by the investigator.
6. Have received endocrine therapy within 7 days prior to randomization.
7. History of other malignant tumors within the past 5 years, except for cured cervical carcinoma *in situ*, skin basal cell carcinoma or squamous cell carcinoma (patients with other malignant tumors that occurred more than 5 years before the date of randomization are allowed to be enrolled only if they have been cured by surgery).
8. Current brain metastases.
9. Subjects with bone or skin as the only target lesion.
10. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin or doxorubicin liposome > 360 mg/m^2
    - Epirubicin > 720 mg/m^2
    - Mitoxantrone > 120 mg/m^2, idarubicin > 90 mg/m^2
    - Others (for example, in case of other anthracyclines or multiple anthracyclines, the cumulative dose > the dose equivalent to 360 mg/m^2 of doxorubicin)
11. Have undergone major surgery or apparent trauma within 4 weeks prior to randomization, or expected to undergo a major surgery during the course of study treatment.

12. With severe cardiovascular disease or discomfort, including but not limited to the following:

    - Medical history of cardiac failure or systolic dysfunction (LVEF < 50%)
    - Angina or arrhythmia that requires treatment or of high risk (such as type 2 second-degree atrioventricular block or third-degree atrioventricular block, ventricular tachycardia)
    - Clinically significant valvular heart disease
    - Transmural myocardial infarction as indicated by ECG
    - Poorly controlled hypertension (systolic pressure > 150 mmHg and/or diastolic pressure > 100 mmHg)

13. With dysphagia, chronic diarrhea, intestinal obstruction, or other factors affecting drug intake and absorption.

14. With known allergies to the components of the study drugs.

15. History of immunodeficiency, including HIV infection or other acquired and congenital immunodeficiencies, or organ transplantation.

16. Presence of third spacing (such as hydrothorax and ascites) that cannot be controlled by drainage or other methods.

17. Pregnant or lactating female subjects, or subjects of childbearing potential who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose.

18. Presence of severe concurrent disease or other concurrent diseases that may interfere with planned treatment, or any other conditions rendering the subjects unsuitable for participating in this study, such as active hepatitis B and lung infection requiring treatment.

5.3. Withdrawal from Study or Treatment Discontinuation

5.3.1. Withdrawal from study

Withdrawal from the study:

1. Subject voluntarily withdraws the ICF and refuses further follow-ups;
2. Investigators may withdraw the subject from the study in the event of major Inclusion/Exclusion protocol violation.

Continue study follow-ups after treatment discontinuation:

1. A tumor assessment shows progressive disease;
2. Meeting criteria for permanent discontinuation of the study drug;
3. Any clinical AE, laboratory abnormality, or medical condition indicating that the subject can no longer benefit from the treatment;
4. Occurrence of pregnancy during the study;
5. Important protocol deviation rendering the subject unsuitable for continuing study treatment;
6. Other reasons for the treatment discontinuation as determined by the investigator.

5.3.2. Procedures for withdrawal from study or treatment discontinuation

The efficacy and safety examinations upon study withdrawal specified in the protocol must be completed and reported as thoroughly as possible. In addition, safety follow-ups and subsequent survival follow-ups should be completed, along with fully documented AEs and their outcomes. The investigator can recommend or provide new or alternative treatments to a subject based on the condition of the subject. Subjects showing no PD need to be continuously followed up for tumor assessment until the subjects begin new anti-tumor treatment or show PD.

Subject's survival status should still be followed up even when the subject refuses to visit the study center, unless the subject withdraws consent to provide further information or consent to be further contacted. In that case, no further study assessments should be conducted and no further data should be collected. The sponsor can retain and continue to use all data collected before withdrawal of informed consent, unless the subject requests a retraction of collected data.

5.4. Premature Termination or Suspension of Study

This study can be terminated prematurely or suspended if there are sufficient reasons. This may result from the decision of regulatory authorities, changes in comments by the ethics committee, efficacy or safety issues of the study drugs, or the judgment of the sponsor. In addition, Hengrui reserves the right to terminate the research and development of pyrotinib at any time. The party who decides to suspend/terminate the study should notify the investigator, sponsor, and regulatory authorities in writing, documenting the reasons for suspension/termination. The investigator must immediately notify the ethics committee and sponsor, and provide relevant reasons.

Termination of study center:

- The sponsor has the right to terminate the study at a study center if it is found that the investigator of the center is seriously or persistently non-compliant to the protocol and other study procedures, which may interfere with the proper implementation of the study. In which case, the sponsor will immediately inform the investigator and the regulatory authorities of the termination.
- If the study is terminated or suspended at a study center by the investigator, the subjects must be informed immediately, and the reasons for termination must be reported in writing to the study center's clinical study institution/ethics committee, the sponsor, and regulatory authorities, as required by regulations.

Reasons for premature termination or suspension of the entire study may include:

- Confirmed unexpected, major, or unacceptable risk to the subjects.
- Existing efficacy data supporting premature study termination.
- Major errors in the protocol found during the implementation of the study;
- Ineffective study drug/treatment, or meaninglessness to continue the study;
- Extreme difficulties in completing the study due to reasons such as severe delays in subject recruitment or frequent protocol deviations.

The study may continue once those issues related to drug safety, protocol compliance, and data quality have been resolved and approved by the sponsor, ethics committee, or CFDA (now NMPA).

5.5. Definition of End of Study

The end of this study is defined as:

- Two years after the collection of 410 PFS events and the sponsor's confirmation that sufficient OS events have been collected;

  or

- Study termination decided by the sponsor.

5.6. Lifestyle Requirements

5.6.1. Contraception

In this study, trastuzumab has been confirmed to have teratogenicity/fetal toxicity; docetaxel and pyrotinib are suspected to have reproductive toxicity, which, however, has not been proven in clinical use. All female subjects of childbearing potential who will take the above study drugs, if the investigator believes that they are at risk of pregnancy, must adopt at least two highly effective contraceptive measures during the entire treatment period from the signing of the ICF until 7 months after the last dose of study drugs. After consulting with subjects, the investigator or designated personnel will select 2 appropriate contraceptive methods from the followings, and confirm the subjects' awareness of correct and consistent use of the contraceptive methods. In addition, the subjects shall be aware that the investigator must be notified immediately once the selected methods of contraception are stopped.

An effective contraception method refers to a method with an annual failure rate of < 1% when correctly used independently or with other methods, including:

1. Correctly inserted intrauterine devices.
2. Male/female condom combined with topical spermicides (i.e., foams, gels, films, creams, or suppositories).
3. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusion (the occlusion should be proven effective by relevant instruments).

6. STUDY MEDICATION

6.1. Description of the Study Drugs and Control Drug

6.1.1. Access to drugs

The investigational drug in this study is pyrotinib maleate tablet (pyrotinib/placebo), manufactured and supplied by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Docetaxel injection (Ai Su®) and trastuzumab (Herceptin®) will be used in the study and are provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

6.1.2. Dosage form, appearance, packaging, and label

- Pyrotinib maleate tablet/placebo

  Dosage form: tablet

  Strength: 80 mg; 160 mg

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

- Docetaxel injection

  Dose form: injection

  Strength: 0.5 mL: 20 mg; 1.5 mL: 60 mg

  Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

- Trastuzumab for injection

  Dosage form: lyophilized powder

  Strength: 440 mg

  Manufacturer: F. Hoffmann-La Roche

Refer to the corresponding packaging information for the labels and outer packaging of the above drugs.

6.1.3. Storage and stability of drugs

The investigator or the authorized representative thereof (e.g., pharmacist) will ensure that all study drugs <including pyrotinib/placebo, docetaxel, and trastuzumab> are stored in a secure and access-controlled area conforming to storage conditions and regulatory requirements.

Docetaxel and trastuzumab should be stored in their original containers and match with the labels. Once the product has been prepared or diluted, it should be stored according to the storage conditions specified in the <Package Insert>.

For inconsistence of the storage conditions on the label with those in other materials (such as IB), the label should be followed.

Daily maximum and minimum temperatures of all storage areas (such as freezer, refrigerator, and room temperature) must be recorded by the study center. The documented period shall begin with the receipt of the study drug until the last subject completes the last visit. Even if a continuous monitoring system is employed, a written log must be kept at the study center to ensure a correct record of storage temperature. The temperature monitoring and storage devices (such as refrigerator) should be regularly inspected to ensure proper operation.

Any deviations related to the labeled conditions on the product should be immediately reported upon discovery. The study center shall take active measures to restore the study drugs under the storage conditions described on the label, and the temperature deviation and the measures taken shall be reported to the sponsor.

Study drugs that are affected by temperature deviations must be temporarily isolated until approved by the sponsor for further use, and such case is not considered a protocol deviation. The use of affected study drugs without the approval of the sponsor is considered a protocol deviation. The sponsor will provide a detailed procedure on reporting temperature deviations to the study center.

For subjects who take the medication at home, the staff at the study center will guide the subjects regarding the proper method of drug storage.

Refer to the Pharmacy Manual for additional storage instructions and actions to be taken when stored outside the specified conditions.

6.1.4. Preparation of study drugs

Trastuzumab and docetaxel should be administered intravenously (IV) at the study center. They should be prepared by qualified or experienced study personnel, such as physicians, pharmacists, or medical assistants (approved by national authorities or study center operating guidelines) according to the corresponding package inserts.

Only qualified personnel who are familiar with reducing inappropriate exposure in themselves and the environment are allowed for the preparation, dispensation, and safe use of study drugs.

6.1.5. Administration of study drugs

Pyrotinib/placebo

Pyrotinib/placebo is orally administered to subjects at 400 mg once a day within 30 min after breakfast in 21-day cycles starting from Day 1 of Cycle 1. Use of loperamide hydrochloride (Imodium®) is allowed (up to 16 mg/day) for secondary preventing diarrhea during pyrotinib/placebo medication in the study.

Subjects swallow pyrotinib/placebo intact and should not hold or chew the drug before swallowing.

The dose of pyrotinib/placebo may be adjusted according to the protocol based on the subject's adverse reactions. The scheduled time of a missed dose and the reason for not taking the dose should be documented in detail. Any vomiting should be documented in the subject diary, original medical records, and the eCRF. Note that missed dose and vomited dose after administration are not made up. The subsequent doses will be taken as scheduled.

The investigator should actively provide symptomatic treatment for adverse events during the study. Concomitant treatments and medications should be documented in detail in the medical records and the EDC system.

Trastuzumab

Trastuzumab is administered intravenously starting from Day 1 of Cycle 1. The subjects will receive 8 mg/kg loading dose of trastuzumab in Cycle 1 and 6 mg/kg dose in subsequent cycles. The dose of trastuzumab will be calculated based on the actual weight of the subject. The body weight should be recorded at baseline and at each visit. If the weight of the subject has increased or decreased by > 10% from baseline, the dose will be recalculated. In the event of dose recalculation due to a change in body weight from baseline by > 10%, the latest body weight will serve as the new baseline to calculate the dose of trastuzumab in subsequent treatment cycles.

Dose modification for reasons other than weight changes are not allowed. Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. If trastuzumab administration must be delayed by one day or longer, docetaxel should be delayed by the same period of time. If the subject misses a dose of trastuzumab for one cycle (e.g., the time interval between 2 sequential administrations is 6 weeks or more apart), the re-loading dose of 8 mg/kg will be administered, and the docetaxel will also be administered on the same day. Maintenance trastuzumab doses of 6 mg/kg will be given every 3 weeks.

Trastuzumab may cause symptoms of infusion reactions, such as nausea, fever, diarrhea, chills, asthenia, and headache. Such reactions generally occur during or shortly after the infusion. Therefore, trastuzumab should be administered in an environment with first aid equipment. The medical staff should be trained on monitoring and responding to medical emergencies. During each infusion, the subjects should be monitored for any adverse reactions. Monitoring should last for at least 90 min after the first trastuzumab infusion.

Supportive treatments with oxygen, beta-agonists, antihistamines, antipyretics, and corticosteroids may help relieve allergic symptoms. Prophylactic treatment with analgesics and antihistamines may be administered in subsequent infusions for subjects who develop infusion-related symptoms during or after the infusion. Infusion reactions may be delayed, and thus the subject should contact the investigator in the rise of any problem.

Docetaxel

The dose of docetaxel is 75 mg/m^2. After the end of the observation period of trastuzumab infusion, docetaxel will be administered by intravenous infusion on Day 1 of each cycle. From the start of docetaxel infusion, the subject will be closely monitored for hypersensitivity reactions, which may occur within a few minutes. In the case of severe hypotension, bronchospasm, or systemic rash/erythema, immediate discontinuation of docetaxel and appropriate treatment are required. In the case of mild symptoms such as flushing or local skin reactions, the infusion may be slowed down. The study treatment should be discontinued in subjects who develop severe hypersensitivity, but follow-up should be continued following the assessment schedule, unless the informed consent is withdrawn.

The risk of hematologic toxicity can be reduced by dose reduction (dose delay when necessary) and/or prophylactic administration of G-CSF. The G-CSF is a long-acting G-CSF preparation, thiopefilgrastim injection (Aiduo®), manufactured and provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd. For intolerant subjects due to contraindications or adverse drug reactions, other G-CSF preparations may be selected.

In the absence of contraindications, prophylactic medications (consisting of oral corticosteroids) may be given on Day -1, Day 1, and Day 2.

Treatment with docetaxel may be delayed in the case of myelosuppression, hepatotoxicity, or other intolerable AEs. If docetaxel administration must be delayed by one day or longer, trastuzumab should be delayed by the same period of time.

The dose of docetaxel is calculated based on the body surface area of the subject. Subjects' baseline weight and height should be recorded, as should their weight at each scheduled visit. If the investigator believes that the height of the subject may change, the height should be re-measured. If the weight of the subject has increased or decreased by > 10% from baseline, the dose will be recalculated. In the event of dose recalculation due to a change in body weight from baseline by > 10%, the latest body weight will serve as the new baseline to calculate the dose of docetaxel in subsequent cycles. The nomograms used to determine the body surface area are shown in Appendix IV. For dose modification of docetaxel and interruption or discontinuation of treatment due to toxicities, see Section 6.1.6 for the guidelines.

6.1.6. Dose modifications and delay

Based on preliminary clinical data, pyrotinib monotherapy is well-tolerated. The incidence of Grade 3/4 adverse events was 25% (2/8) in the 400 mg group and 11.1% (1/9) in the 320 mg group. All Grade 3/4 AEs were diarrhea. Other common adverse reactions included hand and foot syndrome, hepatic function abnormal, vomiting, etc. Thus, active symptomatic treatment or observation is recommended upon occurrence of adverse events during the study. Before intolerance to pyrotinib/placebo is confirmed, it should be ensured that pyrotinib/placebo can be continued as much as possible.

In the case of AEs of intolerance to pyrotinib/placebo during the study, the dose of pyrotinib/placebo may be interrupted after active symptomatic treatment. If the subject is still intolerant, the dose of pyrotinib/placebo may be reduced in the order of 400 mg/day, 320 mg/day, and 240 mg/day.

Dose recalculation of trastuzumab for reasons other than a change of > 10% in body weight is not permitted.

In the case of AEs of intolerance to docetaxel, the dose of docetaxel may be reduced to 60 mg/m^2. Further dose reduction (minimum dose of 60 mg/m^2) is required for subjects persistently intolerant. The investigator and the sponsor will discuss whether to continue the medication or withdraw the subject from all study treatments.

If the subject is still intolerant after dose reduction to the minimum mentioned above, the study drug should be discontinued. Permanent discontinuation of pyrotinib/placebo should be decided based on the discussion between the investigator and the sponsor. In the study, discontinuation of docetaxel and trastuzumab with monotherapy of pyrotinib/placebo is permitted.

6.1.6.1. Management of common adverse events

Diarrhea

The investigator must inform the subject in detail of the potential of diarrhea and appropriate treatment measures prior to starting the oral administration of study drug. Oral administration of loperamide hydrochloride (Imodium®) is allowed (up to 16 mg/day) for secondary preventing diarrhea during pyrotinib medication in the study. For severe diarrhea, electrolytes may be administered orally or intravenously. For Grade ≥ 3 diarrhea that cannot be controlled after prophylactic medication or symptomatic treatment, the dose of study drug will be modified according to Table 3.

Stomatitis

In the case of stomatitis during the study, it is recommended to give symptomatic treatment first, such as gargling with normal saline. Topical medication may be prescribed per the routine diagnosis and treatment of the study center. For Grade ≥ 2 stomatitis that cannot be controlled after symptomatic treatment, the dose of study drug will be modified according to Table 3.

Hand and foot syndrome

In the case of hand and foot syndrome, it is recommended to give symptomatic treatment first and closely follow up. Strengthen skin care, keep skin clean, and avoid secondary infections; avoid pressure or friction; use moisturizers or lubricants, use topical lotions or lubricants containing urea and corticosteroids; use topical antifungal or antibiotic treatment if necessary. For Grade ≥ 2 hand and foot syndrome that cannot be controlled after symptomatic treatment, the dose of study drug will be modified according to Table 3.

Nausea or vomiting

Give symptomatic treatment first, such as acid suppression, gastric protection, and antiemetics and closely follow up. In the case of symptoms seriously affecting eating, pay attention to the water/electrolyte balance. For persisted Grade ≥ 2 vomiting after active treatment, the dose of study drug will be modified according to Table 3.

Hepatic function abnormal

Hepatic function should be monitored regularly per the protocol during the study. Special attention should be paid to the levels of bilirubin, ALT, and AST. In the case of hepatic function abnormal with clinical significance, the investigator should give hepatoprotective and symptomatic treatment based on the subject's condition and adverse events, and determine the frequency of blood biochemistry tests according to clinical requirements. For persisted Grade ≥ 2 hepatic function abnormal after active treatment, the dose of study drug will be modified according to Table 3.

6.1.6.2. Common adverse events of pyrotinib/placebo and docetaxel

The investigator is advised to interrupt and modify the doses of pyrotinib/placebo and docetaxel according to the principles in the table below. In the case of AEs that are considered to be mainly possibly related to docetaxel, including but not limited to myelosuppressive toxicity and hepatic function abnormal, and are not relieved after active symptomatic treatment (≤ 1 treatment cycle), the dose of docetaxel may be delayed or modified in the subsequent cycle according to Table 3.

In the case of AEs that are considered to be possibly related to both pyrotinib/placebo and docetaxel but are not relieved after active symptomatic treatment (≤ 1 treatment cycle), the investigator is advised to interrupt, delay, and modify the dose of one of the study drugs according to Table 3 based on the clinical situation.

The investigator should manage the administration of pyrotinib/placebo and docetaxel as described in this section whenever possible, but may make appropriate adjustments when necessary based on the subject's specific condition and medical judgment.

Table 3. Dose modification for pyrotinib/placebo and docetaxel

NCI CTCAE 4.03*	Pyrotinib/Placebo **(intolerable after active treatment, considered related to pyrotinib/placebo)**[a]	Docetaxel	
		Occurring in a treatment cycle and disappearing by the next treatment cycle[b]	Existing on D1 of scheduled cycle[c]
Neutrophils reduced			
Grade 3-4	Resume medication after interruption	Maintain dose	Delay medication until ANC $\geq$ 1500/mm^3. • If G-CSF is not administered, maintain dose and add G-CSF in the case of recovery within 1-3 weeks • If G-CSF is administered, maintain dose in the case of recovery within 1 week, or reduce dose by 1 level in the case of recovery within 2-3 weeks
Febrile neutropenia (Grade 3-4)	Resume medication after interruption Reduce dose by 1 level when necessary	Add G-CSF and/or reduce dose by 1 level Discontinue when necessary	
Platelets decreased			
Grade 3	Resume medication after interruption	Maintain dose	Delay medication until platelet count $\geq$ 75000/mm^3. • Maintain dose in the case of recovery within 1 week; • Reduce dose by 1 level in the case of recovery within 2-3 weeks
Grade 4	Resume medication after interruption Reduce dose by 1 level when necessary	Reduce dose by 1 level	Reduce dose by 1 level
Diarrhea (not relieved after prophylactic oral administration of loperamide hydrochloride and symptomatic treatment)			
Grade 3 or Grade 1-2 with complications (Grade $\geq$ 2 nausea or vomiting, pyrexia, neutrophils reduced, hematochezia, or dehydration)	First occurrence: resume medication after interruption Second occurrence: reduce dose by 1 level when necessary after interruption	First occurrence: maintain dose Second occurrence: reduce dose by 1 level when necessary after interruption	Delay dose; reduce dose by 1 level when necessary after recovery to Grade $\leq$ 1

NCI CTCAE 4.03*	Pyrotinib/Placebo **(intolerable after active treatment, considered related to pyrotinib/placebo)**[a]	Docetaxel	
		Occurring in a treatment cycle and disappearing by the next treatment cycle[b]	Existing on D1 of scheduled cycle[c]
Grade 4	Discontinue	Discontinue	Discontinue
Other AEs (except those specified in 6.1.6.3 and 6.1.6.4 and those considered tolerable by the investigator)			
Grade 2	Maintain dose Resume after interruption when necessary	Maintain dose	Delay dose; resume after recovery to Grade ≤ 1
Grade 3	First occurrence: resume medication after interruption Second occurrence: reduce dose by 1 level when necessary after interruption	Reduce dose by 1 level when necessary	Delay dose; reduce dose by 1 level when necessary after recovery to Grade ≤ 1
Grade 4	Discontinue	Discontinue	Discontinue

a: Following each dose interruption, medication can be resumed only after the AE recovers to Grade ≤ 1.

b: Disappearance means all events requiring dose modification recover to Grade ≤ 1 (ANC must be ≥ 1500/mm^3) on Day 1 of the next scheduled cycle.

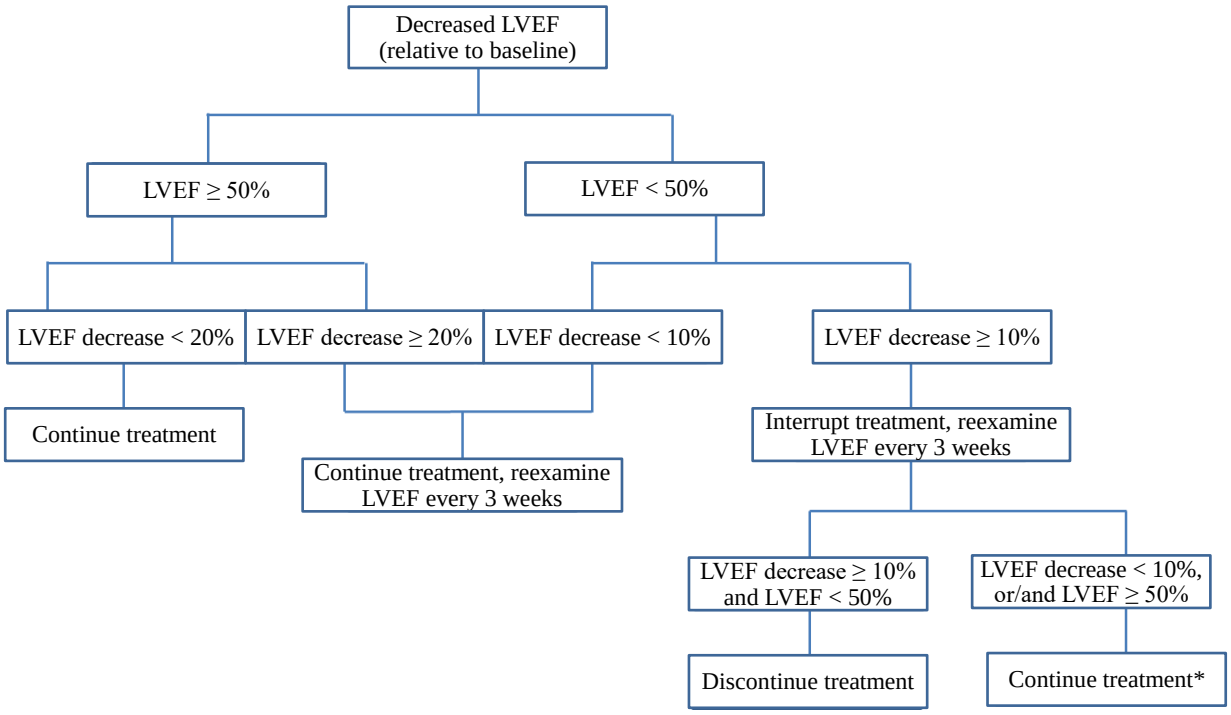
c: Interrupt, examine weekly, and resume treatment when AE recovers to Grade ≤ 1 (ANC must be ≥ 1500/mm^3). Discontinue docetaxel if toxicity is not resolved after dose delay for 3 weeks.

6.1.6.3. Cardiac adverse events

Cardiac AEs, when occurring in the study, should be treated according to the following principles:

- If the investigator considers that a cardiac AE may have occurred, additional LVEF examination is required.
- Once any symptoms or signs suggest the possibility of heart failure, chest X-ray and echocardiography should be performed to confirm the diagnosis. After confirmation, all study drugs should be discontinued, and active symptomatic treatment should be given.
- In the case of cardiac AEs that are considered possibly related to both pyrotinib/placebo and trastuzumab, the dose of pyrotinib may be interrupted/reduced if the condition is not relieved within 2 treatment cycles after active symptomatic treatment and/or dose interruption or delay of trastuzumab.
- In the case of asymptomatic decreased LVEF, treatment should be given following the figure below.

Figure 1. Schematic diagram for the treatment of asymptomatic LVEF decreased



***: Reduce the dose of pyrotinib/placebo by 1 level when resuming medication.**

6.1.6.4. Special requirements for dose interruption and modification of study drugs

6.1.6.4.1. Pyrotinib/placebo

Following each occurrence of dose interruption of pyrotinib/placebo due to intolerable AEs of pyrotinib/placebo, medication should be resumed after the AEs recover to Grade 0-1, unless the investigator believes that AEs have stabilized and the subject can tolerate pyrotinib/placebo medication.

Multiple dose interruptions during the treatment are permitted. Each interruption of pyrotinib/placebo should not exceed 21 days consecutively or within a treatment cycle, so as to maintain the drug intensity of the treatment received by the subject. If the interruption of pyrotinib/placebo treatment due to AE exceeds the criteria above, the subject should withdraw from the study.

6.1.6.4.2. Trastuzumab

The dose of trastuzumab must not be reduced due to any toxicity. However, due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued.

Permanent discontinuation of trastuzumab may be considered in the following cases:

- Decreased LVEF (decreased LVEF below the normal range, and decrease by ≥ 10% from baseline) persisting for more than 8 weeks;
- Interruption of 3 doses of trastuzumab due to trastuzumab-related cardiac events.

Infusion reaction

- In the case of mild or moderate infusion reactions (such as pyrexia, chills, headache, asthenia, pruritus, nausea, vomiting, and diarrhea), slowing the infusion;
- In the case of infusion-related dyspnea or clinically diagnosed hypotension, stopping the infusion;
- In the case of life-threatening infusion reactions, trastuzumab should be permanently discontinued.

6.1.6.4.3. Docetaxel

Hypersensitivity

In the case of docetaxel-related hypersensitivity despite prophylactic treatment, treatment should be given per the package insert of docetaxel and medical routine.

- In the case of Grade ≤ 3 hypersensitivity, the investigator should decide whether to continue treatment with docetaxel based on the situation.
- In the case of Grade 4 hypersensitivity, docetaxel must be permanently discontinued.

Peripheral neuropathy or musculoskeletal pain

In the case of docetaxel-related sensory neurotoxicity or musculoskeletal pain that cannot be controlled by analgesics, docetaxel medication should be adjusted according to the following principles:

- In the case of Grade 2 peripheral neuropathy or musculoskeletal pain persisting for > 7 days per CTCAE v4.0.3, the dose of docetaxel should be reduced by 1 level.
- In the first occurrence of Grade 3 peripheral neuropathy or musculoskeletal pain, medication may be resumed at a reduced dose of docetaxel by 1 level if the condition relieves/recovers within 7 days. However, in the second occurrence of Grade 3 peripheral neuropathy or musculoskeletal pain or in the case of Grade 3 peripheral neuropathy or musculoskeletal pain persisting for > 7 days, docetaxel should be permanently discontinued.

6.1.7. Duration of treatment

Subjects receive study treatment continuously until investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation.

6.1.8. Dose tracking

Pyrotinib/placebo

Subjects are required to document on the Subject Diary Card daily and return all unused study drugs from the previous cycle before the commencement of the next cycle. The quantity of pyrotinib/placebo returned by the subjects will be counted, recorded, and archived.

Trastuzumab and docetaxel

The study center should prepare the drugs and complete the documentation as per the Pharmacy Manual. The documentation system of the study center should include all relevant or required information with regards to preparation and administration.

6.1.9. Precautions for special drug delivery devices

The equipment and precautions required for the infusion of trastuzumab and docetaxel are detailed in their package inserts, Pharmacy Manual, and Sections 6.1.5 and 6.1.6.

6.2. Dosing Regimen

The 590 subjects are randomized in a 1:1 ratio to the treatment group and the control group. The specific dosing regimen is as follows:

Treatment Group	Pyrotinib	400 mg, PO, once daily, administered within 30 min after breakfast, in 21-day cycles
	Trastuzumab	8 mg/kg loading dose in Cycle 1 and 6 mg/kg dose in subsequent cycles, IV, D1, in 21-day cycles
	Docetaxel	75 mg/m^2, IV, D1, in 21-day cycles
Control Group	Placebo	400 mg, PO, once daily, administered within 30 min after breakfast, in 21-day cycles
	Trastuzumab	8 mg/kg loading dose in Cycle 1 and 6 mg/kg dose in subsequent cycles, IV, D1, in 21-day cycles
	Docetaxel	75 mg/m^2, IV, D1, in 21-day cycles

6.3. Drug Management, Dispensation and Return

The management, dispensation and return of the study drugs in this study are in the charge of designated staff. The investigator must ensure that all the study drugs are only used for the subjects participating in this clinical study. The dosage and administration should follow the study protocol. The remaining drugs should be returned to the sponsor. The study drugs should not be transferred to any non-clinical study participant.

The study drugs must be stored according to the label. The drug receipt forms must be signed by two people during drug dispensation. The form is in duplicate copies, of which one is for the study center and the other is for the sponsor. Remaining drugs and empty boxes will be retrieved at the end of the study and a retrieval form will also be signed by both parties. The dispensation and return of each dose of drug should be immediately documented on designated forms.

All remaining study drugs and packages in this study will be returned to the sponsor for destruction.

The CRA is responsible for monitoring the supply, usage, and storage of the study drugs, and the management of remaining drugs.

6.4. Concomitant Treatment

Concomitant treatment refers to treatment that is given for the interest of subjects as determined by the investigator.

All concomitant treatments, blood products, and non-drug interventions (such as puncture) given to the subjects from screening to the end of study visits will be documented in the eCRF.

Subjects are monitored closely if an adverse reaction occurs. Symptomatic treatment is provided when necessary and details are documented in the eCRF. The following medications should be used carefully during the study:

- Drugs that interfere with liver P450 enzymes or P-gp:

1. Strong CYP3A4 inducers (e.g., dexamethasone [except prophylactic medication with docetaxel], phenytoin sodium, carbamazepine, rifampicin, rifabutin, and rifapentine);
2. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit);
3. CYP2C19 substrates (diazepam, imipramine, lansoprazole, and S-mephenytoin);
4. P-gp inhibitors (ritonavir, cyclosporine, and verapamil) and inducers (rifampicin)

- Drugs that prolong the QT interval:

1. Antibacterial agents (such as clarithromycin, azithromycin, erythromycin, roxithromycin, metronidazole, and moxifloxacin)
2. Antiarrhythmic drugs (quinidine, sotalol, amiodarone, propiamine, procainamide, etc.)
3. Antipsychotics (risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, clozapine, etc.)
4. Antifungal drugs (fluconazole, ketoconazole, etc.)
5. Antimalarial drugs (mefloquine, chloroquine, etc.)
6. Antidepressants (amitriptyline, imipramine, clomipramine, dosulepin, doxepin, etc.).

6.4.1. Other anti-tumor/cancer or investigational drugs

Other anti-tumor treatments (chemotherapy, endocrine therapy, immunotherapy, etc.) are not permitted when the subject is receiving treatment with the study drugs. In addition, proprietary Chinese medicines with clear anti-tumor indications are also prohibited. Hormonal contraceptives by oral administration, injection, or implantation are not permitted. Systemic high-dose corticosteroids (daily dose of dexamethasone > 20 mg (or equivalent dose of other corticosteroids) for > 7 consecutive days) are not permitted during treatment.

Palliative radiation may be permitted for the treatment of painful bone lesions, provided that these lesions existed prior to enrollment and the investigators must clearly specify that the palliative radiation does not indicate PD. During palliative radiotherapy, treatment with **pyrotinib/placebo, trastuzumab, and docetaxel** will be interrupted.

6.4.2. Permitted treatments

Comorbidities and all AEs occurred should be actively treated. All concomitant medications should be documented in the eCRF in strict accordance with the GCP regulations.

Patients with bone metastases who have started treatment with bisphosphonate before enrollment are permitted to continue the treatment during the study.

Palliative and supportive care for disease-related symptoms will be based on the investigators' judgment and relevant guidelines.

G-CSF may be used during the study per clinical guidelines and docetaxel's package insert.

Active symptomatic treatment should be given for AEs such as diarrhea, nausea, and vomiting. The treatment recommendations are detailed in Section 6.1.6.

6.5. Subject Compliance

Subject compliance will be assessed by reviewing dispensation and return records of all study treatments. All dose reductions and interruptions must be recorded.

Accurate records must be maintained for each study treatment provided by the sponsor, including trastuzumab and docetaxel for study-defined treatments. These records should contain at least the following information:

- Shipment records of drugs received from the sponsor (date and quantity received)

The drug dispensing log must be kept in real time, including the following information:

- The study number of the subject receiving the study drug
- The date, drug number, and quantity of study drug dispensed to the subject.

Copies of the dispensation and inventory forms must be kept. See Section 6.3 for instructions on the destruction of unused and partially used study drugs or packages.

7. STUDY PROCEDURES

7.1. Screening

Written informed consent form must be obtained before any study-specified medical procedures are performed, except tumor imaging examinations, bone scans, and echocardiography that meet the protocol requirements and are obtained prior to the signing of ICF for participating in this study.

Unless otherwise stated, the following screening procedures must be completed within 21 days prior to randomization; screening visit (Day -21 to Day -1):

- Demographics: name initials, gender, ethnicity, marital status, date of birth, height, weight, and body surface area and body mass index calculated accordingly;
- Complete medical history: including prior medical and treatment history (clinical/histological diagnosis, time of diagnosis, clinical/pathological staging, HER2/ER/PR/expression status; surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy, time of progression, evidence for progression; LVEF before, during, and after administration of trastuzumab must be collected if trastuzumab is used as neoadjuvant/adjuvant therapy; anti-tumor treatments for recurrent/metastatic breast cancer, such as surgery and endocrine therapy), history of smoking and drinking, history of drug allergies (drug name and symptoms), concurrent diseases and

concomitant treatments (disease name, name of concomitant medication, dose, and method of administration);

- ECOG PS;
- Vital signs: including body temperature, blood pressure, respiratory rate, and pulse;
- Physical examination: including general conditions, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental status; height and weight must be measured at baseline;
- Infectious disease screening;
- Echocardiography: Results within 21 days prior to randomization are acceptable (including qualified echocardiography completed before the signing of ICF);
- Tumor assessment: Multidetector spiral CT or contrast-enhanced MRI of the brain, chest, and abdomen should be at least performed during the screening period. The investigator may add other scan sites such as the neck and pelvic cavity based on clinical indications. During the screening period, the results within 21 days prior to randomization are acceptable (including qualified tumor assessments completed before signing the ICF);
- Bone scan: A bone scan is required for subjects who have not undergone a bone scan within 21 days prior to randomization. Positive bone lesions must be reviewed by CT/MRI examination (or X-ray) of bones;
- Prior/concomitant treatment: The patient's medications and treatments should be recorded within at least 28 days prior to randomization;
- Adverse event follow-up: AEs are observed and recorded from the day the subject signs the ICF, but all non-serious adverse events (non-SAEs) that occur prior to the first administration of the study drug will be reported in the medical history unless the investigator believes that they are more appropriate to be reported as AEs.

The following laboratory tests must be completed within 7 days prior to randomization; screening visit (Day -7 to Day -1)

- 12-Lead ECG;
- Hematology;

- Urinalysis;
- Routine stool test;
- Blood biochemistry;
- Blood pregnancy test for women of childbearing potential;

7.2. Enrollment

After completion of all screening assessments, eligible subjects as assessed by the investigator will be assigned a randomization number.

Stratification factors for randomization include:

- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

After obtaining the randomization number, the subject starts the study treatment of the group within 48 h after randomization.

7.3. Treatment Period

The following examinations should be performed according to the time window specified in the Schedule of Activities. In the event of statutory holidays, the examinations may be performed earlier and the reason should be documented in the eCRF. The investigator may add test items or increase the frequency of visits depending on the subjects' clinical conditions:

- ECOG PS: evaluated during the visit in each cycle;
- Vital signs: measured during the visit in each cycle;
- Physical examination: performed during the visit in each cycle;
- Hematology: tested during the visit in each cycle; additional hematology tests are performed on D8 ± 1 day of each cycle in the first 3 cycles of chemotherapy;
- Urinalysis: performed once at the end of every 4 cycles; in case of a urine protein ≥ ++, a 24-h urine protein quantitation should be tested;

- Routine stool test: performed once at the end of every 4 cycles;
- Blood biochemistry: tested during the visit in each cycle; myocardial zymography may be performed when necessary as determined by the investigator based on the subject's condition;
- Pregnancy test: performed if the subject is likely to be pregnant (see Section 8.2.1 for details);
- 12-Lead ECG: performed during the visit in each cycle; if QTcF interval increases by > 30 msec from baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG measurements are required (at least 10 min apart);
- Echocardiography: performed once at the end of every 4 cycles; may be performed if there are symptoms such as chest pain and palpitations during the treatment period;
- Tumor assessment: The tumor assessment schedule during the administration period is determined after the start of treatment (i.e., C1D1) and is not changed regardless of dose interruptions due to toxicity. The time window for tumor assessment is ± 7 days. Specific evaluation time points are as follows:
  - ✓ Once at the end of every 3 cycles in the first 24 cycles and once every 4 cycles thereafter;
  - ✓ In the case of PD, the subject should discontinue the treatment and enter the follow-up period. Other anti-tumor treatments are prohibited prior to PD;
  - ✓ Subjects who request to withdraw from the study due to intolerable adverse events or other reasons must undergo a complete tumor assessment prior to discontinuation of treatment (unless performed within 28 days).
- Concomitant medications/treatments: All concomitant medications/treatments during the study should be documented;
- Adverse events: All adverse events during the study should be monitored and documented.

7.4. End-of-Treatment (EOT) Visit

Following completion of study treatment, the subject should undergo the following examinations within 7 days after treatment discontinuation is determined:

- ECOG PS (unless performed within 7 days);
- Vital signs (unless performed within 7 days);
- Physical examination (unless performed within 7 days);
- Hematology (unless performed within 7 days);
- Urinalysis (unless performed within 7 days);
- Routine stool test (unless performed within 7 days);
- Blood biochemistry (unless performed within 7 days);
- 12-Lead ECG (unless performed within 7 days);
- Echocardiography (unless performed within 28 days);
- Imaging examination (unless performed within 28 days);
- Pregnancy test: Urine pregnancy test can be performed; but if positive for urine pregnancy test, the subject should undergo blood HCG test for confirmation;
- Concomitant medication/treatment: Once the study treatment is interrupted, only concomitant medications or treatments for new or unresolved AEs related to study treatment should be documented. Concomitant medications or treatments for cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has resolved or disappeared, or until 12 months after the last dose;
- Adverse event: AEs that have not recovered after discontinuing the protocol-specified study treatment must be followed and a final assessment must be made. All subjects should record AEs within 28 days after the last dose [cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has resolved or disappeared, or until 12 months after the last dose].

7.5. Follow-up Period

Subjects who discontinue the study medication will immediately enter the follow-up period. The following must be performed until the survival follow-up is completed (randomized subjects who have not received the treatment do not need to be followed):

- Safety follow-up: A safety visit is conducted within 28 ± 7 days after the last dose for ECOG PS, vital signs, and physical examination. Adverse events should continue to be monitored and recorded until the end of follow-up period specified in Section 9.3.
- Efficacy follow-up: Subjects who discontinue treatment for reasons other than PD and death will continue tumor assessments at time points specified by the protocol, starting from the last tumor assessment during the treatment period, until PD, start of a new anti-tumor treatment, or death (whichever occurs first). The time of each follow-up visit, result of tumor imaging assessment, and other anti-tumor treatments should be documented in detail.
- Survival follow-up (OS data collection): All survival subjects who have completed the safety follow-up and efficacy follow-up (whichever is completed later) should undergo survival follow-up. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), starting from the day of completion of safety follow-up and efficacy follow-up (whichever comes later), until death, lost to follow-up, or study termination (whichever occurs first). Data from each survival follow-up should be documented and entered into the appropriate eCRF.

7.6. Visit for Early Discontinuation of Treatment

Subjects who request to withdraw from the study due to intolerable adverse events or other reasons should complete all examinations required at the end-of-treatment (EOT) visit.
A complete tumor assessment is recommended when treatment discontinuation is determined (unless performed within 28 days). Imaging examination should be continued thereafter whenever possible until PD, death, or start of a new anti-tumor treatment (whichever occurs first).

7.7. Unscheduled Visit

The investigator may prescribe unscheduled visits when necessary based on the subject's situation. Details of unscheduled visits should be documented in the original medical record.

8. EVALUATIONS

8.1. Efficacy Evaluation

8.1.1. Tumor assessment

8.1.1.1. Evaluation of efficacy against solid tumors

In this study, the efficacy will be assessed per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for all eligible subjects. The investigators of all study centers and the imaging review experts designated thereby will perform tumor assessment per RECIST 1.1. The primary PFS analysis is based on the assessment results by the investigators.

The CRO for independent tumor assessment consists of 2 independent, qualified imaging radiologists, who will independently conduct blinded evaluation in a designated system with the assistance of a CRA after being trained and tested for imaging review. In the event of disagreement between the two independent radiologists, a third radiologist should make the final judgment under the same conditions as above. The details are listed in the "Third-Party Independent Review Charter" for this study.

The efficacy evaluation of each checkpoint is divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) per RECIST 1.1. Refer to Appendix III for details.

Subjects are required by the study to have at least one measurable lesion. Measurable lesions are defined as tumorous, non-lymphoid lesions ≥ 10 mm in longest diameter, or tumor-associated nodal lesions ≥ 15 mm in longest shorter diameter. In the case of a thickness/spacing of scanning slices > 5 mm, the longest diameter of the measurable lesion must be twice the slice thickness/spacing.

8.1.1.2. Scanning requirements for medical imaging

Qualified multidetector spiral CT should be used for enhanced tumor imaging scan. Subjects allergic to contrast media should undergo contrast-enhanced CT whenever possible according to the study center's guideline for the prevention of allergies to contrast media. CT and MRI are the only acceptable methods of examination in this study. Other imaging methods may only serve as supplementary diagnostic methods. The same method of examination should be used at baseline and during follow-ups per RECIST 1.1. Non-enhanced CT scan of the chest and MRI scan of the abdomen are permitted if the subject is contraindicated to CT contrast media during the treatment or follow-up period. In the case of local recurrence of breast cancer, an MRI scan of the recurrence site is also required. Refer to the "Imaging Manual for Study Centers" for the scanning parameters, requirements, and methods in detail.

At least examinations of the chest, abdomen, and head as well as bone scan should be conducted during the screening period [positive bone lesions must be reviewed by CT/MRI examination (or X-ray) of bones]. Examinations of the neck and pelvic cavity may be added if clinically indicated. During the treatment and follow-up periods, the investigator may also add scan sites for tumor evaluation when clinically indicated. If disease progression is indicated, unscheduled visit may be added for imaging examination based on the condition. Qualified CT scans and other imaging results obtained prior to the signing of ICF within the time window (and within 21 days prior to randomization) may be considered for tumor evaluation during the screening period.

Subsequent tumor assessments should be conducted with the same parameters and conditions as those of the baseline examination whenever possible. The tumor assessment schedule is determined after the start of treatment and should not be changed despite of dose interruption. The time window for tumor assessment is ± 7 days. Specific evaluation time points are as follows:

- First evaluation on Day 21 of Cycle 3, once at the end of every 3 cycles in the first 24 cycles, and once at the end of every 4 cycles thereafter;
- At the end of treatment or upon withdrawal (if not performed within 28 weeks prior) for subjects who withdraw due to reasons other than PD and death;

The thickness of CT scan and reconstruction must be less than or equal to 5 mm per the RECIST 1.1. The dose of contrast media for enhanced scanning, the injection rate, and the enhancement phase of each anatomical site are detailed in the imaging manual and should be kept consistent at all checkpoints.

Locally recurrent cutaneous lesions of breast cancer, if any, should be photographed using a digital camera following the requirements of the imaging manual.

The tumor assessment at the study center should be performed by an experienced, qualified study physician designated by the study center who is unaware of the group assignment. Also, each study center should record all the raw data of imaging examinations related to efficacy evaluation on CD-ROM in DICOM format, and send them to the designated central imaging within the specified time, for medical imaging quality control and efficacy evaluation by an independent, third-party imaging evaluation committee.

8.1.2. Primary endpoint

PFS: The time between the date of randomization and the first PD or death due to any cause based on the investigator's imaging review results. Tumor assessments are performed based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If no PD or death is observed at the study cut-off date, or the subject has received other anti-tumor treatments, the cut-off date or the date of the last tumor evaluation prior to the start of a new anti-tumor treatment (whichever occurs first) should be used as the censored date.

8.1.3. Secondary endpoints

PFS: The time between the date of randomization and the first PD or death due to any cause based on the IRC's imaging review results. Tumor assessments are performed based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If no PD or death is observed at the study cut-off date, or the subject has received other anti-tumor treatments, the cut-off date or the date of the last tumor evaluation prior to the start of a new anti-tumor treatment (whichever occurs first) should be used as the censored date.

ORR: Refers to the percentage of subjects in the analysis set with best overall response of CR or PR from the start of study treatment to subject withdrawal due to PD. Evaluated based on the RECIST 1.1.

DoR: Refers to the time period from the first evaluation of CR or PR (whichever occurs first) to PD or death. Evaluated based on the RECIST 1.1.

CBR: Refers to the percentage of subjects in the analysis set with CR, PR, and SD (≥ 24 weeks). Evaluated based on the RECIST 1.1.

OS: Refers to the time from the date of randomization to the date of death due to any cause. For subjects who are still alive at the last follow-up, their OS will be censored at the date of last follow-up. For subjects who are lost to follow-up, their OS will be censored at the last confirmed survival time before lost to follow-up. The OS for data censoring is defined as the time from randomization to censoring.

Except for OS, the above endpoints are the results of efficacy evaluation and evaluated per RECIST 1.1 during the study period. The analysis of OS includes all tumor evaluations during the treatment period and the follow-up period.

8.2. Safety Evaluation

8.2.1. Pregnancy test

Female subjects of childbearing potential will undergo blood HCG test before the start of administration. The test must have a sensitivity of at least 25 mIU/mL for HCG. After a negative result is obtained from the pregnancy test during the screening period, appropriate contraceptive measures should be taken. Subsequently, urine/blood pregnancy test should be performed at least during the end-of-treatment visit and safety visit. During the study, additional pregnancy test may be prescribed per the diagnosis and treatment routine of the study center. Subjects positive for urine pregnancy test during the study should undergo blood HCG test for confirmation. If HCG test shows positive result, the subject should discontinue medication and be treated in according to Section 9.4.

8.2.2. Adverse event

The assessments of AEs include type, incidence, severity (according to NCI CTCAE v4.03), start and end date, actions taken, whether it is an SAE, causality, and outcome.

AEs that occur during the study, including signs and symptoms at screening, will be recorded on the AE page of the eCRF.

8.2.3. Laboratory safety evaluation

Samples for laboratory tests are collected at time points specified in the "Schedule of Activities". The study centers will be responsible for sampling and testing the following laboratory indicators. Unscheduled laboratory tests may be carried out at any time for safety reasons.

Table 4. Laboratory tests

Hematology	Blood Biochemistry	Routine Stool Test	Urinalysis[a]
Hemoglobin Red blood cell White blood cell Neutrophil count Lymphocyte count Platelet count	Total bilirubin Conjugated bilirubin Unconjugated bilirubin ALT AST Alkaline phosphatase γ-GT Total protein Albumin A/G Urea/urea nitrogen Creatinine Uric acid Blood glucose Triglyceride Cholesterol	Fecal occult blood	Urine protein Urine glucose Urine occult blood

Hematology	Blood Biochemistry	Routine Stool Test	Urinalysis[a]
	Potassium Sodium Chlorine Calcium Phosphorus Magnesium		
Infectious Disease Screening	**Others**		
Hepatitis B test HIV antibody HCV antibody	Pregnancy test[b]		

Note: a. If the protein results of the semi-quantitative method (such as urine test paper) are ≥ 2+, a quantitative test of 24-h urine protein should be performed.

b. Women of childbearing potential must undergo a blood HCG test to rule out pregnancy during screening. For other time points, a urine HCG test is required.

8.2.4. Vital signs and physical examination

The investigator is responsible for physical examination. The examination items include: general condition, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental status. Weight will be measured during each physical examination, but height will only be measured during screening. If the investigator believes that the height of the subject may change, the height should be re-measured.

Vital signs include: body temperature, blood pressure, respiratory rate, and pulse.

ECOG PS is assessed by the investigator based on Appendix I "ECOG Performance Status Score".

8.2.5. 12-Lead ECG

12-Lead ECG should be performed by a qualified physician at the time points specified in the "Schedule of Activities".

Subjects are required to rest for at least 10 min in a supine position prior to the ECG examination. The ECG should include at least heart rate, QT, QTc, and P-R intervals.

To assess the safety of the subject, the investigator will compare the ECG results with those at baseline. If the QTcF interval increases by > 30 msec compared to baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG tests are required, at least 10 minutes apart, to verify the accuracy of the initial measurement and to rule out incorrect electrode placement causing the abnormality. If the device judges that the QTc value is prolonged, as described above, but a qualified physician considers that the QTc value is still within the acceptable range, there is no need to repeat the measurement.

9. ADVERSE EVENT REPORTING

9.1. Adverse Events (AEs)

9.1.1. Definition of adverse event

AE is defined as adverse medical events that occur after the subject receives a drug in clinical trial, but do not necessarily have a causal relationship with the treatment. In this study, all AEs occurring from the time that the subject provides informed consent, through and including 28 days of the last dose of study treatment will be collected. AEs can be any undesirable and unexpected symptoms, signs, laboratory abnormalities, or diseases, including at least the following conditions:

1) Worsening of pre-existing (prior to enrollment of clinical trial) medical conditions/diseases (including worsening of symptoms, signs, or laboratory abnormalities);

2) Any new onset of AE: Any adverse medical conditions newly occurring (including symptoms, signs, and newly diagnosed diseases);

3) Abnormal laboratory test or result with clinical significance.

All AEs that occur in the subjects should be documented in detail by the investigators, including: the name of the AE and description of all relevant symptoms, time of onset, severity, causality with study drugs, duration, measures taken, as well as final outcomes and prognosis.

9.1.2. AE severity assessment criteria

Refer to NCI-CTCAE v4.03 for grading criteria. Refer to the following criteria for AEs not listed in NCI-CTCAE v4.03:

Table 5. AE severity grading criteria

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild clinical symptoms; clinical or laboratory test abnormality only; intervention not indicated.
2	Moderate; minimal, local, or non-invasive interventions indicated; limiting age-appropriate instrumental activities of daily living (ADL), e.g., preparing meals, shopping, using the telephone, managing money, etc.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening; urgent intervention indicated.
5	Death related to AE.

9.1.3. Causality assessment

AEs should be collected and recorded from the time that the subject provides informed consent up to 28 days after the last dose of study treatment, regardless of whether the event is related to the study drug, whether the subject is assigned to an experimental arm, or whether the medication is administered or not. All subject complaints and abnormal changes in laboratory tests during the treatment should be documented truthfully. Meanwhile, the severity, duration, measures taken, and outcome of the AE should be recorded. The investigators should determine the relationship between the AE and study drugs, such as whether there is a plausible temporal relationship between the AE occurrence and the study drugs, the characteristics of the study drugs, the toxicological and pharmacological effects of the study drugs, the use of concomitant medications, the subject's underlying diseases, medical history, family history, as well as challenge and rechallenge. The causality assessment should be made using the following five-category scale: "definitely related, possibly related, unlikely related, not related, and unassessable".

Table 6. Criteria for the causality assessment between AEs and study drug

Classification	Criteria
Definitely Related	The AE occurs in a plausible temporal relationship to drug administration. The event is a recognized pharmacological phenomenon of the suspected drug. The event resolves with drug discontinuation and recurs with drug re-administration.
Possibly Related	The AE occurs in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Unlikely Related	The AE does not occur in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Not Related	The AE does not occur in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments. The event resolves when patient's clinical status improves or other treatments are discontinued. The event recurs upon restarting other treatment.
Unassessable	The temporal relationship between the AE and drug administration is unclear. The event is similar to a recognized pharmacological phenomenon of the product. It can also be explained by concomitant medications.

9.2. Serious Adverse Events (SAEs)

9.2.1. Definition of SAE

An SAE is defined as any medical event during the clinical trial that requires hospitalization or prolonged hospitalization, or results in disability, impairment of work ability, life-threatening, death, or congenital malformation. The following medical events are included:

- Events leading to death;
- Life-threatening events (defined as when the subject is at immediate risk of death at the time of the event);
- Events requiring hospitalization or prolonged hospitalization;
- Events leading to persistent or significant disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require intervention to prevent any of the above outcomes).

9.2.2. Hospitalization

AEs resulting in hospitalization (even less than 24 hours) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

- Rehabilitation facilities
- Nursing homes
- Routine emergency room visit (observation for less than 24 hours)
- Same day surgery (such as outpatient/same day/ambulatory surgery)
- Social reasons (medical insurance reimbursement, etc.)

Hospitalization or prolonged hospitalization in the absence of the worsening of an AE is not in itself an SAE. For example:

- Admission due to pre-existing conditions without the occurrence of new AEs or worsening of the pre-existing diseases (e.g., for work-up of persistent pre-treatment laboratory abnormalities);
- Administrative admission (e.g., annual physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Elective admission not associated with the worsening of AEs (e.g., elective surgery);
- Pre-planned treatment or surgery. This should be noted in the baseline documentation for the entire study protocol and/or for the individual subject;

- Admission exclusively for the administration of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendicectomy should be recorded as treatment of the AE.

9.2.3. Disease progression and death

Disease progression is defined as the worsening of the subject's conditions caused by the indications of the study, including radiological progressions and/or progressions in clinical symptoms and signs. New metastases relative to the primary tumor or progressions of the previous metastases are recognized as PD. Events that are life-threatening, require hospitalization or prolonged hospitalization, or result in persistent or significant disability/incapacity/impairment of work ability due to symptoms and signs of disease progression, and congenital anomalies or birth defects are not reported as SAEs. Death caused by the symptoms and signs of PD will be reported as an SAE.

Death of a subject during the study, regardless of whether a new anti-tumor treatment is administrated, must be reported as an SAE. The term "death" should not be reported as an AE or SAE term, but as the outcome of the event. Events that result in death should be recorded as AEs or SAEs. If the cause of death is unknown and cannot be determined at the time of reporting, the AE or SAE term "death unexplained" shall be used for documentation.

9.2.4. Potential drug-induced liver injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations of TBIL that meet all of the following criteria in the absence of other etiologies causing the liver injury should be considered as drug-induced liver injury, and should be reported as important medical events and reported as SAEs.

Potential drug-induced liver injury is defined as follows:

Baseline Period	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT and TBIL)
Treatment Period	• ALT or AST ≥ 3 × ULN • With TBIL ≥ 2 × ULN • And ALP ≤ 2 × ULN • And no hemolysis	• AST or ALT ≥ 2 × baseline level, and values ≥ 3 × ULN; or AST or ALT ≥ 8 × ULN • With TBIL increase ≥ 1 × ULN or TBIL ≥ 3 × ULN

The subject should return to the study center and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include the

laboratory tests, detailed history, and physical assessment. The possibility of hepatic tumor (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, TBIL, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, may be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) may be warranted. If compliance with the above laboratory criteria is confirmed upon re-examination, the possibility of potential drug-induced liver injury should be considered in the absence of any other causes of abnormal liver function, without waiting for all liver function test results. Potential drug-induced liver injury should be reported as an SAE.

9.2.5. SAE reporting

The period for SAE collection begins from the time that the subject provides informed consent, through and including 28 calendar days after the last dose of study treatment. All SAEs should be reported to the sponsor by the investigator on the "Serious Adverse Event Report Form" (signed and dated) within 24 hours of awareness, regardless of whether this is an initial report or a follow-up report. The investigator should also report the SAEs to relevant organizations in a timely manner as required by local regulations.

The sponsor's email address for SAE reporting is: **hengrui_drug_safety@hrglobe.cn**

SAEs that occur 28 days after the last study dose are generally not reported unless they are suspected to be related to the study drug(s). The detailed record content of SAE should include symptoms, severity, causality with study drugs, time of onset, time of treatment, action taken with study drugs, follow-up time and method as well as outcome. If the investigator considers that an SAE is not related to study drugs, while potentially related to the study conditions (e.g., termination of the original treatment or complications during the study), the relationship should be described in detail in the narrative section of SAE report form. If there is a change in the severity of an ongoing SAEs or its relationship with the study drug, follow-up reports should be submitted immediately. If misinformation is considered to be present in the previously reported SAE, it can be corrected, retracted or downgraded in the follow-up report in accordance with the SAE reporting procedures.

9.3. Follow-up of AEs/SAEs

During treatment until safety follow-up visit

All AEs/SAEs should be followed up until the following conditions, and every effort should be made to ensure the best outcome and that definite causality assessment is obtained:

- The AE disappeared, or improved to baseline level or Grade ≤ 1
- No further improvement is expected for the AE per investigator's assessment
- Death

For the AEs that persist at safety follow-up visit

AEs should be followed up until the following occurs (whichever occurs first):

- The AE disappeared, or improved to baseline level or Grade ≤ 1
- The AE stabilized and no further improvement is expected per investigator's assessment
- Death
- New anti-tumor treatment affects the determination of AE outcome
- Data collection for the clinical trial is terminated

Event of cardiotoxicity should be followed if persisting at the end-of-treatment visit (regardless of causality with the study drugs) until the AE has recovered or disappeared, or until 12 months after the last dose of study treatment.

Investigators should inquire about AE/SAE after the last visit at each visit and provide follow-up data in time according to the sponsor's queries.

9.4. Pregnancy

If a female subject becomes pregnant during the study, the subject must immediately discontinue the study treatment. The investigators should report the pregnancy to the sponsor within 24 hours of awareness and to the ethics committee timely using Hengrui Clinical Trial Pregnancy Report/Follow-Up Form.

The investigator should follow up the pregnancy outcome until 1 month after delivery, and report the outcome to the sponsor and the ethics committee.

The email address for pregnancy reporting is: hengrui_drug_safety@hrglobe.cn.

Pregnancy outcomes such as stillbirth, spontaneous abortion, and fetal malformation are considered SAEs and need to be reported according to the time requirements for SAEs.

If a subject experiences any SAE during pregnancy, then "Serious Adverse Event Report Form" should be filled out and reported according to SAE reporting procedure.

9.5. AEs of Special Interest

All AEs of special interest (SIEs) specified in the study protocol should be reported to the sponsor by the investigator on the "Clinical Trial SIE Report Form" within 24 hours of awareness. If an SIE is also an SAE, it should also be reported on Serious Adverse Event Report Form in accordance with SAE reporting procedures.

Cardiac events are adverse events of special interest in this study, including:

- Asymptomatic LVEF decrease by ⩾ 10% and the value < 50%
- Symptomatic LVEF decrease, left ventricular systolic dysfunction
- Prolonged QTcF (average QTcF > 500 ms)
- Events possibly due to abnormal cardiac function: e.g., syncope and seizure
- Other Grade 3 or 4 cardiac events

The following principles are recommended for reporting AEs and SAEs of special interest in this study.

Left ventricular systolic dysfunction and asymptomatic LVEF decrease should be reported using the AE terms in the table below.

Table 7. Reporting rules for left ventricular systolic dysfunction

Symptom	Clinical Result	Reported Term	Grading Scale
Asymptomatic	Asymptomatic LVEF decrease from baseline by ⩾ 10% and value < 50%	Ejection fraction decreased	Refer to AE term of "ejection fraction decreased" in CTCAE 4.0.3
	Asymptomatic LVEF decrease requiring treatment or leading to dose interruption or reduction of any study drug	Ejection fraction decreased	Refer to AE term of "ejection fraction decreased" in CTCAE 4.0.3
Symptomatic	Symptomatic left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Refer to AE term of "left ventricular systolic dysfunction" in CTCAE 4.0.3

10. CLINICAL MONITORING

The clinical research associate (CRA) is responsible for monitoring whether the study is carried out in accordance with relevant regulations, the GCP, and study protocol; whether the CRF is entered accurately and completely, and consistent with source documents such as medical records and physical and chemical test reports, and free from errors and omissions. The CRA must check the content in eCRF against the source documents item by item, ensuring that the data in eCRF are consistent with the source data. This process is also known as source data verification (SDV).

11. DATA ANALYSIS/STATISTICAL METHODS

The detailed statistical analysis of this study will be included in the Statistical Analysis Plan (SAP) and kept by the sponsor. The plan marked in the protocol can be appropriately modified in the SAP. However, any significant revisions to the definitions and analyses of primary study endpoints should be reflected in the amendment versions of the protocol.

11.1. Sample Size

In this study, PFS is used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to evaluate the efficacy of the drugs and to determine whether to terminate or continue the study. The assumptions for sample size calculation are as follows:

- Enrollment duration = 24 months, minimum follow-up = 18 months (overall duration of 42 months)
- Randomization in a 1:1 ratio
- Overall $\alpha = 0.025$ (one-sided)
- The power of test is 80%
- Hazard ratio (HR) = 0.76 (estimated median PFS is 12.5 months in the control group and 16.5 months in the treatment group)
- An interim analysis will be performed when 50% of PFS events (205 events) are collected to evaluate the efficacy of the drugs, and to decide whether to terminate or continue the study.

Based on the above parameters, at least 410 PFS events should be collected according to the log rank test for PFS comparison between two groups and the Lan-DeMets α spending function (EAST 6.4.1) constrained by the O'Brien & Fleming boundaries. Assuming that the PFS dropout rate is 15% for 24 months, approximately 590 subjects should be enrolled.

11.2. Statistical Analysis Plan

In this study, SAS 9.4 or above will be used for data processing and analysis.

The time-to-event variables (such as PFS, OS, and DoR) will be analyzed using the Kaplan-Meier (KM) method, the survival functions of the two groups will be estimated, and the survival curves will be plotted. In addition, the Cox regression model will be used to estimate the hazard ratio between the two groups and its 95% CI.

For binary variables, the Cochran-Mantel-Haenszel (CMH)/Chi-square/Non-parametric test (if applicable) methods can be used to test the inter-group difference and compute its 95% CI.

The safety data will be summarized using descriptive statistics.

The detailed analysis plan will be described in the Statistical Analysis Plan (SAP).

11.3. Statistical Hypothesis and Decision Rules

The primary endpoint of this study is PFS. The log-rank test is used for the inter-group comparison of the investigational drug and the control drug.

Hypothesis:

- H_0: The survival function of the pyrotinib group is the same as that of the placebo group
- H_1: The survival function of the pyrotinib group is different from that of the placebo group
- α level: 0.025 (one-sided)

11.4. Analysis Sets

- Full analysis set (FAS): all subjects who are screened eligible per the ITT principle and receive the study drugs after randomization and enrollment. The FAS is the primary analysis set for the efficacy analysis of this study.
- Per-protocol set (PPS): a subset of the FAS, excluding subjects with important protocol deviations which significantly impact study results.
- Safety analysis set (SS): all randomized subjects who have received at least one dose of the study drug and have at least one safety assessment.

The statistical analysis is performed for drug efficacy based on both the FAS and PPS. Before database is locked, the principal investigator, statistician and sponsor should determine the final PPS through the data review meeting.

11.5. Statistical Method

The following sections include the description of the planned statistical methods.

11.5.1. Basic methods

This study is a phase III, randomized, placebo-controlled, multicenter study. This study plans to perform 2 analyses by IDMC (including one interim analysis) and one final analysis. One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the blinded safety evaluation. The interim analysis will be carried out when 50% of PFS events (205 events) are collected to evaluate the efficacy of the drugs and to decide whether to terminate or continue the study. The final analysis will be performed when the number of PFS events reaches 410.

11.5.2. Analysis of primary efficacy endpoints

The primary endpoint of the study is PFS. The primary analysis will be based on the FAS. The survival functions of PFS of the two groups will be compared using both stratified and non-stratified log-rank tests. In addition, the Kaplan-Meier method will be used for estimating the PFS by group, the survival curves will be plotted, and the median PFS and its 95% CI will be estimated. The analysis with stratification factors will be used as the primary analysis.

In addition, as a supporting analysis, under the assumption of proportional hazards, the Cox models with and without considering stratification factors will be used to estimate the hazard ratio between the two groups and calculate the corresponding 95% CI.

The analysis methods for PPS will be the same as those for FAS.

11.5.3. Analysis of secondary efficacy endpoints

The secondary endpoints OS and DoR will be statistically described based on the FAS and PPS using methods similar to those of the primary endpoint.

The objective response rate (ORR) and clinical benefit rate (CBR) of the two groups and their two-sided 95% CIs will be estimated based on the FAS and PPS, and the inter-group differences of the rates and their two-sided 95% CIs will be calculated.

Other endpoints will be statistically summarized in accordance with general principles.

11.5.4. Handling of missing data

In this study, the missing data of the efficacy endpoints will not be treated specially, and the missing values will not be estimated in the safety evaluation.

11.5.5. Safety analysis

AEs that occur during the study will be coded according to the latest version of MedDRA. The frequency and incidence of AEs will be summarized by system organ class and preferred term. The causality and severity of AEs will be further tabulated for description. Descriptive statistics will be used to summarize other safety endpoints. Summarize the incidence of AEs, adverse drug reactions, AEs resulting in withdrawal from the study, AEs resulting in death, and SAEs; severity of AEs and adverse drug reactions: For the same AE with multiple occurrences in the same subject, the highest severity will be included in the analysis; for different AEs occurring in the same subject, the most severe AE will be included in the analysis.

Laboratory tests: Abnormal laboratory values will be summarized using descriptive statistics.

Vital signs: Measured values and changes will be summarized using mean, maximum, minimum, median, and SD.

Physical examination and 12-Lead ECG will be summarized using descriptive statistics.

Baseline is defined as the most recent test data before the first dose.

11.5.6. Interim analysis

In this study, an interim analysis will be carried out for the primary endpoint. The interim analysis will be conducted when 50% of PFS events (205 events) are collected. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:

Table 8. Termination criteria and significance level in the interim analysis and final analysis of PFS

Time Point	Number of PFS Events	Boundary Z-Value (Corresponding HR)	One-Sided Nominal Significance Level
Interim (1st)	205 (50%)	-2.963 (HR = 0.66)	0.002
Final	410	-1.969 (HR = 0.82)	0.024

Note: HR = Hazard ratio; PFS = Progression-free survival;

Results will be subjected to boundary testing and analysis based on z-scores simulated by EAST 6.4.1 and using the Lan-DeMets α spending function constrained by the O'Brien & Fleming boundaries

The unblinded interim analysis will be completed by independent statisticians and their programming team. The results of the unblinded interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study based on the results.

11.5.7. Safety analysis and evaluation by IDMC

In this study, a safety evaluation is scheduled upon enrollment of 10% (59) of subjects. The results will be reviewed by the IDMC, which will recommend whether to continue the study based on the results.

11.5.8. Subgroup analysis

Subgroup analyses will be performed for primary endpoint PFS according to (including but not limited to) the following factors, and the forest plot on HR will be produced:

Stratification factors:

- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

Baseline factors; critical baseline factors, including but not limited to age, ECOG PS, pathological grade, and lesion site, will undergo subgroup analysis.

11.5.9. Multiple comparison/multiplicity

The overall type I error rate in the interim and final analyses of the primary endpoint PFS will be strictly controlled at 0.025 (one-sided) by the O'Brien & Fleming method for the Lan-DeMets alpha spending function.

11.5.10. Exploratory analysis

Not applicable.

12. DATA MANAGEMENT METHOD

12.1. Data Recording

Data will be collected and managed using the electronic case report form (eCRF).

12.1.1. Filing of study medical records

As source documents, the medical records should be completely retained. The investigators should be responsible for filling and keeping the study medical record. The subject information on the cover of the medical record should be checked each time before filling the record. The medical record should be written in a neat and legible way so that the sponsor's CRA could verify the data with eCRF during each monitoring visit.

12.1.2. eCRF entry

Clinical study data will be collected using the HRTAU EDC system.

Entry: The data in the eCRF are from and should be consistent with the source documents, such as the original medical records and laboratory test reports. Any observations or test results in the study should be entered in the eCRF in a timely, accurate, complete, clear, normative, and verifiable manner. Data should not be changed arbitrarily. All items in the eCRF should be filled out, with no blank or omissions.

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the clinical study data entered into the EDC system and generate an error message prompt for questionable data. The PI or CRC will be permitted to modify or explain the problematic data. If necessary, multiple inquiries can be raised until the event of problematic data is resolved.

12.1.3. eCRF review

The investigator must complete, review, and submit the eCRF within <3> working days after the end of each subject's treatment course. The investigator or the data input operator (CRC) should promptly respond to queries raised by CRA, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

12.2. Data Monitoring

Implemented by: CRA.

Monitoring content: To confirm that whether the study protocol is adhered to; whether the records in eCRF are correct and complete, and consistent with the source documents such as study medical records and laboratory test reports, and whether there are errors or omissions in the data. According to the monitoring plan, the CRA will verify the completeness, consistency, and accuracy of study data in the database. The CRA will discuss problematic data with study personnel and direct them to add or correct the data whenever necessary. Ensure that the data in the eCRF are consistent with source data. This process is also known as source data verification (SDV).

12.3. Data Management

12.3.1. EDC database establishment

The data administrator will establish a study-related database according to the study protocol, which will be available for online usage within one week before the first subject is enrolled. All EDC users must submit Form for EDC User Permission and be sufficiently trained, with training records in hard copy, before obtaining the accounts of the EDC system for the project.

12.3.2. Data entry and verification

The investigators or CRC should input data into the EDC system in accordance with the requirements of the visit procedures and the eCRF completion guideline. After submitting the eCRF, the CRA, data manager, and medical reviewer should review the data. Questions during the review will be submitted to the investigators or CRC in the form of queries. After data cleaning is completed, the investigator should sign the completed eCRF for verification.

12.3.3. Blind review and database lock

After the clinical study is completed, the study director, sponsor, statistician, and data administrator will conduct a joint blind review before statistical analysis mainly to determine the analysis data set (including FAS, PPS, and SS) for each case, the judgment of missing values, and the handling of outliers. All decisions made under blind review cannot be modified after unblinding, and every decision must be documented.

After the established database is considered correct by blind review, the database will locked and unblinded. After the database is locked, the data must be properly stored for future reviews. The blind code and the database should be statistically analyzed by the statistician.

12.3.4. Data archiving

After the study is completed, the eCRFs of the subjects must be generated from the EDC system in the PDF format and kept on non-rewritable CD-ROMs, which will be archived by the sponsor and various institutions for auditing and/or inspection.

All materials should be preserved and managed in accordance with GCP requirements, and necessary documents of clinical trials should be preserved until 2 years after the investigational drug is approved for marketing or 5 years after the termination of the clinical study.

13. SOURCE DATA AND DOCUMENTS

According to ICH E6, relevant regulations, and requirements for subject's personal information protection of the study centers, each study center must properly keep all treatment and scientific records related to this study. As a part of the study that Hengrui sponsors or participates in, each study center must allow the authorized representative of Hengrui and regulatory authorities to inspect the clinical records (which may be copied if permissible by law) for quality review, audit, and evaluations of safety, study progress, and data validity.

Source data are information required to reconstruct and evaluate the clinical study, and are the original documentation of clinical findings, observations, and other activities. These source documents and data records include but are not limited to: hospital record, laboratory records, memos, subject diary cards, pharmacy dispensing records, recordings of advisory meetings, recorded data from automated devices, copies or transcripts that are verified to be accurate and intact, microfiche, photographic negatives, microfilms or magnetic disks, X-ray films, and subject's documents and records that are kept in the pharmacies, laboratories, and medical technology departments that are involved in this study.

14. QUALITY ASSURANCE AND QUALITY CONTROL

To ensure study quality, the sponsor and the investigators will jointly discuss and formulate a clinical study plan before the formal study initiation. All study personnel participating in the study will receive GCP training.

All the study centers must comply with the SOPs for the management of the study drugs, including receipt, storage, dispensation, return, and destruction (if applicable).

According to the GCP guidelines, necessary measures must be taken at the design and implementation phases of the study to ensure that all collected data are accurate, consistent, intact, and reliable. All observed results and abnormal findings in the clinical study must be verified and recorded in a timely manner to ensure data reliability. All devices, equipment, reagents, and standards used in various tests in the clinical study must have stringent specifications and be operated under normal conditions.

The investigators will input data required by the protocol into the eCRF. The CRA will check whether the eCRF is completely and accurately filled and guide the study site personnel for necessary correction and addition.

The drug regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), sponsor's CRA and/or auditor may carry out systemic inspection of study-related activities or documents to assess whether the study is implemented based on the study

protocol, SOPs, and relevant regulations (such as Good Laboratory Practices [GLP] and Good Manufacturing Practices [GMP]) and whether the study data are recorded in a prompt, truthful, accurate, and complete manner. The audit should be performed by personnel not directly involved in this clinical study.

15. REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

15.1. Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the CFDA (now NMPA) before starting a new drug study and the study can only be carried out after approval is obtained. The clinical approval numbers of pyrotinib applicable for this study include 2016L03115 and 2016L03116.

The legal basis for the design of this protocol is as follows:

1) Provisions for Drug Registration
2) Good Clinical Practice
3) Technical Guidelines for Clinical Pharmacokinetic Study of Chemical Drugs
4) Consensus on ethical principles based on international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines
5) ICH Guidelines
6) Other applicable laws and regulations

15.2. Ethical Standards

The investigator will ensure that the trial in this study is fully implemented in accordance with the requirements for subject protection in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and/or ICH E6.

This study protocol must first be reviewed and approved in writing by the ethics committee of the hospital before being implemented. The study protocol, protocol amendments, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical study must comply with the "Declaration of Helsinki", CFDA's (now NMPA) "Good Clinical Practice" (GCP), and other relevant regulations. Before the study is initiated, approval must be obtained from the ethics committee of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and the investigators. The investigators can modify or deviate from the study protocol before obtaining an approval from the ethics committee/institutional review board only when in purpose of eliminating direct and immediate harm to the subject. Besides, the deviation or change and the corresponding reason, and the recommended protocol amendment should be submitted to the EC/IRB for review. The investigators must provide explanations and document any protocol deviation.

During the study, any changes to this study protocol must be submitted to the ethics committee. If necessary, corresponding changes should be simultaneously made to other study documents and be submitted and/or approved according to the pertinent requirements of the ethics committee. The investigator is responsible for submitting the interim reports regularly according to the pertinent requirements of the ethics committee. After the end of the study, the completion should be informed to the ethics committee.

15.3. Independent Ethics Committee

The protocol, ICF, recruitment material, and all subject materials must be reviewed and approved by the ethics committee. Subjects may be enrolled only after the protocol and ICF have been approved. Any revisions to the protocol must be reviewed and approved by the ethics committee prior to being implemented. All revisions to the ICF must be approved by the ethics committee, who will decide whether the subjects who have signed the previous version of the ICF are required to sign the new one.

15.4. Informed Consent

15.4.1. Informed consent form and other written information for subjects

The informed consent form describes the investigational drug and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures.

15.4.2. Informed consent process and records

Informed consent will begin before an individual decides to participate in the clinical study and continues during the entire clinical study. The risks and potential benefits of participating in the study should be discussed fully and in detail with subjects or their legally acceptable representatives. Subjects will be asked to read and review the ICF that has been approved by the ethics committee. The investigator will explain the clinical study to the subjects and answer any questions posed by the subjects. Subjects can only participate in the study after they have signed the ICF. During the clinical study, subjects can withdraw the informed consents at any time. One copy of the signed ICF will be kept by subjects. Even if a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

15.5. Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigators, participating study personnel, sponsor, and its representative. In addition to the clinical information, confidentiality also simultaneously covers biosamples and genetic tests of the subjects. Therefore, the study protocol, documentation, data, and other information generated from these materials will be kept strictly confidential. All relevant study or data information should not be disclosed to any unauthorized third-party without prior written approval from the sponsor.

Other authorized representatives of the sponsor, IRB or regulatory authorities, and the representatives of the pharmaceutical company that provides the investigational drugs can examine all the documents and records that are maintained by the investigators, including but not limited to the medical records and subject's administration records. The study center should allow access to these records.

The contact information of the subjects will be safely kept in each study center and only used internally during the study. When the study is ended, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of subjects collected for statistical analysis and scientific reports will be uploaded and stored in the study centers. This should not include the contact information or identification information of subjects. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the study personnel at study centers should be confidential and password-protected. At the end of the study, all identification information in the study database will be erased and archived in the study center.

16. PUBLICATION OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. If the investigators plan to publish any study-related data and information, Hengrui should be provided with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to the submission of documents for publication or other forms of release.

17. CLINICAL STUDY PROGRESS

Anticipated enrollment of the first subject: Mar. 2019

Anticipated enrollment of the last subject: Mar. 2021

Anticipated study completion: Jul. 2024

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Appendix I Clinical Staging for Breast Cancer (AJCC Breast Cancer TNM Staging)

Stage 0	TisN0M0
Stage I	T1N0M0
Stage IIA	T0N1M0
	T1N1M0
	T2N0M0
Stage IIB	T2N1M0
	T3N0M0
Stage IIIA	T0N2M0
	T1N2M0
	T2N2M0
	T3N1, 2M0
Stage IIIB	T4N0M0, T3N1M0, T4N2M0
Stage IIIC	Any T, N3M0
Stage IV	Any T and N, M1

Appendix II Performance Status Criteria (ECOG)

(Eastern Cooperative Oncology Group)

Score	Description
0	Asymptomatic, fully active, able to carry on all performance without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any physical activities; up and about more than 50% of waking hours (confined to bed < 50% of waking hours).
3	Symptomatic, capable of only limited self-care; confined to bed or chair more than 50% of waking hours, but not totally confined to bed.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Death.

Appendix III Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

(New Response Evaluation Criteria in Solid Tumors: Revised RECIST Version 1.1)

Note: This appendix is translated internally and is for reference only. Please refer to the English version during practice.

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definition

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1 Measurable lesions

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15 mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

3.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Non-measurable lesions include: meningeal disorder, ascites, pleural or pericardial effusion, breast carcinoma inflammatory, lymphangitis carcinomatosa of skin or lung, abdominal masses unable to be diagnosed or followed by imaging techniques, and cystic lesions.

3.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by tomography techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts shall not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion. Study protocols shall detail the conditions under which such lesions are considered measurable.

3.2 Methods of Measurement

3.2.1 Measurements of lesions

All measurements shall be recorded in metric notation if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

3.2.2 Method of assessment

The same method and technique shall be used to assess lesions at baseline and during follow-up. Imaging based evaluation shall always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., nodule skin). For the case of cutaneous lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both imaging and clinical examination, tumor assessment shall be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, especially when tumor progression is an important clinical endpoint, since CT is more sensitive, particularly in identifying new lesions. Chest X-ray is only applicable when the measured lesion boundary is clear and the lungs are well ventilated.

CT and MRI: CT is currently the best available and reproducible method for efficacy evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for whole body scans).

Ultrasound: Ultrasound shall not be used as a method to measure lesion size. Ultrasound examinations are operation-dependent, and cannot be reproduced at a later date. It cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead.

Endoscopy, celioscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained, or to determine relapse in studies where recurrence following CR or surgical excision is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. However, if the marker levels exceed the upper normal limit at baseline, they must return to the normal levels for evaluation of complete response. Because tumor markers are disease specific, instructions for their measurement shall be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

4 TUMOR RESPONSE ASSESSMENT

4.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor load at baseline and use this as a comparator for subsequent measurements. Only patients with measurable lesions at baseline should be included in protocols where objective response is the primary endpoint. Measurable lesion is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if enrollment is restricted to those with measurable lesions or whether patients with non-measurable lesions are also eligible.

4.2 Baseline Documentation of "Target" and "Non-target" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions shall be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition shall be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly shall be selected.

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smallest of these measures is the short axis. For example, an abdominal nodule which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable nodule. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference.

All other lesions including pathological lymph nodes shall be identified as non-target lesions, and while measurements are not required, they shall be recorded at baseline. These lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3 Response Criteria

4.3.1 Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, compared to baseline.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each nodule must achieve a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodules is to be included in the sum of target lesions.

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value is recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph nodule is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce: When non-nodal lesions fragmented, the longest diameters of the fragmented portions shall be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that will aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance shall be the maximal longest diameter for the coalesced lesion.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead shall be assessed only qualitatively at the time points specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodules must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered PD.

4.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that the overall tumor load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that will be

required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a peritoneal effusion from trace to large, an increase in lymphangiopathy from localized to widespread, or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesion

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion shall be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study that is not scanned at baseline will be considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example, because of its small size, continued treatment and follow-up evaluation are required to clarify if it represents a truly new disease. If repeated scans confirm there is definitely a new lesion, then progression shall be declared using the date of the initial identification.

While FDG-PET response assessments generally need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible new disease). New lesions on the basis of FDG-PET imaging can be identified according to the following process:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study until the end of study taking into account any necessary requirement for confirmation. On occasion a response may not be documented until after the end of treatment, so protocols should be clear if post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The patient's best overall response evaluation will depend on the findings of both target and non-target diseases and will also take into consideration the characteristics of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to determine either one is the best overall response.

4.4.1 Time point response

It is assumed that at each time point specified in protocol, an efficacy response occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1. Time point response: patients with target (+/- non-target) disease

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all evaluable	Non	PR
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2. Time point response: patients with non-target disease only

Non-Target Lesion	New Lesion	Overall Response
CR	Non	CR
Non-CR/Non-PD	Non	Non-CR/Non-PD[a]
Not all evaluable	Non	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

[a]: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for efficacy evaluation, non-CR/non-PD response is developed to address the absence of lesion measurability.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all time points

The BOR is determined once all the data for the patient are known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time calculated from baseline. If the minimum time is not met when SD is otherwise the best overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at Cycle 1, PD at Cycle 2 and does not meet minimum duration for SD, will have a best overall response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

BOR determination in studies where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3. Best overall response when confirmation of CR and PR required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
PR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
[a]: If a CR is truly met at first time point, then response of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still evaluated as PD at that point (since disease will reappear after CR). Best response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions are likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR shall be changed to PR and the best response is PR.

4.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement shall be recorded even though the nodules are normal in order not to overstate progression shall it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have "zero" recorded on the case report form (CRF).

In studies where confirmation of response is required, repeated "NE" time point evaluations may complicate best response determination. The analysis plan for the study must address how missing data/evaluations will be addressed in determination of response and progression. For

example, in most studies it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Patients with an overall deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time shall be reported as symptomatic deterioration. Efforts shall be made to evaluate objective progression even after discontinuation of treatment. Symptomatic deterioration is not a description of an objective response: it is a reason for discontinuation of treatment. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 1-Table 3.

Conditions that are defined as early progression, early death and not evaluable are study specific and shall be clearly described in each protocol (depending on treatment duration and treatment cycle).

In some circumstances, it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended that the local lesion be investigated before assigning a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled evaluation. If at the next scheduled assessment, progression is confirmed, the date of progression shall be the earlier date when progression is suspected.

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment shall be protocol-specific and consistent with the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. The protocol shall specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After treatment, the need for tumor re-evaluations depends on whether the study has made the response rate or the time to an event (progression/death) an endpoint. If "time to an event" (e.g. TTP/DFS/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment group in the timing of disease assessment.

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

4.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time criteria are first met for CR until the first date that recurrent or progressive disease is truly documented.

4.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency shall take into account many parameters including disease types and stages, treatment cycle and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

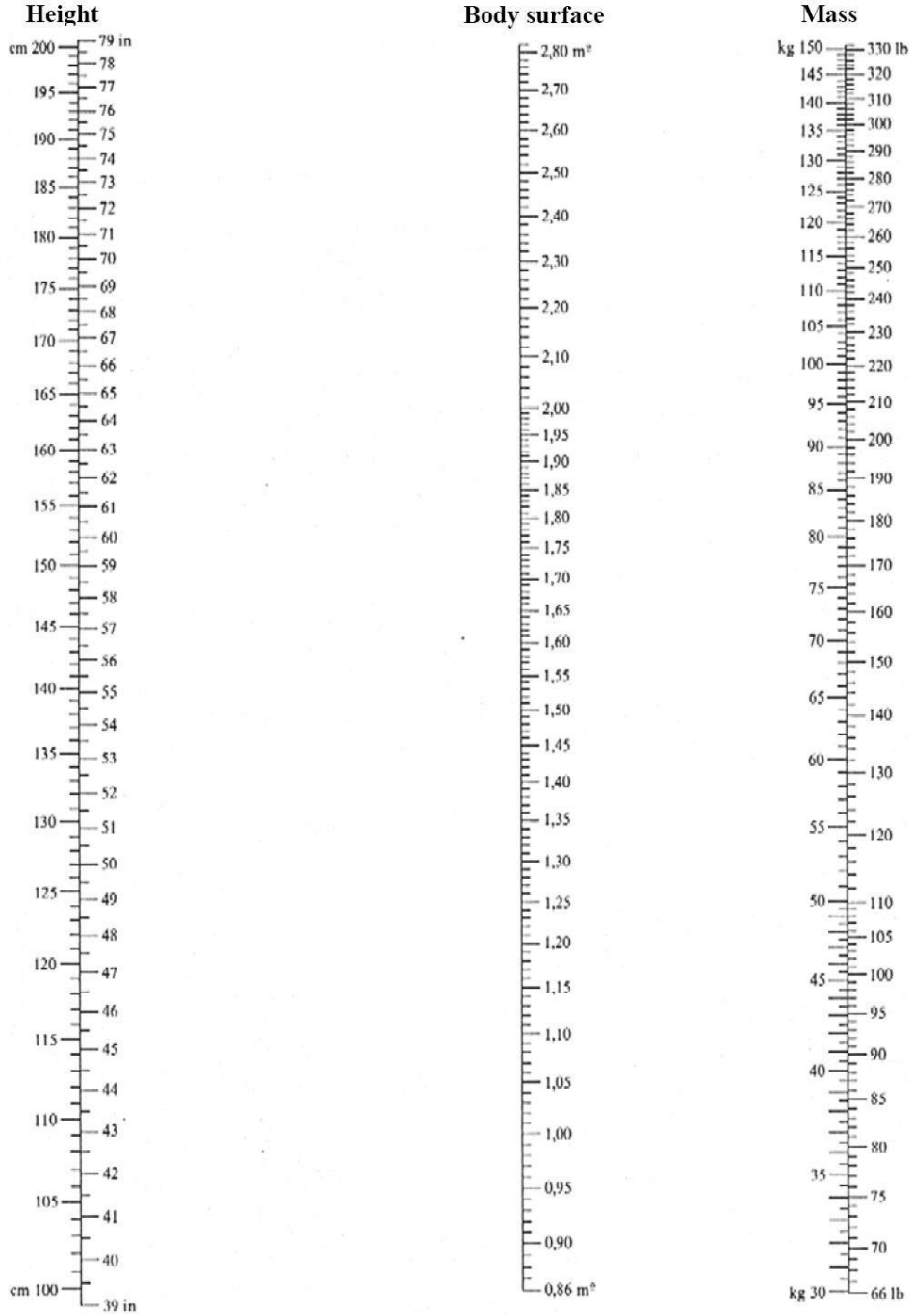
4.7 PFS/TTP

4.7.1 Phase II clinical trials

This guideline is primarily focused on the use of objective response as study endpoints for phase II studies. In some circumstances, response rate may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, PFS/PPF at landmark time points might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled study, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening studies utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor) that a non-randomized study is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF in the absence of a treatment effect.

Appendix IV Nomogram for Determining the Body Surface Area

Nomogram for Determining the Body Surface Area



Formula from Du Bois and Du Bois, Arch. Intern. Med., 17, 863 (1916): $0 = M^{0,425} \times L^{0,725} + 71,84$ resp. $\log 0 = \log M \times 0,425 + \log L \times 0,725 + 1,8564$ (0: body surface area [cm^2], M; weight [kg]: L: height [cm]

A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF PYROTINIB MALEATE TABLETS COMBINED WITH TRASTUZUMAB AND DOCETAXEL VS. PLACEBO COMBINED WITH TRASTUZUMAB AND DOCETAXEL IN HER2-POSITIVE RECURRENT/METASTATIC BREAST CANCER

Protocol No.:	HR-BLTN-III-MBC-C
Study Phase:	III
Compound Code:	SHR-1258
Compound Name:	Pyrotinib maleate tablets
Medical Director:	Xiaoyu Zhu
Leading Center of Clinical Study:	Cancer Hospital, Chinese Academy of Medical Sciences
Principal Investigator:	Prof. Binghe Xu
Version No.:	5.0
Version Date:	12 Jan., 2022

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu 222047, China

VERSION HISTORY/REVISION HISTORY

Document	Version Date	Amendment Rationale and Summary of Changes
Initial Version	21 Dec., 2018	Not applicable
Version 2.0	20 Jan., 2020	1. Updated the progress in studies of pyrotinib; 2. Specified the administration duration of docetaxel; 3. Updated the standardized treatment for diarrhea; 4. Updated the dose modification of pyrotinib/placebo and added safety visits; 5. Specified the procedures of safety visits and tumor assessments; 6. Added pharmacokinetic study.
Version 3.0	31 Oct., 2020	1. Updated the contraceptive measures for women of childbearing potential; 2. Updated the time point of interim analysis; 3. Clarified the dose modification of pyrotinib/placebo after permanent discontinuation of docetaxel; 4. Deleted CYP2C19 substrates from drugs to be used with caution during the study; 5. Clarified the reporting requirements for deaths during the study, standardized the SAE terms related to disease progression, and updated the pregnancy reporting procedures; 6. Updated the number of subjects undergoing blood sampling for pharmacokinetic studies; 7. Updated the description of statistical methods; 8. Corrected the survival follow-up procedures under the Schedule of Activities; 9. Corrected clerical errors in the entire text.
Version 4.0	1 Dec., 2020	1. Added the investigational drug, trastuzumab (Zercepac®).
Version 5.0	12 Jan., 2022	1. Modified the information for subjects switching to trastuzumab (Herceptin®).

Sponsor's Protocol Signature Page

I have read and confirmed this clinical study protocol (protocol no.: HR-BLTN-III-MBC-C; version no.: 5.0; version date: 12 Jan, 2022). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Xiaoyu Zhu		
Study Director (print)	Study Director (signature)	Signature Date (DD/MM/YYYY)

Statistical Institution's Signature Page

I have read and confirmed this protocol (protocol no.: HR-BLTN-III-MBC-C; version no.: 5.0; version date: 12 Jan, 2022). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Statistical Institution: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Ping Yan		
Statistical Director (print)	Statistical Director (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Protocol Signature Page (Leading Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational drug; and I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial or economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Site: Cancer Hospital, Chinese Academy of Medical Sciences

Binghe Xu		
Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Protocol Signature Page (Participating Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational drug; and I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial or economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Site: _____

_____	_____	_____
Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

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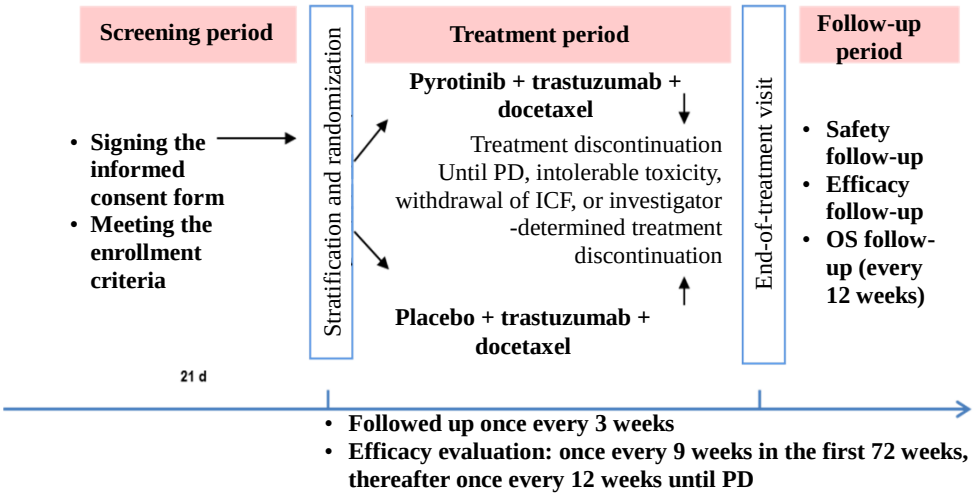
PROTOCOL SYNOPSIS

Study Title	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer
Protocol No.	HR-BLTN-III-MBC-C
Version No.	5.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigator	Prof. Binghe Xu
Participating Study Centers	Approximately 41 study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences
Study Objectives	**Primary objective** • To evaluate the progression-free survival (PFS) of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer **Secondary objectives** • To evaluate the safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer • To compare the efficacy between two groups in overall survival (OS), objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR) • To evaluate the pharmacokinetics (PK) of pyrotinib maleate tablets combined with trastuzumab and docetaxel in patients with HER2-positive recurrent/metastatic breast cancer.
Study Endpoints	**Primary endpoint:** • PFS (investigator-assessed) **Secondary endpoints** • PFS (IRC-assessed) • OS • ORR • DoR • CBR

	• Safety endpoints: incidence and severity of adverse events (AEs) and serious adverse events (SAEs), according to NCI-CTCAE v4.03; changes in the following parameters from baseline: ECOG PS, vital signs, physical examination, laboratory tests (hematology, urinalysis, routine stool test, and blood biochemistry), 12-lead electrocardiogram (ECG), and echocardiography. • Blood concentrations of pyrotinib
Study Population	Female patients with HER2-positive recurrent/metastatic breast cancer who have not received systematic anti-tumor therapy for their metastatic diseases (except first-line endocrine therapy)
Study Design	This is a phase III, randomized, double-blind, placebo-controlled, multicenter study. This study plans to enroll a total of 590 subjects. Eligible subjects will be randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). Randomization is stratified by the following factors: • Prior neoadjuvant/adjuvant therapy: with or without trastuzumab • ER/PR status: positive or negative Subjects will receive study treatment within 48 h after randomization in 21-day cycles. Pyrotinib/placebo and trastuzumab will be administered until investigator-assessed progressive disease (PD), intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The tumor assessments will be performed by the investigators and independent review committee according to RECIST v1.1. The primary PFS analysis is based on the assessment results by the investigators. For subjects who discontinue the study treatment, the safety visit should occur on D28 ± 7 d after the last administration of study drug, then the subjects should start the survival follow-up period until death or study termination (whichever occurs first). For subjects who discontinue the study treatment due to reasons other than PD or death, scheduled tumor assessments need to be collected until PD, start of a new anti-tumor treatment, or death (whichever occurs first). This study plans to perform 1 safety assessment and 1 interim analysis by Independent Data Monitoring Committee (IDMC). After the data review, the IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study.

	An overview of the study design is shown below: 
Study Drugs	Pyrotinib maleate tablets (hereinafter referred to as "pyrotinib") Dummy of pyrotinib maleate tablets (hereinafter referred to as "placebo") Trastuzumab for injection (Herceptin® or Zercepac®, hereinafter referred to as "trastuzumab") Docetaxel injection (Ai Su®, hereinafter referred to as "docetaxel")
Method of Administration	Subjects will receive study treatment in 21-day cycles. Pyrotinib/placebo and trastuzumab will be administered until investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The specific methods of administration are as follows: **Pyrotinib/Placebo** Oral administration (PO), 400 mg/day, once a day. Dose modification and delay may be carried out according to the protocol (Section 6.1.6) if an intolerable adverse event occurs during study drug administration. If pyrotinib/placebo is interrupted for more than 21 days due to intolerable toxicity, all study treatments of the subjects will be discontinued. **Trastuzumab** Intravenous infusion (IV), 8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose in subsequent cycles. The dose of trastuzumab dose not need to be recalculated except for a change of > 10% in body weight. The drug is given on Day 1 of each cycle (D1) via intravenous injection, once every 3 weeks. Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. No dose reduction will be allowed. If the subject misses a dose of trastuzumab for one cycle (e.g., the time interval between 2 sequential administrations is 6 weeks or more apart), the re-loading dose of 8 mg/kg will be administered, and the docetaxel will also be administered on the same day. Maintenance trastuzumab doses of 6 mg/kg will be given every 3 weeks.

Docetaxel

IV, at a starting dose of 75 mg/m^2. D1, once every 3 weeks. The dose of docetaxel does not need to be recalculated if the body weight increases/decreases by < 10% from baseline.

Dose modification and delay may be carried out according to the protocol (Section 6.1.6) if an intolerable adverse event occurs during study drug administration. If the administration of docetaxel must be delayed by one or more days, the administration of trastuzumab also needs to be delayed for the same period of time.

Treatment Group	Pyrotinib	400 mg, once daily, consecutive administration
	Trastuzumab	8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles
	Docetaxel	75 mg/m^2, D1
Control Group	Placebo	400 mg, once daily, consecutive administration
	Trastuzumab	8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles
	Docetaxel	75 mg/m^2, D1

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for study entry:

1. Females aged ≥ 18 and ≤ 75 years old.
2. Histologically confirmed HER2-positive invasive breast cancer, while meeting the following conditions:
   - HER2 positive is defined as 3+ by immunohistochemistry (IHC) or an *in situ* hybridization (ISH) result of HER2 gene amplification. A HER2-positive breast cancer confirmed by the pathology department of the participating study center.
   - Tumor staging: recurrent or metastatic breast cancer; locally recurrent disease must not be amenable to resection with curative intent.
3. Have at least one measurable lesion according to RECIST v1.1.
4. ECOG PS: 0-1.
5. The functional levels of major organs must meet the following requirements (no blood transfusion or treatment with leukogenic and thrombopoietin drugs within 2 weeks prior to screening):
   - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L;
   - Platelet count (PLT) ≥ 90 × 10^9/L;
   - Hemoglobin (Hb) ≥ 90 g/L;
   - Total bilirubin (TBIL) ≤ upper limit of normal (ULN); for patients with Gilbert's syndrome, TBIL ≤ 2 × ULN;
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN; for patients with liver metastases, ALT and AST ≤ 5 × ULN;
   - Alkaline phosphatase ≤ 2.5 × ULN;

	• Urea/urea nitrogen (BUN) and creatinine (Cr) ≤ 1.5 × ULN; • Left ventricular ejection fraction (LVEF) ≥ 50%; • Fridericia-corrected QT interval (QTcF) < 470 msec. *6.* Participate in the study voluntarily, sign the informed consent form, have good compliance, and willing to cooperate with follow-up visits.
Exclusion Criteria	Subjects meeting any of the following exclusion criteria are not eligible to participate in this study: *1.* Have received any systemic anti-tumor therapy for the recurrent/metastatic diseases, including any anti-EGFR or anti-HER2 agents, systemic chemotherapy, immunotherapy, and more than one prior hormonal regimen, as well as other anti-tumor therapies that shall be excluded as judged by the investigator. *2.* History of anti-HER tyrosine kinase inhibitor (TKI) or macromolecular antibody for breast cancer in any treatment setting, except trastuzumab used in the (neo) adjuvant therapy. *3.* History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (except endocrine therapy) to metastatic diagnosis of < 12 months. *4.* Current Grade ≥ 3 peripheral neuropathy as per CTCAE v4.03. *5.* Not suitable for systemic chemotherapy as judged by the investigator. *6.* Have received endocrine therapy within 7 days prior to randomization. *7.* History of other malignant tumors within the past 5 years, except for cured cervical carcinoma *in situ*, skin basal cell carcinoma or squamous cell carcinoma (patients with other malignant tumors that occurred more than 5 years before the date of randomization are allowed to be enrolled only if they have been cured by surgery). *8.* Current brain metastases. *9.* Subjects with bone or skin as the only target lesion. *10.* History of exposure to the following cumulative doses of anthracyclines: • Doxorubicin or doxorubicin liposome > 360 mg/m^2 • Epirubicin > 720 mg/m^2 • Mitoxantrone > 120 mg/m^2, idarubicin > 90 mg/m^2 • Others (for example, in case of other anthracyclines or multiple anthracyclines, the cumulative dose > the dose equivalent to 360 mg/m^2 of doxorubicin) *11.* Have undergone major surgery or apparent trauma within 4 weeks prior to randomization, or expected to undergo a major surgery during the course of study treatment. *12.* With severe cardiovascular disease or discomfort, including but not limited to the following: • Medical history of cardiac failure or systolic dysfunction (LVEF < 50%)

	• Angina or arrhythmia that requires treatment or of high risk (such as type 2 second-degree atrioventricular block or third-degree atrioventricular block, ventricular tachycardia) • Clinically significant valvular heart disease • Transmural myocardial infarction as indicated by ECG • Poorly controlled hypertension (systolic pressure > 150 mmHg and/or diastolic pressure > 100 mmHg) 13. With dysphagia, chronic diarrhea, intestinal obstruction, or other factors affecting drug intake and absorption. 14. With known allergies to the components of the study drugs. 15. History of immunodeficiency, including HIV infection or other acquired and congenital immunodeficiencies, or organ transplantation. 16. Presence of third spacing (such as hydrothorax and ascites) that cannot be controlled by drainage or other methods. 17. Pregnant or lactating female subjects, or subjects of childbearing potential who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose. 18. Presence of severe concurrent disease or other concurrent diseases that may interfere with planned treatment, or any other conditions rendering the subjects unsuitable for participating in this study, such as active hepatitis B and lung infection requiring treatment.
Determination of Sample Size	In this study, PFS is used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to evaluate the efficacy of the drugs and to determine whether to terminate or continue the study. The assumptions for sample size calculation are as follows: • Enrollment duration = 24 months, minimum follow-up = 18 months (overall duration of 42 months) • Randomization in a 1:1 ratio • Overall alpha = 0.025 (one-sided) • The power of test is approximately 80% • Hazard ratio (HR) = 0.76 (median PFS is 12.5 months in the control group and 16.5 months in the treatment group) • An interim analysis will be performed when 67% of PFS events (275 events) are collected to evaluate the efficacy of the drugs, and to decide whether to terminate or continue the study. Based on the above parameters, at least 410 PFS events should be collected according to the log rank test for PFS comparison between two groups and the Lan-DeMets α spending function (EAST 6.4.1) constrained by the O'Brien & Fleming boundaries. Assuming that the PFS dropout rate is 15% for 24 months, approximately 590 subjects should be enrolled.

<table>
<tr><td>Data Analysis/ Statistical Methods</td><td>This study plans to perform 2 IDMC meetings (including 1 safety assessment and 1 interim analysis) and 1 final analysis. One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the safety evaluation. The interim analysis will be carried out when 67% of PFS events (275 events) are collected to evaluate the efficacy of the drugs and to decide whether to terminate or continue the study. The final analysis will be performed when the number of PFS events reaches 410.
The primary analysis of PFS, the primary endpoint of this study, will be based on all randomized subjects. The survival functions of PFS of the two groups will be compared using stratified log-rank tests considering randomization stratification factors. In addition, under the assumption of proportional hazards, the Cox models considering stratification factors will be used to estimate the hazard ratio between the two groups and calculate the corresponding 95% confidence interval (95% CI).
The time-to-event variables (such as PFS, OS, and DoR) will be analyzed using the Kaplan-Meier (KM) method, the survival functions of the two groups will be estimated, and the survival curves will be plotted. In addition, the Cox proportional hazards model will be used to estimate the hazard ratio between the two groups and its 95% CI.
For binary variables, the Cochran-Mantel-Haenszel (CMH)/Chi-square/Non-parametric test (if applicable) methods can be used to test the inter-group difference and compute its 95% CI.
The safety data will be summarized using descriptive statistics.</td></tr>
<tr><td>Interim Analysis</td><td>In the study, one interim analysis will be performed for the primary efficacy endpoint. The main objectives of interim analysis include but are not limited to:
1. Early termination of the study due to superiority;
2. Continuation of the study as planned;
The interim analysis will be conducted when 67% of PFS events (275 events) are collected. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:
<table>
<tr><th>Time Point</th><th>Number of PFS Events</th><th>Boundary Z-Value (Corresponding HR)</th><th>One-Sided Nominal Significance Level</th></tr>
<tr><td>Interim (1st)</td><td>275 (67%)</td><td>-2.500 (HR = 0.74)</td><td>0.0062</td></tr>
<tr><td>Final</td><td>410</td><td>-1.994 (HR = 0.82)</td><td>0.0231</td></tr>
</table>
Note: HR = Hazard ratio; PFS = Progression-free survival;
The interim analysis will be completed by independent statisticians and their programming team. The results of interim analysis will be reviewed by the Independent Data Monitoring Committee (IDMC), which will recommend whether to continue the study based on the results.</td></tr>
<tr><td>Study Period</td><td>Anticipated enrollment of the first subject: Mar. 2019
Anticipated enrollment of the last subject: Mar. 2021
Anticipated study completion: Jul. 2024</td></tr>
</table>

SCHEDULE OF ACTIVITIES

Time / Item	Screening Period		Treatment Period		End-of-Treatment Visit	Follow-up Period		
						Safety	Efficacy[22]	Survival[23]
	D-21 to D-1	D-7 to D-1	Cycle 1	Every cycle (except for C1D1)[21]		28 days after the last dose		
				± 3 d		7 d	± 7 d	± 7 d
Visit	**Screening period**		**C1D1**	**C2 + D1**	**EOT**	**Safety visit**	**Efficacy follow-up**	**Survival follow-up**
Signing of Informed Consent Form[1]	×							
Demographics[2]	×							
Complete Medical History[3]	×							
ECOG PS	×			×	×	×		
Vital Signs[4]	×			×	×	×		
Physical Examination[5]	×			×	×	×		
Hematology[6]		×		×	×	As needed		
Urinalysis[7]		×		Every 4 cycles	×	As needed		
Routine Stool Test[8]		×		Every 4 cycles	×	As needed		
Blood Biochemistry[9]		×		×	×	As needed		
Infectious Disease Screening[10]	×							
Pregnancy Test[11]		×		When necessary	×	As needed		
12-Lead ECG[12]		×		×	×	As needed		
Echocardiography[13]	×			Every 4 cycles	×	As needed		

Time / Item	Screening Period		Treatment Period		End-of-Treatment Visit	Follow-up Period		
						Safety	Efficacy[22]	Survival[23]
	D-21 to D-1	D-7 to D-1	Cycle 1	Every cycle (except for C1D1)[21]		28 days after the last dose		
				± 3 d		7 d	± 7 d	± 7 d
Tumor Assessment[14]	×		Once every 9 weeks in the first 72 weeks, thereafter once every 12 weeks until PD					
Bone Scan[15]	×		When necessary					
Review of Inclusion and Exclusion Criteria	×							
Randomization	×							
PK Blood Sampling[16]				As per footnote				
Pyrotinib/Placebo[17]			Once daily	Once daily				
Trastuzumab[17]			D1	D1 in each cycle				
Docetaxel[17]			D1	D1 in each cycle				
Subject Diary Card			×	×	×			
Drug Return			×	×	×			
Prior/Concomitant Treatment[18]	×							
Adverse Events[19]	×							
Time of PD/Death							×	×
Subsequent Anti-Tumor Treatment[20]					×	×	×	×

Note: The following examinations should be performed according to the time window specified in the Schedule of Activities. In the event of statutory holidays, the examinations may be performed earlier and the reason should be documented. The investigator may add test items or increase the frequency of visits depending on the subjects' clinical conditions.

1. Informed consent form: signed with 21 days prior to randomization.
2. Demographics (name initials, gender, ethnicity, marital status, date of birth, height, weight, and body surface area and body mass index calculated accordingly).
3. Complete medical history: including prior medical and treatment history (clinical/histological diagnosis, time of diagnosis, clinical/pathological staging, HER2/ER/PR status; surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy, time of progression, evidence for progression; LVEF before, during, and after administration of trastuzumab must be collected if trastuzumab is used as neoadjuvant/adjuvant therapy; anti-tumor treatments for recurrent/metastatic breast cancer, such as surgery and endocrine therapy), history of smoking and drinking, history of drug allergies (drug name and symptoms), concurrent diseases and concomitant treatments (disease name, name of concomitant medication, dose, and method of administration).
4. Vital signs: including body temperature, blood pressure, respiratory rate, and pulse.
5. Physical examination: including general condition, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental state; height is only measured at baseline, and weight is measured during each physical examination.
6. Hematology: including absolute counts of WBC, ANC, LC, RBC, Hb, and PLT; for the first 3 cycles of chemotherapy, additional hematology tests should be performed on D8 ± 1 day of each cycle.
7. Urinalysis: including urine protein, urine glucose, and urine occult blood; in case of a urine protein ≥ ++, a 24-h urine protein quantitation should be tested.
8. Routine stool test: including fecal occult blood.
9. Blood biochemistry: including glucose, TP, A/G, ALT, AST, ALP, γ-GT, ALB, TBIL, DBIL, IBIL, TG, CHOL, UA, BUN, Cr, K^+, Na^+, Mg^{2+}, Cl^-, Ca^{2+}, and P; the investigator may perform myocardial zymography as needed based on subjects' conditions.
10. Infectious disease screening: including hepatitis B test (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HIV antibodies, and HCV antibodies.
11. Pregnancy test: Pregnancy must be ruled out in female subjects of childbearing potential by blood HCG test during the screening period; urine pregnancy test may be used subsequently, but a positive urine pregnancy test result must be confirmed by a blood HCG test.
12. 12-Lead ECG: The heart rate, QT, QTc, and P-R interval should be monitored. If QTcF interval increases by > 30 msec from baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG measurements are required (at least 10 min apart).
13. Echocardiography: The results obtained within 21 days prior to randomization (including qualified echocardiography completed before signing the ICF) can be used. If a subject shows symptoms such as precordial pain and palpitations during the study, additional examinations can be carried out.

14. Tumor assessments: Multidetector spiral CT or contrast-enhanced MRI of the brain, chest, and abdomen should be at least performed during the screening period. For patients with local recurrent breast cancer, contrast-enhanced MRI scan of the recurrence site of breast is required. Multidetector spiral CT or contrast-enhanced MRI of the chest and abdomen should at least be performed at subsequent visits. The investigator may decide to perform brain imaging evaluation depending on subjects' clinical symptoms. The investigator may add other scan sites such as the neck and pelvic cavity in the tumor assessments at baseline or later based on clinical indications. The time window for tumor assessments is ± 7 days. During the screening period, reports issued within 21 days prior to randomization (including qualified tumor assessments completed before signing the ICF) should be used. The tumor assessment schedule during the administration period is determined after the start of treatment and is not changed regardless of dose interruptions due to toxicity. Tumor assessments are continued until investigator-assessed PD. The tumor assessments should be continued whenever possible for those who withdraw from study due to intolerable toxicities until PD, start of a new anti-tumor treatment, or lost to follow-up.
15. Bone scan: A bone scan is required for subjects who have not undergone a bone scan within 21 days prior to randomization. Positive bone lesions should be reviewed by CT/MRI examinations (or X-ray), and metastatic bone lesions should be followed up subsequently as per the tumor assessment schedule with the same imaging method for baseline. During treatment period and follow-up period, the investigator may decide to perform bone scan or CT/MRI of bones depending on subjects' clinical symptoms.
16. PK blood sampling: For approximately 50 subjects, 2 mL of peripheral venous blood should be collected before pyrotinib administration on D1 ± 3 days of Cycle 2, Cycle 4, and Cycle 10, and on D1 ± 3 days of every 6 cycle subsequently. The administration time should be relatively stable for the 3 days prior to PK blood sampling. The actual administration time should be documented.
17. Dosing regimen:

    - Pyrotinib/placebo: 400 mg orally once a day within 30 min after breakfast in 21-day cycles.
    - Trastuzumab: 8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose on D1 of subsequent cycles. Trastuzumab is administered once every 3 weeks. The dose of trastuzumab does not need to be recalculated except for a change of > 10% in body weight.
    - Docetaxel (75 mg/m^2, D1, the dose of docetaxel does not need to be recalculated if the body weight increases/decreases by < 10% from baseline). The calculated dose may be rounded, but should not exceed ± 5%. Docetaxel is administered once every 3 weeks.

    Subjects will continue to receive treatment with pyrotinib/placebo and trastuzumab until PD, intolerable toxicity, withdrawal of ICF, or investigator-determined treatment discontinuation. Subjects should receive docetaxel for at least 6 cycles if there is no PD, intolerable toxicity, withdrawal of ICF, or investigator-determined treatment discontinuation. Refer to Sections 6.1.5 and 6.1.6 for the detailed method of administration and dose modifications.

18. Prior/concomitant treatment: Concomitant medications within 28 days prior to randomization and during the study should be documented. Once the study treatment is permanently discontinued, only concomitant medications or treatments for new or unresolved AEs related to study treatment should be documented. Concomitant medications or treatments for cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has returned to baseline or Grade ≤ 1, or until 12 months after the last dose;
19. Observation and recording of AEs: AEs should be monitored starting from the signing of the ICF until 28 days after the last study drug administration or start of a new anti-tumor treatment [cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has returned to baseline or Grade ≤ 1, or until 12 months after the last dose]. AEs, concomitant medications/treatments, and unscheduled examinations should be documented in detail. Refer to Section 9.3 for details.
20. Subsequent anti-tumor treatment: Other anti-tumor treatments from the date of discontinuation of study treatment to the end of survival follow-up should be documented. Only anti-tumor treatments should be recorded for the survival follow-up, and concomitant medications for other diseases may not be recorded.
21. Telephone follow-up: During the treatment with pyrotinib/placebo combined with trastuzumab and docetaxel, if the dose of pyrotinib/placebo was reduced, the dose of pyrotinib/placebo should be increased to 400 mg after permanent discontinuation of docetaxel. If, per the investigator's assessment, the dose cannot be increased to 400 mg, after reporting to the sponsor, the dose of pyrotinib/placebo can be maintained at the dose before docetaxel discontinuation or increased to an appropriate dose (two increases are allowed, up to 400 mg). On D8 ± 1 day (CxD8 ± 1 d) after the dose is increased, a telephone visit should be conducted to collect information on AEs and concomitant medications after the dose increase.
22. Efficacy follow-up: Subjects who discontinue study treatment for reasons other than PD and death should continue to receive efficacy follow-ups based on the tumor assessment schedule specified in the protocol until PD, start of a new anti-tumor treatment, or death (whichever occurs first); The follow-up time, tumor assessment results, and other anti-tumor treatments should be documented.
23. Survival follow-up (OS data collection): All survival subjects who have completed the safety follow-up and efficacy follow-up (whichever is completed later) should undergo survival follow-up. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), starting from the day of completion of safety follow-up and efficacy follow-up (whichever comes later), until death, lost to follow-up, or study termination (whichever occurs first). Data from each survival follow-up should be documented and entered into the appropriate eCRF.

ABBREVIATIONS

Abbreviations	Full Name
12-Lead ECG	12-Lead electrocardiogram
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CK	Creatine kinase
CK-MB	Creatine kinase-MB
Cl^-	Blood chlorine
Cr	Creatinine
CRF	Case report form
D	Day
EC	Ethics committee
GCP	Good Clinical Practice
GLU	Blood glucose
GLU-U	Uglu urine glucose
H	Hour
Hb	Hemoglobin
HDL-C	High-density lipoproteincholesterol
IB	Investigator’s brochure
K^+	Serum potassium
KET	Urine acetone bodies
Kg	Kilogram
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LYMPH	Lymphocyte
mg	Milligram
min	Minimum
mL	Milliliter
mm	Millimeter
Na^+	Plasma sodium
NEUT	Neutrophil
PK	Pharmacokinetics
PLT	Blood platelet

Abbreviations	Full Name
PRO	Protein in urine
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical analysis plan
T-BIL	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
UA	Uric acid
UBIL	Urine bilirubin
URBC	Urine red blood cell
WBC	White blood cell count

1. KEY FUNCTIONAL ROLES

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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

2.1.1. Overview of breast cancer and HER2-targeted therapy

Breast cancer is one of the most common malignancies in women and its incidence is increasing year by year. It has been estimated that in 2012, approximately 1.67 million cases of breast cancer were newly diagnosed worldwide. The morbidity and mortality of breast cancer vary worldwide depending on the region. The incidence of breast cancer is higher in developed regions (73.4/100,000) than in less developed regions (31.3/100,000). The mortality of breast cancer is close between developed regions (14.9/100,000) and less developed regions (11.5/100,000)[1]. This is likely because the early screening, diagnosis, and treatment system in developed regions are more complete, and more new drugs are commercially available. In China, the prevalence of breast cancer is about 37.86/100000 and ranks the first among all cancers in women[2], and the onset age of breast cancer in China was younger than that in Western countries.

In the 1980s, scientists discovered that HER2 overexpression is directly related to the aggressive growth and poor prognosis of tumor[3]. About 10%-34% of subjects with invasive breast cancer have overexpression of human epidermal growth factor receptor 2 (HER2, also known as erbB2, neu, and p185HER2) or amplification of HER2 gene[4]. So far, no ligand has been found to bind to the HER2 receptor. The HER2 molecule mainly forms heterodimers with other receptors of the epidermal growth factor receptor (EGFR) family, further activating MAPK, JAK, PI3K, STAT3, and other pathways to promote the occurrence and progression of cancers. Normal epithelial cells have low levels of HER2 expression. The HER2 gene is amplified/overexpressed

in over 30% of human cancers, including breast cancer, gastric cancer, and lung cancer. HER2 molecule is an independent factor for the poor prognosis of breast cancer. With the standardization of HER2 amplification testing, targeted therapy for HER2 positive subjects has become a focus of basic and clinical research[5]. At present, several anti-HER2 drugs have been approved worldwide (see Table 1).

Table 1. Existing anti-HER2 drugs on the market

	Drug Name	**Company**	**Marketed in the U.S.**	**Indication**	**Marketed in China**
Macromolecular Drugs	Trastuzumab -	Roche -	1998 Herceptin	HER2+ breast cancer; metastatic HER2+ gastric cancer and gastroesophageal junction adenocarcinoma	2002 Herceptin
	Pertuzumab -	Roche -	2012 Perjeta	In combination with trastuzumab and docetaxel: for the treatment of advanced HER2+ (metastatic) breast cancer; used as early preoperative neoadjuvant therapy and postoperative adjuvant therapy	2018 Perjeta®
Antibody-Drug Conjugate (ADC)	T-DM1	Roche -	2013 Kadcyla	Monotherapy: for patients with HER2+ metastatic breast cancer who previously have received trastuzumab or taxane, separately or in combination	——
First-Generation Small Molecule Inhibitor	Lapatinib -	GlaxoSmithKline -	2007 Tykerb	In combination with capecitabine: for the treatment of patients with HER2+ metastatic breast cancer who previously have received trastuzumab or taxane, separately or in combination; In combination with letrozole: for the treatment of postmenopausal women with ER+, HER2+ metastatic breast cancer	2013 Tykerb
Second-Generation Small Molecule Inhibitor	Neratinib (HKI-272) -	Puma	2017 Nerlynx	Adjuvant therapy for breast cancer and systemic treatment for advanced disease	——

Approximately 20% to 30% of breast cancer subjects in China have HER2 amplification/overexpression. About 42.6% (1342/3149) of the subjects were tested positive for HER2 (2+/3+) by immunohistochemistry (IHC) and 46.9% (1477/3149) were tested positive by fluorescence *in situ* hybridization (FISH) [6]. Currently, in China, all HER2-targeted drugs are imported, including trastuzumab and lapatinib. According to the 2016 Expert Consensus on Clinical Diagnosis and Treatment of Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer[7], the National Comprehensive Cancer Network (NCCN) guidelines recommend pertuzumab and trastuzumab combined with taxanes as the preferred first-line regimen for the treatment of HER2-positive advanced breast cancer.

2.1.2. Main information of pyrotinib

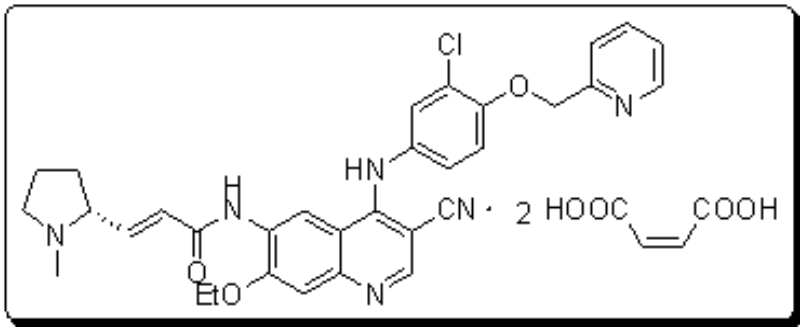
2.1.2.1. Drug name and molecular structure

Generic name: Pyrotinib Maleate Tablets

R&D code: SHR1258

Chemical name (IUPAC): (R,E)-N-(4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino-3-cyano-7-ethoxyquinolin-6-yl)-3-(1-methylpyrrolidin-2-yl)) acrylamide, maleate (1:2)

CAS No.: 1397922-61-0



Molecular formula: $C_{32}H_{31}ClN_6O_3 \cdot 2C_4H_4O_4$

Molecular weight: 815.22

Dosage form and strength:

This product is a film-coated tablet. A tablet of the 40 mg, 60 mg, 200 mg, 160 mg, and 80 mg strengths contains 55.9 mg, 83.9 mg, 279.6 mg, 223.7 mg, and 111.8 mg of pyrotinib maleate, respectively, equivalent to 40 mg, 60 mg, 200 mg, 160 mg, and 80 mg of pyrotinib, respectively.

2.1.2.2. Pharmacological type and mechanism of action of pyrotinib

Pyrotinib is an irreversible dual-receptor tyrosine kinase inhibitor (TKI) targeting mainly epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). *In vitro* and *in vivo* studies of pyrotinib have been conducted to assess the mechanism of action as well as the effect on tumor growth inhibition and tyrosine phosphorylation. Studies investigating the effects of pyrotinib on several human tumor cell lines were performed in both cell culture and mice xenograft models.

Pyrotinib significantly inhibited EGFR1 and EGFR2/HER2 at the molecular level, with median half-maximal inhibitory concentrations (IC_{50}) of 5.6 nM and 8.1 nM, respectively, which were comparable to the IC_{50} values of the positive control neratinib. It was observed that pyrotinib slightly inhibited the activity of the SRC proto-oncogene non-receptor tyrosine kinase (c-Src), with an IC_{50} of 790.3 nM, which was comparable to that of the positive control. Pyrotinib showed no significant inhibitory effect on the following kinases: KIT proto-oncogene receptor tyrosine kinase (c-Kit), kinase insert domain receptor (KDR), MET proto-oncogene receptor tyrosine kinase (c-Met), and beta platelet-derived growth factor receptor (PDGFRβ), suggesting that pyrotinib is a receptor tyrosine kinase inhibitor that targets mainly EGFR and HER2.

Growth inhibition of pyrotinib on tumor cells was evaluated in HER2 over-expression cell lines, EGFR over-expression cell lines, and HER2 and EGFR low-expression cell lines. The results showed that pyrotinib significantly inhibited the proliferation of HER2 over-expression cell lines, and it also significantly inhibited the proliferation of EGFR over-expression cell lines. As expected, pyrotinib showed no significant inhibitory effect on the proliferation of cells with low HER2 and EGFR expression.

In EGFR-overexpressing A431 cells, pyrotinib significantly inhibited the phosphorylation of EGFR receptor and its downstream signals ERK1/2 and AKT serine/threonine kinase (Akt), with comparable potency to that of neratinib. In HER2-overexpressing BT-474 cells, pyrotinib significantly inhibited the activation of HER2 and its downstream signals ERK1/2 and Akt, with comparable inhibitory potency to that of neratinib. Furthermore, the inhibitory effect of pyrotinib on HER2 was irreversible. In c-Kit-overexpressing Mo7e cells and PDGFRβ-overexpressing NIH-3T3 cells, pyrotinib showed no significant inhibitory effect on the phosphorylation of c-Kit and PDGFR kinases stimulated by SCF-1 and $PDGF_{BB}$, respectively, while the positive control sunitinib significantly inhibited the phosphorylation of these kinases.

The *in vivo* anti-tumor effects of pyrotinib and HKI-272 (neratinib) in cell lines with HER2 overexpression such as BT-474 (human breast cancer), SK-OV-3 (human ovarian cancer), Calu-3 (human non-small cell lung cancer), as well as human epidermoid carcinoma A431 cell line with high expression of EGFR were compared in nude mice xenografts. The results showed that

pyrotinib significantly inhibited the growth of HER2-overexpressing tumor models, such as SK-OV-3, Calu-3, and BT-474. The tumor growth inhibition was significant and dose-dependent, and resulted in tumor size shrinkage. The overall efficacy was comparable to or superior to that of neratinib without increased toxicity. When it wa administered at an effective dose comparable to the models with high expression of HER2, pyrotinib showed no significant effect on A431 of EGFR overexpression model. The above results suggested that pyrotinib is a small-molecule tyrosine kinase inhibitor that primarily targets HER2.

2.1.2.3. Safety pharmacology

Safety pharmacology studies were conducted to evaluate the effects of pyrotinib on locomotor activity and general behaviors of mice and on the cardiovascular and respiratory systems of anesthetized dogs.

Single dose intragastric administration of pyrotinib was given to mice at the dose levels of 20, 60 and 200 mg/kg. Within 24 hours, there were no changes in appearance, posture and gait, salivation and muscle trembling in each dose group. The mice of all dose groups had normal food and water intake, and no other abnormal reactions. No noticeable changes in locomotor activity were observed in mice. These results suggested that pyrotinib had no effect on the general behavior of the mice and little or no effect on locomotor activity.

Single dose intraduodenal administration of pyrotinib at dose levels of 5, 15 and 50 mg/kg to anesthetized beagle dogs produced no arrhythmia when measured at up to 240 minutes after administration. No change in PR, QRS, and corrected QT interval (QTc) on ECG was observed in the animals of all dose groups during the 240 min observation period after administration, nor in systolic and diastolic blood pressure and mean arterial pressure. The heart rhythm of the anesthetized dog was normal. These results suggested that pyrotinib at doses of 50 mg/kg or lower had no adverse effects on blood pressure, heart rate, heart rhythm, or ECG, nor on respiratory rate or amplitude (measured 240 min after administration) in anesthetized dogs.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for details.

2.1.2.4. Preclinical pharmacokinetic study of pyrotinib

The pharmacokinetics (PK), absorption, distribution, metabolism, and excretion (ADME) of pyrotinib were investigated *in vitro* and in Sprague Dawley (SD) rats and beagle dogs orally and/or intravenously (IV) administered with unlabeled drugs.

Absorption:

SD rats were given pyrotinib orally (gavage) at 1.0, 3.0 and 10 mg/kg, or IV at 3.0 mg/kg. After pyrotinib was administered to the rats orally (gavage), the average time to maximum plasma concentration (T_{max}) was 4.86 h. The elimination half-life ($t_{1/2}$) of pyrotinib was 3.23 h. After intravenous administration of pyrotinib, the average plasma clearance, the volume of distribution (Vd), and the $t_{1/2}$ was 0.21 mL/h/kg, 1.35 mL/kg, and 4.42 h, respectively. After gavage administration to the rats at various doses, the logarithmic values of C_{max} and AUC_{0-t} of pyrotinib were calculated against the logarithmic dose values using linear regression. Within the dose range of 1-10 mg/kg, the increase of the C_{max} was proportional to the increase of the dose of pyrotinib, while the increase of AUC_{0-t} was slightly higher than the increase of the dose.

Pyrotinib was given to beagle dogs orally (gavage) at 0.5, 1.5, and 5 mg/kg or IV at 1.5 mg/kg. Pyrotinib was quickly absorbed in beagle dogs after gavage administration. The average time to maximum plasma concentration was 1.5 h, and the plasma $t_{1/2}$ was 2.45 h for gavage administration. For IV administration, the average plasma clearance, apparent Vd, and plasma $t_{1/2}$ of pyrotinib were 2.57 L/h/kg, 10.7 L/kg, and 2.99 h, respectively. The logarithmic values of C_{max} and AUC_{0-t} against the logarithmic value of pyrotinib oral doses were calculated using linear regression. Within the dose range of 0.5-5.0 mg/kg, the C_{max} of pyrotinib was proportional to the increase of the dose, while the increase of $AUC_{0-\infty}$ was slightly higher than the increase of the dose.

Distribution:

In this study, the plasma protein binding rates of pyrotinib in human, rat, dog, monkey, and mouse plasma proteins at 10, 100, and 4000 ng/mL dose levels were investigated using equilibrium dialysis assay. Pyrotinib showed no species differences in plasma protein binding rate, no significant differences at various concentration levels, and its plasma protein binding rate was not concentration-dependent.

The distribution of pyrotinib in major tissues and plasma of rats was evaluated at 1, 4, and 8 h after oral (gavage) administration of pyrotinib to rats at 3.0 mg/kg. Pyrotinib mainly resided in the lungs, spleen, fat, and gastrointestinal (GI) tract and other tissues. Except in stomach, small intestine, spleen, fat, and lungs, the concentrations of pyrotinib in other tissues were all lower than the that in plasma. The time to maximum concentration of pyrotinib in tissues was the same as that in the plasma (4 h). The concentrations of pyrotinib in most of the tissues were about half of the maximum concentration at 8 h after administration. The concentrations of pyrotinib in brain tissues and cerebrospinal fluid were measurable and were much lower when compared to other tissues.

Metabolism:

The *in vitro* metabolic stability of pyrotinib in the liver microsomes from mice, rats, dogs, monkeys, and humans was determined using liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS). After 60-min incubation, the contents of pyrotinib in the liver microsome incubation systems of mice, rats, dogs, monkeys, and humans were 10.79%, 19.34%, 22.0%, 0.05%, and 2.09% of the initial dose, respectively. Pyrotinib was stable in human liver microsome 450 (CYP450) isoenzymes CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP4A11, with less than 2% degradation of the parent drug. Pyrotinib had no obvious inhibitory effect on cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (IC_{50} > 25 μM) but had a relatively weak inhibitory effect on CYP2C19 (IC_{50} = 18.52 μM). Pyrotinib at final concentrations of 1 μM and 10 μM was incubated with human primary hepatocytes for two days, respectively. The results showed that pyrotinib did not induce CYP1A2 and CYP3A4.

Excretion:

After a single oral dose of pyrotinib at 3.0 mg/kg in SD rats, the potential metabolites in plasma, urine, feces, and bile samples were detected using ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS). Of the seven metabolites detected in the rat plasma, the peak areas of extracted ion chromatograms of individual metabolites in plasma were less than 10% of that of the parent compound. Of the seven metabolites detected in the rat feces, the peak area of the major metabolite was 11.6% of that of the parent compound, while the corresponding results for the remaining 6 metabolites were less than 8.0%. Five metabolites were detected in rat urine and four in rat bile. In terms of the amount and relative ratios of metabolites, no significant gender difference in the *in vivo* metabolism of pyrotinib in rats was observed. The excretion amount of the parent compound in fecal samples within 0-48 h accounted for 17.45 ± 3.37% of the dose administered; the excretion amount of the parent compound in urine samples within 0-48 h accounted for 0.50 ± 0.47% of the dose administered; the excretion of parent compound in bile samples within 0-48 h accounted for 0.16 ± 0.15% of the dose administered; and the excretion in fecal and urine samples in total accounted for 17.95 ± 3.25% of the dose administered. After a single oral dose of [^{14}C]pyrotinib at 3 mg/kg in SD rats, the parent drug and its metabolites were mainly excreted in bile (about 44%) and feces (about 59%), and in a small proportion in urine (less than 1%). No significant difference in the total cumulative excretion in urine and feces was observed between male and female rats.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for details.

2.1.2.5. Clinical studies of pyrotinib

As of 31 Mar., 2019, 12 clinical studies of pyrotinib have been conducted in China: 7 phase I clinical studies, including 4 in healthy subjects, 2 in subjects with HER2-positive metastatic breast cancer (mBC) (BLTN-Ib, BLTN-Ic), and 1 in subjects with advanced gastric cancer (BLTN-Id); a phase I/II clinical study in subjects with mBC (HR-BLTN-I/II-mBC); an ongoing phase II clinical study in subjects with HER2-mutant non-small cell lung cancer (NSCLC) (HR-BLTN-II-NSCLC), and 3 phase III clinical studies in subjects with breast cancer (HR-BLTN-III-MBC-A, HR-BLTN-III-MBC, and HR-BLTN-III-NeoBC). There is currently a phase I clinical study underway in the United States involving subjects with HER2-positive and HER2-mutant solid tumors who develop PD following prior HER2-targeted therapy.

Table 2. Summary of ongoing or completed clinical studies of pyrotinib

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
Phase I Study in Healthy Chinese Subjects					
BLTN-Ia	Healthy males and females Age: 18-45 years	**Primary objective:** To evaluate the tolerability and safety of a single oral dose of pyrotinib in healthy subjects **Secondary objective:** To characterize the PK of pyrotinib in healthy subjects.	**Design:** A phase I, randomized, double-blind, single-dose study to evaluate the safety and to characterize the PK of pyrotinib in healthy male and female subjects. Subjects are randomized to either the pyrotinib group or placebo group. **Dose:** Pyrotinib: 20, 40, 80, 160, 240, 320, or 400 mg, given as a single oral dose within 30 min after breakfast	56/56 46: pyrotinib 10: placebo	Completed
BLTN-Ie (also known as HR-BLTN-FDI/MB)	Healthy males Age: 18-45 years	**Primary objectives:** To determine the food effect on the PK of pyrotinib, to investigate the metabolic pathway, excretion pathway, and excretion level of pyrotinib in the human body, and to further confirm the safety of a single oral dose of 320 mg pyrotinib maleate tablets.	**Design:** A phase I, randomized, open-label, single-dose, two-stage crossover study to determine the food effect on the PK of pyrotinib in healthy male subjects. The study also aims to further investigate the metabolic pathway, excretion pathway, and excretion level after a single oral dose of 320 mg pyrotinib. Further studies on safety evaluation will be conducted. **Dose:** Pyrotinib: single oral dose at 320 mg, administered to subjects under fasting or fed condition (within 30 min after the meal)	12/12	Completed

Protocol No.	**Study Population**	**Objectives**	**Study Design/Dose of Pyrotinib**	**Enrollment: Planned/ Completed**	**Study Status**
Mass balance study	Healthy males Age: 18-45 years	**Primary objective:** To evaluate the mass balance and metabolic transformation pathways of [^{14}C]pyrotinib maleate in healthy male Chinese subjects after a single oral dose.	**Design:** A single center, single-dose, non-randomized, and open-label study Dose: Administration of 200 mL of a suspension containing 402 mg of pyrotinib (approximately 5.55 MBq radioactivity, 150 μCi) under fasting condition.	4-6/6	Completed
BE	Healthy males and females Age: 18-65 years	**Primary objective:** To investigate the human bioavailability and bioequivalence of pyrotinib maleate tablets (160 mg × 2 tablets + 80 mg × 1 tablet) after the process change using the pyrotinib maleate tablets before the process change (200 mg × 2 tablets) as the reference product. **Secondary objective:** To investigate the safety of pyrotinib maleate tablets in healthy subjects before and after the change of preparation process.	**Design:** A single-center, randomized, open-label, single-dose, two-period, crossover bioequivalence study **Dose:** 42 male and female subjects. In Cycle 1, 21 subjects are given oral dose of pyrotinib maleate tablets before the process change (200 mg × 2 tablets) under fed condition, and the other 21 subjects are given oral dose of pyrotinib maleate tablets after the process change (160 mg × 2 tablets + 80 mg × 1 tablet) under fed condition. The subjects cross over to receive Cycle 2 treatment after 8 days.	42/43	Completed

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
Study in Chinese Subjects with HER2-Positive Breast Cancer					
BLTN-Ib	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective:** To determine the DLT and MTD of pyrotinib by oral administration once daily at escalating doses in female subjects with advanced HER2-positive metastatic breast cancer. **Secondary objectives:** 1) To evaluate the PK and clinical efficacy of pyrotinib by oral administration, 2) To explore the relationship between HER2 expression status and efficacy	**Design:** A phase I, single-arm, open-label, dose-escalation study to determine the DLT, MTD, and RP2D of pyrotinib by oral administration and to evaluate the PK and clinical efficacy. The study also aims to explore the relationship between HER2 expression status and clinical efficacy at various dose levels. **Dose:** Pyrotinib: multiple ascending doses at 80, 160, 240, 320, 400, or 480 mg, once daily, orally administered within 30 min after breakfast	40/38	Completed
BLTN-Ic	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective:** To determine the MTD and evaluate the safety of pyrotinib combined with capecitabine in female subjects with advanced HER2-positive metastatic breast cancer **Secondary objective:** To evaluate the PK and clinical efficacy of pyrotinib by oral administration.	**Design:** A phase I, single-arm, open-label, dose-escalation study to determine the MTD of pyrotinib combined with capecitabine by oral administration in female subjects with advanced HER2-positive metastatic breast cancer and to evaluate the safety, PK, and clinical efficacy. **Dose:** Pyrotinib: multiple ascending doses at 160, 240, 320, or 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle)	29/29	Completed

Protocol No.	**Study Population**	**Objectives**	**Study Design/Dose of Pyrotinib**	**Enrollment: Planned/ Completed**	**Study Status**
HR-BLTN-I/II mBC	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective:** To compare the safety and efficacy of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer. **Secondary objective:** To determine the PFS, TTP, and DoR of pyrotinib combined with capecitabine	**Design:** A phase I/II, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose:** Pyrotinib: 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle) Lapatinib: 1250 mg, in combination with capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)	128/128	Enrollment completed, final report completed (data cutoff date: 15 Mar., 2017)
HR-BLTN-III-MBC-A	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-75 years	**Primary objective:** To evaluate the superiority of pyrotinib combined with capecitabine vs. placebo combined with capecitabine in the treatment of HER2-positive metastatic breast cancer in terms of progression-free survival (PFS). **Secondary objectives** 1. To compare the objective response rate (ORR), duration of response (DoR), disease control rate (DCR),	**Design:** A phase III, randomized, double-blind, placebo-controlled, multicenter study comparing pyrotinib combined with capecitabine vs. placebo combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose:** Pyrotinib/placebo: 400 mg, once daily continuously, orally administered within 30 min after breakfast (in 21-day cycles)	350/279**	Enrollment completed, final report completed (data cutoff date: 27 May, 2018)

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		clinical benefit rate (CBR), and overall survival (OS) between the pyrotinib combined with capecitabine group and the placebo combined with capecitabine group. 2. To compare the safety of pyrotinib combined with capecitabine vs. placebo combined with capecitabine in the treatment of HER2-positive metastatic breast cancer.	Capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)		
HR-BLTN-III-MBC	Female patients with advanced HER2-positive metastatic breast cancer Age: 18-70 years	**Primary objective:** To confirm that the PFS of pyrotinib combined with capecitabine is superior to that of lapatinib combined with capecitabine in treatment of HER2-positive metastatic breast cancer. **Secondary objectives** • To compare the overall survival (OS), objective response rate (ORR), time to progression (TTP), duration of response (DoR), and clinical benefit rate of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer	**Design:** A phase III, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in female subjects with HER2-positive metastatic breast cancer **Dose:** Pyrotinib: 400 mg, once daily continuously, orally administered within 30 min after breakfast, in combination with capecitabine BID at 1000 mg/m^2 (administered on D1-D14 of each 21-day cycle) Lapatinib: 1250 mg, in combination with capecitabine: 1000 mg/m^2 BID (administered on D1-D14 of each 21-day cycle)	240/267*	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		• To compare the safety of pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer.			
HR-BLTN-III-NeoBC	Treatment-naive patients with early or locally advanced HER2-positive breast cancer Age: 18-75 years	**Primary objective:** To compare the efficacy of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer in terms of tpCR (ypT0/is, ypN0) pathologically evaluated by the Independent Review Committee (IRC). **Secondary objective:** To compare the efficacy of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer based on pathologically assessed tpCR, event-free survival	**Design:** A phase III, multicenter, randomized, placebo-controlled, double-blind study comparing pyrotinib combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in patients with early or locally advanced HER2-positive breast cancer. **Dose:** Treatment group: pyrotinib (400 mg/day); trastuzumab (8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose in Cycles 2-4); docetaxel (100 mg/m^2 in Cycles 1-4). Control group: placebo (400 mg/day); trastuzumab (8 mg/kg loading dose in Cycle 1, and 6 mg/kg dose in Cycles 2-4); docetaxel (100 mg/m^2 in Cycles 1-4). 21 days/cycle, for a total of 4 cycles.	294/144*	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		(EFS), disease-free survival (DFS), distant disease-free survival (DDFS), and objective response rate (ORR). **Safety objective:** To compare the safety and tolerability of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel in the preoperative treatment of early or locally advanced HER2-positive breast cancer.			
Phase I Study in Chinese Subjects with Advanced Gastric Cancer					
BLTN-Id	Male and female patients with advanced HER2-positive gastric cancer Age: 18-70 years	**Primary objectives:** To determine the MTD and safety of pyrotinib maleate tablets in monotherapy and in combination with docetaxel in patients with advanced HER2-positive gastric cancer; and to determine the RP2D of pyrotinib maleate tablets in monotherapy and in combination with docetaxel **Secondary objective:** To evaluate the PK and clinical efficacy of pyrotinib by oral administration.	**Design:** A phase I, single-arm, open-label, dose-escalation study to determine the MTD (monotherapy or combination therapy), safety, RP2D, and PK of pyrotinib in monotherapy or in combination with docetaxel in patients with HER2-positive gastric cancer and to observe the clinical efficacy **Dose:** **Part 1:** Pyrotinib monotherapy, at a dose of 240, 320, 400, or 480 mg/day, continuously orally administered within 30 min after breakfast (in 21-day cycles)	70/26	Enrollment discontinued. Project closing.

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
			Part 2: Pyrotinib, at multiple ascending doses of 240, 320, 400, or 480 mg/day, once daily continuously, orally administered within 30 min after breakfast, in monotherapy or in combination with docetaxel 60 mg/m^2 IV (on Day 1 of each 21-day cycle)		
Phase II Study in Chinese Subjects with Advanced Non-Small Cell Lung Cancer					
HR-BLTN-II-NSCLC	Male and female patients with HER2-mutant advanced non-small cell lung adenocarcinoma Age: 18-75 years	To evaluate efficacy and safety of pyrotinib maleate tablets in patients with HER2-mutated advanced non-small cell lung adenocarcinoma.	**Design:** A phase II, multicenter, open-label, single-arm study to evaluate the efficacy and safety of pyrotinib in subjects with HER2-mutant advanced non-small cell lung adenocarcinoma who have been treated with at least one platinum-based chemotherapy **Dose:** Pyrotinib 400 mg, once daily continuously, orally administered within 30 min after breakfast	55/60*	Ongoing
Phase I Clinical Study in the United States: involving subjects with HER2-positive solid tumors who develop PD following prior HER2-targeted therapy					
SHRUS 1001	Patients with HER2-positive solid tumors and patients with HER2-mutant NSCLC who develop PD following prior HER2-targeted therapy	**Primary objectives:** **Part 1:** To evaluate the safety and tolerability of pyrotinib in patients with HER2-positive advanced solid tumors and to determine the MTD of pyrotinib. **Part 2:** To estimate the ORR in patients with HER2-positive metastatic	A phase I, open-label, dose-escalation study containing two parts to evaluate the safety, tolerability, and PK of pyrotinib in patients with HER2-positive solid tumors who develop PD following prior HER2-targeted therapy Dose: **Part 1:** Pyrotinib: at ascending doses of 320, 400, 480, 560, and 640 mg, once daily, orally administered 30 min after a meal.	Part 1: 15-30/9 Part 2: 60/54***	Ongoing

Protocol No.	Study Population	Objectives	Study Design/Dose of Pyrotinib	Enrollment: Planned/ Completed	Study Status
		breast cancer or HER2-mutant NSCLC treated at the MTD or RP2D. **Secondary objectives:** **Part 1:** To preliminarily obtain information on anti-tumor activity and PK. **Part 2:** To confirm the MTD from Part 1 of the study and determine the RP2D, so as to obtain safety and evaluate additional efficacy parameters, including clinical benefit rate: complete response + partial response + stable disease for ≥ 6 months (for metastatic breast cancer) or for ≥ 6 months (for HER2-mutant NSCLC), duration of response with pyrotinib, and TTP.	**Part 2:** During the study expansion stage, 2 independent groups (at least 20 subjects in each group) are investigated to assess the safety and preliminary efficacy of pyrotinib: Group A includes patients with HER2-positive metastatic breast cancer and Group B includes patients with HER2-mutant NSCLC. Subjects in each group are randomized and treated at 2 selected dose levels based on the preliminary safety, PK, and clinical activity observed in Part 1 to determine the most appropriate RP2D.		

Abbreviations: BID, bis in die; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase II dose; TTP, time to progression; yrs, years.

* As of 31 Mar., 2019

** As of 27 May, 2018

*** As of 30 Mar., 2019

2.1.2.5.1. Clinical safety

The most common adverse events (AEs) are similar across all clinical studies. Gastrointestinal disorders, skin reactions, and subcutaneous reactions are the common AEs reported in clinical studies to date. Most notable AEs are diarrhea, nausea, vomiting, and palmar-plantar erythrodysaesthesia syndrome.

Gastrointestinal disorders

AEs involving gastrointestinal disorders, including diarrhea, nausea, vomiting, and mouth ulceration, are frequently reported in the studies. Diarrhea is the most common AE across studies and the most common Grade ≥ 3 AE. The incidence, severity, and duration of diarrhea, and the frequency in individual subjects are generally dose-dependent. In the BLTN-Ib study, the incidence of diarrhea was 87.5% (7/8 subjects) in the pyrotinib 400 mg group, and the incidence of Grade 3 diarrhea was 25.0% (2/8 subjects). In the HR-BLTN-I/II mBC study, the incidence of diarrhea was 96.9% (63/65 subjects) in the pyrotinib (400 mg QD) combined with capecitabine (1000 mg/m^2 BID) group, and the incidence of Grade 3 diarrhea was 15.4% (10/65 subjects). In the HR-BLTN-II-NSCLC study, the incidence of diarrhea was 93.3% (56/60 subjects) in the pyrotinib (400 mg QD) group, and the incidence of Grade 3 diarrhea was 20.0% (12/60 subjects). In the HR-BLTN-III-MBC study, the incidence of diarrhea was 94.8% (127/134 subjects) in the pyrotinib (400 mg QD) combined with capecitabine group, and the incidence of Grade 3 diarrhea was 31.3% (42/134 subjects). In the HR-BLTN-III-MBC-A study, the incidence of diarrhea was 98.4% (182/185 subjects) in the pyrotinib (400 mg QD) combined with capecitabine group, and the incidence of Grade 3 diarrhea was 31.4% (58/185 subjects).

AEs related to hematology and blood biochemistry tests

The AEs related to hematology and blood biochemistry tests showed that the most common AEs included: white blood cell count decreased, neutrophil count decreased, hemoglobin decreased, aspartate aminotransferase increased, alanine aminotransferase increased, and blood bilirubin increased. Grade ≥ 3 AEs of laboratory abnormalities reported in the studies mainly include: aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, hemoglobin decreased, white blood cell count decreased, glutamyltransferase increased, blood triglycerides increased, neutrophil count decreased, and hypokalemia.

Skin and subcutaneous tissue AEs

Palmar-plantar erythrodysaesthesia syndrome is the most common skin-related AE. In the study of pyrotinib monotherapy (BLTN-Ib), palmar-plantar erythrodysaesthesia syndrome was observed in 3 (3/38) subjects, and no Grade 3 palmar-plantar erythrodysaesthesia syndrome occurred. However, the incidence and severity of palmar-plantar erythrodysaesthesia syndrome

were apparently increased in the combination therapy of pyrotinib and capecitabine. Grade ≥ 3 PPE syndrome was reported in 16 subjects (24.6%) in the HR-BLTN-I/II mBC study and 22 subjects (16.4%) in the HR-BLTN-III-MBC study who received pyrotinib combined with capecitabine. No Grade 3 PPE occurred in NSCLC subjects. In the HR-BLTN-III-MBC-A study, Grade ≥ 3 PPE syndrome was reported in 17.3% (32/185) of subjects treated with pyrotinib (400 mg QD) combined with capecitabine. In the SHRUS 1001 study (pyrotinib 400 mg group) in the U.S., 1 subject developed Grade 3 Stevens-Johnson syndrome, which was possibly related to the investigational drug.

Cardiac adverse events

Although animal toxicity studies up to now have not suggested any significant effect of pyrotinib on cardiac function, careful monitoring for possible cardiotoxicity is required in clinical studies. In the HR-BLTN-I/II mBC study, 8 subjects (12.3%) in the pyrotinib group experienced asymptomatic Grade 2 LVEF decreased (decrease by ≥ 10% and < 20% relative to baseline); but all subjects had LVEF above 50%. In addition, 11 subjects (16.9%) had a maximum QTcF interval of ≥ 480 msec or an increase by ≥ 60 msec from baseline, and 5 subjects (7.7%) had an absolute maximum QTcF interval of ≥ 480 msec. None of these subjects showed symptoms related to malignant arrhythmia and syncope, etc. QT interval prolongation may be partially related to the use of drugs that prolong QT interval and hypocalcemia during the treatment period. One SAE of arrhythmia was considered possibly related to the study treatment (BLTN-Id study). One AE of sinus tachycardia leading to the subject's withdrawal from study was reported (HR-BLTN-III-MBC-A study). The subject developed Grade 2 AE sinus tachycardia 7 days after medication, which did not relieve after symptomatic treatment. Thus, medication was permanently discontinued and the medical history was traced. During the subject's previous THC treatment, medication was also discontinued due to palpitations, the symptoms of which disappeared after more than 2 months of discontinuation. The AE of sinus tachycardia was considered related to the study drug as considered by the investigator.

One SAE of palpitation was reported (HR-BLTN-III-MBC-A study). The subject experienced 4 intermittent occurrences of Grade 2 SAE palpitation (important medical event), mainly manifested as heart pounding and/or heart rate increased with a duration of 1-2 min at 121 days after the first dose. No dose modification was made in the first occurrence. Treatment was interrupted in the second occurrence and resumed later. The paroxysmal palpitation was of unknown cause and possibly related to the study drug as considered by the investigator.

No SAE related to cardiac function was reported in the U.S. study (SHRUS 1001 study).

2.1.2.5.2. Clinical efficacy

BLTN-Ib study that has been completed is a phase I, single-center, single-arm, open-label, dose-escalation study of pyrotinib in the treatment of HER2-positive metastatic breast cancer. Efficacy data as of 31 Dec., 2015: The best overall response rates (ORR) at doses of 80, 160, 240, 360, and 400 mg were 0, 50%, 25%, 55.6%, and 87.5%, respectively. The median progression-free survivals (PFS) were 23.7, 31.7, 14.6, 31.9, and 59.7 weeks, respectively.

BLTN-Ic study that has been completed is a phase I, single-arm, open-label, dose-escalation study of pyrotinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer. Among the 28 subjects, 0, 22 (78.6%), 5 (17.9%), and 0 subjects had a best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively; 1 subject (3.6%) did not complete the first efficacy evaluation due to withdrawal of informed consent. The efficacy mentioned above has been confirmed after at least 4 weeks. The overall ORR was 78.6%, with a 95% CI of (59.0%, 91.7%). The ORRs were 66.7%, 66.7%, 72.7%, and 90.9% at pyrotinib doses of 160 mg, 240 mg, 320 mg, and 400 mg, respectively, suggesting a certain dose dependence. The median PFS was 22.1 months, with a 95% CI of (9.0 months, 26.2 months).

HR-BLTN-I/II mBC study is a phase I/II, randomized, open-label, multicenter study comparing pyrotinib combined with capecitabine vs. lapatinib combined with capecitabine in the treatment of HER2-positive metastatic breast cancer. Among the subjects included in the FAS, in the pyrotinib group and in the lapatinib group, 3 subjects (4.6% of the same group) and 1 subject (1.6% of the same group) achieved a 12-cycle BOR of CR, respectively; 48 subjects (73.8% of the same group) and 35 subjects (55.6% of the same group) achieved PR, respectively; 14 subjects (21.5% of the same group) and 22 subjects (34.9% of the same group) achieved SD, respectively. In addition, 5 subjects (7.9% of the same group) in the lapatinib group and 0 in the pyrotinib group had a BOR of PD. The results showed that the 12-cycle ORRs in the pyrotinib and lapatinib groups were 78.5% (95% CI: 68.5%, 88.5%) and 57.1% (95% CI: 44.9%, 69.4%), respectively. Using CMH chi-squared test with the stratification factor "with/without previous treatment with macromolecular anti-HER2 antibody" being corrected, the ORR was improved by 21.3% (95% CI: 4.0%, 38.7%) in the pyrotinib group compared to the lapatinib group with statistically significant difference, $P = 0.01$.

2.1.2.5.3. Clinical pharmacokinetics

In BLTN-Ia study, the PK analysis showed that the $t_{1/2}$ (mean) was 15.0, 20.9, 18.4, 18.1, and 18.8 h after a single oral dose of pyrotinib at 80, 160, 240, 320, and 400 mg, respectively. The median time to maximum plasma concentration of pyrotinib (T_{max}) ranged within 4-5.5 h. Within the dose range of 80-400 mg, the AUC and C_{max} of pyrotinib increased with increasing dose;

C_{max} increased proportionally with the increasing dose (β = 1.0349), and AUC_{0-t} was roughly proportional to the increase in dose (β = 1.2). No significant change in Cl/F was observed in all dose groups, suggesting a linear PK profile for pyrotinib within the dose range of 80-400 mg.

The results of the BLTN-Ie study showed that compared with administration in fasted condition, the bioavailability of pyrotinib increased after administration in post-prandial condition, with an increase in AUC by 43.31% and an increase in C_{max} by 78.89%. However, the time to C_{max} or elimination half-life ($t_{1/2}$) was not altered in general. These results suggested that it would be more rational to administer pyrotinib after meals, which supports the method of administration adopted in the phase I study.

In BLTN-Ib study, the PK analysis showed median T_{max} of 3.00-5.00 h, geometric mean $t_{1/2}$ of 9.43-16.5 h, and geometric mean C_{max} of 38.8, 80.8, 98.7, 143, and 147 ng/mL on Day 1 after oral pyrotinib doses at 80, 160, 240, 320, and 400 mg, respectively, in Chinese subjects with breast cancer. On the 8th day of continuous administration, the plasma concentrations reached a steady state. At steady state, the median T_{max} was 2.00-4.00 h, and the geometric mean $t_{1/2}$ was 11.4-15.9 h. At steady state (Day 28) after continuous administration of pyrotinib at 80-400 mg once daily, the geometric mean accumulation ratios R (in terms of AUC_{0-24h}) were 1.32, 1.35, 1.57, 1.35, and 1.22, respectively, suggesting that continuous administration did not produce significant dose-dependent accumulation. The geometric mean C_{max} was 43.0, 102, 156, 175, and 170 ng/mL, respectively, and the geometric mean AUC_{0-24h} was 549, 1260, 2080, 2660, and 2270 h·ng/mL, respectively. The increase of C_{max} was roughly proportional to the increase of dose (β = 0.8092), and the increase of AUC_{0-24h} was roughly proportional to the increase of dose (β = 0.9066), suggesting that PK parameters of pyrotinib in steady state basically conformed to the linear kinetic characteristics.

In BLTN-Ic study, the PK showed that after pyrotinib maleate was administered at doses of 160-400 mg once a day in combination with capecitabine, the time to maximum concentration (T_{max}) and the elimination half-life ($t_{1/2z}$) on Day 14 were nearly equal to that on Day 1, with no significant changes occurring due to continuous administration. T_{max} and $t_{1/2z}$ did not change significantly with the increasing dose of pyrotnib. On Day 14, the geometric mean of accumulation ratio R (in terms of AUC) was approximately 1, suggesting no obvious accumulation with continuous administration. The $AUC_{0-24\,h}$ and C_{max} of pyrotinib increased with dose in an almost dose-proportional manner (β = 1.0088 and 0.8177, respectively) over the dose range of 160-400 mg, indicating that pyrotinib had basically linear PK when used in combination with capecitabine. The pharmacokinetics of capecitabine and 5-fluorouracil after combined administration showed that capecitabine was rapidly absorbed and converted to active metabolite, 5-fluorouracil, after administered at 2000 mg/m^2/day, twice daily. Most subjects had concentrations below

quantitation limit at 8 h after administration. There were no significant differences in primary PK parameters ($AUC_{0\text{-}24h}$ and C_{max}) of capecitabine and its metabolite 5-fluorouracil between the each dose groups.

Refer to the "Investigator's Brochure for Pyrotinib Maleate" for the safety, efficacy, and pharmacokinetic data from clinical studies of pyrotinib in detail.

2.2. Scientific Rationale

2.2.1. Study rationale

The incidence of breast cancer is the highest among all cancers diagnosed in Chinese women and is on the rise. In addition, breast cancer is a common malignancy that hazards to women. Positive HER2 status is an independent factor with poor prognosis in breast cancer. Approximately 20% to 30% of breast cancer patients in China have HER2 amplification/overexpression. Targeted therapy should be used as soon as possible for HER2-positive recurrent and metastatic breast cancer, and earlier use may bring the greater benefit[8, 9].

Pyrotinib is a novel small molecule irreversible inhibitor of tyrosine kinases EGFR and HER2 independently developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd./Shanghai Hengrui Pharmaceutical Co., Ltd. Preclinical *in vivo* studies showed that pyrotinib could significantly inhibit HER2-positive breast cancer. Pyrotinib is an irreversible small molecule inhibitor with dual targets (EGFR and HER2), and has different sites of action and additional EGFR target compared with trastuzumab, a macromolecule antibody directed at the HER2 receptor.

Small molecule inhibitor of HER2 and trastuzumab block different HER2 target regions and have some non-overlapping mechanisms of action[10]. A phase II clinical study of lapatinib combined with trastuzumab and paclitaxel in treatment naive patients with advanced breast cancer showed ORRs of 79%, 71%, and 70% in the lapatinib (1000 mg/d) + paclitaxel (80 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week), lapatinib (1000 mg/d) + paclitaxel (70 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week), and lapatinib (750 mg/d) + paclitaxel (80 mg/m^2, once a week) + trastuzumab (2 mg/kg, once a week) groups, respectively. The results showed a certain efficacy of dual-targeted drugs (trastuzumab + lapatinib) combined with first-line therapy in the treatment of HER2-positive advanced breast cancer[11]. In addition, in the NSABP FB-8 study of neratinib, paclitaxel (80 mg/m^2, on D1, D8, and D15, in 28-day cycles), trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg once a week), and neratinib (by oral administration, at 120, 160, or 240 mg, once daily) were administered. The study results of the three-agent combination: overall ORR: 38%; CBR: 52%; median time to progression (mTTP): 3.7 m. The study results showed a certain efficacy of the combination of dual-targeted drugs (neratinib and trastuzumab) in patients with advanced breast cancer previously treated with trastuzumab, lapatinib, T-DM1, taxanes, and multiple lines of

chemotherapy[12]. In conclusion, small molecule targeted inhibitor of HER2 combined with monoclonal antibody trastuzumab showed good efficacy in patients with HER2-positive advanced breast cancer. The efficacy and safety need to be further explored in future studies.

The current clinical study results showed that pyrotinib is well tolerated, and has significant anti-tumor efficacy both as a single agent and in combination with docetaxel or capecitabine in patients with HER2-positive and HER2-mutant advanced solid tumors. This study intends to further explore the efficacy and safety of pyrotinib combined with trastuzumab and docetaxel in patients with advanced HER2-positive breast cancer.

2.2.2. Rationale for the dose of docetaxel and trastuzumab

Docetaxel (100 mg/m^2 for every 3 weeks) combined with trastuzumab showed a positive benefit-risk ratio compared with docetaxel monotherapy in the treatment of HER2-overexpressing metastatic breast cancer[13]. That is, adding anti-HER2 targeted therapy on the basis of chemotherapy can provide clinical benefit to subjects. Studies have shown a significantly higher incidence of febrile neutropenia in Asian subjects than in other populations with docetaxel 75 mg/m^2. This result is consistent with the overall observation of tolerability of taxane in such a population[14, 15]. However, lapatinib (1000 mg/day)[16] (small molecule tyrosine kinase inhibitor of HER2) and neratinib (240 mg/day)[17] combined with trastuzumab at standard dose and paclitaxel (80 mg/m^2, once a week) may result in a higher incidence of Grade 3 diarrhea. Considering the subjects' tolerance, efficacy, race, and other factors, the dose of docetaxel in this study is set at 75 mg/m^2.

In this study, following one of the recommended dosing regimens in the instruction for use, trastuzumab will be administered once every 3 weeks, with an initial loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary objective

- To evaluate the progression-free survival (PFS) of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer

3.1.2. Secondary objectives

- To evaluate the safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer

- To compare the efficacy between two groups in overall survival (OS), objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR).
- To evaluate the pharmacokinetics (PK) of pyrotinib maleate tablets combined with trastuzumab and docetaxel in patients with HER2-positive recurrent/metastatic breast cancer.

3.2. Study Endpoints

3.2.1. Primary endpoint:

- PFS (investigator-assessed)

3.2.2. Secondary endpoints

- PFS (IRC-assessed)
- OS
- ORR
- DoR
- CBR
- Safety endpoints: incidence and severity of adverse events (AEs) and serious adverse events (SAEs), according to NCI-CTCAE v4.03; changes in the following parameters from baseline: ECOG PS, vital signs, physical examination, laboratory tests (hematology, urinalysis, routine stool test, and blood biochemistry), ECG, and echocardiography.
- Blood concentrations of pyrotinib

4. STUDY DESIGN

4.1. Overview of Study Design

This is a phase III, randomized, double-blind, placebo-controlled, multicenter study.

This study plans to enroll a total of 590 subjects. Eligible subjects will be randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). Randomization is stratified by the following factors:

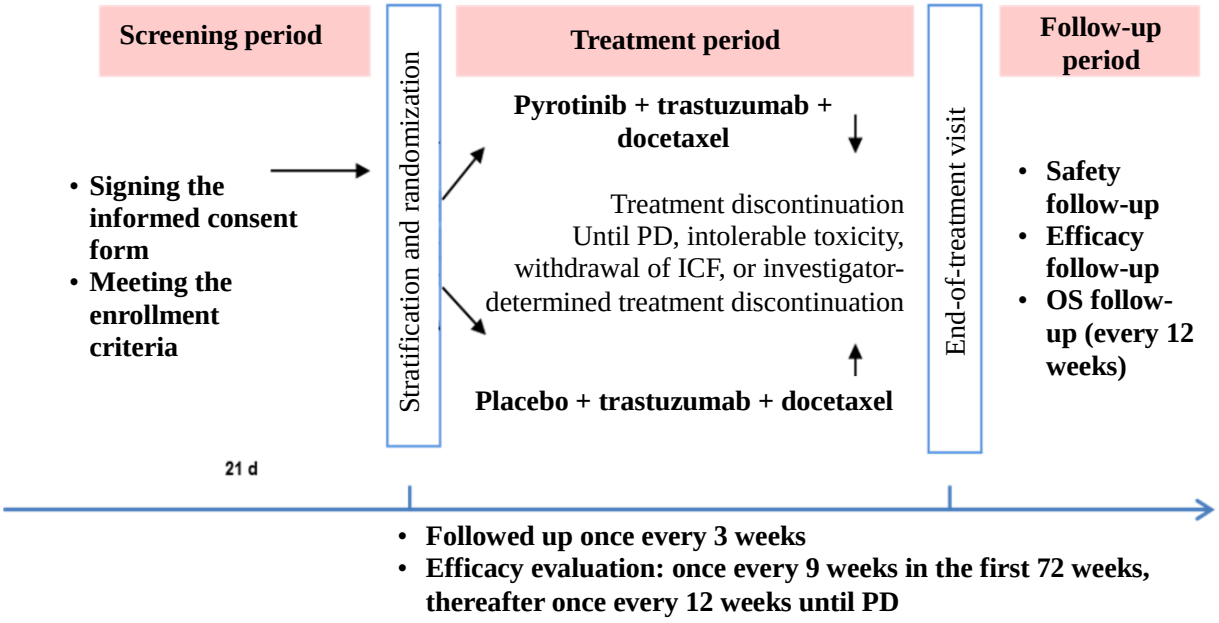
- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

Subjects will receive study treatment within 48 h after randomization in 21-day cycles. Pyrotinib/placebo and trastuzumab will be administered until investigator-assessed progressive disease (PD), intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The tumor assessments will be performed by the investigators and independent review committee according to RECIST v1.1. The primary PFS analysis is based on the assessment results by the investigators.

For subjects who discontinue the study treatment, the safety visit should occur on D28 ± 7 d after the last administration of study drug, then the subjects should start the survival follow-up period until death or study termination (whichever occurs first). For subjects who discontinue the study treatment due to reasons other than PD or death, scheduled tumor assessments need to be collected until PD, start of a new anti-tumor treatment, or death (whichever occurs first).

This study plans to perform 1 safety assessment and 1 interim analysis by Independent Data Monitoring Committee (IDMC). After the data review, the IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study.

An overview of the study design is shown below:



4.2. Methods to Reduce Bias

4.2.1. Enrollment/randomization/blinding

This is a randomized, double-blind clinical study. The sponsor's randomization specialist uses SAS (version 9.4 or higher) to simulate the generation of the randomization table and drug number list, which are kept by the randomization specialist. The generation process is reproducible. The subjects, investigators, and all medical personnel participating in the study or clinical evaluation as well as the sponsor's research team are blinded to the subject's medication assignment.

The subjects are randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). The study centers screen for subjects who meet all the inclusion criteria and do not meet any exclusion criteria. The personnel with relevant authority log in to the Interactive Web Response System (IWRS) for stratified randomization. The stratification factors include: 1) prior neoadjuvant/adjuvant therapy: with or without trastuzumab; 2) ER/PR status: positive or negative. The screening information is entered into the system. Randomization number and drug number are obtained. The subjects must start the assigned study medication within 48 h after randomization.

4.2.2. Unblinding

When the principal investigator of a study center (or the drug regulatory authority (such as the National Center for Drug Evaluation)) believes it necessary to know the group assignment for the safety of the subject, the principal investigator of the study center applies for emergency unblinding in the IWRS and contacts the sponsor's research team. The project manager or CRA contacts the randomization specialist. The randomization specialist logs in the IWRS to confirm the application for emergency unblinding and executes unblinding, and informs the project manager or CRA of the completion of unblinding. The investigator logs in the IWRS to obtain the grouping information of the subject. If the IWRS cannot be used when applying for emergency unblinding, the principal investigator of the study center fills out a notice of emergency unblinding and mail it to the sponsor's research team. The project manager or CRA forwards it to the randomization specialist. The randomization specialist provides a Blind Code Handover Sheet of the corresponding subject by email.

The clinical care for the subject should remain unchanged regardless of the blinded treatment assignment.

Unblinding by the Independent Data Monitoring Committee (IDMC) during the safety monitoring should be performed by an independent statistician and the integrity of the study should be guaranteed.

The subjects, study center personnel, sponsor's MA, CRA, project manager, and project statisticians participating in the study are kept blinded. Upon deterministic analysis of the primary efficacy endpoint, after review under blinding, the database will be locked. The statistician will apply to the randomization specialist for unblinding, i.e., inform the statistician of the corresponding group of each subject's number for statistical analysis of all data.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

The enrollment of eligible subjects is critical to ensure the outcome of the study. Subjects must meet the following inclusion criteria to be allowed to participate in this study. Any medical or non-medical conditions of a subject are considered for his/her eligibility.

Before the subject's enrollment in the study, the investigator should review, confirm, and document whether the subject is suitable for participating in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for study entry:

1. Females aged ≥ 18 and ≤ 75 years old.
2. Histologically confirmed HER2-positive invasive breast cancer, while meeting the following conditions:
    - HER2 positive is defined as 3+ by immunohistochemistry (IHC) or an *in situ* hybridization (ISH) result of HER2 gene amplification. A HER2-positive breast cancer confirmed by the pathology department of the participating study center.
    - Tumor staging: recurrent or metastatic breast cancer; locally recurrent disease must not be amenable to resection with curative intent.
3. Have at least one measurable lesion according to RECIST v1.1.
4. ECOG PS: 0-1.
5. The functional levels of major organs must meet the following requirements (no blood transfusion or treatment with leukogenic and thrombopoietin drugs within 2 weeks prior to screening):
    - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L;
    - Platelet count (PLT) ≥ 90×10^9/L;

- Hemoglobin (Hb) ≥ 90 g/L;
- Total bilirubin (TBIL) ≤ upper limit of normal (ULN); for patients with Gilbert's syndrome, TBIL ≤ 2 × ULN;
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN; for patients with liver metastases, ALT and AST ≤ 5 × ULN;
- Alkaline phosphatase ≤ 2.5 × ULN;
- Urea/urea nitrogen (BUN) and creatinine (Cr) ≤ 1.5 × ULN;
- Left ventricular ejection fraction (LVEF) ≥ 50%;
- Fridericia-corrected QT interval (QTcF) < 470 msec.

6. Participate in the study voluntarily, sign the informed consent form, have good compliance, and willing to cooperate with follow-up visits.

5.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to participate in this study:

1. Have received any systemic anti-tumor therapy for the recurrent/metastatic diseases, including any anti-EGFR or anti-HER2 agents, systemic chemotherapy, immunotherapy, and more than one prior hormonal regimen, as well as other anti-tumor therapies that shall be excluded as judged by the investigator.
2. History of anti-HER tyrosine kinase inhibitor (TKI) or macromolecular antibody for breast cancer in any treatment setting, except trastuzumab used in the (neo) adjuvant therapy.
3. History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (except endocrine therapy) to metastatic diagnosis of < 12 months.
4. Current Grade ≥ 3 peripheral neuropathy as per CTCAE v4.03.
5. Not suitable for systemic chemotherapy as judged by the investigator.
6. Have received endocrine therapy within 7 days prior to randomization.
7. History of other malignant tumors within the past 5 years, except for cured cervical carcinoma *in situ*, skin basal cell carcinoma or squamous cell carcinoma (patients with other malignant tumors that occurred more than 5 years before the date of randomization are allowed to be enrolled only if they have been cured by surgery).

8. Current brain metastases.
9. Subjects with bone or skin as the only target lesion.
10. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin or doxorubicin liposome > 360 mg/m^2
    - Epirubicin > 720 mg/m^2
    - Mitoxantrone > 120 mg/m^2, idarubicin > 90 mg/m^2
    - Others (for example, in case of other anthracyclines or multiple anthracyclines, the cumulative dose > the dose equivalent to 360 mg/m^2 of doxorubicin)
11. Have undergone major surgery or apparent trauma within 4 weeks prior to randomization, or expected to undergo a major surgery during the course of study treatment.
12. With severe cardiovascular disease or discomfort, including but not limited to the following:
    - Medical history of cardiac failure or systolic dysfunction (LVEF < 50%)
    - Angina or arrhythmia that requires treatment or of high risk (such as type 2 second-degree atrioventricular block or third-degree atrioventricular block, ventricular tachycardia)
    - Clinically significant valvular heart disease
    - Transmural myocardial infarction as indicated by ECG
    - Poorly controlled hypertension (systolic pressure > 150 mmHg and/or diastolic pressure > 100 mmHg)
13. With dysphagia, chronic diarrhea, intestinal obstruction, or other factors affecting drug intake and absorption.
14. With known allergies to the components of the study drugs.
15. History of immunodeficiency, including HIV infection or other acquired and congenital immunodeficiencies, or organ transplantation.
16. Presence of third spacing (such as hydrothorax and ascites) that cannot be controlled by drainage or other methods.
17. Pregnant or lactating female subjects, or subjects of childbearing potential who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose.
18. Presence of severe concurrent disease or other concurrent diseases that may interfere with planned treatment, or any other conditions rendering the subjects unsuitable for participating in this study, such as active hepatitis B and lung infection requiring treatment.

5.3. Withdrawal from Study or Treatment Discontinuation

5.3.1. Withdrawal from study

Withdrawal from the study:

1. Subject voluntarily withdraws the ICF and refuses further follow-ups;
2. Investigators may withdraw the subject from the study in the event of major Inclusion/Exclusion protocol violation.

Continue study follow-ups after treatment discontinuation:

1. A tumor assessment shows progressive disease;
2. Meeting criteria for permanent discontinuation of the study drug;
3. Any clinical AE, laboratory abnormality, or medical condition indicating that the subject can no longer benefit from the treatment;
4. Occurrence of pregnancy during the study;
5. Important protocol deviation rendering the subject unsuitable for continuing study treatment;
6. Other reasons for the treatment discontinuation as determined by the investigator.

5.3.2. Procedures for withdrawal from study or treatment discontinuation

The efficacy and safety examinations upon study withdrawal specified in the protocol must be completed and reported as thoroughly as possible. In addition, safety follow-ups and subsequent survival follow-ups should be completed, along with fully documented AEs and their outcomes. The investigator can recommend or provide new or alternative treatments to a subject based on the condition of the subject. Subjects showing no PD need to be continuously followed up for tumor assessment until the subjects begin new anti-tumor treatment or show PD.

Subject's survival status should still be followed up even when the subject refuses to visit the study center, unless the subject withdraws consent to provide further information or consent to be further contacted. In that case, no further study assessments should be conducted and no further data should be collected. The sponsor can retain and continue to use all data collected before withdrawal of informed consent, unless the subject requests a retraction of collected data.

5.4. Premature Termination or Suspension of Study

This study can be terminated prematurely or suspended if there are sufficient reasons. This may result from the decision of regulatory authorities, changes in comments by the ethics committee, efficacy or safety issues of the study drugs, or the judgment of the sponsor. In addition, Hengrui

reserves the right to terminate the research and development of pyrotinib at any time. The party who decides to suspend/terminate the study should notify the investigator, sponsor, and regulatory authorities in writing, documenting the reasons for suspension/termination. The investigator must immediately notify the ethics committee and sponsor, and provide relevant reasons.

Termination of study center:

- The sponsor has the right to terminate the study at a study center if it is found that the investigator of the center is seriously or persistently non-compliant to the protocol and other study procedures, which may interfere with the proper implementation of the study. In which case, the sponsor will immediately inform the investigator and the regulatory authorities of the termination.
- If the study is terminated or suspended at a study center by the investigator, the subjects must be informed immediately, and the reasons for termination must be reported in writing to the study center's clinical study institution/ethics committee, the sponsor, and regulatory authorities, as required by regulations.

Reasons for premature termination or suspension of the entire study may include:

- Confirmed unexpected, major, or unacceptable risk to the subjects.
- Existing efficacy data supporting premature study termination.
- Major errors in the protocol found during the implementation of the study;
- Ineffective study drug/treatment, or meaninglessness to continue the study;
- Extreme difficulties in completing the study due to reasons such as severe delays in subject recruitment or frequent protocol deviations.

The study may continue once those issues related to drug safety, protocol compliance, and data quality have been resolved and approved by the sponsor, ethics committee, or CFDA (now NMPA).

5.5. Definition of End of Study

The end of this study is defined as:

- Two years after the collection of 410 PFS events and the sponsor's confirmation that sufficient OS events have been collected;

or

- Study termination decided by the sponsor.

5.6. Lifestyle Requirements

5.6.1. Contraception

In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after amniotic index improved and oligohydramnios recurred

Cases of impaired fetal renal development and/or function due to oligohydramnios were reported in pregnant women treated with trastuzumab in post-marketing reports, as well as some cases associated with fatal fetal lung hypoplasia. Trastuzumab can cause fetal harm when administered to a pregnant woman. Preclinical studies suggested that docetaxel is genotoxic. Results from animal studies suggested that pyrotinib may have reproductive toxicity (including teratogenicity), but it has not been clinically proven.

Female subjects are considered non-childbearing potential if they are either:

1) postmenopausal, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative medical reasons; a high follicle stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a post-menopausal state in female subjects younger than 45 years of age and not using hormonal contraception or hormonal replacement therapy; However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient);

or

2) have undergone a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

or

3) have a congenital or acquired condition that prevents childbearing.

Female subjects of childbearing potential must agree to avoid becoming pregnant and are required to use the following contraception methods, from the time the subject signs the informed consent form until 7 months after the last dose of study treatment:

1) practice abstinence from heterosexual activity*.

or

2) female subjects (or male partners) use acceptable non-hormonal contraceptive methods during heterosexual activity.

Acceptable non-hormonal contraceptive methods include:

Single method (one of the following is acceptable):

- copper-containing intrauterine device (IUD)
- vasectomy of female subject's male partner

Combination method (requires use of two of the following):

- vaginal diaphragm with spermicide (cannot to be used in combination with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot to be used together)

*Abstinence (avoiding heterosexual intercourse) can be used as the sole method of contraception if this is the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), and withdrawal (coitus interruptus) are not acceptable methods of contraception.

In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject.

6. STUDY MEDICATION

6.1. Description of the Study Drugs and Control Drug

6.1.1. Access to drugs

The investigational drug in this study is pyrotinib maleate tablet (pyrotinib/placebo), manufactured and supplied by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Docetaxel injection (Ai Su®) and trastuzumab (Herceptin® or Zercepac®) will be used in the study and are provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Following the ethics approval of Protocol Version 5.0, subjects who are treated with Zercepac® at study centers that have no supply of Zercepac® will be switched to treatment with Herceptin® until the subjects withdraw from the study treatment or withdraw from the study. Newly randomized subjects will be treated with Herceptin® until the subjects withdraw from the study treatment or withdraw from the study.

6.1.2. Dosage form, appearance, packaging, and label

- Pyrotinib maleate tablet/placebo

  Dosage form: tablet

  Strength: 80 mg; 160 mg

  Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

- Docetaxel injection

  Dose form: injection

  Strength: 0.5 mL: 20 mg; 1.5 mL: 60 mg

  Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

- Trastuzumab for injection (Zercepac®)

  Dosage form: lyophilized powder

  Strength: 150 mg/vial

  Manufacturer: Shanghai Henlius Biopharmaceuticals Co., Ltd.

- Trastuzumab for injection (Herceptin®)

  Dosage form: lyophilized powder

  Strength: 440 mg

  Manufacturer: F. Hoffmann-La Roche

  Refer to the corresponding packaging information for the labels and outer packaging of the above drugs.

6.1.3. Storage and stability of drugs

The investigator or the authorized representative thereof (e.g., pharmacist) will ensure that all study drugs <including pyrotinib/placebo, docetaxel, and trastuzumab> are stored in a secure and access-controlled area conforming to storage conditions and regulatory requirements.

Docetaxel and trastuzumab should be stored in their original containers and match with the labels. Once the product has been prepared or diluted, it should be stored according to the storage conditions specified in the <Package Insert>.

For inconsistence of the storage conditions on the label with those in other materials (such as IB), the label should be followed.

Daily maximum and minimum temperatures of all storage areas (such as freezer, refrigerator, and room temperature) must be recorded by the study center. The documented period shall begin with the receipt of the study drug until the last subject completes the last visit. Even if a continuous monitoring system is employed, a written log must be kept at the study center to ensure a correct record of storage temperature. The temperature monitoring and storage devices (such as refrigerator) should be regularly inspected to ensure proper operation.

Any deviations related to the labeled conditions on the product should be immediately reported upon discovery. The study center shall take active measures to restore the study drugs under the storage conditions described on the label, and the temperature deviation and the measures taken shall be reported to the sponsor.

Study drugs that are affected by temperature deviations must be temporarily isolated until approved by the sponsor for further use, and such case is not considered a protocol deviation. The use of affected study drugs without the approval of the sponsor is considered a protocol deviation. The sponsor will provide a detailed procedure on reporting temperature deviations to the study center.

For subjects who take the medication at home, the staff at the study center will guide the subjects regarding the proper method of drug storage.

Refer to the Pharmacy Manual for additional storage instructions and actions to be taken when stored outside the specified conditions.

6.1.4. Preparation of study drugs

Trastuzumab and docetaxel should be administered intravenously (IV) at the study center. They should be prepared by qualified or experienced study personnel, such as physicians, pharmacists, or medical assistants (approved by national authorities or study center operating guidelines) according to the corresponding package inserts.

Only qualified personnel who are familiar with reducing inappropriate exposure in themselves and the environment are allowed for the preparation, dispensation, and safe use of study drugs.

6.1.5. Administration of study drugs

Pyrotinib/placebo

Pyrotinib/placebo is orally administered to subjects at 400 mg once a day within 30 min after breakfast in 21-day cycles starting from Day 1 of Cycle 1. Use of loperamide hydrochloride (Imodium®) is allowed (up to 16 mg/day) for secondary preventing diarrhea during pyrotinib/placebo medication in the study.

Subjects swallow pyrotinib/placebo intact and should not hold or chew the drug before swallowing.

During the treatment with pyrotinib/placebo combined with trastuzumab and docetaxel, the dose of pyrotinib/placebo may be reduced per the protocol based on the adverse reactions of the subject. The dose of pyrotinib/placebo should be increased to 400 mg after permanent discontinuation of docetaxel. If, per the investigator's comprehensive assessment, the dose cannot be increased to 400 mg, after reporting to the sponsor, the dose of pyrotinib/placebo can be maintained at the dose before docetaxel discontinuation or increased to an appropriate dose (two increases are allowed, up to 400 mg).

The scheduled time of a missed dose and the reason for not taking the dose should be documented in detail. Any vomiting should be documented in the subject diary, original medical records, and the eCRF. Note that missed dose and vomited dose after administration are not made up. The subsequent doses will be taken as scheduled.

The investigator should actively provide symptomatic treatment for adverse events during the study. Concomitant treatments and medications should be documented in detail in the medical records and the EDC system.

Trastuzumab

Trastuzumab is administered intravenously starting from Day 1 of Cycle 1. The subjects will receive 8 mg/kg loading dose of trastuzumab in Cycle 1 and 6 mg/kg dose in subsequent cycles. The dose of trastuzumab will be calculated based on the actual weight of the subject. The body weight should be recorded at baseline and at each visit. If the weight of the subject has increased or decreased by > 10% from baseline, the dose will be recalculated. In the event of dose recalculation due to a change in body weight from baseline by > 10%, the latest body weight will serve as the new baseline to calculate the dose of trastuzumab in subsequent treatment cycles.

Dose modification for reasons other than weight changes are not allowed. Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. If trastuzumab administration must be delayed by one day or longer, docetaxel should be delayed by the same period of time. If the subject misses a dose of trastuzumab for one cycle (e.g., the time interval between 2 sequential administrations is 6 weeks or more apart), the re-loading dose of 8 mg/kg will be administered, and the docetaxel will also be administered on the same day. Maintenance trastuzumab doses of 6 mg/kg will be given every 3 weeks.

Trastuzumab may cause symptoms of infusion reactions, such as nausea, fever, diarrhea, chills, asthenia, and headache. Such reactions generally occur during or shortly after the infusion. Therefore, trastuzumab should be administered in an environment with first aid equipment. The medical staff should be trained on monitoring and responding to medical emergencies. During each infusion, the subjects should be monitored for any adverse reactions. Monitoring should last for at least 90 min from the start of the first trastuzumab infusion.

Supportive treatments with oxygen, beta-agonists, antihistamines, antipyretics, and corticosteroids may help relieve allergic symptoms. Prophylactic treatment with corticosteroids and antihistamines may be administered in subsequent infusions for subjects who develop infusion-related symptoms during or after the infusion. Infusion reactions may be delayed, and thus the subject should contact the investigator in the rise of any problem.

Docetaxel

The dose of docetaxel is 75 mg/m^2. After the end of the observation period of trastuzumab infusion, docetaxel will be administered by intravenous infusion on Day 1 of each cycle. From the start of docetaxel infusion, the subject will be closely monitored for hypersensitivity reactions, which may occur within a few minutes. In the case of severe hypotension, bronchospasm, or systemic rash/erythema, immediate discontinuation of docetaxel and appropriate treatment are required. In the case of mild symptoms such as flushing or local skin reactions, the infusion may be slowed down. Treatment with docetaxel should be discontinued in subjects who develop severe hypersensitivity, but follow-up should be continued following the assessment schedule, unless the informed consent is withdrawn.

The risk of hematologic toxicity can be reduced by dose reduction (dose delay when necessary) and/or prophylactic administration of G-CSF. The G-CSF is a long-acting G-CSF preparation, thiopefilgrastim injection (Aiduo®), manufactured and provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd. For intolerant subjects due to contraindications or adverse drug reactions, other G-CSF preparations may be selected.

In the absence of contraindications, prophylactic medications (consisting of oral corticosteroids) may be given on Day -1, Day 1, and Day 2.

Treatment with docetaxel may be delayed in the case of hematologic and clinical biochemistry AEs or other intolerable adverse events. If docetaxel administration must be delayed by one day or longer, trastuzumab should be delayed by the same period of time.

The dose of docetaxel is calculated based on the body surface area of the subject. The calculated dose may be rounded, but should not exceed ± 5%. Subjects' baseline weight and height should be recorded, as should their weight at each scheduled visit. If the investigator believes that the height of the subject may change, the height should be re-measured. If the weight of the subject has increased or decreased by > 10% from baseline, the dose will be recalculated. In the event of dose recalculation due to a change in body weight from baseline by > 10%, the latest body weight will serve as the new baseline to calculate the dose of docetaxel in subsequent cycles. For dose modification of docetaxel and interruption or discontinuation of treatment due to toxicities, see Section 6.1.6 for the guidelines.

6.1.6. Dose modifications and delay

Based on preliminary clinical data, pyrotinib monotherapy is well-tolerated. The incidence of Grade 3/4 adverse events was 25% (2/8) in the 400 mg group and 11.1% (1/9) in the 320 mg group. All Grade 3/4 AEs were diarrhea. Other common adverse reactions included hand and foot syndrome, hepatic function abnormal, vomiting, etc. Thus, active symptomatic treatment or observation is recommended upon occurrence of adverse events during the study. Before intolerance to pyrotinib/placebo is confirmed, it should be ensured that pyrotinib/placebo can be continued as much as possible.

In the case of AEs of intolerance to pyrotinib/placebo during the study, the dose of pyrotinib/placebo may be interrupted after active symptomatic treatment. If the subject is still intolerant, the dose of pyrotinib/placebo may be reduced in the order of 400 mg/day, 320 mg/day, and 240 mg/day.

Dose recalculation of trastuzumab for reasons other than a change of > 10% in body weight is not permitted.

In the case of AEs due to intolerance to docetaxel, the dose of docetaxel may be reduced to a minimum of 60 mg/m^2 per the package insert and the investigator's assessment. Further dose reduction (minimum dose of 60 mg/m^2) is required for subjects persistently intolerant. The investigator and the sponsor will discuss whether to continue the medication or withdraw the subject from all study treatments.

If the subject is still intolerant after dose reduction to the minimum mentioned above, the study drug should be discontinued. Permanent discontinuation of pyrotinib/placebo should be decided based on the discussion between the investigator and the sponsor. In the study, discontinuation of docetaxel and trastuzumab with monotherapy of pyrotinib/placebo is permitted.

6.1.6.1. Management of common adverse events

Diarrhea

The investigator must inform the subject in detail of the potential of diarrhea and appropriate treatment measures prior to starting the oral administration of study drug. **Instruct the subject to prepare anti-diarrheal drugs; pay attention to changes in the appearance of stool and frequency of defecation during the study drug administration; start anti-diarrheal treatment as soon as possible in the case of loose stool; and adjust the diet. Loperamide may serve as an anti-diarrheal drug.**

Oral administration of loperamide hydrochloride (Imodium®) is allowed (up to 16 mg/day) for secondary preventing diarrhea during the study. In the case of interruption or delay of study medication (pyrotinib/placebo, trastuzumab, or docetaxel), the investigator may prescribe loperamide to prevent diarrhea after evaluation. For severe diarrhea, electrolytes may be administered orally or intravenously. For Grade ≥ 3 diarrhea that cannot be controlled after prophylactic medication or symptomatic treatment, the dose of study drug will be modified according to Table 3.

Stomatitis

In the case of stomatitis during the study, it is recommended to give symptomatic treatment first, such as gargling with normal saline. Topical medication may be prescribed per the routine diagnosis and treatment of the study center. For Grade ≥ 2 stomatitis that cannot be controlled after symptomatic treatment, the dose of study drug will be modified according to Table 3.

Hand and foot syndrome

In the case of hand and foot syndrome, it is recommended to give symptomatic treatment first and closely follow up. Strengthen skin care, keep skin clean, and avoid secondary infections; avoid pressure or friction; use moisturizers or lubricants, use topical lotions or lubricants containing urea and corticosteroids; use topical antifungal or antibiotic treatment if necessary. For Grade ≥ 2 hand and foot syndrome that cannot be controlled after symptomatic treatment, the dose of study drug will be modified according to Table 3.

Nausea or vomiting

Give symptomatic treatment first, such as acid suppression, gastric protection, and antiemetics and closely follow up. In the case of symptoms seriously affecting eating, pay attention to the water/electrolyte balance. For persisted Grade ≥ 2 vomiting after active treatment, the dose of study drug will be modified according to Table 3.

Hepatic function abnormal

Hepatic function should be monitored regularly per the protocol during the study. Special attention should be paid to the levels of bilirubin, ALT, and AST. In the case of hepatic function abnormal with clinical significance, the investigator should give hepatoprotective and symptomatic treatment based on the subject's condition and adverse events, and determine the frequency of blood biochemistry tests according to clinical requirements. For persisted Grade ≥ 2 hepatic function abnormal after active treatment, the dose of study drug will be modified according to Table 3.

6.1.6.2. Common adverse events of pyrotinib/placebo and docetaxel

The investigator is advised to interrupt and modify the doses of pyrotinib/placebo and docetaxel according to the principles in the table below. In the case of AEs that are considered to be mainly related to docetaxel, including but not limited to hematologic and clinical biochemistry AEs, and are not relieved after active symptomatic treatment (≤ 1 treatment cycle), the dose of docetaxel may be delayed or modified in the subsequent cycle according to Table 3.

In the case of AEs that are considered to be possibly related to both pyrotinib/placebo and docetaxel but are not relieved after active symptomatic treatment (≤ 1 treatment cycle), the investigator is advised to interrupt, delay, and modify the dose of one of the study drugs according to Table 3 based on the clinical situation.

The investigator should manage the administration of pyrotinib/placebo and docetaxel as described in this section whenever possible, but may make appropriate adjustments when necessary based on the subject's specific condition and medical judgment.

Table 3. Dose modification for pyrotinib/placebo and docetaxel

NCI CTCAE 4.03*	Pyrotinib/placebo **(intolerable after active treatment, considered related to pyrotinib/placebo)[a]**	Docetaxel	
		Occurring in a treatment cycle and disappearing by the next treatment cycle[b]	Existing on D1 of scheduled cycle[c]
Neutrophils reduced			
Grade 3-4	Resume medication after interruption	Maintain dose	Delay medication until ANC ≥ 1500/mm^3. If G-CSF is not administered, maintain dose and add G-CSF in the case of recovery within 1-3 weeks If G-CSF is administered, maintain dose in the case of recovery within 1 week, or reduce dose by 1 level in the case of recovery within 2-3 weeks

NCI CTCAE 4.03*	Pyrotinib/placebo **(intolerable after active treatment, considered related to pyrotinib/placebo)[a]**	Docetaxel	
		Occurring in a treatment cycle and disappearing by the next treatment cycle[b]	Existing on D1 of scheduled cycle[c]
Febrile neutropenia (Grade 3-4)	Resume medication after interruption Reduce dose by 1 level when necessary	Add G-CSF and/or reduce dose by 1 level Discontinue when necessary	
Platelets decreased			
Grade 3	Resume medication after interruption	Maintain dose	Delay medication until platelet count ≥ 75000/mm^3. Maintain dose in the case of recovery within 1 week; Reduce dose by 1 level in the case of recovery within 2-3 weeks
Grade 4	Resume medication after interruption Reduce dose by 1 level when necessary	Reduce dose by 1 level	Reduce dose by 1 level
Diarrhea (not relieved after prophylactic oral administration of loperamide hydrochloride and symptomatic treatment)			
Grade 3 for > 2 days or Grade 1-2 with complications (Grade ≥ 2 nausea or vomiting, pyrexia, hematochezia, or dehydration, or Grade 3-4 neutrophils reduced)	First occurrence: interrupt dose; remain original dose in the case of recovery to Grade ≤ 1 or baseline within 1 week; reduce dose by 1 level in the case of recovery to Grade ≤ 1 or baseline within 1-3 weeks. Second occurrence: interrupt dose; reduce dose by 1 level after recovery to Grade ≤ 1 or baseline.	First occurrence: maintain dose Second occurrence: reduce dose by 1 level when necessary after interruption	Delay dose; reduce dose by 1 level when necessary after recovery to Grade ≤ 1 or baseline
Grade 4	Discontinue	Discontinue	Discontinue
Other AEs (except those specified in 6.1.6.3 and 6.1.6.4 and those considered tolerable by the investigator)			
Grade 2	Maintain dose Resume after interruption when necessary	Maintain dose	Delay dose; resume after recovery to Grade ≤ 1 or baseline
Grade 3	First occurrence: resume medication after interruption Second occurrence: reduce dose by 1 level when necessary after interruption	Reduce dose by 1 level when necessary	Delay dose; reduce dose by 1 level when necessary after recovery to Grade ≤ 1 or baseline
Grade 4	Discontinue	Discontinue	Discontinue

a: Following each dose interruption, medication can be resumed only after the AE recovers to Grade ≤ 1 or baseline.

b: Disappearance means all AEs requiring dose modification recover to Grade ≤ 1 (ANC must be ≥ 1500/mm^3) on Day 1 of the next scheduled cycle.

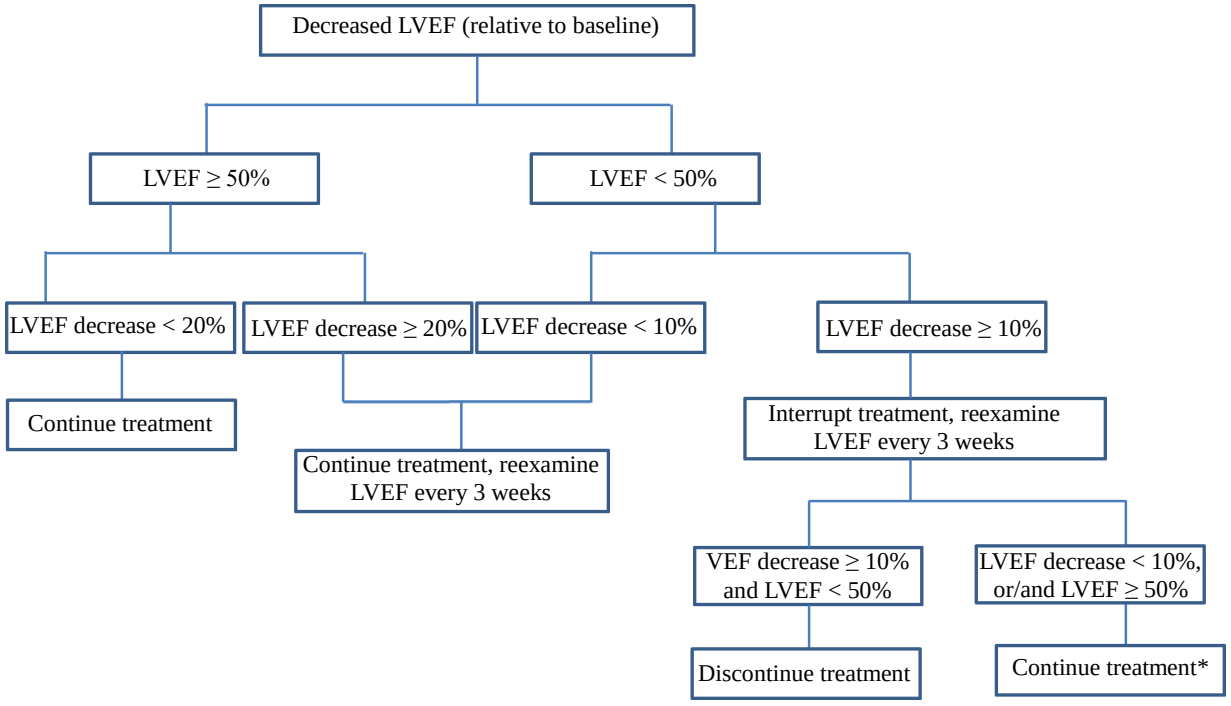
c: Interrupt, examine weekly, and resume treatment when AE recovers to Grade ≤ 1 (ANC must be ≥ 1500/mm^3). Discontinue docetaxel if toxicity is not relieved after dose delay for 3 weeks.

6.1.6.3. Cardiac adverse events

Cardiac AEs, when occurring in the study, should be treated according to the following principles:

- If the investigator considers that a cardiac AE may have occurred, additional LVEF examination is required.
- Once any symptoms or signs suggest the possibility of heart failure, chest X-ray and echocardiography should be performed to confirm the diagnosis. After confirmation, all study drugs should be discontinued, and active symptomatic treatment should be given.
- In the case of cardiac AEs that are considered possibly related to trastuzumab, the dose of pyrotinib/placebo may be reduced if the condition is not relieved within 2 treatment cycles after active symptomatic treatment and/or dose interruption or delay of trastuzumab.
- In the case of asymptomatic decreased LVEF, treatment should be given following the figure below.

Figure 1. Schematic diagram for the treatment of asymptomatic LVEF decreased



***: Reduce the dose of pyrotinib/placebo by 1 level when resuming medication.**

6.1.6.4. Special requirements for dose interruption and modification of study drugs

6.1.6.4.1. Pyrotinib/placebo

Following each occurrence of dose interruption of pyrotinib/placebo due to intolerable AEs of pyrotinib/placebo, medication should be resumed after the AEs recover to Grade ≤ 1 or baseline, unless the investigator believes that AEs have stabilized and the subject can tolerate pyrotinib/placebo medication.

Multiple dose interruptions during the treatment are permitted. Each interruption of pyrotinib/placebo should not exceed 21 days consecutively, so as to maintain the drug intensity of the treatment received by the subject. If the interruption of pyrotinib/placebo treatment due to AE exceeds the criteria above, the subject should withdraw from the study.

6.1.6.4.2. Trastuzumab

The dose of trastuzumab must not be reduced due to any toxicity. However, due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued.

Permanent discontinuation of trastuzumab may be considered in the following cases:

- Decreased LVEF (decreased LVEF below the normal range, and decrease by ≥ 10% from baseline) persisting for more than 8 weeks;
- Interruption of 3 doses of trastuzumab due to trastuzumab-related cardiac events.

Infusion reaction

- In the case of mild or moderate infusion reactions (such as pyrexia, chills, headache, asthenia, pruritus, nausea, vomiting, and diarrhea), slowing the infusion;
- In the case of infusion-related dyspnea or clinically diagnosed hypotension, stopping the infusion;
- In the case of life-threatening infusion reactions, trastuzumab should be permanently discontinued.

6.1.6.4.3. Docetaxel

Hypersensitivity

In the case of docetaxel-related hypersensitivity despite prophylactic treatment, treatment should be given per the package insert of docetaxel and medical routine.

- In the case of Grade ≤ 3 hypersensitivity, the investigator should decide whether to continue treatment with docetaxel based on the situation.
- In the case of Grade 4 hypersensitivity, docetaxel must be permanently discontinued.

Peripheral neuropathy or musculoskeletal pain

In the case of docetaxel-related sensory neurotoxicity or musculoskeletal pain that cannot be controlled by analgesics, docetaxel medication should be adjusted according to the following principles:

- In the case of Grade 2 peripheral neuropathy or musculoskeletal pain persisting for > 7 days per CTCAE v4.0.3, the dose of docetaxel should be reduced by 1 level.
- In the first occurrence of Grade 3 peripheral neuropathy or musculoskeletal pain, medication may be resumed at a reduced dose of docetaxel by 1 level if the condition relieves/recovers within 7 days. However, in the second occurrence of Grade 3 peripheral neuropathy or musculoskeletal pain or in the case of Grade 3 peripheral neuropathy or musculoskeletal pain persisting for > 7 days, docetaxel should be permanently discontinued.

6.1.7. Duration of treatment

Subjects receive study treatment continuously. Pyrotinib/placebo and trastuzumab are administered until investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation.

6.1.8. Dose tracking

Pyrotinib/placebo

Subjects are required to document on the Subject Diary Card daily and return all unused study drugs from the previous cycle before the commencement of the next cycle. The quantity of pyrotinib/placebo returned by the subjects will be counted, recorded, and archived.

Trastuzumab and docetaxel

The study center should prepare the drugs and complete the documentation as per the Pharmacy Manual. The documentation system of the study center should include all relevant or required information with regards to preparation and administration.

6.1.9. Precautions for special drug delivery devices

The equipment and precautions required for the infusion of trastuzumab and docetaxel are detailed in their package inserts, Pharmacy Manual, and Sections 6.1.5 and 6.1.6.

6.2. Dosing Regimen

The 590 subjects are randomized in a 1:1 ratio to the treatment group and the control group. The specific dosing regimen is as follows:

Treatment Group	Pyrotinib	400 mg, PO, once daily, administered within 30 min after breakfast, in 21-day cycles
	Trastuzumab	8 mg/kg loading dose in Cycle 1 and 6 mg/kg dose in subsequent cycles, IV, D1, in 21-day cycles
	Docetaxel	75 mg/m^2, IV, D1, in 21-day cycles
Control Group	Placebo	400 mg, PO, once daily, administered within 30 min after breakfast, in 21-day cycles
	Trastuzumab	8 mg/kg loading dose in Cycle 1 and 6 mg/kg dose in subsequent cycles, IV, D1, in 21-day cycles
	Docetaxel	75 mg/m^2, IV, D1, in 21-day cycles

6.3. Drug Management, Dispensation and Return

The management, dispensation and return of the study drugs in this study are in the charge of designated staff. The investigator must ensure that all the study drugs are only used for the subjects participating in this clinical study. The dosage and administration should follow the study protocol. The remaining drugs should be returned to the sponsor. The study drugs should not be transferred to any non-clinical study participant.

The study drugs must be stored according to the label. The drug receipt forms must be signed by two people during drug dispensation. The form is in duplicate copies, of which one is for the study center and the other is for the sponsor. Remaining drugs and empty boxes will be retrieved at the end of the study and a retrieval form will also be signed by both parties. The dispensation and return of each dose of drug should be immediately documented on designated forms.

All remaining study drugs and packages in this study will be returned to the sponsor for destruction.

The CRA is responsible for monitoring the supply, usage, and storage of the study drugs, and the management of remaining drugs.

6.4. Concomitant Treatment

Concomitant treatment refers to treatment that is given for the interest of subjects as determined by the investigator.

All concomitant treatments, blood products, and non-drug interventions (such as puncture) given to the subjects from screening to the end of study visits will be documented in the eCRF.

Subjects are monitored closely if an adverse event occurs. Symptomatic treatment is provided when necessary and details are documented in the eCRF. The following medications should be used carefully during the study:

- Drugs that interfere with liver P450 enzymes or P-gp:

1. Strong CYP3A4 inducers (carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, and St. John's wort) and moderate inducers (bosentan, efavirenz, etravirin, and modafinil);
2. Strong CYP3A4 inhibitors (boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir/dasabuvir, posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, and voriconazole) and moderate inhibitors (aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofesopar, and verapamil);
3. P-gp inhibitors (amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, and verapamil).

- Drugs that prolong the QT interval:

1. Antibacterial agents (such as clarithromycin, azithromycin, erythromycin, roxithromycin, metronidazole, and moxifloxacin)
2. Antiarrhythmic drugs (quinidine, sotalol, amiodarone, propiamine, procainamide, etc.)
3. Antipsychotics (risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, clozapine, etc.)
4. Antifungal drugs (fluconazole, ketoconazole, etc.)
5. Antimalarial drugs (mefloquine, chloroquine, etc.)
6. Antidepressants (amitriptyline, imipramine, clomipramine, dosulepin, doxepin, etc.).

6.4.1. Other anti-tumor/cancer or investigational drugs

Other anti-tumor treatments (chemotherapy, endocrine therapy, immunotherapy, etc.) are not permitted when the subject is receiving treatment with the study drugs. In addition, proprietary Chinese medicines with clear anti-tumor indications are also prohibited. Hormonal contraceptives by oral administration, injection, or implantation are not permitted. Systemic high-dose corticosteroids (daily dose of dexamethasone > 20 mg (or equivalent dose of other corticosteroids) for > 7 consecutive days) are not permitted during treatment.

Palliative radiation may be permitted for the treatment of painful bone lesions, provided that these lesions existed prior to enrollment and the investigators must clearly specify that the palliative radiation does not indicate PD. During palliative radiotherapy, treatment with **pyrotinib/placebo, trastuzumab, and docetaxel** will be interrupted.

6.4.2. Permitted treatments

Comorbidities and all AEs occurred should be actively treated. All concomitant medications should be documented in the eCRF in strict accordance with the GCP regulations.

Patients with bone metastases who have started treatment with bisphosphonate before enrollment are permitted to continue the treatment during the study.

Palliative and supportive care for disease-related symptoms will be based on the investigators' judgment and relevant guidelines.

G-CSF may be used during the study per clinical guidelines and docetaxel's package insert.

Active symptomatic treatment should be given for AEs such as diarrhea, nausea, and vomiting. The treatment recommendations are detailed in Section 6.1.6.

6.5. Subject Compliance

Subject compliance will be assessed by reviewing dispensation and return records of all study treatments. All dose reductions and interruptions must be recorded.

Accurate records must be maintained for each study treatment provided by the sponsor, including trastuzumab and docetaxel for study-defined treatments. These records should contain at least the following information:

- Shipment records of drugs received from the sponsor (date and quantity received)

The drug dispensing log must be kept in real time, including the following information:

- The study number of the subject receiving the study drug
- The date, drug number, and quantity of study drug dispensed to the subject.

Copies of the dispensation and inventory forms must be kept. See Section 6.3 for instructions on the destruction of unused and partially used study drugs or packages.

7. STUDY PROCEDURES

7.1. Screening

Written informed consent form must be obtained before any study-specified medical procedures are performed, except tumor imaging examinations, bone scans, and echocardiography that meet the protocol requirements and are obtained prior to the signing of ICF for participating in this study.

Unless otherwise stated, the following screening procedures must be completed within 21 days prior to randomization; screening visit (Day -21 to Day -1):

- Demographics: name initials, gender, ethnicity, marital status, date of birth, height, weight, and body surface area and body mass index calculated accordingly;
- Complete medical history: including prior medical and treatment history (clinical/histological diagnosis, time of diagnosis, clinical/pathological staging, HER2/ER/PR/expression status; surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy, time of progression, evidence for progression; LVEF before, during, and after administration of trastuzumab must be collected if trastuzumab is used as neoadjuvant/adjuvant therapy; anti-tumor treatments for recurrent/metastatic breast cancer, such as surgery and endocrine therapy), history of smoking and drinking, history of drug allergies (drug name and symptoms), concurrent diseases and concomitant treatments (disease name, name of concomitant medication, dose, and method of administration);
- ECOG PS;
- Vital signs: including body temperature, blood pressure, respiratory rate, and pulse;
- Physical examination: including general conditions, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental status; height and weight must be measured at baseline;
- Infectious disease screening;
- Echocardiography: Results within 21 days prior to randomization are acceptable (including qualified echocardiography completed before the signing of ICF);

- Tumor assessment: Multidetector spiral CT or contrast-enhanced MRI of the brain, chest, and abdomen should be at least performed during the screening period. The investigator may add other scan sites such as the neck and pelvic cavity based on clinical indications. During the screening period, the results within 21 days prior to randomization are acceptable (including qualified tumor assessments completed before signing the ICF);
- Bone scan: A bone scan is required for subjects who have not undergone a bone scan within 21 days prior to randomization. Positive bone lesions must be reviewed by CT/MRI examination (or X-ray) of bones;
- Prior/concomitant treatment: The patient's medications and treatments should be recorded within at least 28 days prior to randomization;
- Adverse event follow-up: AEs are observed and recorded from the day the subject signs the ICF, but all non-serious adverse events (non-SAEs) that occur prior to the first administration of the study drug will be reported in the medical history unless the investigator believes that they are more appropriate to be reported as AEs.

The following laboratory tests must be completed within 7 days prior to randomization; screening visit (Day -7 to Day -1)

- 12-Lead ECG;
- Hematology;
- Urinalysis;
- Routine stool test;
- Blood biochemistry;
- Blood pregnancy test for women of childbearing potential;

7.2. Enrollment

After completion of all screening assessments, eligible subjects as assessed by the investigator will be assigned a randomization number.

Stratification factors for randomization include:

- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

After obtaining the randomization number, the subject starts the study treatment of the group within 48 h after randomization.

7.3. Treatment Period

The following examinations should be performed according to the time window specified in the Schedule of Activities. In the event of statutory holidays, the examinations may be performed earlier and the reason should be documented in the eCRF. The safety visit cycle is determined according to the infusion date of the drug (i.e., trastuzumab and/or docetaxel), that is, the safety examinations should be completed within 3 days before the infusion date of the drug.

The investigator may add test items or increase the frequency of visits depending on the subjects' clinical conditions:

- ECOG PS: evaluated during the visit at the end of each cycle;
- Vital signs: measured during the visit at the end of each cycle;
- Physical examination: performed during the visit at the end of each cycle;
- Hematology: tested during the visit at the end of each cycle; additional hematology tests are performed on D8 ± 1 day of each cycle in the first 3 cycles of chemotherapy;
- Urinalysis: performed once at the end of every 4 cycles; in case of a urine protein ≥ ++, a 24-h urine protein quantitation should be tested;
- Routine stool test: performed once at the end of every 4 cycles;
- Blood biochemistry: tested during the visit at the end of each cycle; myocardial zymography may be performed when necessary as determined by the investigator based on the subject's condition;
- Pregnancy test: performed if the subject is likely to be pregnant (see Section 错误!未找到引用源。.1 for details);
- 12-Lead ECG: performed during the visit at the end of each cycle; if QTcF interval increases by > 30 msec from baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG measurements are required (at least 10 min apart);
- Echocardiography: performed once at the end of every 4 cycles; may be performed if there are symptoms such as chest pain and palpitations during the treatment period;
- Tumor assessment: The tumor assessment schedule during the administration period is determined after the start of treatment (i.e., C1D1) and is not changed regardless of dose interruptions due to toxicity. The time window for tumor assessment is ± 7 days. Specific evaluation time points are as follows:

- ✓ Once every 9 weeks in the first 72 weeks after the start of study treatment and once every 12 weeks thereafter;
- ✓ In the case of PD, the subject should discontinue the treatment and enter the follow-up period. Other anti-tumor treatments are prohibited prior to PD.
- ✓ Subjects who request to withdraw from the study due to intolerable adverse events or other reasons must undergo a complete tumor assessment prior to discontinuation of treatment (unless performed within 28 days).

- Concomitant medications/treatments: All concomitant medications/treatments during the study should be documented;
- Telephone follow-up: On D8 ± 1 day (CxD8 ± 1 d) during the treatment cycle of dose increase of pyrotinib/placebo, a telephone follow-up should be conducted to collect information on AEs and concomitant medications.
- Adverse events: All adverse events during the study should be monitored and documented.
- PK blood sampling: For at least 50 subjects, 2 mL of peripheral venous blood should be collected before pyrotinib administration on D1 ± 3 days of Cycle 2, Cycle 4, and Cycle 10, and on D1 ± 3 days of every 6 cycle subsequently. The administration time should be relatively stable for the 3 days prior to PK blood sampling. The actual administration time should be documented.

7.4. End-of-Treatment (EOT) Visit

Following completion of study treatment, the subject should undergo the following examinations within 7 days after treatment discontinuation is determined:

- ECOG PS (unless performed within 7 days);
- Vital signs (unless performed within 7 days);
- Physical examination (unless performed within 7 days);
- Hematology (unless performed within 7 days);
- Urinalysis (unless performed within 7 days);
- Routine stool test (unless performed within 7 days);
- Blood biochemistry (unless performed within 7 days);
- 12-Lead ECG (unless performed within 7 days);
- Echocardiography (unless performed within 28 days);

- Imaging examination (unless performed within 28 days);
- Pregnancy test: Urine pregnancy test can be performed; but if positive for urine pregnancy test, the subject should undergo blood HCG test for confirmation;
- Concomitant medication/treatment: Once the study treatment is interrupted, only concomitant medications or treatments for new or unresolved AEs related to study treatment should be documented. Concomitant medications or treatments for cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has returned to baseline or Grade ≤ 1, or until 12 months after the last dose;
- Adverse event: AEs that have not recovered after discontinuing the protocol-specified study treatment must be followed and a final assessment must be made. All subjects should record AEs within 28 days after the last dose [cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has returned to baseline or Grade ≤ 1, or until 12 months after the last dose].

7.5. Follow-up Period

Subjects who discontinue the study medication will immediately enter the follow-up period. The following must be performed until the survival follow-up is completed (randomized subjects who have not received the treatment do not need to be followed):

- Safety follow-up: A safety visit is conducted within 28 ± 7 days after the last dose for ECOG PS, vital signs, and physical examination. Adverse events should continue to be monitored and recorded until the end of follow-up period specified in Section 9.3.
- Efficacy follow-up: Subjects who discontinue treatment for reasons other than PD and death will continue tumor assessments at time points specified by the protocol, starting from the last tumor assessment during the treatment period, until PD, start of a new anti-tumor treatment, or death (whichever occurs first). The time of each follow-up visit, result of tumor imaging assessment, and other anti-tumor treatments should be documented in detail.
- Survival follow-up (OS data collection): All survival subjects who have completed the safety follow-up and efficacy follow-up (whichever is completed later) should undergo survival follow-up. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), starting from the day of completion of safety follow-up and efficacy follow-up (whichever comes later), until death, lost to follow-up, or study termination (whichever occurs first). Data from each survival follow-up should be documented and entered into the appropriate eCRF.

7.6. Visit for Early Discontinuation of Treatment

Subjects who request to withdraw from the study due to intolerable adverse events or other reasons should complete all examinations required at the end-of-treatment (EOT) visit. **A complete tumor assessment is recommended when treatment discontinuation is determined (unless performed within 28 days).** Imaging examination should be continued thereafter whenever possible until PD, death, or start of a new anti-tumor treatment (whichever occurs first).

7.7. Unscheduled Visit

The investigator may prescribe unscheduled visits when necessary based on the subject's situation. Details of unscheduled visits should be documented in the original medical record.

8. EVALUATIONS

8.1. Efficacy Evaluation

8.1.1. Tumor assessment

8.1.1.1. Evaluation of efficacy against solid tumors

In this study, the efficacy will be assessed per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for all eligible subjects. The investigators of all study centers and the imaging review experts designated thereby will perform tumor assessment per RECIST 1.1. The primary PFS analysis is based on the assessment results by the investigators.

The CRO for independent tumor assessment consists of 2 independent, qualified imaging radiologists, who will independently conduct blinded evaluation in a designated system with the assistance of a CRA after being trained and tested for imaging review. In the event of disagreement between the two independent radiologists, a third radiologist should make the final judgment under the same conditions as above. The details are listed in the "Third-Party Independent Review Charter" for this study.

The efficacy evaluation of each checkpoint is divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) per RECIST 1.1. Refer to Appendix III for details.

Subjects are required by the study to have at least one measurable lesion. Measurable lesions are defined as tumorous, non-lymphoid lesions ≥ 10 mm in longest diameter, or tumor-associated nodal lesions ≥ 15 mm in longest shorter diameter. In the case of a thickness/spacing of scanning slices > 5 mm, the longest diameter of the measurable lesion must be twice the slice thickness/spacing.

8.1.1.2. Scanning requirements for medical imaging

Qualified multidetector spiral CT should be used for enhanced tumor imaging scan. Subjects allergic to contrast media should undergo contrast-enhanced CT whenever possible according to the study center's guideline for the prevention of allergies to contrast media. CT and MRI are the only acceptable methods of examination in this study. Other imaging methods may only serve as supplementary diagnostic methods. The same method of examination should be used at baseline and during follow-ups per RECIST 1.1. Non-enhanced CT scan of the chest and MRI scan of the abdomen are permitted if the subject is contraindicated to CT contrast media during the treatment or follow-up period. In the case of local recurrence of breast cancer, an MRI scan of the recurrence site of the breast is also required. Refer to the "Imaging Manual for Study Centers" for the scanning parameters, requirements, and methods in detail.

At least examinations of the chest, abdomen, and head as well as bone scan should be conducted during the screening period [positive bone lesions must be reviewed by CT/MRI examination (or X-ray) of bones]. Examinations of the neck and pelvic cavity may be added if clinically indicated. During the treatment and follow-up periods, the investigator may also add scan sites for tumor evaluation when clinically indicated. If disease progression is indicated, unscheduled visit may be added for imaging examination based on the condition. Qualified CT scans and other imaging results obtained prior to the signing of ICF within the time window (and within 21 days prior to randomization) may be considered for tumor evaluation during the screening period.

Subsequent tumor assessments should be conducted with the same parameters and conditions as those of the baseline examination whenever possible. The tumor assessment schedule is determined after the start of treatment and should not be changed despite of dose interruption. The time window for tumor assessment is ± 7 days. Specific evaluation time points are as follows:

- The first evaluation is performed at Week 9 of medication. Evaluations are conducted once every 9 weeks in the first 72 weeks after the start of study treatment and once every 12 weeks thereafter;
- At the end of treatment or upon withdrawal (if not performed within 28 weeks prior) for subjects who withdraw due to reasons other than PD and death

The thickness of CT scan and reconstruction must be less than or equal to 5 mm per the RECIST 1.1. The dose of contrast media for enhanced scanning, the injection rate, and the enhancement phase of each anatomical site are detailed in the imaging manual and should be kept consistent at all checkpoints.

Locally recurrent cutaneous lesions of breast cancer, if any, should be photographed using a digital camera following the requirements of the imaging manual.

It is recommended that the tumor assessment at the study center be performed by an experienced, qualified study physician designated by the study center who is unaware of the group assignment. Also, each study center should record all the raw data of imaging examinations related to efficacy evaluation on CD-ROM in DICOM format, and send them to the designated central imaging within the specified time, for medical imaging quality control and efficacy evaluation by an independent, third-party imaging evaluation committee.

8.1.2. Primary endpoint

PFS: The time between the date of randomization and the first PD or death due to any cause based on the investigator's imaging review results. Tumor assessments are performed based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If no PD or death is observed at the study cut-off date, or the subject has received other anti-tumor treatments, the cut-off date or the date of the last tumor evaluation prior to the start of a new anti-tumor treatment (whichever occurs first) should be used as the censored date.

8.1.3. Secondary endpoints

PFS: The time between the date of randomization and the first PD or death due to any cause based on the IRC's imaging review results. Tumor assessments are performed based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If no PD or death is observed at the study cut-off date, or the subject has received other anti-tumor treatments, the cut-off date or the date of the last tumor evaluation prior to the start of a new anti-tumor treatment (whichever occurs first) should be used as the censored date.

ORR: Refers to the percentage of subjects in the analysis set with best overall response of CR or PR from the start of study treatment to subject withdrawal due to PD. Evaluated based on the RECIST 1.1.

DoR: Refers to the time period from the first evaluation of CR or PR (whichever occurs first) to PD or death. Evaluated based on the RECIST 1.1.

CBR: Refers to the percentage of subjects in the analysis set with CR, PR, and SD (≥ 24 weeks). Evaluated based on the RECIST 1.1.

OS: Refers to the time from the date of randomization to the date of death due to any cause. For subjects who are still alive at the last follow-up, their OS will be censored at the date of last follow-up. For subjects who are lost to follow-up, their OS will be censored at the last confirmed survival time before lost to follow-up. The OS for data censoring is defined as the time from randomization to censoring.

Except for OS, the above endpoints are the results of efficacy evaluation and evaluated per RECIST 1.1 during the study period. The analysis of OS includes all tumor evaluations during the treatment period and the follow-up period.

8.2. Safety Evaluation

8.2.1. Pregnancy test

Female subjects of childbearing potential will undergo blood HCG test before the start of administration. The test must have a sensitivity of at least 25 mIU/mL for HCG. After a negative result is obtained from the pregnancy test during the screening period, appropriate contraceptive measures should be taken. Subsequently, urine/blood pregnancy test should be performed at least during the end-of-treatment visit. During the study, additional pregnancy test may be prescribed per the diagnosis and treatment routine of the study center. Subjects positive for urine pregnancy test during the study should undergo blood HCG test for confirmation. If HCG test shows positive result, the subject should discontinue medication and be treated in according to Section 9.4.

8.2.2. Adverse event

The assessments of AEs include type, incidence, severity (according to NCI CTCAE v4.03), start and end date, actions taken, whether it is an SAE, causality, and outcome.

AEs that occur during the study, including signs and symptoms at screening, will be recorded on the AE page of the eCRF.

8.2.3. Laboratory safety evaluation

Samples for laboratory tests are collected at time points specified in the "Schedule of Activities". The study centers will be responsible for sampling and testing the following laboratory indicators. Unscheduled laboratory tests may be carried out at any time for safety reasons.

Table 4. Laboratory tests

Hematology	**Blood Biochemistry**	**Routine Stool Test**	**Urinalysis[a]**
Hemoglobin Red blood cell White blood cell Neutrophil count Lymphocyte count Platelet count	Total bilirubin Conjugated bilirubin Unconjugated bilirubin ALT AST Alkaline phosphatase γ-GT Total protein Albumin A/G Urea/urea nitrogen Creatinine	Fecal occult blood	Urine protein Urine glucose Urine occult blood

Hematology	Blood Biochemistry	Routine Stool Test	Urinalysis[a]
	Uric acid Blood glucose Triglyceride Cholesterol Potassium Sodium Chlorine Calcium Phosphorus Magnesium		
Infectious Disease Screening	**Others**		
Hepatitis B test HIV antibody HCV antibody	Pregnancy test[b]		

Note: a. If the protein results of the semi-quantitative method (such as urine test paper) are ≥ 2+, a quantitative test of 24-h urine protein should be performed.

b. Women of childbearing potential must undergo a blood HCG test to rule out pregnancy during screening. For other time points, a urine HCG test is required.

8.2.4. Vital signs and physical examination

The investigator is responsible for physical examination. The examination items include: general condition, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental status. Weight will be measured during each physical examination, but height will only be measured during screening. If the investigator believes that the height of the subject may change, the height should be re-measured.

Vital signs include: body temperature, blood pressure, respiratory rate, and pulse.

ECOG PS is assessed by the investigator based on Appendix I "ECOG Performance Status Score".

8.2.5. 12-Lead ECG

12-Lead ECG should be performed by a qualified physician at the time points specified in the "Schedule of Activities".

Subjects are required to rest for at least 10 min prior to undergoing the ECG. The ECG should include at least heart rate, QT, QTc, and P-R intervals.

To assess the safety of the subject, the investigator will compare the ECG results with those at baseline. If the QTcF interval increases by > 30 msec compared to baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG tests are required, at least 10 minutes apart, to verify the accuracy of the initial measurement and to rule out incorrect electrode placement causing the abnormality. If the device judges that the QTc value is prolonged, as described above, but a qualified physician considers that the QTc value is still within the acceptable range, there is no need to repeat the measurement.

9. ADVERSE EVENT REPORTING

9.1. Adverse Events (AEs)

9.1.1. Definition of adverse event

AE is defined as adverse medical events that occur after the subject receives a drug in clinical trial, but do not necessarily have a causal relationship with the treatment. In this study, all AEs occurring from the time that the subject provides informed consent, through and including 28 days of the last dose of study treatment will be collected. AEs can be any undesirable and unexpected symptoms, signs, laboratory abnormalities, or diseases, including at least the following conditions:

1) Worsening of pre-existing (prior to enrollment of clinical trial) medical conditions/diseases (including worsening of symptoms, signs, or laboratory abnormalities);
2) Any new onset of AE: Any adverse medical conditions newly occurring (including symptoms, signs, and newly diagnosed diseases);
3) Abnormal laboratory test or result with clinical significance.

All AEs that occur in the subjects should be documented in detail by the investigators, including: the name of the AE and description of all relevant symptoms, time of onset, severity, causality with study drugs, duration, measures taken, as well as final outcomes and prognosis.

9.1.2. AE severity assessment criteria

Refer to NCI-CTCAE v4.03 for grading criteria. Refer to the following criteria for AEs not listed in NCI-CTCAE v4.03:

Table 5. AE severity grading criteria

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild clinical symptoms; clinical or laboratory test abnormality only; intervention not indicated.
2	Moderate; minimal, local, or non-invasive interventions indicated; limiting age-appropriate instrumental activities of daily living (ADL), e.g., preparing meals, shopping, using the telephone, managing money, etc.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening; urgent intervention indicated.
5	Death related to AE.

9.1.3. Causality assessment

AEs should be collected and recorded from the time that the subject provides informed consent up to 28 days after the last dose of study treatment, regardless of whether the event is related to the study drug, whether the subject is assigned to an experimental arm, or whether the medication is administered or not. All subject complaints and abnormal changes in laboratory tests during the treatment should be documented truthfully. Meanwhile, the severity, duration, measures taken, and outcome of the AE should be recorded. The investigators should determine the relationship between the AE and study drugs, such as whether there is a plausible temporal relationship between the AE occurrence and the study drugs, the characteristics of the study drugs, the toxicological and pharmacological effects of the study drugs, the use of concomitant medications, the subject's underlying diseases, medical history, family history, as well as challenge and rechallenge. The causality assessment should be made using the following five-category scale: "definitely related, possibly related, unlikely related, not related, and unassessable".

Table 6. Criteria for the causality assessment between AEs and study drug

Classification	Criteria
Definitely Related	The AE occurs in a plausible temporal relationship to drug administration. The event is a recognized pharmacological phenomenon of the suspected drug. The event resolves with drug discontinuation and recurs with drug re-administration.
Possibly Related	The AE occurs in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Unlikely Related	The AE does not occur in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Not Related	The AE does not occur in a plausible temporal relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments. The event resolves when patient's clinical status improves or other treatments are discontinued. The event recurs upon restarting other treatment.
Unassessable	The temporal relationship between the AE and drug administration is unclear. The event is similar to a recognized pharmacological phenomenon of the product. It can also be explained by concomitant medications.

9.2. Serious Adverse Events (SAEs)

9.2.1. Definition of SAE

An SAE is defined as any medical event during the clinical trial that requires hospitalization or prolonged hospitalization, or results in disability, impairment of work ability, life-threatening, death, or congenital malformation. The following medical events are included:

- Events leading to death;
- Life-threatening events (defined as when the subject is at immediate risk of death at the time of the event);
- Events requiring hospitalization or prolonged hospitalization;
- Events leading to persistent or significant disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require intervention to prevent any of the above outcomes).

9.2.2. Hospitalization

AEs resulting in hospitalization (even less than 24 hours) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

- Rehabilitation facilities
- Nursing homes
- Routine emergency room visit (generally less than 24 hours)
- Same day surgery (such as outpatient/same day/ambulatory surgery)
- Social reasons (medical insurance reimbursement, etc.)

Hospitalization or prolonged hospitalization in the absence of the worsening of an AE is not in itself an SAE. For example:

- Admission due to pre-existing conditions not associated with the occurrence of new AEs or with worsening of the pre-existing diseases (e.g., for work-up of persistent pre-treatment laboratory abnormalities);
- Administrative admission (e.g., annual physical examination);

- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Elective admission not associated with the worsening of AEs (e.g., elective surgery);
- Pre-planned treatment or surgery. This should be noted in the baseline documentation for the entire study protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendicectomy should be recorded as treatment of the AE.

9.2.3. Disease progression and death

Events that are life-threatening, require hospitalization or prolonged hospitalization, or result in persistent or significant disability/incapacity/impairment of work ability due to symptoms and signs of disease progression are not reported as SAEs. If there is any uncertainty over the whether the SAE is caused by disease progression, it should be reported as an SAE.

All deaths occurring within the AE/SAE collection period must be reported as SAEs, regardless of whether it is likely related to disease progression per the investigator's judgment, or whether the subject has received any other anti-tumor treatments. The term "death" should not be reported as an SAE term, but as the outcome of the event. Events that result in death should be recorded as SAEs. The medical condition/disease (including deterioration of symptoms and signs) that causes or contributes to fatal outcome should be recorded in the eCRF as an SAE term, and reported as an SAE. If the cause of death cannot be determined at the time of reporting, the AE or SAE should be recorded as "unexplained death"; if the cause of death later becomes available, "unexplained death" should be replaced by the established cause of death.

If the subject dies from disease progression as assessed by the investigator, the grade 5 event caused by disease progression should be recorded in the eCRF and reported as an SAE; if the death caused by disease progression cannot be attributed to a specific medical event, then a Grade 5 "Tumor progression" should be recorded in the eCRF and reported as an SAE. Evidence that the death is due to disease progression (e.g., radiological changes suggesting tumor growth or progression, clinical deterioration associated with a disease process) should be provided by the investigator.

9.2.4. Potential drug-induced liver injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations of TBIL that meet all of the following 3 criteria in the absence of other etiologies causing the liver injury should be reported as important medical events and reported as SAEs.

Condition	Criteria
(1) ALT or AST abnormal	For subjects with AST or ALT baseline values within the normal range: subsequent ALT or AST ≥ 3 × ULN during treatment; For subjects with AST or ALT baseline values above the upper limit of normal: subsequent ALT or AST ≥ 2 × baseline values and ≥ 3 × ULN during treatment; or the value ≥ 8 × ULN.
(2) TBIL abnormal	For subjects with TBIL baseline values within the normal range: subsequent TBIL > 2 × ULN during treatment; For subjects with TBIL baseline values above the upper limit of normal: subsequent TBIL increased from baseline by at least 1 × ULN or value > 3 × ULN during treatment.
(3) No evidence of hemolysis, and alkaline phosphatase < 2 × ULN or not available	

This evaluation should include laboratory tests, detailed history, and physical assessment.

The subject should return to the study center and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include the laboratory tests, detailed history, and physical assessment. The possibility of hepatic tumor (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, TBIL, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, may be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) may be warranted.

9.2.5. SAE reporting requirements

The period for SAE collection begins from the time that the subject provides informed consent, through and including 28 calendar days after the last dose of study treatment. All SAEs should be reported to the sponsor by the investigator on the "Serious Adverse Event Report Form" (signed and dated) within 24 hours of awareness, regardless of whether this is an initial report or a follow-up report. The investigator should also report the SAEs to relevant organizations in a timely manner as required by local regulations.

The email address for the sponsor to receive the report of SAEs (as well as SIE and pregnancy) is hengrui_drug_safety@hrglobe.cn.

SAEs that occur 28 days after the last study dose are generally not reported unless they are suspected to be related to the study drug(s). The detailed record content of SAE should include symptoms, severity, causality with study drugs, time of onset, time of treatment, action taken with study drugs, follow-up time and method as well as outcome. If the investigator considers that an SAE is not related to study drugs, while potentially related to the study conditions (e.g., termination of the original treatment or complications during the study), the relationship should be described in detail in the narrative section of SAE report form. If there is a change in the severity of an ongoing SAEs or its relationship with the study drug, follow-up reports should be submitted immediately. If misinformation is considered to be present in the previously reported SAE, it can be corrected, retracted or downgraded in the follow-up report in accordance with the SAE reporting procedures.

9.3. Collection and Follow-Up of AEs/SAEs

AEs/SAEs in this study are collected from the time that the subject signs the informed consent form. Refer to Table 7. AEs/SAEs.

All AEs/SAEs should be followed up until the following conditions, and every effort should be made to ensure the final outcome and that definite causality assessment is obtained:

During treatment until safety follow-up visit

- The AE disappeared, or improved to baseline level or Grade ≤ 1
- No further improvement is expected for the AE per investigator's assessment
- Death

For the AEs that persist at safety follow-up visit

AEs should be followed up until the following occurs (whichever occurs first):

- The AE disappeared, or improved to baseline level or Grade ≤ 1
- The AE stabilized and no further improvement is expected per investigator's assessment
- Death
- New anti-tumor treatment affects the determination of AE outcome
- Data collection for the clinical trial is terminated

Event of cardiotoxicity should be followed if persisting at the end-of-treatment visit (regardless of causality with the study drugs) until the AE has recovered to baseline or Grade ≤ 1, or until 12 months after the last dose of study treatment.

Investigators should inquire about AE/SAE after the last visit at each visit and provide follow-up data in time according to the sponsor's queries.

Table 7. AEs/SAEs collection period

Classification	Collection/Documentation Requirement
AEs[a] Unrelated to Study Treatment	Until 28 days after the last dose of the study drugs or the start of a new anti-tumor treatment (whichever comes first)
Suspected Treatment-Related AEs[a]	Until 28 days after the last dose of the study drugs
SAE[b] Unrelated to Study Treatment	·Fatal SAEs: until 28 days after the last dose of the study drugs; ·Non-fatal SAEs: until 28 days after the last dose of the study drugs or the start of a new anti-tumor treatment (whichever comes first)
Suspected Treatment-Related SAE[b]	No time limit

[a]: Non-serious AEs
[b]: Including fatal and non-fatal SAEs.

9.4. Pregnancy

If a female subject becomes pregnant during the study, the subject must immediately discontinue the study treatment. The investigators should report the pregnancy to the sponsor within 24 hours of awareness using Hengrui Clinical Trial Pregnancy Report/Follow-Up Form.

The investigator should follow up the pregnancy outcome (including any early termination of pregnancy or childbirth) until 1 month after delivery, and notify the sponsor of the pregnancy outcome. If the pregnancy outcome meets the seriousness criteria (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), it must be reported as an SAE (other important medical events).

9.5. AEs of Special Interest

All AEs of special interest (SIEs) specified in the study protocol should be reported to the sponsor by the investigator on the "Clinical Trial SIE Report Form" within 24 hours of awareness. If an SIE is also an SAE, it should also be reported on Serious Adverse Event Report Form in accordance with SAE reporting procedures.

Cardiac events are adverse events of special interest in this study, including:

- Asymptomatic LVEF decrease by ≥ 10% and the value < 50%
- Symptomatic LVEF decrease, left ventricular systolic dysfunction
- Prolonged QTcF (average QTcF > 500 ms)
- Events possibly due to abnormal cardiac function: e.g., syncope and seizure
- Other Grade 3 or 4 cardiac events

The following principles are recommended for reporting AEs and SAEs of special interest in this study.

Left ventricular systolic dysfunction and asymptomatic LVEF decrease should be reported using the AE terms in the table below.

Table 8. Reporting rules for left ventricular systolic dysfunction

Symptom	Clinical Result	Reported Term	Grade
Asymptomatic	Asymptomatic LVEF decrease from baseline by ≥ 10% and value < 50%	Ejection fraction decreased	Refer to AE term of "ejection fraction decreased" in CTCAE 4.0.3
	Asymptomatic LVEF decrease requiring treatment or leading to dose interruption or reduction of any study drug	Ejection fraction decreased	Refer to AE term of "ejection fraction decreased" in CTCAE 4.0.3
Symptomatic	Symptomatic left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Refer to AE term of "left ventricular systolic dysfunction" in CTCAE 4.0.3

10. CLINICAL MONITORING

The clinical research associate (CRA) is responsible for monitoring whether the study is carried out in accordance with relevant regulations, the GCP, and study protocol; whether the CRF is entered accurately and completely, and consistent with source documents such as medical records and physical and chemical test reports, and free from errors and omissions. The CRA must check the content in eCRF against the source documents item by item, ensuring that the data in eCRF are consistent with the source data. This process is also known as source data verification (SDV).

11. DATA ANALYSIS/STATISTICAL METHODS

The detailed statistical analysis of this study will be included in the Statistical Analysis Plan (SAP) and kept by the sponsor. The plan marked in the protocol can be appropriately modified in the SAP. However, any significant revisions to the definitions and analyses of primary study endpoints should be reflected in the amendment versions of the protocol.

11.1. Sample Size

In this study, PFS is used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to evaluate the efficacy of the drugs and to determine whether to terminate or continue the study. The assumptions for sample size calculation are as follows:

- Enrollment duration = 24 months, minimum follow-up = 18 months (overall duration of 42 months)

- Randomization in a 1:1 ratio
- Overall $\alpha = 0.025$ (one-sided)
- The power of test is approximately 80%
- Hazard ratio (HR) = 0.76 (estimated median PFS is 12.5 months in the control group and 16.5 months in the treatment group)
- An interim analysis will be performed when 67% of PFS events (275 events) are collected to evaluate the efficacy of the drugs, and to decide whether to terminate or continue the study.

Based on the above parameters, at least 410 PFS events should be collected according to the log rank test for PFS comparison between two groups and the Lan-DeMets α spending function (EAST 6.4.1) constrained by the O'Brien & Fleming boundaries. Assuming that the PFS dropout rate is 15% for 24 months, approximately 590 subjects should be enrolled.

11.2. Statistical Analysis Plan

In this study, SAS 9.4 or above will be used for data processing and analysis.

The time-to-event variables (such as PFS, OS, and DoR) will be analyzed using the Kaplan-Meier (KM) method, the survival functions of the two groups will be estimated, and the survival curves will be plotted. In addition, the Cox proportional hazards model will be used to estimate the hazard ratio between the two groups and its 95% CI.

For binary variables, the Cochran-Mantel-Haenszel (CMH)/Chi-square/Non-parametric test (if applicable) methods can be used to test the inter-group difference and compute its 95% CI.

The safety data will be summarized using descriptive statistics.

The detailed analysis plan will be described in the Statistical Analysis Plan (SAP).

11.3. Statistical Hypothesis and Decision Rules

The primary endpoint of this study is PFS. Stratified log-rank test is used for the primary analysis of the inter-group comparison of the investigational drug and the control drug.

Hypothesis:

- H_0: The survival function of the pyrotinib group is the same as that of the placebo group
- H_1: The survival function of the pyrotinib group is different from that of the placebo group
- Overall α level: 0.025 (one-sided)

11.4. Analysis Sets

- Full analysis set (FAS): all subjects who are screened eligible per the ITT principle and are randomized and enrolled. The FAS is the primary analysis set for the efficacy analysis of this study.
- Per-protocol set (PPS): a subset of the FAS, excluding subjects with important protocol deviations which significantly impact study results.
- Safety analysis set (SS): all randomized subjects who have received at least one dose of the study drug.

The statistical analysis is performed for drug efficacy based on both the FAS and PPS. Before database is locked, the principal investigator, statistician and sponsor should determine the final PPS through the data review meeting.

11.5. Statistical Method

The following sections include the description of the planned statistical methods.

11.5.1. Basic methods

This study is a phase III, randomized, placebo-controlled, multicenter study. This study plans to perform 2 analyses by IDMC (including one interim analysis) and one final analysis. One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the safety evaluation. The interim analysis will be carried out when 67% of PFS events (275 events) are collected to evaluate the efficacy of the drugs and to decide whether to terminate or continue the study. The final analysis will be performed when the number of PFS events reaches 410.

11.5.2. Analysis of primary efficacy endpoints

The primary endpoint of the study is PFS. The primary analysis will be based on the FAS. The analysis based on the PPS will serve as a sensitive analysis. The survival functions of PFS of the two groups will be compared using both stratified and non-stratified log-rank tests. The analysis with stratification factors will be used as the primary analysis. In addition, the Kaplan-Meier method will be used for estimating the PFS by group, the survival curves will be plotted, and the median PFS and its 95% CI will be estimated.

In addition, under the assumption of proportional hazards, the Cox models with and without considering stratification factors will be used to estimate the hazard ratio between the two groups and calculate the corresponding 95% CI. The analysis with stratification factors will be used as the primary analysis.

11.5.3. Analysis of secondary efficacy endpoints

The secondary endpoints OS and DoR will be statistically described based on the FAS and PPS using methods similar to those of the primary endpoint.

The objective response rate (ORR) and clinical benefit rate (CBR) of the two groups and their two-sided 95% CIs will be estimated based on the FAS and PPS, and the inter-group differences of the rates and their two-sided 95% CIs will be calculated.

Other endpoints will be statistically summarized in accordance with general principles.

Refer to the SAP for more details on statistical analysis including censoring rules.

11.5.4. Pharmacokinetic analysis

The blood concentration data of pyrotinib may be summarized using descriptive statistics and analyzed. In addition to the statistics used for continuous variables, PK data may also be summarized using coefficient of variation, geometric mean, geometric standard deviation, and geometric coefficient of variation depending on the nature of data.

The blood concentration data of pyrotinib will also be listed by time points.

11.5.5. Handling of missing data

In this study, the missing data of the efficacy endpoints will not be treated specially, and the missing values will not be estimated in the safety evaluation.

11.5.6. Safety analysis

AEs that occur during the study will be coded according to the latest version of MedDRA. The frequency and incidence of AEs will be summarized by system organ class and preferred term. The causality and severity of AEs will be further tabulated for description. Descriptive statistics will be used to summarize other safety endpoints. Summarize the incidence of AEs, adverse drug reactions, AEs resulting in withdrawal from the study, AEs resulting in death, and SAEs; severity of AEs and adverse drug reactions: For the same AE with multiple occurrences in the same subject, the highest severity will be included in the analysis; for different AEs occurring in the same subject, the most severe AE will be included in the analysis.

Laboratory tests: Abnormal laboratory values will be summarized using descriptive statistics.

Vital signs: Measured values and changes will be summarized using mean, maximum, minimum, median, and SD.

Physical examination and 12-Lead ECG will be summarized using descriptive statistics.

Baseline is defined as the most recent test data before the first dose.

11.5.7. Interim analysis

In this study, an interim analysis will be carried out for the primary endpoint. The interim analysis will be conducted when 67% of PFS events (275 events) are collected. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:

Table 9. Termination criteria and significance level in the interim analysis and final analysis of PFS

Time Point	Number of PFS Events	Boundary Z-Value (Corresponding HR)	One-Sided Nominal Significance Level
Interim (1st)	275 (67%)	-2.500 (HR = 0.74)	0.0062
Final	410	-1.994 (HR = 0.82)	0.0231

Note: HR = Hazard ratio; PFS = Progression-free survival;

The unblinded interim analysis will be completed by independent statisticians and their programming team. The results of the unblinded interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study based on the results.

11.5.8. Safety analysis and evaluation by IDMC

In this study, a safety evaluation is scheduled upon enrollment of 10% (59) of subjects. The results will be reviewed by the IDMC, which will recommend whether to continue the study based on the results.

11.5.9. Subgroup analysis

Subgroup analyses will be performed for primary endpoint PFS according to (including but not limited to) the following factors, and the forest plot on HR will be produced:

Stratification factors:

- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

Baseline factors; critical baseline factors, including but not limited to age, ECOG PS, pathological grade, and lesion site, will undergo subgroup analysis.

11.5.10. Multiple comparison/multiplicity

The overall type I error rate in the interim and final analyses of the primary endpoint PFS will be strictly controlled at 0.025 (one-sided) by the O'Brien & Fleming method for the Lan-DeMets alpha spending function.

11.5.11. Exploratory analysis

Not applicable.

12. DATA MANAGEMENT METHOD

12.1. Data Recording

Data will be collected and managed using the electronic case report form (eCRF).

12.1.1. Filing of study medical records

As source documents, the medical records should be completely retained. The investigators should be responsible for filling and keeping the study medical record. The subject information on the cover of the medical record should be checked each time before filling the record. The medical record should be written in a neat and legible way so that the sponsor's CRA could verify the data with eCRF during each monitoring visit.

12.1.2. eCRF entry

Clinical study data will be collected using the HRTAU EDC system.

Entry: The data in the eCRF are from and should be consistent with the source documents, such as the original medical records and laboratory test reports. Any observations or test results in the study should be entered in the eCRF in a timely, accurate, complete, clear, normative, and verifiable manner. Data should not be changed arbitrarily. All items in the eCRF should be filled out, with no blank or omissions.

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the clinical study data entered into the EDC system and generate an error message prompt for questionable data. The PI or CRC will be permitted to modify or explain the problematic data. If necessary, multiple inquiries can be raised until the event of problematic data is resolved.

12.1.3. eCRF review

The investigator must complete, review, and submit the eCRF within <3> working days after the end of each subject's treatment course. The investigator or the data input operator (CRC) should promptly respond to queries raised by CRA, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

12.2. Data Monitoring

Implemented by: CRA.

Monitoring content: To confirm that whether the study protocol is adhered to; whether the records in eCRF are correct and complete, and consistent with the source documents such as study medical records and laboratory test reports, and whether there are errors or omissions in

the data. According to the monitoring plan, the CRA will verify the completeness, consistency, and accuracy of study data in the database. The CRA will discuss problematic data with study personnel and direct them to add or correct the data whenever necessary. Ensure that the data in the eCRF are consistent with source data. This process is also known as source data verification (SDV).

12.3. Data Management

12.3.1. EDC database establishment

The data administrator will establish a study-related database according to the study protocol, which will be available for online usage within one week before the first subject is enrolled. All EDC users must submit Form for EDC User Permission and be sufficiently trained, with training records in hard copy, before obtaining the accounts of the EDC system for the project.

12.3.2. Data entry and verification

The investigators or CRC should input data into the EDC system in accordance with the requirements of the visit procedures and the eCRF completion guideline. After submitting the eCRF, the CRA, data manager, and medical reviewer should review the data. Questions during the review will be submitted to the investigators or CRC in the form of queries. After data cleaning is completed, the investigator should sign the completed eCRF for verification.

12.3.3. Blind review and database lock

After the clinical study is completed, the study director, sponsor, statistician, and data administrator will conduct a joint blind review before statistical analysis mainly to determine the analysis data set (including FAS, PPS, and SS) for each case, the judgment of missing values, and the handling of outliers. All decisions made under blind review cannot be modified after unblinding, and every decision must be documented.

After the established database is considered correct by blind review, the database will locked and unblinded. After the database is locked, the data must be properly stored for future reviews. The blind code and the database should be statistically analyzed by the statistician.

12.3.4. Data archiving

After the study is completed, the eCRFs of the subjects must be generated from the EDC system in the PDF format and kept on non-rewritable CD-ROMs, which will be archived by the sponsor and various institutions for auditing and/or inspection.

All materials should be preserved and managed in accordance with GCP requirements, and necessary documents of clinical trials should be preserved until 2 years after the investigational drug is approved for marketing or 5 years after the termination of the clinical study.

13. SOURCE DATA AND DOCUMENTS

According to ICH E6, relevant regulations, and requirements for subject's personal information protection of the study centers, each study center must properly keep all treatment and scientific records related to this study. As a part of the study that Hengrui sponsors or participates in, each study center must allow the authorized representative of Hengrui and regulatory authorities to inspect the clinical records (which may be copied if permissible by law) for quality review, audit, and evaluations of safety, study progress, and data validity.

Source data are information required to reconstruct and evaluate the clinical study, and are the original documentation of clinical findings, observations, and other activities. These source documents and data records include but are not limited to: hospital record, laboratory records, memos, subject diary cards, pharmacy dispensing records, recordings of advisory meetings, recorded data from automated devices, copies or transcripts that are verified to be accurate and intact, microfiche, photographic negatives, microfilms or magnetic disks, X-ray films, and subject's documents and records that are kept in the pharmacies, laboratories, and medical technology departments that are involved in this study.

14. QUALITY ASSURANCE AND QUALITY CONTROL

To ensure study quality, the sponsor and the investigators will jointly discuss and formulate a clinical study plan before the formal study initiation. All study personnel participating in the study will receive GCP training.

All the study centers must comply with the SOPs for the management of the study drugs, including receipt, storage, dispensation, return, and destruction (if applicable).

According to the GCP guidelines, necessary measures must be taken at the design and implementation phases of the study to ensure that all collected data are accurate, consistent, intact, and reliable. All observed results and abnormal findings in the clinical study must be verified and recorded in a timely manner to ensure data reliability. All devices, equipment, reagents, and standards used in various tests in the clinical study must have stringent specifications and be operated under normal conditions.

The investigators will input data required by the protocol into the eCRF. The CRA will check whether the eCRF is completely and accurately filled and guide the study site personnel for necessary correction and addition.

The drug regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), sponsor's CRA and/or auditor may carry out systemic inspection of study-related activities or documents to assess whether the study is implemented based on the study protocol, SOPs, and relevant regulations (such as Good Laboratory Practices [GLP] and Good Manufacturing Practices [GMP]) and whether the study data are recorded in a prompt, truthful, accurate, and complete manner. The audit should be performed by personnel not directly involved in this clinical study.

15. REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

15.1. Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the CFDA (now NMPA) before starting a new drug study and the study can only be carried out after approval is obtained. The clinical approval numbers of pyrotinib applicable for this study include 2016L03115 and 2016L03116.

The legal basis for the design of this protocol is as follows:

1) Provisions for Drug Registration
2) Good Clinical Practice
3) Technical Guidelines for Clinical Pharmacokinetic Study of Chemical Drugs
4) Consensus on ethical principles based on international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines
5) ICH Guidelines
6) Other applicable laws and regulations

15.2. Ethical Standards

The investigator will ensure that the trial in this study is fully implemented in accordance with the requirements for subject protection in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and/or ICH E6.

This study protocol must first be reviewed and approved in writing by the ethics committee of the hospital before being implemented. The study protocol, protocol amendments, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical study must comply with the "Declaration of Helsinki", CFDA's (now NMPA) "Good Clinical Practice" (GCP), and other relevant regulations. Before the study is initiated, approval must be obtained from the ethics committee of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and the investigators. The investigators can modify or deviate from the study protocol before obtaining an approval from the ethics committee/institutional review board only when in purpose of eliminating direct and immediate harm to the subject. Besides, the deviation or change and the corresponding reason, and the recommended protocol amendment should be submitted to the EC/IRB for review. The investigators must provide explanations and document any protocol deviation.

During the study, any changes to this study protocol must be submitted to the ethics committee. If necessary, corresponding changes should be simultaneously made to other study documents and be submitted and/or approved according to the pertinent requirements of the ethics committee. The investigator is responsible for submitting the interim reports regularly according to the pertinent requirements of the ethics committee. After the end of the study, the completion should be informed to the ethics committee.

15.3. Independent Ethics Committee

The protocol, ICF, recruitment material, and all subject materials must be reviewed and approved by the ethics committee. Subjects may be enrolled only after the protocol and ICF have been approved. Any revisions to the protocol must be reviewed and approved by the ethics committee prior to being implemented. All revisions to the ICF must be approved by the ethics committee, who will decide whether the subjects who have signed the previous version of the ICF are required to sign the new one.

15.4. Informed Consent

15.4.1. Informed consent form and other written information for subjects

The informed consent form describes the investigational drug and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures.

15.4.2. Informed consent process and records

Informed consent will begin before an individual decides to participate in the clinical study and continues during the entire clinical study. The risks and potential benefits of participating in the study should be discussed fully and in detail with subjects or their legally acceptable representatives. Subjects will be asked to read and review the ICF that has been approved by the ethics committee. The investigator will explain the clinical study to the subjects and answer any questions posed by the subjects. Subjects can only participate in the study after they have signed the ICF. During the clinical study, subjects can withdraw the informed consents at any time. One copy of the signed ICF will be kept by subjects. Even if a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

15.5. Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigators, participating study personnel, sponsor, and its representative. In addition to the clinical information, confidentiality also simultaneously covers biosamples and genetic tests of the subjects. Therefore, the study protocol, documentation, data, and other information generated from these materials will be kept strictly confidential. All relevant study or data information should not be disclosed to any unauthorized third-party without prior written approval from the sponsor.

Other authorized representatives of the sponsor, IRB or regulatory authorities, and the representatives of the pharmaceutical company that provides the investigational drugs can examine all the documents and records that are maintained by the investigators, including but not limited to the medical records and subject's administration records. The study center should allow access to these records.

The contact information of the subjects will be safely kept in each study center and only used internally during the study. When the study is ended, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of subjects collected for statistical analysis and scientific reports will be uploaded and stored in the study centers. This should not include the contact information or identification information of subjects. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the study personnel at study centers should be confidential and password-protected. At the end of the study, all identification information in the study database will be erased and archived in the study center.

16. PUBLICATION OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. If the investigators plan to publish any study-related data and information, Hengrui should be provided with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to the submission of documents for publication or other forms of release.

17. CLINICAL STUDY PROGRESS

Anticipated enrollment of the first subject: Mar. 2019

Anticipated enrollment of the last subject: Mar. 2021

Anticipated study completion: Jul. 2024

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Appendix I Clinical Staging for Breast Cancer (AJCC Breast Cancer TNM Staging)

Stage 0	TisN0M0
Stage I	T1N0M0
Stage IIA	T0N1M0
	T1N1M0
	T2N0M0
Stage IIB	T2N1M0
	T3N0M0
Stage IIIA	T0N2M0
	T1N2M0
	T2N2M0
	T3N1, 2M0
Stage IIIB	T4N0M0, T3N1M0, T4N2M0
Stage IIIC	Any T, N3M0
Stage IV	Any T and N, M1

Appendix II Performance Status Criteria (ECOG)

(Eastern Cooperative Oncology Group)

Score	Description
0	Asymptomatic, fully active, able to carry on all performance without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any physical activities; up and about more than 50% of waking hours (confined to bed < 50% of waking hours).
3	Symptomatic, capable of only limited self-care; confined to bed or chair more than 50% of waking hours, but not totally confined to bed.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Death.

Appendix III Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

(New Response Evaluation Criteria in Solid Tumors: Revised RECIST Version 1.1)

Note: This appendix is translated internally and is for reference only. Please refer to the English version during practice.

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definition

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1.1 Measurable lesions

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15 mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm).

  At baseline and during follow-up, only the short axis will be measured and followed.

3.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Non-measurable lesions include: meningeal disorder, ascites, pleural or pericardial effusion, breast carcinoma inflammatory, lymphangitis carcinomatosa of skin or lung, abdominal masses unable to be diagnosed or followed by imaging techniques, and cystic lesions.

3.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by tomography techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts shall not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion. Study protocols shall detail the conditions under which such lesions are considered measurable.

3.2 Methods of Measurement

3.2.1 Measurements of lesions

All measurements shall be recorded in metric notation if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

3.2.2 Method of assessment

The same method and technique shall be used to assess lesions at baseline and during follow-up. Imaging based evaluation shall always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., nodule skin). For the case of cutaneous lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both imaging and clinical examination, tumor assessment shall be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, especially when tumor progression is an important clinical endpoint, since CT is more sensitive, particularly in identifying new lesions. Chest X-ray is only applicable when the measured lesion boundary is clear and the lungs are well ventilated.

CT and MRI: CT is currently the best available and reproducible method for efficacy evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for whole body scans).

Ultrasound: Ultrasound shall not be used as a method to measure lesion size. Ultrasound examinations are operation-dependent, and cannot be reproduced at a later date. It cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead.

Endoscopy, celioscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained, or to determine relapse in studies where recurrence following CR or surgical excision is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. However, if the marker levels exceed the upper normal limit at baseline, they must return to the normal levels for evaluation of complete response. Because tumor markers are disease specific, instructions for their measurement shall be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

4 TUMOR RESPONSE ASSESSMENT

4.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor load at baseline and use this as a comparator for subsequent measurements. Only patients with measurable lesions at baseline should be included in protocols where objective response is the primary endpoint. Measurable lesion is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if enrollment is restricted to those with measurable lesions or whether patients with non-measurable lesions are also eligible.

4.2 Baseline Documentation of "Target" and "Non-target" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions shall be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition shall be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly shall be selected.

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image

is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smallest of these measures is the short axis. For example, an abdominal nodule which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable nodule. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference.

All other lesions including pathological lymph nodes shall be identified as non-target lesions, and while measurements are not required, they shall be recorded at baseline. These lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3 Response Criteria

4.3.1 Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, compared to baseline.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each nodule must achieve a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodules is to be included in the sum of target lesions.

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value is recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph nodule is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce: When non-nodal lesions fragmented, the longest diameters of the fragmented portions shall be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that will aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance shall be the maximal longest diameter for the coalesced lesion.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead shall be assessed only qualitatively at the time points specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodules must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered PD.

4.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that the overall tumor load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that will be required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a peritoneal effusion from trace to large, an increase in lymphangiopathy from localized to widespread, or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If

unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesion

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion shall be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study that is not scanned at baseline will be considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example, because of its small size, continued treatment and follow-up evaluation are required to clarify if it represents a truly new disease. If repeated scans confirm there is definitely a new lesion, then progression shall be declared using the date of the initial identification.

While FDG-PET response assessments generally need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible new disease). New lesions on the basis of FDG-PET imaging can be identified according to the following process:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study until the end of study taking into account any necessary requirement for confirmation. On occasion a response may not be documented until after the end of treatment, so protocols should be clear if post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The patient's best overall response evaluation will depend on the findings of both target and non-target diseases and will also take into consideration the characteristics of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to determine either one is the best overall response.

4.4.1 Time point response

It is assumed that at each time point specified in protocol, an efficacy response occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1. Time point response: patients with target (+/- non-target) disease

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all evaluable	Non	PR
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2. Time point response: patients with non-target disease only

Non-Target Lesion	New Lesion	Overall Response
CR	Non	CR
Non-CR/Non-PD	Non	Non-CR/Non-PD[a]
Not all evaluable	Non	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

[a]: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for efficacy evaluation, non-CR/non-PD response is developed to address the absence of lesion measurability.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all time points

The BOR is determined once all the data for the patient are known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time calculated from baseline. If the minimum time is not met when SD is otherwise the best overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at Cycle 1, PD at Cycle 2 and does not meet minimum duration for SD, will have a best overall response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

BOR determination in studies where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3. Best overall response when confirmation of CR and PR required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
PR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a]: If a CR is truly met at first time point, then response of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still evaluated as PD at that point (since disease will reappear after CR). Best response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions are likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR shall be changed to PR and the best response is PR.

4.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement shall be recorded even though the nodules are normal in order not to overstate progression shall it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have "zero" recorded on the case report form (CRF).

In studies where confirmation of response is required, repeated "NE" time point evaluations may complicate best response determination. The analysis plan for the study must address how missing data/evaluations will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Patients with an overall deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time shall be reported as symptomatic deterioration. Efforts shall be made to evaluate objective progression even after discontinuation of treatment. Symptomatic deterioration is not a description of an objective response: it is a reason for discontinuation of treatment. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 1-Table 3.

Conditions that are defined as early progression, early death and not evaluable are study specific and shall be clearly described in each protocol (depending on treatment duration and treatment cycle).

In some circumstances, it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended that the local lesion be investigated before assigning a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled evaluation. If at the next scheduled assessment, progression is confirmed, the date of progression shall be the earlier date when progression is suspected.

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment shall be protocol-specific and consistent with the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. The protocol shall specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After treatment, the need for tumor re-evaluations depends on whether the study has made the response rate or the time to an event (progression/death) an endpoint. If "time to an event" (e.g. TTP/DFS/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment group in the timing of disease assessment.

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

4.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time criteria are first met for CR until the first date that recurrent or progressive disease is truly documented.

4.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency shall take into account many parameters including disease types and stages, treatment cycle and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

4.7 PFS/TTP

4.7.1 Phase II clinical trials

This guideline is primarily focused on the use of objective response as study endpoints for phase II studies. In some circumstances, response rate may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, PFS/PPF at landmark time points might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled study, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening studies utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor) that a non-randomized study is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF in the absence of a treatment effect.

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer

Study Protocol Amendments

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
Version No. of Study Protocol	1.0	2.0	Uniform amendments to the full text and header/footer.
Version Date of Study Protocol	21 Dec., 2018	20 Jan., 2020	Uniform amendments to the full text and header/footer.
Page 11	Participating study centers: Approximately 25 study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences	Participating study centers: Approximately 37 study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences	Updated the number of participating study centers
Pages 11, 23-24, 50, and 76		Secondary objective: To evaluate the pharmacokinetics (PK) of pyrotinib maleate tablets combined with trastuzumab and docetaxel in patients with HER2-positive recurrent/metastatic breast cancer. Study endpoint: Blood concentrations of pyrotinib. Study procedures PK blood sampling: For approximately 100 subjects, 2 mL of peripheral venous blood	Blood samples should be collected for pharmacokinetic study of three-agent combination. Added the pharmacokinetic study objective, study endpoint, blood sampling time and procedures.

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
		should be collected before pyrotinib administration on D1 ± 3 days of Cycle 2, Cycle 4, and Cycle 10, and on D1 ± 3 days of every 6 cycle subsequently. The administration time should be relatively stable for the 3 days prior to PK blood sampling. The actual administration time should be documented.	
Pages 13-14, 24, 51, and 69	Study design	Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation.	Specified the administration duration of docetaxel for the efficacy benefits of subjects and in combination with clinical practice
Pages 14 and 62	Method of administration: Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. No dose reduction will be allowed	Method of administration: Due to trastuzumab-related toxicity, trastuzumab may be interrupted, delayed, or discontinued. No dose reduction will be allowed	Corrigendum
Pages 15 and 53	Inclusion criteria: Females aged ≥ 18 and ≤ 75 years old	Inclusion criteria: Females aged ≥ 18 and ≤ 75 years old	Clarified the description of age in the inclusion and exclusion criteria
Pages 19 and 93	Data analysis/statistical methods: One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the blinded safety evaluation.	Data analysis/statistical methods: One of the IDMC's assessments is carried out when the number of enrolled subjects reaches 10% (59) for the safety evaluation.	Revised the evaluation content based on the IDMC charter and actual practice.
Pages 21, 76, and 79	Efficacy evaluation: Once every 3 cycles in the first 24 cycles, thereafter once every 4 cycles until PD	Efficacy evaluation: Once every 9 weeks in the first 72 weeks, thereafter once every 12 weeks until PD	Clarified the tumor assessment schedule

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
Pages 24 and 63	Administration of study drugs: The dose of docetaxel is calculated based on the body surface area of the subject.	Administration of study drugs: The dose of docetaxel is calculated based on the body surface area of the subject. The calculated dose may be rounded, but should not exceed ± 5%.	Clarified the dose range of docetaxel according to clinical practice.
Pages 24, 61, and 76	Administration of study drugs	Administration of study drugs: During the treatment with pyrotinib/placebo combined with trastuzumab and docetaxel, the dose of pyrotinib/placebo may be adjusted per the protocol based on the adverse reactions of the subject. If Grade ≥ 3 pyrotinib-/placebo-related non-hematologic toxicities do not occur after the dose of pyrotinib/placebo is reduced, then based on assessment, the investigator may increase the dose of pyrotinib/placebo by one level after permanent discontinuation of docetaxel, that is, during the treatment with pyrotinib/placebo combined with trastuzumab. During the treatment with three-agent combination, if the dose of pyrotinib/placebo is reduced to 320 mg, and Grade ≥ 3 pyrotinib-/ placebo-related non-hematologic toxicities do not occur during the treatment at 320 mg, then based on assessment, the investigator may increase the dose of pyrotinib/placebo to 400 mg after permanent discontinuation of docetaxel.	Added the description of dose increase of pyrotinib/placebo and corresponding safety visits for the safety and benefits of subjects

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
	Study procedures - treatment period	Telephone follow-up: On D8 ± 1 day (CxD8 ± 1 d) during the treatment cycle of dose increase of pyrotinib/placebo by one level based on the investigator's assessment, a telephone follow-up should be conducted to collect information on AEs and concomitant medications.	
Pages 35-45	Main information of pyrotinib	Updated the summary table of ongoing or completed clinical studies of pyrotinib and clinical safety data.	Updated the progress in studies of pyrotinib
Page 62	Administration of study drugs: During each infusion, the subjects should be monitored for any adverse reactions. Monitoring should last for at least 90 min after the first trastuzumab infusion.	Administration of study drugs: During each infusion, the subjects should be monitored for any adverse reactions. Monitoring should last for at least 90 min from the start of the first trastuzumab infusion.	Clarified the time of monitoring after the first trastuzumab infusion
Page 63	Dose modification and delay: In the case of AEs of intolerance to docetaxel, the dose of docetaxel may be reduced to 60 mg/m^2.	Dose modification and delay: In the case of AEs due to intolerance to docetaxel, the dose of docetaxel may be reduced to a minimum of 60 mg/m^2 per the package insert and the investigator's assessment.	Clarified the docetaxel modification principle based on the docetaxel's package insert and actual practice.
Pages 64 and 66	Management of common adverse events - diarrhea: The investigator must inform the subject in detail of the potential of diarrhea and appropriate treatment measures prior to starting the oral administration of study drug. Oral administration of loperamide hydrochloride (Imodium®) is allowed (up to	Management of common adverse events - diarrhea: The investigator must inform the subject in detail of the potential of diarrhea and appropriate treatment measures prior to starting the oral administration of study drug. Instruct the subject to prepare anti-diarrheal drugs; pay attention to	Clarified the standardized treatment and dose reduction for common adverse events - diarrhea

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	16 mg/day) for secondary preventing diarrhea during pyrotinib medication in the study. For severe diarrhea, electrolytes may be administered orally or intravenously. For Grade ≥ 3 diarrhea that cannot be controlled after prophylactic medication or symptomatic treatment, the dose of study drug will be modified according to Table 3.	changes in the appearance of stool and frequency of defecation during the study drug administration; start anti-diarrheal treatment as soon as possible in the case of loose stool; and adjust the diet. Loperamide may serve as an anti-diarrheal drug. Oral administration of loperamide hydrochloride (Imodium®) is allowed (up to 16 mg/day) for secondary preventing diarrhea during the study. In the case of interruption or delay of study medication (pyrotinib/placebo, trastuzumab, or docetaxel), the investigator may prescribe loperamide to prevent diarrhea after evaluation. For severe diarrhea, electrolytes may be administered orally or intravenously. For Grade ≥ 3 diarrhea that cannot be controlled after prophylactic medication or symptomatic treatment, the dose of study drug will be modified according to Table 3.	
	Dose modification for pyrotinib/placebo and docetaxel in Table 3: Grade 3 or Grade 1-2 with complications (Grade ≥ 2 nausea or vomiting, pyrexia, neutrophils reduced, hematochezia, or dehydration), and intolerable after active treatment, considered related to pyrotinib: First occurrence: resume medication after interruption	Dose modification for pyrotinib/placebo and docetaxel in Table 3: Grade 3 for > 2 days or Grade 1-2 with complications (Grade ≥ 2 nausea or vomiting, pyrexia, hematochezia, or dehydration, or Grade 3-4 neutrophils reduced), and intolerable after active treatment, considered related to pyrotinib/placebo:	

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
	Second occurrence: reduce dose by 1 level when necessary after interruption.	First occurrence: interrupt dose; remain original dose in the case of recovery to Grade ≤ 1 or baseline within 1 week; reduce dose by 1 level in the case of recovery to Grade ≤ 1 or baseline within 1-3 weeks. Second occurrence: interrupt dose; reduce dose by 1 level after recovery to Grade ≤ 1 or baseline.	
Page 67	Management of common adverse events - cardiac adverse events: In the case of cardiac AEs that are considered possibly related to both pyrotinib/placebo and trastuzumab, the dose of pyrotinib may be interrupted/reduced if the condition is not relieved within 2 treatment cycles after active symptomatic treatment and/or dose interruption or delay of trastuzumab.	Management of common adverse events - cardiac adverse events: In the case of cardiac AEs that are considered possibly related to trastuzumab, the dose of pyrotinib/placebo may be reduced if the condition is not relieved within 2 treatment cycles after active symptomatic treatment and/or dose interruption or delay of trastuzumab.	Clarified the treatment for cardiac adverse events.
Page 71	Concomitant treatment: The following medications should be used carefully during the study: Strong CYP3A4 inducers (e.g., dexamethasone [except prophylactic medication with docetaxel], phenytoin sodium, carbamazepine, rifampicin, rifabutin, and rifapentine); Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir,	Concomitant treatment: The following medications should be used carefully during the study: Strong CYP3A4 inducers (carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, and St. John's wort) and moderate inducers (bosentan, efavirenz, etravirin, and modafinil); Strong CYP3A4 inhibitors (boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir	Updated the list of drugs that should be used with caution

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	ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit); CYP2C19 substrates (diazepam, imipramine, lansoprazole, and S-mephenytoin); P-gp inhibitors (ritonavir, cyclosporine, and verapamil) and inducers (rifampicin)	and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir/dasabuvir, posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, and voriconazole) and moderate inhibitors (aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofesopar, and verapamil); CYP2C19 substrate (S-mephenytoin, omeprazole, diazepam, lansoprazole, rabeprazole, and voriconazole); P-gp inhibitors (amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, and verapamil).	
Page 75	Study procedures - treatment period	The safety visit cycle is determined according to the infusion date of the drug (i.e., trastuzumab and/or docetaxel), that is, the safety examinations should be completed within 3 days before the infusion date of the drug.	Clarified that the safety visit cycle is determined according to the infusion date of the drug.

Revised Item	**Original Protocol** **Version Date: 21 Dec., 2018** **Version No.: 1.0**	**Amended Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amendment Description**
Page 79	Scanning requirements for medical imaging: In the case of local recurrence of breast cancer, an MRI scan of the recurrence site is also required.	Scanning requirements for medical imaging: In the case of local recurrence of breast cancer, an MRI scan of the recurrence site of the breast is also required.	Updated the requirements for MRI examination of the recurrence site
Page 81	Pregnancy test: Subsequently, urine/blood pregnancy test should be performed at least during the end-of-treatment visit and safety visit.	Pregnancy test: Subsequently, urine/blood pregnancy test should be performed at least during the end-of-treatment visit.	Updated the time point of pregnancy test
Page 82	12-Lead ECG: Subjects are required to be in a supine position for at least 10 minutes prior to the ECG examination. The ECG should include at least heart rate, QT, QTc, and P-R intervals.	12-Lead ECG: Subjects are required to rest for at least 10 min prior to undergoing the ECG. The ECG should include at least heart rate, QT, QTc, and P-R intervals.	Updated the requirements for ECG examination based on actual practice.
Page 87	Potential drug-induced liver injury Abnormal values in AST and/or ALT concurrent with abnormal elevations of TBIL that meet all of the following criteria in the absence of other etiologies causing the liver injury should be considered as drug-induced liver injury, and should be reported as important medical events and reported as SAEs. Potential drug-induced liver injury is defined as follows:	Abnormal values in AST and/or ALT concurrent with abnormal elevations of TBIL that meet all of the following 3 criteria in the absence of other etiologies causing the liver injury should be reported as important medical events and reported as SAEs.	Updated the evaluation criteria and recommendation for potential drug-induced liver injury

<table>
<tr><th>Revised Item</th><th>Original Protocol
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<tr><td></td><td>
<table>
<tr><td>Baseline Period</td><td>Normal (AST/ALT and TBIL)</td><td>Abnormal (AST/ALT and TBIL)</td></tr>
<tr><td>Treatment Period</td><td>ALT or AST
≥ 3 × ULN
With TBIL
≥ 2 × ULN
And ALP
≤ 2 × ULN
And no hemolysis</td><td>AST or ALT
≥ 2 × baseline level, and values
≥ 3 × ULN; or
AST or ALT
≥ 8 × ULN
With TBIL increase
≥ 1 × ULN or
TBIL ≥ 3 × ULN</td></tr>
</table>
</td><td>
<table>
<tr><td>Condition</td><td>Criteria</td></tr>
<tr><td>(1) ALT or AST abnormal</td><td>For subjects with AST or ALT baseline values within the normal range: subsequent ALT or AST ≥ 3 × ULN during treatment;
For subjects with AST or ALT baseline values above the upper limit of normal: subsequent ALT or AST ≥ 2 × baseline values and ≥ 3 × ULN during treatment; or the value ≥ 8 × ULN.</td></tr>
<tr><td>(2) TBIL abnormal</td><td>For subjects with TBIL baseline values within the normal range: subsequent TBIL > 2 × ULN during treatment;
For subjects with TBIL baseline values above the upper limit of normal: subsequent TBIL increased from baseline by at least 1 × ULN or value > 3 × ULN during treatment.</td></tr>
<tr><td colspan="2">(3) No evidence of hemolysis, and alkaline phosphatase < 2 × ULN or not available</td></tr>
</table>
</td><td></td></tr>
<tr><td>Page 87</td><td>Potential drug-induced liver injury:</td><td>Deleted "If compliance with the above laboratory criteria is confirmed upon re-examination, the possibility of potential drug-induced liver injury should be considered in the absence of any other causes of abnormal liver function, without waiting for all liver function test results. Potential drug-induced liver injury should be reported as an SAE."</td><td></td></tr>
</table>

<table>
<tr><th>Revised Item</th><th>Original Protocol
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<tr><td>Page 89</td><td>Collection and follow-up of AEs/SAEs</td><td>Added "Table 7. AEs/SAEs collection period"
<table>
<tr><th>Classification</th><th>Collection/Documentation Requirement</th></tr>
<tr><td>AEs[a] Unrelated to Study Treatment</td><td>Until 28 days after the last dose of the study drugs or the start of a new anti-tumor treatment (whichever comes first)</td></tr>
<tr><td>Suspected Treatment-Related AEs[a]</td><td>Until 28 days after the last dose of the study drugs</td></tr>
<tr><td>SAE[b] Unrelated to Study Treatment</td><td>Fatal SAEs: until 28 days after the last dose of the study drugs;
Non-fatal SAEs: until 28 days after the last dose of the study drugs or the start of a new anti-tumor treatment (whichever comes first)</td></tr>
<tr><td>Suspected Treatment-Related SAE[b]</td><td>No time limit</td></tr>
</table>
a: Non-serious AEs
b: Including fatal and non-fatal SAEs.</td><td>Added the table of AEs/SAEs collection period</td></tr>
</table>

Revised Item	Original Protocol Version Date: 21 Dec., 2018 Version No.: 1.0	Amended Protocol Version Date: 20 Jan., 2020 Version No.: 2.0	Amendment Description
Page 93	Analysis of primary efficacy endpoints: The primary endpoint of the study is PFS. The primary analysis will be based on the FAS. The survival functions of PFS of the two groups will be compared using both stratified and non-stratified log-rank tests. In addition, the Kaplan-Meier method will be used for estimating the PFS by group, the survival curves will be plotted, and the median PFS and its 95% CI will be estimated. The analysis with stratification factors will be used as the primary analysis. In addition, as a supporting analysis, under the assumption of proportional hazards, the Cox models with and without considering stratification factors will be used to estimate the hazard ratio between the two groups and calculate the corresponding 95% CI. The analysis methods for PPS will be the same as those for FAS.	The primary endpoint of the study is PFS. The primary analysis will be based on the FAS. The analysis based on the PPS will serve as a sensitive analysis. The survival functions of PFS of the two groups are compared using both stratified and non-stratified log-rank tests. In addition, the Kaplan-Meier method will be used for estimating the PFS by group, the survival curves will be plotted, and the median PFS and its 95% CI will be estimated. The analysis with stratification factors will be used as the primary analysis. In addition, as a supporting analysis, under the assumption of proportional hazards, the Cox models with and without considering stratification factors will be used to estimate the hazard ratio between the two groups and calculate the corresponding 95% CI. Censoring rules for PFS: If the baseline tumor response of the subject is not evaluable, then the randomization date will be censored. If there is no post-baseline objective tumor response evaluation or death, then the randomization date will be censored. If there is no PD or death as per RECIST v1.1, the date of the last objective tumor response evaluation will be censored.	Updated the description of the analysis of primary efficacy endpoints.

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		If there is no radiographic PD or death before the start of any new anti-tumor treatment, then the date of the last objective tumor response evaluation prior to the start of new anti-tumor treatment will be censored. Before PD or death, if a subject has missed ≥ 2 consecutive scheduled imaging evaluation, then the date of the last objective tumor response evaluation prior to the missing ones will be censored.	
Page 94		Added pharmacokinetic analysis "The blood concentration data of pyrotinib will be summarized using descriptive statistics and analyzed. In addition to the statistics used for continuous variables, PK data may also be summarized using coefficient of variation, geometric mean, geometric standard deviation, and geometric coefficient of variation depending on the nature of data."	Added the statistical methods for pharmacokinetic analysis.
	Appendix IV "Nomogram for Determining the Body Surface Area"	Deleted Appendix IV "Nomogram for Determining the Body Surface Area"	The body surface area will be calculated according to the software and others of each center, and the nomogram for determining the body surface area is deleted

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer

Study Protocol Amendments

Revised Item	**Modified Page Number**	**Original Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amended Protocol** **Version Date: 31 Oct., 2020** **Version No.: 3.0**	**Amendment Description**
Version No. of Study Protocol	Full Text	2.0	3.0	Uniform amendments to the full text and header/footer.
Version Date of Study Protocol	Full Text	20 Jan., 2020	31 Oct., 2020	Uniform amendments to the full text and header/footer.
Synopsis: Number of Participating Study Centers	Page 11	Participating study centers: Approximately ~~37~~ study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences	Participating study centers: Approximately **41** study centers in China, including the Cancer Hospital, Chinese Academy of Medical Sciences	Updated the number of participating study centers
Synopsis: Study Population	Page 12	Female patients with HER2-positive recurrent/metastatic breast cancer who have not received systematic anti-tumor therapy for their metastatic diseases	Female patients with HER2-positive recurrent/metastatic breast cancer who have not received systematic anti-tumor therapy for their metastatic diseases **(except first-line endocrine therapy)**	Corrigendum, to be consistent with the exclusion criterion 1
Full Text: Exclusion Criterion 17;	Pages 18 and 57	Pregnant or lactating female subjects, or subjects ~~of childbearing potential~~ who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose.	Pregnant or lactating female subjects, or subjects **of childbearing potential** who are unwilling to take effective contraceptive measures during the entire study period and within 7 months after the last dose.	To be consistent with the content described in the contraception section

Revised Item	**Modified Page Number**	**Original Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amended Protocol** **Version Date: 31 Oct., 2020** **Version No.: 3.0**	**Amendment Description**
Schedule of Activities 23	Page 25	Survival follow-up (collection of OS data): Subjects will continue to receive survival follow-up ~~after completing the end-of-treatment visit~~. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), ~~starting from the day of completion of the end-of-treatment visit~~	Survival follow-up (OS data collection): All survival subjects **who have completed the safety follow-up and efficacy follow-up (whichever is completed later)** should undergo survival follow-up. Survival (date and cause of death) and post-treatment information (including subsequent treatments) should be collected from the subjects, family members, or local physicians via telephone interview or clinical follow-up at least once every 12 weeks (± 7 days), **starting from the day of completion of safety follow-up and efficacy follow-up (whichever comes later)**	Corrigendum, to be consistent with Section 7.5
Main Text: 5.6.1 Contraception	Pages 58-59	~~In this study, trastuzumab has been confirmed to have teratogenicity/fetal toxicity; docetaxel and pyrotinib are suspected to have reproductive toxicity, which, however, has not been proven in clinical use. All female subjects of childbearing potential who will take the above study drugs, if the investigator believes that they are at risk of pregnancy, must adopt at least two highly effective contraceptive measures during the entire treatment period from the signing of the ICF until 7 months after the last dose of study drugs. After consulting with subjects, the investigator or designated personnel will select 2 appropriate~~	**Cases of impaired fetal renal development and/or function due to oligohydramnios were reported in pregnant women treated with trastuzumab in post-marketing reports, as well as some cases associated with fatal fetal lung hypoplasia. Trastuzumab can cause fetal harm when administered to a pregnant woman. Preclinical studies suggested that docetaxel is genotoxic. Results from animal studies suggested that pyrotinib may have reproductive toxicity (including teratogenicity), but it has not been clinically proven.**	Updated the contraception section: 1. Updated the reproductive toxicity of the study drugs. 2. Added the definition of women of childbearing potential, and updated the corresponding description in the protocol. 3. Updated the acceptable contraceptive measures.

Revised Item	Modified Page Number	Original Protocol Version Date: 20 Jan., 2020 Version No.: 2.0	Amended Protocol Version Date: 31 Oct., 2020 Version No.: 3.0	Amendment Description
		~~contraceptive methods from the followings, and confirm the subjects' awareness of correct and consistent use of the contraceptive methods. In addition, the subjects shall be aware that the investigator must be notified immediately once the selected methods of contraception are stopped.~~ ~~An effective contraception method refers to a method with an annual failure rate of < 1% when correctly used independently or with other methods, including:~~ ~~1. Correctly inserted intrauterine devices.~~ ~~2. Male/female condom combined with topical spermicides (i.e., foams, gels, films, creams, or suppositories).~~ ~~3. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusion (the occlusion should be proven effective by relevant instruments)~~	**Female subjects are considered non-childbearing potential if they are either:** **1) postmenopausal, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative medical reasons; a high follicle stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a post-menopausal state in female subjects younger than 45 years of age and not using hormonal contraception or hormonal replacement therapy; However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient);** **or** **2) have undergone a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;** **or**	

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			3) have a congenital or acquired condition that prevents childbearing. **Female subjects of childbearing potential must agree to avoid becoming pregnant and are required to use the following contraception methods, from the time the subject signs the informed consent form until 7 months after the last dose of study treatment:** **1) practice abstinence from heterosexual activity*.** **or** **2) female subjects (or male partners) use acceptable non-hormonal contraceptive methods during heterosexual activity.** **Acceptable non-hormonal contraceptive methods include:** **Single method (one of the following is acceptable):** **• copper-containing intrauterine device (IUD)** **• vasectomy of female subject's male partner**	

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			Combination method (requires use of two of the following): • **vaginal diaphragm with spermicide (cannot to be used in combination with cervical cap/spermicide)** • **cervical cap with spermicide (nulliparous women only)** • **contraceptive sponge (nulliparous women only)** • **male condom or female condom (cannot to be used together)** * **Abstinence (avoiding heterosexual intercourse) can be used as the sole method of contraception if this is the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), and withdrawal (coitus interruptus) are not acceptable methods of contraception.** **In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject.**	

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Full Text: Schedule of Activities 21 6.1.5 Administration of study drugs	Pages 24 and 62	During the treatment with pyrotinib/placebo combined with trastuzumab and docetaxel, the dose of pyrotinib/placebo may be adjusted per the protocol based on the adverse reactions of the subject. ~~If Grade ≥ 3 pyrotinib-/placebo-related non-hematologic toxicities do not occur after the dose of pyrotinib/placebo is reduced, then based on assessment, the investigator may increase the dose of pyrotinib/placebo by one level after permanent discontinuation of docetaxel, that is, during the treatment with pyrotinib/placebo combined with trastuzumab. During the treatment with three-agent combination, if the dose of pyrotinib/placebo is reduced to 320 mg, and Grade ≥ 3 pyrotinib-/ placebo-related non-hematologic toxicities do not occur during the treatment at 320 mg, then based on assessment, the investigator may increase the dose of pyrotinib/placebo to 400 mg after permanent discontinuation of docetaxel.~~	During the treatment with pyrotinib/placebo combined with trastuzumab and docetaxel, the dose of pyrotinib/placebo may be reduced per the protocol based on the adverse reactions of the subject. **The dose of pyrotinib/placebo should be increased to 400 mg after permanent discontinuation of docetaxel. If, per the investigator's comprehensive assessment, the dose cannot be increased to 400 mg, after reporting to the sponsor, the dose of pyrotinib/placebo can be maintained at the dose before docetaxel discontinuation or increased to an appropriate dose (two increases are allowed, up to 400 mg).**	Clarified the dose increase of pyrotinib/placebo, with the reasons as follows: 1. Safety: In this study, it is observed that the safety of pyrotinib/ placebo combined with trastuzumab is acceptable after permanent discontinuation of docetaxel; 2. More potential benefits: Data from the phase I clinical study of pyrotinib indicated that the PFS for pyrotinib (400 mg) alone or combined with capecitabine was greater than that for 320 mg; 3. Study design of similar drug: The dose of lapatinib was increased when combined with trastuzumab after discontinuation of taxanes.

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Main Text: Concomitant Treatment	Page 72	CYP2C19 substrate (S-mephenytoin, omeprazole, diazepam, lansoprazole, rabeprazole, and voriconazole);	~~CYP2C19 substrate (S-mephenytoin, omeprazole, diazepam, lansoprazole, rabeprazole, and voriconazole);~~	Updated the list of drugs that should be used with caution
Full Text: Schedule of Activities 21 7.3 Treatment Period	Pages 24 and 77	Telephone follow-up: On D8 ± 1 day (CxD8 ± 1 d) during the treatment cycle of dose increase of pyrotinib/placebo ~~by one level based on the investigator's assessment~~, a telephone follow-up should be conducted to collect information on AEs and concomitant medications.	Telephone follow-up: On D8 ± 1 day (CxD8 ± 1 d) during the treatment cycle of **dose increase of pyrotinib/placebo**, a telephone follow-up should be conducted to collect information on AEs and concomitant medications.	Updated the description of telephone follow-up
Main Text 7.3 Treatment Period	Page 77	PK blood sampling: For ~~approximately 100~~ subjects	PK blood sampling: For **at least 50** subjects	Clarified the minimum number of subjects for PK blood sampling.
Main Text 9.2.2 Hospitalization;	Page 87	AEs resulting in hospitalization (even less than 24 hours) or prolonged hospitalization during the clinical study should be considered as SAEs. Hospitalization does not include the following: • …… • Routine emergency room visit (~~observation~~ for less than 24 hours) • …… Hospitalization or prolonged hospitalization in the absence of the worsening of an AE is not in itself an SAE. For example:	AEs resulting in hospitalization (even less than 24 hours) or prolonged hospitalization during the clinical study should be considered as SAEs. Hospitalization does not include the following: • …… • Routine emergency room visit (**generally** less than 24 hours) • ……	1. Provided the investigator with a certain time window for medical judgment. Refined the description.

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		• Admission due to pre-existing conditions ~~without the occurrence of new AEs or worsening of the pre-existing diseases~~ (e.g., for work-up of persistent pre-treatment laboratory abnormalities);	Hospitalization or prolonged hospitalization in the absence of the worsening of an AE is not in itself an SAE. For example: • Admission due to pre-existing conditions **not associated with the occurrence of new AEs or with worsening of the pre-existing diseases** (e.g., for work-up of persistent pre-treatment laboratory abnormalities); ……	
Main Text 9.2.3 Disease progression and death;	Pages 88-89	~~Disease progression is defined as the worsening of the subject's conditions caused by the indications of the study, including radiological progressions and/or progressions in clinical symptoms and signs. New metastases relative to the primary tumor or progressions of the previous metastases are recognized as PD.~~ Events that are life-threatening, require hospitalization or prolonged hospitalization, or result in persistent or significant disability/incapacity/impairment of work ability due to symptoms and signs of disease progression, ~~and congenital anomalies or birth defects are not reported as SAEs. Death caused by the symptoms and signs of PD will be reported as an SAE.~~	Events that are life-threatening, require hospitalization or prolonged hospitalization, or result in persistent or significant disability/incapacity/impairment of work ability due to symptoms and signs of disease progression are not reported as SAEs. **If there is any uncertainty over the whether the SAE is caused by disease progression, it should be reported as an SAE.** **All deaths occurring within the AE/SAE collection period must be reported as SAEs, regardless of whether it is likely related to disease progression per the investigator's judgment, or whether the subject has received any other anti-tumor treatments. The term "death" should not**	1. It has been clarified in the full text that the investigator should be responsible for the evaluation of PD, and the tumor assessment should be conducted according to RECIST v1.1. This is the SAE reporting of PD and death, and is not repeated. 2. Pregnancy abnormalities complying with the Section 9.4 (including

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		• ~~Death of a subject during the study, regardless of whether a new anti-tumor treatment is administrated, must be reported as an SAE. The term "death" should not be reported as an AE or SAE term, but as the outcome of the event. Events that result in death should be recorded as AEs or SAEs. If the cause of death is unknown and cannot be determined at the time of reporting, the AE or SAE term "death unexplained" shall be used for documentation.~~	**be reported as an SAE term, but as the outcome of the event. Events that result in death should be recorded as SAEs. The medical condition/disease (including deterioration of symptoms and signs) that causes or contributes to fatal outcome should be recorded in the eCRF as an SAE term, and reported as an SAE. If the cause of death cannot be determined at the time of reporting, the AE or SAE should be recorded as "unexplained death"; if the cause of death later becomes available, "unexplained death" should be replaced by the established cause of death.** **If the subject dies from disease progression as assessed by the investigator, the Grade 5 event caused by disease progression should be recorded in the eCRF and reported as an SAE; if the death caused by disease progression cannot be attributed to a specific medical event, then a Grade 5 "Tumor progression" should be recorded in the eCRF and reported as an SAE. Evidence that the death is due to disease progression (e.g., radiological changes suggesting tumor growth or progression, clinical**	congenital anomalies or birth defects) will be reported as SAEs, so the content is deleted. 3. Reporting requirements for death during the study are clarified. 2. SAE terms related to PD are coded according to the reporting requirements specified by the company.

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			deterioration associated with a disease process) should be provided by the investigator.	
Main Text 9.2.5 SAE reporting requirements	Page 89	The sponsor's email address for SAE reporting is: hengrui_drug_safety@hrglobe.cn	The email address for the sponsor to receive the report of SAEs (**as well as SIE and pregnancy**) is: hengrui_drug_safety@hrglobe.cn	4. Clarified the email address for the report of SIE and pregnancy.
Main Text 9.4 Pregnancy	Page 90	If a female subject becomes pregnant during the study, the subject must immediately discontinue the study treatment. The investigators should report the pregnancy to the sponsor within 24 hours of awareness and ~~to the ethics committee timely~~ using Hengrui Clinical Trial Pregnancy Report/Follow-Up Form. ~~The investigator should follow up the pregnancy outcome until 1 month after delivery, and report the outcome to the sponsor and the ethics committee.~~	If a female subject becomes pregnant during the study, the subject must immediately discontinue the study treatment. The investigators should report the pregnancy to the sponsor within 24 hours of awareness using Hengrui Clinical Trial Pregnancy Report/Follow-Up Form. **The investigator should follow up the pregnancy outcome (including any early termination of pregnancy or childbirth) until 1 month after delivery, and notify the sponsor of the pregnancy outcome. If the pregnancy outcome meets the seriousness criteria (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), it must be reported as an SAE (other important medical events).**	Updated the report of pregnancy and follow-up procedures;

<table>
<tr><th>Revised Item</th><th>Modified Page Number</th><th>Original Protocol
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<tr><td>Full Text
Data Analysis/ Statistical Methods</td><td>Pages 19-20, 92, and 94-95</td><td>In this study, an interim analysis will be carried out for the primary endpoint. The interim analysis will be conducted when ~~50% of PFS events (205 events)~~ are collected. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:
Table 9. Termination criteria and significance level in the interim analysis and final analysis of PFS
<table>
<tr><td>Time Point</td><td>Number of PFS Events</td><td>Boundary Z-Value (Corresponding HR)</td><td>One-Sided Nominal Significance Level</td></tr>
<tr><td>Interim (1st)</td><td>~~205 (50%)~~</td><td>~~-2.963 (HR = 0.66)~~</td><td>~~0.002~~</td></tr>
<tr><td>Final</td><td>410</td><td>~~-1.969 (HR = 0.82)~~</td><td>~~0.024~~</td></tr>
</table></td><td>In this study, an interim analysis will be carried out for the primary endpoint. The interim analysis will be conducted <u>when 67% of PFS events (275 events) are collected</u>. The α spending function of the interim analysis is based on the O'Brien-Fleming method, and the boundaries of superiority determined by this method are as follows:
Table 9. Termination criteria and significance level in the interim analysis and final analysis of PFS
<table>
<tr><td>Time Point</td><td>Number of PFS Events</td><td>Boundary Z-Value (Corresponding HR)</td><td>One-Sided Nominal Significance Level</td></tr>
<tr><td>Interim (1st)</td><td><u>275 (67%)</u></td><td><u>-2.500 (HR = 0.74)</u></td><td><u>0.0062</u></td></tr>
<tr><td>Final</td><td>410</td><td><u>-1.994 (HR = 0.82)</u></td><td><u>0.0231</u></td></tr>
</table></td><td>Updated the time point, termination criteria and significance level of the interim analysis.</td></tr>
<tr><td>Main Text
11.4 Analysis Sets</td><td>Page 93</td><td>• Full analysis set (FAS): all subjects who are screened eligible per the ITT principle and ~~receive the study drugs~~ after randomization and enrollment. The FAS is the primary analysis set for the efficacy analysis of this study.</td><td>• Full analysis set (FAS): all subjects who are screened eligible per the ITT principle and are randomized and enrolled. The FAS is the primary analysis set for the efficacy analysis of this study.</td><td>Updated the definition of analysis sets</td></tr>
</table>

Revised Item	Modified Page Number	Original Protocol Version Date: 20 Jan., 2020 Version No.: 2.0	Amended Protocol Version Date: 31 Oct., 2020 Version No.: 3.0	Amendment Description
		• Per-protocol set (PPS): a subset of the FAS, excluding subjects with important protocol deviations which significantly impact study results. Safety analysis set (SS): all randomized subjects who have received at least one dose of the study drug ~~and have at least one safety assessment~~.	• Per-protocol set (PPS): a subset of the FAS, excluding subjects with important protocol deviations which significantly impact study results. • Safety analysis set (SS): all randomized subjects who have received at least one dose of the study drug	
Main Text Analysis of primary efficacy endpoints	Page 94	Censoring rules for PFS: – If the baseline tumor response of the subject is not evaluable, then the randomization date will be censored. – If there is no post-baseline objective tumor response evaluation or death, then the randomization date will be censored. – If there is no PD or death as per RECIST v1.1, the date of the last objective tumor response evaluation will be censored. – If there is no radiographic PD or death before the start of any new anti-tumor treatment, then the date of the last objective tumor response evaluation prior to the start of new anti-tumor treatment will be censored.	~~Censoring rules for PFS:~~ ~~– If the baseline tumor response of the subject is not evaluable, then the randomization date will be censored.~~ ~~– If there is no post-baseline objective tumor response evaluation or death, then the randomization date will be censored.~~ ~~– If there is no PD or death as per RECIST v1.1, the date of the last objective tumor response evaluation will be censored.~~ ~~– If there is no radiographic PD or death before the start of any new anti-tumor treatment, then the date of the last objective tumor response evaluation prior to the start of new anti-tumor treatment will be censored.~~	The content will be specified in the statistical analysis plan, so it is not repeated in the protocol.

Revised Item	**Modified Page Number**	**Original Protocol** **Version Date: 20 Jan., 2020** **Version No.: 2.0**	**Amended Protocol** **Version Date: 31 Oct., 2020** **Version No.: 3.0**	**Amendment Description**
		• Before PD or death, if a subject has missed ≥ 2 consecutive scheduled imaging evaluation, then the date of the last objective tumor response evaluation prior to the missing ones will be censored.	• ~~Before PD or death, if a subject has missed ≥ 2 consecutive scheduled imaging evaluation, then the date of the last objective tumor response evaluation prior to the missing ones will be censored.~~	
Main Text 11.5.4 Pharmacokinetic analysis	Page 94	The blood concentration data of pyrotinib will be summarized using descriptive statistics and analyzed. In addition to the statistics used for continuous variables, PK data may also be summarized using coefficient of variation, geometric mean, geometric standard deviation, and geometric coefficient of variation depending on the nature of data.	The blood concentration data of pyrotinib **may** be summarized using descriptive statistics and analyzed. In addition to the statistics used for continuous variables, PK data may also be summarized using coefficient of variation, geometric mean, geometric standard deviation, and geometric coefficient of variation depending on the nature of data. **The blood concentration data of pyrotinib will also be listed by time points.**	Clarified the description of pharmacokinetic analysis.
Corrected the clerical errors found in the full text				

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer

Study Protocol Amendments

Revised Item	**Modified Page Number**	**Original Protocol Version Date: 31 Oct., 2020 Version No.: 3.0**	**Amended Protocol Version Date: 1 Dec., 2020 Version No.: 4.0**	**Amendment Description**
Version No. of Study Protocol	Full Text	3.0	4.0	Uniform amendments to the full text and header/footer.
Version Date of Study Protocol	Full Text	31 Oct., 2020	1 Dec., 2020	Uniform amendments to the full text and header/footer.
Full Text: Study Drugs	Pages 14 and 59-60	Trastuzumab for injection (Herceptin®, hereinafter referred to as "trastuzumab") Trastuzumab for injection (Herceptin®) Dosage form: lyophilized powder Strength: 440 mg Manufacturer: F. Hoffmann-La Roche	Trastuzumab for injection (Herceptin® **or Zercepac®**, hereinafter referred to as "trastuzumab") **Trastuzumab for injection (Zercepac®)** **Dosage form: lyophilized powder** **Strength: 150 mg/vial** **Manufacturer: Shanghai Henlius Biopharmaceuticals Co., Ltd.** Trastuzumab for injection (Herceptin®) Dosage form: lyophilized powder Strength: 440 mg Manufacturer: F. Hoffmann-La Roche	On 14 Aug., 2020, the NMPA approved the domestic trastuzumab Zercepac® developed by Henlius for the treatment of HER2-positive early breast cancer, metastatic breast cancer, and metastatic gastric cancer, covering all indications of originator trastuzumab approved in China.
Main Text 6.1.1 Access to drugs	Page 59	NA	**Following the ethics approval of Protocol Version 4.0, the newly enrolled subjects will receive Zercepac®, and subjects who are already in screening or have received Herceptin® still receive Herceptin®. Crossover use of Herceptin® and Zercepac® is not allowed.**	After the change of the study drug, different medication for subjects who sign informed consent form at different time points is clarified.
Corrigendum in full text				

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer

Study Protocol Amendments

Revised Item	**Modified Page Number**	**Original Protocol Version Date: 1 Dec., 2020 Version No.: 4.0**	**Amended Protocol Version Date: 12 Jan., 2022 Version No.: 5.0**	**Amendment Description**
Version No. of Study Protocol	Full Text	4.0	5.0	Uniform amendments to the full text and header/footer.
Version Date of Study Protocol	Full Text	1 Dec., 2020	12 Jan., 2022	Uniform amendments to the full text and header/footer.
Main Text 6.1.1 Access to drugs	Page 59	~~Following the ethics approval of Protocol Version 4.0, the newly enrolled subjects will receive Zercepac®, and subjects who are already in screening or have received Herceptin® still receive Herceptin®. Crossover use of Herceptin® and Zercepac® is not allowed.~~	**Following the ethics approval of Protocol Version 5.0, subjects who are treated with Zercepac® at study centers that have no supply of Zercepac® will be switched to treatment with Herceptin® until the subjects withdraw from the study treatment or withdraw from the study. Newly randomized subjects will be treated with Herceptin® until the subjects withdraw from the study treatment or withdraw from the study.**	The supply of Zercepac® is limited. It is clarified that trastuzumab will be used for subjects with different conditions.
Main Text 8.1.2 Scanning requirements for medical imaging	Page 81	The tumor assessment at the study center should be performed by an experienced, qualified study physician designated by the study center who is unaware of the group assignment.	**It is recommended that** the tumor assessment at the study center be performed by an experienced, qualified study physician designated by the study center who is unaware of the group assignment.	Updated according to the clinical practice
Corrigendum in full text				

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Pyrotinib Maleate Tablets Combined with Trastuzumab and Docetaxel vs. Placebo Combined with Trastuzumab and Docetaxel in HER2-Positive Recurrent/Metastatic Breast Cancer

Statistical Analysis Plan
(SAP)

Author: Fangli Dong

Company: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Version: 1.0/Initial Version

Date: 23 Jun., 2022

This statistical analysis plan has been reviewed by the following personnel before being approved and effective.

Functional Role	Reviewer
Medicine	Xiaoyu Zhu
Statistics	Ping Yan

ABBREVIATIONS

Abbreviation	Full Name
12-Lead ECG	12-Lead Electrocardiograph
BMI	Body Mass Index
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
DoR	Duration of Response
ECOG-PS	Eastern Cooperative Oncology Group Physical Status Score
eCRF	Electronic Case Report Form
ER	Estrogen Receptor
FAS	Full Analysis Set
HER-2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
NALQ	Number of Above Limit Quantitation
NCI-CTC	National cancer institute Common Terminology Criteria
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
p	p Value
PD	Progressive Disease
PFS	Progression Free Survival
PPS	Per-Protocol Analysis Set
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SOC	System Organ Classification
SS	Safety Analysis Set
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event

TABLE OF CONTENTS

1. REVISION

Not applicable.

2. INTRODUCTION

This statistical analysis plan (SAP) is formulated to provide the specific methods or strategies of statistical analysis and reporting for a phase III, randomized, double-blind, placebo-controlled, multicenter study comparing the efficacy and safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in subjects with HER2-positive recurrent/metastatic breast cancer. The contents of this SAP are based on the study protocol (version No.: 5.0, version date: 12 Jan., 2022).

This SAP is finalized before database locked and signed by cross-functional departments for confirmation.

2.1. Study Design

This is a phase III, randomized, double-blind, placebo-controlled, multicenter study.

This study plans to enroll a total of 590 subjects. Eligible subjects will be randomized in a 1:1 ratio to the pyrotinib combined with trastuzumab and docetaxel group (treatment group) or the placebo combined with trastuzumab and docetaxel group (control group). Randomization is stratified by the following factors:

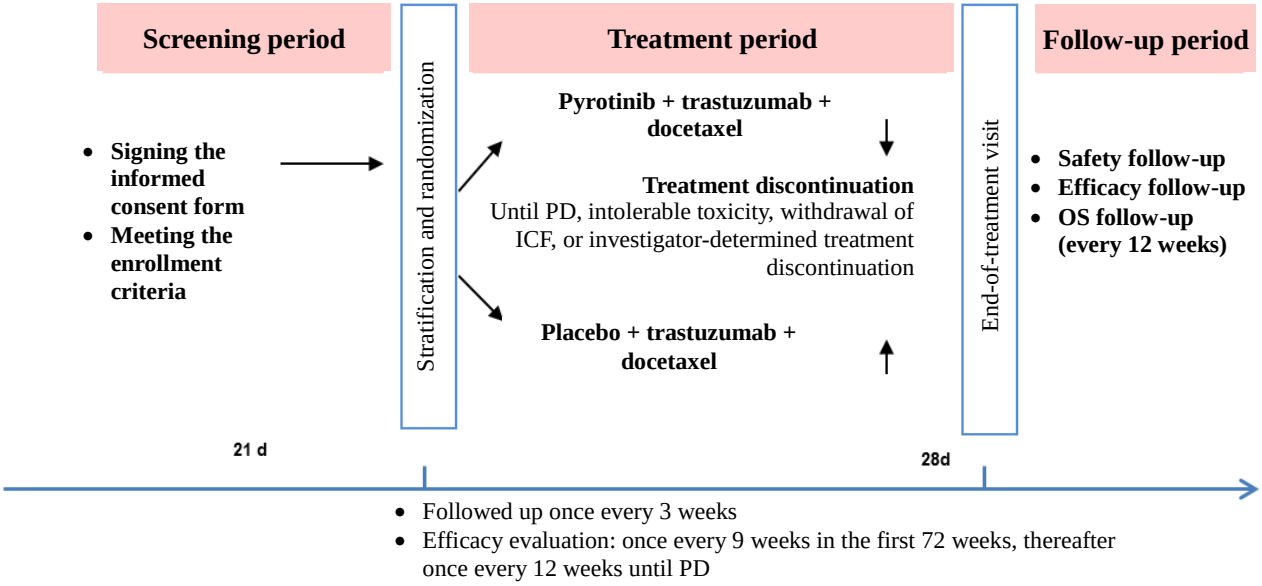
- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab
- ER/PR status: positive or negative

Subjects will receive study treatment within 48 h after randomization in 21-day cycles. Pyrotinib/placebo and trastuzumab will be administered until investigator-assessed progressive disease (PD), intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. Subjects will receive docetaxel for at least 6 cycles if there is no investigator-assessed PD, intolerable toxicity, withdrawal of informed consent form, or investigator-determined treatment discontinuation. The tumor assessments will be performed by the investigators and independent review committee according to RECIST v1.1. The primary PFS analysis is based on the assessment results by the investigators.

For subjects who discontinue the study treatment, the safety visit should occur on D28 ± 7 d after the last administration of study drug, then the subjects should start the survival follow-up period until death or study termination (whichever occurs first). For subjects who discontinue the study treatment due to reasons other than PD or death, scheduled tumor assessments need to be collected until PD, start of a new anti-tumor treatment, or death (whichever occurs first).

This study plans to perform 2 IDMC meetings (including 1 safety assessment and 1 interim analysis). After the data review, the IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study.

An overview of the study design is shown below:



2.2. Study Objectives

2.2.1. Primary objective

- To evaluate the progression-free survival (PFS) of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer

2.2.2. Secondary objectives

- To evaluate the safety of pyrotinib maleate tablets combined with trastuzumab and docetaxel vs. placebo combined with trastuzumab and docetaxel as first-line treatment in patients with HER2-positive recurrent/metastatic breast cancer
- To compare the efficacy between two groups in overall survival (OS), objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR)
- To evaluate the pharmacokinetics (PK) of pyrotinib maleate tablets combined with trastuzumab and docetaxel in patients with HER2-positive recurrent/metastatic breast cancer.

2.3. Sample Size

In this study, PFS is used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to evaluate the efficacy of the drugs and to determine whether to terminate or continue the study. The assumptions for sample size calculation are as follows:

- Enrollment duration = 24 months, minimum follow-up = 18 months (overall duration of 42 months)
- Randomization in a 1:1 ratio
- Overall type I error rate $\alpha = 0.025$ (one-sided)
- The power of test is approximately 80%
- Hazard ratio (HR) = 0.76 (estimated median PFS is 12.5 months in the control group and 16.5 months in the treatment group)
- An interim analysis will be performed when 67% of PFS events (275 events) are collected to evaluate the efficacy of the drugs, and to decide whether to terminate or continue the study.

Based on the above parameters, at least 410 PFS events should be collected according to the log rank test for PFS comparison between two groups and the Lan-DeMets α spending function (EAST 6.4.1) constrained by the O'Brien & Fleming boundaries. Assuming that the PFS dropout rate is 15% for 24 months, approximately 590 subjects should be enrolled.

3. STATISTICAL HYPOTHESIS AND DECISION RULE

The primary endpoint of this study is PFS (investigator-assessed). The following superiority hypotheses for the primary endpoint will be tested:

- H_0: HR ≥ 1
- H_1: HR < 1
- α level: 0.025 (one-sided)

In this study, an interim efficacy analysis will be conducted for the primary endpoint when 67% of PFS events (275 events) are collected, with an $\alpha = 0.0062$ (one-sided) for the interim analysis and an $\alpha = 0.0231$ (one-sided) for the final analysis to control the overall type I error rate to not exceed 0.025 (one-sided). The α for the interim and final analyses will be adjusted as necessary based on the proportion of events in the actual interim analysis. The PFS of the treatment group and the control group will be compared using stratified log-rank test.

For the comparison between the pyrotinib maleate tablet combined with trastuzumab and docetaxel group and the placebo combined with trastuzumab and docetaxel group, if the *p* value for the inter-group comparison is ≤ α in the interim or final analysis, then it is considered that pyrotinib maleate tablet combined with trastuzumab and docetaxel is superior to placebo combined with trastuzumab and docetaxel and can significantly prolong the PFS of subjects.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Primary efficacy endpoint

Progression-free survival (PFS): Defined as the time from the date of randomization to the occurrence date of a PFS event. A PFS event refers to 1) the first documented PD (as per RECIST v1.1, see Section 4.4.1 of Appendix III in the protocol), or 2) death (due to any cause), whichever occurs first. Therefore, the occurrence date of a PFS event is 1) the date of tumor imaging examination [1] corresponding to the first documented PD, or 2) the date of death, whichever is earlier.

If a subject does not experience any PFS event before study discontinuation or the analysis cutoff date (whichever occurs first), the subject's PFS will be censored at the date of tumor imaging examination corresponding to the last adequate tumor assessment[2] (if there is no adequate post-baseline tumor assessment, PFS will be censored at the date of randomization).

Based on this, for subjects who receive new anti-tumor treatment[3], and subjects who miss some of the adequate scheduled tumor assessments before the PFS event, the following censoring rules for PFS will be used if applicable:

- If after baseline, a subject does not experience any PFS event before receiving new anti-tumor treatment, the subject's PFS will be censored at the date of imaging examination corresponding to the last adequate tumor assessment prior to the initiation of the new anti-tumor treatment (or censored at the date of randomization if there is no adequate post-baseline tumor assessment);
- If after baseline, a subject experiences a PFS event after missing two or more consecutive adequate scheduled tumor assessments[4], the subject's PFS will be censored at the date of imaging examination corresponding to the last adequate tumor assessment before missing (or censored at the date of randomization if there is no adequate post-baseline tumor assessment);
- If a subject fits both of the above cases, the subject's PFS will be censored at the earlier date of the above dates.

The censoring categories and censoring dates are summarized in the table below, with censoring categories listed in descending order of priority:

Censoring Category	**Censoring Date**
Receive new anti-tumor treatment	Censored at the date of imaging examination corresponding to the last adequate tumor assessment prior to the initiation of the new anti-tumor treatment (or censored at the date of randomization if there is no adequate post-baseline tumor assessment)

Censoring Category	Censoring Date
Missing two or more consecutive adequate scheduled tumor assessments prior to PD/death	Censored at the date of imaging examination corresponding to the last adequate tumor assessment prior to PD/death (or censored at the date of randomization if there is no adequate post-baseline tumor assessment)
No PD/death, have adequate post-baseline assessment, study discontinued	Censored at the date of imaging examination corresponding to the last adequate tumor assessment
No PD/death, no adequate post-baseline assessment, study discontinued	Censored at the date of randomization
No PD/death, follow-up ongoing	Censored at the date of imaging examination corresponding to the last adequate tumor assessment (or censored at the date of randomization if there is no adequate post-baseline tumor assessment)

[1] Date of imaging examination:

1) If the overall tumor assessment result is PD, then the corresponding imaging examination date should be the earliest imaging examination date at this imaging visit;

2) If the overall tumor assessment result is not PD, then the corresponding imaging examination date should be the latest imaging examination date at this imaging visit.

[2] An adequate tumor assessment refers to an overall tumor response assessment with the result of complete response (CR)/partial response (PR)/stable disease (SD)/PD.

[3] New anti-tumor treatments include the following treatments recorded on the electronic case report form (eCRF): all subsequent systemic anti-tumor treatments, subsequent radiotherapy for target lesions (except radiotherapy with bone as the site of radiotherapy), and subsequent surgeries for radical cure.

[4] Missing two or more consecutive adequate scheduled tumor assessments is judged as follows:

1) If the occurrence date of PFS event is $\leq 72 + 1$ weeks after randomization, and the visit interval is > 20 weeks, a subject is considered missing two or more consecutive adequate scheduled tumor assessments;

2) If the occurrence date of PFS event is $> 72 + 12 \times 2 + 1$ weeks after randomization, and the visit interval is > 26 weeks, a subject is considered missing two or more consecutive adequate scheduled tumor assessments;

3) If the occurrence date of PFS event is $> 72 + 1$ weeks after randomization and $\leq 72 + 12 \times 2 + 1$ weeks after randomization, and the visit interval is > 23 weeks, a subject is considered missing two or more consecutive adequate scheduled tumor assessments.

In the efficacy analysis, PFS (in months) will be calculated as follows:

PFS (months) = (occurrence or censoring date of PFS event - date of randomization + 1)/30.4375.

The primary efficacy endpoint of this study is investigator-assessed PFS as per RECIST v1.1.

4.1.2. Secondary efficacy endpoints

The secondary efficacy endpoints of this study include:

- IRC-assessed PFS as per RECIST v1.1;
- Overall survival (OS);
- Objective response rate (ORR);
- Duration of response (DoR);
- Clinical benefit rate (CBR).

4.1.2.1. Progression-free survival (PFS)

Refer to Section 4.1.1 for the definition and calculation of PFS. IRC-assessed PFS as per RECIST v1.1 is one of the secondary efficacy endpoints of this study.

4.1.2.2. Overall survival (OS)

Overall survival (OS): Defined as the time from the date of randomization to the date of death due to any cause (refer to Section 5.1.6.4 for the imputation rules). The censoring rules for OS are as follows:

- For subjects who are alive and still in the study at the cutoff date, OS will be censored at the last survival date (refer to Section 5.1.5);
- For subjects who are alive and have discontinued the study at the cutoff date, OS will be censored at the last survival date;
- For subjects who died, if the date of death is completely missing, OS will be censored at the last survival date;
- For subjects who died, if the month and day of death are missing, OS will be censored at max (last survival date, 1 Jan. of the year of the death date - 1 day).

In the efficacy analysis, OS (in months) will be calculated as follows:

OS (months) = (occurrence or censoring date of OS event - date of randomization + 1)/30.4375.

4.1.2.3. Objective response rate (ORR)

Objective response rate (ORR): the proportion of subjects who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) as per RECIST v1.1.

Best overall response (BOR) refers to the best response recorded from the date of randomization to the objective documentation of PD as per RECIST v1.1 or to the start of a new anti-tumor treatment (whichever occurs first). In this study, the BOR does not need to be confirmed. For subjects without documented PD or new anti-tumor treatment, BOR will be determined based on all response assessments. BOR is classified into: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE), and will be determined based on the following rules:

- CR: response evaluated as CR.
- PR: response evaluated as PR without response evaluated as CR.
- SD: response evaluated as SD without response evaluated as CR or PR, and with at least one SD with an interval (from the randomization date to the corresponding imaging examination date) not less than the minimum interval (6 weeks, i.e., 42 days).
- PD: response evaluated as PD, without response evaluated as CR or PR, and without response evaluated as SD with an interval not less than the minimum interval (6 weeks, i.e., 42 days).
- NE: all other situations.

Refer to Section 4.4.3 of RECIST v1.1 in Appendix III of the protocol for details.

4.1.2.4. Clinical benefit rate (CBR)

CBR: the proportion of subjects with a best overall response of CR, PR, or SD as per RECIST v1.1 for ≥ 24 weeks from the date of randomization.

4.1.2.5. Duration of response (DoR)

Duration of response (DoR): the time from the date of first record of objective response (CR or PR, as per RECIST v1.1) to the occurrence date of PFS event (including first documented PD assessed as per RECIST v1.1 or death of any cause, whichever occurs first).

DoR will only be calculated for subjects with a BOR of objective response after treatment. According to the definition of DoR, the end date of response must be consistent with either the date of PD or death of PFS. The censoring rules for DoR are the same as those for PFS. The correspondence between DoR censoring category and PFS censoring category is as follows:

PFS Censoring Category	DoR Censoring Category
Receive new anti-tumor treatment	Receive new anti-tumor treatment
Missing two or more consecutive adequate scheduled tumor assessments prior to PD/death	Others
No PD/death, have adequate post-baseline assessment, study discontinued	
No PD/death, no adequate post-baseline assessment, study discontinued	
No PD/death, follow-up ongoing	Still in remission

DoR (in months) will be calculated as follows:

DoR (months) = (occurrence or censoring date of PFS event - date of first CR/PR + 1)/30.4375.

4.2. Safety Endpoints

4.2.1. Adverse events

All adverse events (AEs) will be coded using MedDRA V24.0, and graded according to NCI-CTCAE v4.0.3 and Section 9.1.2 of the study protocol. In the analysis, an AE with a start date (refer to Section 5.1.6.2 for imputation rules of incomplete dates) being on or later than the date of the first study dose (refer to Section 5.1.5) will be considered as a **treatment-emergent adverse event (TEAE)**. Refer to Section 9.1.3 of the protocol for the causality assessment criteria. In the analysis, if "Related", "Possibly related", or "Unassessable" is ticked for the question "Causality with pyrotinib/placebo" or "Causality with trastuzumab" or "Causality with docetaxel" on the AE page of the CRF, the TEAE is considered as a **treatment-related adverse event (TRAE)**. In addition, a TEAE should also be considered as a TRAE if the answer to either of the above three questions is missing.

Refer to Section 9.2.1 of the protocol for the judgment rules of **serious adverse events (SAEs)** in the study. In the analysis, if "Yes" is ticked for the question "Serious Adverse Event or Not" on the AE page of the CRF, the AE is considered as an SAE.

See Section 9.5 of the protocol for **AEs of special interest (AESIs)** in the study. In the analysis, if "Yes" is ticked for the question "AESI or Not" on the AE page of the CRF, the AE is considered as an AESI.

See Section 9.3 of the protocol for the collection of AEs/SAEs in the study.

4.2.2. Prior/concomitant treatment

Prior medications within 28 days prior to study medication and concomitant medications and concomitant non-drug treatments during the study should be documented. Once the study treatment is permanently discontinued, only concomitant medications or treatments for new or unresolved AEs related to study treatment should be documented. Concomitant medications or treatments for cardiotoxicity that is still present at the end-of-treatment visit (regardless of causality with the study drugs) should be followed until the AE has returned to baseline or Grade ≤ 1, or until 12 months after the last dose.

Non-study drugs documented will be coded using WHODrug (GLOBALB3Mar20).

Prior medication is defined as non-study medication with a start date earlier than the date of the first study dose (refer to Section 5.1.5). Non-study medication with a completely or partially missing start date is also considered prior medication if any of the following conditions is met:

- The start date is completely missing;
- The start date is partially missing, and the non-missing part is not later than the date of the first dose.

Concomitant medication is defined as non-study medication with a start date that is not later than 28 days after the last dose (refer to Sections 5.1.5 and 5.1.6.8) and an end date that is not earlier than the first dose. Non-study medication with a completely or partially missing start or end date is also considered concomitant medication if any of the following conditions is met:

- The start and end dates are completely missing;
- The start date is completely missing, the end date is partially missing or not missing, and the non-missing part is not earlier than the date of the first dose;
- The end date is completely missing, the start date is partially missing or not missing, and the non-missing part is not later than 28 days after the date of the last dose;
- The start date is partially missing or not missing, the end date is partially missing or not missing, the non-missing part of the start date is not later than 28 days after the last dose, and the non-missing part of the end date is not earlier than the first dose.

4.2.3. Laboratory test

Laboratory data such as hematology, blood biochemistry, urinalysis, routine stool test, infectious disease screening, and pregnancy test will be collected at the visit time points specified in the protocol.

4.2.4. Vital signs

Vital signs such as body temperature, blood pressure, respiratory rate, and pulse will be collected at the time points specified in the protocol.

4.2.5. 12-Lead electrocardiogram

Heart rate, P-R interval, QT interval, QTc, QTcF, and other data will be collected/calculated at the time points specified in the protocol. If the QTcF interval increases by > 30 msec from baseline, or if any one of the measured QTcF interval has an absolute value ≥ 470 msec, then 2 additional ECG measurements are required (at least 10 min apart).

4.2.6. Physical examination

The physical examination items include general condition, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal system, nerve reflex, respiratory system, cardiovascular system, reproductive-urinary system (when necessary), and mental status. These data will be collected at the visits/time points specified in the protocol.

4.2.7. Other safety endpoints

Echocardiography, ECOG PS, etc.

4.3. Other Study Endpoints

4.3.1. Pharmacokinetics and pharmacodynamics

PK blood sampling will be conducted at the visits/time points specified in the protocol. Pharmacodynamics is not involved in this study.

4.3.2. Immunogenicity

Not applicable.

4.3.3. Quality of life index

Not applicable.

4.3.4. Biomarker

Not applicable.

5. STATISTICAL ANALYSIS

5.1. General Considerations

5.1.1. Analysis sets

5.1.1.1. Full analysis set (FAS)

Includes all randomized subjects per the ITT principle. The FAS is the primary analysis set for the efficacy analysis of this study. All baseline and primary efficacy analyses will be conducted based on the groups allocated according to randomization.

5.1.1.2. Per-protocol set (PPS)

A subset of the FAS, excluding subjects with important protocol deviations that significantly impact study results. The exclusion criteria should be finalized prior to database locked, and the list of subjects included in and excluded from the PPS should be reviewed and determined by the sponsor and the principal investigator prior to database locked.

5.1.1.3. Safety set (SS)

All randomized subjects who have received at least one dose of the study drugs constitute the SS of this study. SS is the primary analysis set for the safety analysis of this study. All safety analyses will be conducted based on the actual study treatment received by the subjects.

5.1.2. General rule and analysis

General analysis

Unless otherwise specified, the following descriptive statistics will be summarized by the type of variables:

- Continuous variables will be summarized using mean, standard deviation, median, maximum, and minimum;
- Categorical variables will be summarized using frequency and percentage.
- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median survival time, and the survival curve will be plotted.
- The PK concentration data will be summarized using number of subjects, number above the lower limit of quantitation (NALQ), mean, geometric mean, standard deviation, coefficient of variation, geometric coefficient of variation, median, maximum, and minimum.

Number of decimal places

Unless otherwise specified, number of decimal places in the analysis report will be determined as follows:

- The decimal places of the minimum and maximum will remain the same as those of the raw data in the CRF. Mean and quantile should have one more decimal place than those of the raw data, and the standard deviation should have 2 more decimal places than that of the raw data. However, there can only be at most 4 decimal places.
- The percentage will be rounded to 1 decimal place. If the frequency is 0, the percentage is not displayed.
- The *p* value will retain 4 decimal places. If the *p* value is < 0.0001, it will be expressed as "< 0.0001"; if the *p* value is > 0.9999, it will be reported as "> 0.9999".
- Hazard ratio will be rounded to 4 decimal places.

Analysis software

All statistical analyses will be conducted using SAS® 9.4 or above.

Results of laboratory tests

The results of laboratory tests are generally continuous numerical variables or character variables. If continuous numerical variables recorded in eCRF contain special characters (such as < xx and > xx), the following rules will be applied:

- In the case of < xx, half of the xx value will be used for analysis;
- In the case of > xx or ≥ xx, the value of xx will be used for analysis.

5.1.3. Derived variables

Refer to Section 5.5.1 "Extent of exposure" for the derived variables related to study drug exposure information, and for other derived variables, refer to the corresponding definition of derived rules in each section for details.

5.1.4. Covariates and subgroups

See Section 5.4.4 "Subgroup analysis" for details.

5.1.5. Analysis window

Date of first dose

The date of first dose is defined as the earliest among all administration dates of trastuzumab or docetaxel and start dates of pyrotinib/placebo documented on the "Combined Administration" and "Administration Record (Pyrotinib/Placebo)" pages of the eCRF.

Date of last dose

The date of last dose is defined as the latest among all administration dates of trastuzumab or docetaxel and end dates of pyrotinib/placebo (imputed according to Section 5.1.6.8) documented on the "Combined Administration" and "Administration Record (Pyrotinib/Placebo)" pages of the eCRF.

Last survival date

Only the dates of actual examinations/visits can be used to derive the last survival date. The dates of examinations/visits carried out after the cutoff date will not be used to calculate the last survival date. The last survival date refers to the latest among all the complete and unimputed dates including but not limited to the following:

- All examination dates (imaging examination, bone scan, blood tests (laboratory, PK), weight measurement, vital signs measurement, physical examination, ECOG PS scoring, pregnancy test, urinalysis, routine stool test, echocardiography, 12-lead ECG, unscheduled tests, sampling date of pregnancy test, etc.)
- The start and end dates of new anti-tumor treatment after the discontinuation of study treatment
- The start and end dates of concomitant medications and concomitant non-drug treatments
- The start and resolve dates of AEs
- The last known "alive" date on the survival follow-up page
- The start and end dates of study treatment and the start/end dates of treatment interruption/dose modification

- The date of informed consent and the date of withdrawal of informed consent
- The date of clinical diagnosis during screening, the date of pathological specimen collection, and the date of randomization
- The date on the end of study page, the last known survival date and the date of study discontinuation (if the reason for discontinuation is "lost to follow up", "withdrawal of informed consent", or "death", the date of study discontinuation will not be included for calculation).

If the derived last survival date is later than the date of withdrawal of informed consent, the date of withdrawal of informed consent will be taken as the last survival date.

Baseline

Unless otherwise stated, "baseline" in this study is defined as the last non-missing measurement before the first dose of the study drugs. Unscheduled examinations will also be used for baseline assessment.

For the measurements on the day of the first dose, a scheduled measurement will be assumed to be conducted before the first dose and included in baseline calculation; an unscheduled measurement will be assumed to be conducted after the first dose and will not be included in baseline calculation. If the date of the first dose and the date of the end of the treatment both occurred on C1D1 (one in the treatment period and the other at the end-of-treatment visit), then the end-of-treatment examination will be assumed to be conducted after the first dose and will not be included in baseline calculation.

In case of repeated measurements on the same day, the mean value of a continuous variable will serve as baseline value, or the lower-severity grade of a categorical variable will serve as baseline value.

Study days

The date of first dose is defined as the start day of the study (Day 1). Then, based on the start day of the study, the number of days of study corresponding to examination or event is calculated by the following formula:

- Study days = examination/event date - start date of the study, if the date of an examination/event is before the start date of the study;
- Study days = examination/event date - start date of the study + 1, if the date of an examination/event is on or after the start day of the study.

Analysis by visit

Safety data that need to be analyzed by visit will be summarized by scheduled visits. Unscheduled visits do not need to be presented. Scheduled post-baseline visits will be summarized using examination records corresponding to the visits in the eCRF (if there are several records corresponding to the visit, the average value will be included in the summary), with no need to consider whether the actual examination date exceeds the protocol-specified visit window or include the records of unscheduled examinations falling within the visit window.

5.1.6. Handling of missing dates and missing data

Unless otherwise stated, missing data of examinations or records will not be imputed in principle. If the following conditions are met, missing dates of examinations or records will be imputed according to the corresponding rules. No imputation will be done for other missing dates in principle.

5.1.6.1. Dates related to medical history

Missing recurrence/metastasis dates on the clinical diagnosis page of the eCRF will be imputed as follows:

- If the date is partially missing (day is missing or day and month are missing), impute the missing part with the last day of the month (day is missing) or the last day of the year (day and month are missing);
- No imputation will be done if the date is completely missing.

5.1.6.2. Adverse event onset date

AE refers to records on the AE page of the eCRF. Missing AE onset dates will be imputed according to the following rules, by regarding the date of first dose (refer to Section 5.1.5) as the reference date:

- If the AE onset date is completely missing, then compare the unimputed end date with the reference date:
  - If the end date is not available or if its non-missing part is not earlier than the corresponding part of the reference date, then impute with the reference date;
  - If the non-missing part of the end date is earlier than the corresponding part of the reference date, then impute the onset date with 1 Jan. of the end year;
- If the AE onset date is partially missing, then compare the unimputed end date with the reference date:
  - If the end date is not available or if its non-missing part is not earlier than the corresponding part of the reference date and the non-missing part of the onset date is equal to the corresponding part of the reference date, then impute the onset date with the corresponding part of the reference date;

- In other cases, impute the missing part of the onset date with 1 (the 1st day of the month or 1 Jan. of the year).

All imputed AE onset dates must not be earlier than the informed consent date; otherwise impute the onset date with the informed consent date.

5.1.6.3. Adverse event resolve date

Missing AE resolve dates will be imputed as follows:

- If the date is partially missing (day is missing or day and month are missing), impute the missing part with the earlier date of either the last day of the month (day is missing) or the year (day and month are missing) or the cutoff date. If the imputed resolve date is later than the death date, then impute with the death date;
- If the resolve date is completely missing, then impute with the analysis cutoff date. If the imputed resolve date is later than the death date, then impute with the death date.

5.1.6.4. Death date

Death dates are from the end of study page of the eCRF. The completely or partially missing death dates will be imputed by regarding the last survival date (refer to Section 5.1.5) as the reference date.

By referring to the last survival date, the death dates will be imputed as follows:

- No imputation will be done if the death date is completely missing or only the month and day are missing;
- If only the day is missing and the non-missing part is equal to the corresponding part of the last survival date, then impute with the last survival date + 1 day;
- If only the day is missing and the non-missing part is later than the corresponding part of the last survival date, then impute the missing part with 1 (the 1st day of the month).

5.1.6.5. Systemic treatment start date

Systemic treatment histories include surgical history, neoadjuvant therapy history, adjuvant therapy history, recurrence/metastasis treatment history, and radiotherapy history in the eCRF.

The start date of systemic treatment history will not be imputed.

5.1.6.6. Systemic treatment end date

For missing end dates of chemotherapy and targeted therapy on the adjuvant therapy history page of the eCRF:

- If the date is partially missing (day is missing or day and month are missing), impute the missing part with the last day of the month (day is missing) or the last day of the year (day and month are missing);
- No imputation will be done if the date is completely missing.

5.1.6.7. Study drug first dose date

Refer to the first dose date defined in Section 5.1.5. No imputation will be done.

5.1.6.8. Study drug last dose date (pyrotinib/placebo)

Completely or partially missing last dose dates on the administration record (pyrotinib/placebo) page of the eCRF will be imputed according to the following rules, by regarding the earlier date of either the treatment end date of pyrotinib/placebo (if available) or the complete and unimputed death date (if available) as the reference date:

- For subjects with no death dates or no end-of-treatment records of pyrotinib/placebo:
  - If the last dose date of pyrotinib/placebo is partially missing (day is missing or day and month are missing), impute the missing part with the earlier date of either the last day of the month (day is missing) or the year (day and month are missing) or the cutoff date.
  - If the last dose date is completely missing, impute with the cutoff date.
- For subjects with death dates or end-of-treatment records of pyrotinib/placebo:
  - If the last dose date of pyrotinib/placebo is completely missing, impute it with the reference date;
  - If the last dose date of pyrotinib/placebo is partially missing and the non-missing part is earlier than the corresponding part of the reference date, then impute the missing part with the earlier date of either the last day of the month (day is missing) or the year (day and month are missing) or the cutoff date;
  - If the last dose date of pyrotinib/placebo is partially missing and the non-missing part is equal to the corresponding part of the reference date, impute it with the reference date;

All imputed dates must be earlier than the date of end of study (e.g., date of study discontinuation).

5.1.6.9. Study drug dose adjustment/interruption dates

Missing start and end dates of interruption/adjustment in the dose interruption/adjustment page of the eCRF will not be imputed.

5.1.6.10. New anti-cancer therapy related dates

For the start and end dates of subsequent systemic anti-cancer therapy, start and end dates of subsequent radiotherapy, and date of subsequent surgery in the eCRF:

1) Partially or completely missing end dates of subsequent systemic anti-cancer therapy and subsequent radiotherapy will be imputed as follows:

- If only the day is missing, impute the missing part with the earlier date of either the last day of the month or the cutoff date;
- If both day and month are missing, impute the missing part with the earlier date of either the last day of the year (31 Dec.) or the cutoff date;
- If the date is completely missing, impute it with the cutoff date.

2) The start date of subsequent systemic anti-cancer therapy and subsequent radiotherapy as well as the date of subsequent surgery may be used for the censoring of efficacy endpoints. The following dates will be used to impute these partially or completely missing dates:

- The last dose date (see Section 5.1.5) and the date of first assessment of PD by investigator (if available);
- The end date of subsequent anti-cancer therapy imputed according to 1) in Section 5.1.6.10 (if available).

Completely or partially missing start dates of subsequent systemic anti-cancer therapy and subsequent radiotherapy as well as date of subsequent surgery will be imputed according to the following rules:

- If the date is completely missing, impute it with min [max (last dose date + 1, date of first assessment of PD by investigator + 1), imputed end date of subsequent anti-cancer therapy];
- If the date is partially missing, e.g., only day is missing or both day and month are missing, compare (1) the non-missing part of the date with (2) the corresponding non-missing part of min [max (last dose date + 1, date of first assessment of PD by investigator + 1), imputed end date of subsequent anti-cancer therapy]:
  - If (1) is earlier than the corresponding non-missing part of (2), impute the missing part with the last day of the month (day is missing) or the year (day and month are missing);
  - If (1) is equal to the corresponding non-missing part of (2), impute the missing part with (2);
  - If (1) is later than the corresponding non-missing part of (2), impute the missing part with 1 (the 1st day of the month or 1 Jan. of the year).

5.1.6.11. General prior and concomitant medication related date

No imputation will be done. Refer to Section 4.2.2 for the determination of prior and concomitant medications based on missing or partially missing dates.

5.1.6.12. Concomitant non-drug treatment related date

No imputation will be done.

5.2. Study Subjects

Unless otherwise stated, the descriptive analysis described in this section will be conducted by randomized group based on the FAS.

5.2.1. Subjects disposition

For all subjects who have signed the informed consent form and participated in screening, descriptive statistics will be used to summarize the screening status of subjects, including the number of screen failures and categories of reasons for screen failure.

All randomized subjects will be summarized by randomized group using frequency and percentage.

In addition, in the disposition of subjects, the following information will be summarized using frequency and percentage:

- Randomized subjects (including those treated and untreated after randomization)
- Subjects who are still under combination therapy, have discontinued any study drug, or have discontinued study treatment/reasons for treatment discontinuation
- Subjects who are still in the study or who have discontinued study/reasons for study discontinuation
- Subjects in each analysis set, including FAS, PPS, and SS

The reasons for not receiving the study treatment or discontinuing the study treatment will be listed. Subjects not included in the PPS will be listed.

5.2.2. Demographics and baseline characteristics

The gender, age (years), age group (< 65 years old vs. ≥ 65 years old), ethnicity, height [m], weight [kg], body mass index (BMI) [kg/m^2], body surface area [m^2], ECOG, alcohol use status, smoking status, etc., will be summarized using descriptive statistics based on the FAS. In addition, the stratification factor information (prior neoadjuvant/adjuvant therapy: with or without trastuzumab and ER/PR status) collected in the randomization system and electronic data capture (EDC) database will also be summarized using descriptive statistics.

Age will be calculated with the number of full years between date of birth and date of signing informed consent form. Age (years) is calculated using the following formula: (date of signing informed consent form - date of birth + 1)/365.25, rounded to the nearest integer.

In addition, a detailed listing of subjects will be provided.

5.2.3. Medical history

Medical history will be coded using MedDRA V24.0, and summarized by system organ class (SOC) and preferred term (PT) using descriptive statistics based on the FAS. The presence of history of allergy will be summarized.

Virological examination results will be summarized and listed. Medical history and history of allergy of subjects will be listed.

5.2.4. Tumor diagnosis

Based on the FAS, the tumor diagnostic information (including clinical diagnosis and pathological diagnosis), recurrence/metastasis, visceral metastasis, initial AJCC stage, pathological grade, hormone receptor status (including estrogen receptor (ER) and progesterone receptor (PR)), human epidermal growth factor receptor 2 status (ICH test results, FISH test results), etc., will be summarized by treatment group using descriptive statistics including number and percentage of subjects.

The "recurrence/metastasis" will be taken from subjects with history of radical mastectomy, and other situations will be defined as "initial diagnosis".

Visceral metastasis will be taken from the lesion sites on the target lesion and non-target lesion pages of the eCRF during the screening. Lesion sites except for lymph nodes, bone, bone marrow, pelvis, breast, skin, and soft tissues will be classified as visceral metastasis.

In addition, the treatment-free interval (TFI), the number of metastatic sites, and the sum of diameters (SOD) of target lesions will be summarized. The calculation methods are as follows:

TFI (months) = (recurrence/metastasis date - end date of adjuvant therapy + 1)/30.4375, rounded to the nearest integer. The recurrence/metastasis date in the equation refers to the recurrence/metastasis date on the clinical diagnosis page of the eCRF. The end date of adjuvant therapy refers to the latest end date of chemotherapy or targeted therapy on the adjuvant therapy history page of the eCRF. Refer to Section 5.1.6.1 and Section 5.1.6.6 for imputation rules.

The number of metastatic sites will be counted only for the screening period by using the lesion sites on the target lesion and non-target lesion pages of the eCRF, while the breast ticked for the metastatic site on the target lesion and non-target lesion pages of the eCRF during the screening period will be excluded from the counting. In particular, if both bone and pelvis are ticked for the lesion site, they should be combined as one bone lesion, and each of other ticked lesion sites will be counted as one separately.

The SOD of target lesions will be calculated only for the screening period by using the long diameter of the lesion and short diameter of the lesion (only for the lymph nodes) on target lesion page of the eCRF (sum of diameters (mm) = long diameter of the lesion + short diameter of the lesion (only for the lymph nodes)).

A detailed listing of subjects for tumor diagnosis will be provided.

5.2.5. Tumor treatment history

Tumor treatment histories mainly include tumor surgery history, neoadjuvant/adjuvant therapy history, recurrence/metastasis treatment history, and radiotherapy history.

For tumor treatment history, the following descriptive statistics will be provided:

- Number and percentage of subjects who have received any of the above tumor treatments
- Number and percentage of subjects who have received breast cancer surgery which is further categorized as radical surgery and palliative surgery
- Number and percentage of subjects who have received neoadjuvant/adjuvant therapy which is further categorized as history of endocrine therapy, use of anthracyclines, and use of taxanes
- Number and percentage of subjects who have received recurrence/metastasis treatment which is further categorized as history of endocrine therapy
- Number and percentage of subjects who have received radiotherapy;

In addition, a detailed listing of subjects will be provided.

5.2.6. Prior/concomitant medication and/or non-drug therapy

All prior and concomitant medications will be coded according to WHODrug (GLOBALB3Mar20), and the prior and concomitant medications (based on the SS) will be summarized by ATC2 and PT using frequency and percentage.

All prior and concomitant medications and concomitant non-drug therapy will be listed.

5.2.7. Protocol deviations

Before database lock, relevant researchers of the sponsor's study team and the investigators will review and discuss all protocol deviations and determine whether subjects with important protocol deviations should be excluded from relevant analysis sets.

Important protocol deviations include but are not limited to the following:

- Serious violation of the inclusion/exclusion criteria;
- Not taking study drugs according to the protocol, such as using the wrong drugs;

- Use of any prohibited drug.

The protocol deviations will be listed by subjects and summarized by treatment group, type of protocol deviation, description of protocol deviation, etc.

Whether a subject is excluded from an analysis set due to a protocol deviation is decided prior to the database lock.

5.2.8. Subsequent anti-cancer therapies

The number and percentage of subjects receiving various subsequent anti-cancer therapies (including subsequent systemic anti-cancer therapy, subsequent radiotherapy, and subsequent surgery) will be summarized, including the number and percentage of subjects receiving anti-HER2 drugs/treatment such as pertuzumab and pyrotinib during subsequent systemic anti-cancer therapy, the number and percentage of subjects receiving subsequent radiotherapy, and the number and percentage of subjects receiving subsequent surgery.

The subsequent anti-cancer therapies will be listed.

5.3. Treatment Compliance

Based on the SS, the use of study drugs: 1) pyrotinib/placebo, 2) trastuzumab, 3) docetaxel during the treatment period will be summarized by group using descriptive statistics.

Treatment compliance will be summarized by group using indexes such as relative dose intensity. See Section 5.5.1 for details.

5.4. Efficacy Analysis

The analysis of primary efficacy endpoint will be performed based on the FAS and PPS. The analysis of secondary efficacy endpoints and the subgroup analysis, unless otherwise specified, will be performed based on the FAS. All efficacy analyses will be presented by randomized group. Unless otherwise stated, the randomization stratification factors mentioned in the efficacy analyses of this study refer to the stratification information in the randomization system.

5.4.1. Analysis of primary endpoint

The primary efficacy endpoint of this study is investigator-assessed progression-free survival (PFS). The following primary analysis and sensitivity analysis of primary endpoint will be performed:

5.4.1.1. Primary analysis of primary endpoint

Investigator-assessed PFS will be summarized by group using descriptive statistics, including number and percentage of PFS events (including PD and PD-free death), number and percentage of censored subjects, and summary by censoring reason.

The probabilities of PFS will be estimated using the Kaplan-Meier method and the probability of PFS vs. time curves will be plotted by group. Also, the probabilities at 6-, 12-, 24-, and 36-month of PFS will be estimated along with the corresponding 95% CIs. Specifically, a 95% CI of the log-log transformation of the probability of PFS is calculated by using normal approximation, then the 95% CI of the probability of PFS will be obtained by a reverse transformation. In addition, the quartiles and medians (25%, 50%, and 75%) of PFS in each group will be estimated using the Kaplan-Meier method, and the corresponding 95% CIs will be estimated using the Brookmeyer-Crowley method.

For inter-group comparison, a stratified log-rank test (considering randomization stratification factors) will be used to calculate the *p*-value. A stratified Cox proportional hazards model (considering randomization stratification factors) will be used to estimate the hazard ratio (HR, treatment group vs. control group) and the corresponding 95% CI. Randomization stratification factors are collected from the randomization system:

- Prior neoadjuvant/adjuvant therapy: with or without trastuzumab;
- ER/PR status: positive or negative;

In addition, given that this study is a group sequential design, Repeated Confidence Interval (RCI) method proposed by Jennison & Turnbull (1984, 1989)[1] will be used to calculate two-sided RCIs of inter-group PFS hazard ratios in interim and final analyses. Refer to Appendix 1.1 for the key SAS codes for PFS analysis.

The above analyses will be repeated in the PPS.

5.4.1.2. Sensitivity analysis of primary endpoint

In addition to the above primary analysis of primary endpoint (investigator-assessed PFS), the following sensitivity analyses will also be performed.

Sensitivity analysis 1:

Based on the FAS, the analysis using 1) log-rank test and 2) Cox proportional hazards model described above without considering stratification factors will be repeated as one of the sensitivity analyses.

Sensitivity analysis 2:

Based on the FAS, 1) log-rank test and 2) Cox proportional hazards model analysis will be repeated by considering the randomization stratification factors collected in the EDC system (i.e., stratification factors collected in the inclusion and exclusion criteria page of the eCRF).

In addition, if necessary, the plot of the Schoenfeld residuals of the stratified Cox proportional hazards model vs. time will be plotted to assess whether the proportional hazard assumption is valid. If the proportional hazard assumption is invalid, the Wilcoxon method and/or Max-Combo method[2] will be used to compare the distributions of survival functions of the two groups. Refer to Andrea et al. (2020)[3] for the SAS macro of the Max-Combo test.

5.4.2. Analysis of secondary endpoints

5.4.2.1. IRC-assessed PFS

The primary analysis of secondary efficacy endpoint IRC-assessed PFS is the same as the primary analysis of primary endpoint (investigator-assessed PFS) (see Section 5.4.1.1) and will be conducted based on the FAS and PPS. The sensitivity analysis is the same as that of primary endpoint (investigator-assessed PFS) (see Section 5.4.1.2) and will be conducted based on the FAS.

5.4.2.2. Overall survival (OS)

Overall survival (OS) is defined in Section 4.1.2.2. OS will be summarized by group using descriptive statistics, including number and percentage of OS events, number and percentage of censored subjects, and summary by censoring reason.

The probabilities of OS will be estimated using the Kaplan-Meier method and the probability of OS vs. time curves will be plotted by group. Also, the probabilities at 12-, 24-, and 48-month of OS will be estimated along with the corresponding 95% CIs for each group. Refer to the corresponding part in Section 5.4.1.1 for the calculation method. The quartiles and medians (25%, 50%, and 75%) of OS in each group will be estimated using the Kaplan-Meier method, and the corresponding 95% CIs will be estimated using the Brookmeyer-Crowley method.

For inter-group comparison, a stratified log-rank test (considering randomization stratification factors) will be used to calculate the nominal *p*-value. A stratified Cox proportional hazards model (considering randomization stratification factors) will be used to estimate the hazard ratio (HR, treatment group vs. control group) and the corresponding 95% CI.

In addition, 1) log-rank test and 2) Cox proportional hazards model analysis (without considering stratification factors) will be repeated. The follow-up time (months) of the subjects will be summarized using descriptive statistics.

5.4.2.3. Objective response rate (ORR)

Objective response rate (ORR) is defined in Section 4.1.2.3.

The BOR will be summarized by group based on investigator and IRC assessments, respectively. The ORR of each group and the corresponding two-sided 95% CI (Clopper-Pearson) in the FAS will be calculated.

Based on the randomization stratification factors collected in randomization system, the Cochran-Mantel-Haenszel (CMH) method will be used to test the inter-group difference in the FAS, and the inter-group difference (treatment group vs. control group) and its two-sided 95% CI (Wald method) will be calculated. Refer to Appendix 1.1 for the key SAS codes for ORR analysis.

If response evaluation data of one subject are missing or unknown, then the subject is not evaluable (NE) and will be included in the denominator for percentage calculation.

In addition, the BOR assessment, tumor measurement methods, and other information will be listed.

5.4.2.4. Clinical benefit rate (CBR)

Clinical benefit rate (CBR) is defined in Section 4.1.2.4.

The analysis of secondary endpoint CBR also includes the investigator and IRC assessments as per RECIST v1.1. Based on the FAS, the analytical method is the same as that of ORR.

5.4.2.5. Duration of response (DoR)

Duration of response (DoR) is defined in Section 4.1.2.5.

Based on investigator and IRC assessments, for subjects with CR or PR in the FAS, the quartiles and medians (25%, 50%, and 75%) of DoR in each group will be estimated using the Kaplan-Meier method, and the corresponding 95% CIs will be estimated using the Brookmeyer-Crowley method. In addition, the number of subjects with objective response will be summarized and the persistence of objective response will be classified and summarized.

5.4.3. Exploratory analyses

Not applicable.

5.4.4. Subgroup analysis

In order to evaluate whether the efficacy of this study is consistent among various subgroups, based on the FAS, the unstratified Cox proportional hazards model will be used to estimate the hazard ratio (treatment group vs. control group) of investigator- and IRC-assessed PFS, respectively, of each subgroup and its 95% CI will be calculated. The forest plot will also be generated. The subgroups include:

- Prior neoadjuvant/adjuvant therapy (with or without trastuzumab);
- ER/PR status (positive or negative);
- Age (< 65 years old vs. ≥ 65 years old);
- Baseline ECOG PS (0 vs. 1);

- IHC test results for HER2 (2+/1+ vs. 3+);
- TFI (12 months ≤ X < 24 months vs. X ≥ 24 months)
- Presence of visceral metastasis (yes vs. no); lesion sites, except for lymph nodes, bone, bone marrow, pelvis, breast, skin, and soft tissues, on the target lesion and non-target lesion pages of the eCRF during the screening will be classified as visceral metastasis;
- Liver metastasis (yes vs. no); with liver ticked for the lesion site on the target lesion and non-target lesion pages of the eCRF during the screening period;
- Lung metastasis (yes vs. no); with lung ticked for the lesion site on the target lesion and non-target lesion pages of the eCRF during the screening period;
- Liver and lung metastases (yes vs. no); with liver and lung ticked for the lesion site on the target lesion and non-target lesion pages of the eCRF during the screening period;
- History of neoadjuvant/adjuvant therapy (yes vs. no).

Based on the FAS, the ORR for each subgroup will be estimated by randomized group based on the investigator assessment results, and the corresponding 95% CI will be calculated (based on Clopper-Pearson method).

5.4.5. Other analysis

In consistency analysis of investigator-assessed data versus IRC-assessed data, the discrepancy rate between investigator- and IRC-assessed PFS events will be presented.

5.5. Safety Analysis

All safety analyses will be conducted based on the SS by actual group.

5.5.1. Extent of exposure

Based on the SS, the extent of exposure of pyrotinib/placebo will be summarized using descriptive statistics, including duration of drug exposure (months), cumulative dose (mg), dose intensity (mg/day), and relative dose intensity (%).

Based on the SS, the number of trastuzumab treatment cycles will be summarized using descriptive statistics.

Based on the SS, the extent of exposure of docetaxel will be summarized using descriptive statistics, including number of treatment cycles, cumulative dose (mg), dose intensity (mg/3 weeks), and relative dose intensity (%).

Duration of exposure of pyrotinib/placebo (months) = (last dose date of pyrotinib/placebo - first dose date of pyrotinib/placebo + 1)/30.4375. Refer to Section 5.1.6.8 for imputation rules for last dose date of pyrotinib/placebo.

The number of trastuzumab and docetaxel treatment cycles: According to the protocol, trastuzumab and docetaxel will be given once per cycle, so the number of treatment cycles is that between the first dose date (see Section 5.1.5) and the last dose date (see Section 5.1.5) when the dose of drug is not 0.

Cumulative dose of pyrotinib/placebo and docetaxel (mg) = sum of actual administered dose.

Dose intensity of pyrotinib/placebo (mg/day) = cumulative dose of pyrotinib/placebo (mg) / planned duration of treatment (days). For pyrotinib/placebo, planned duration of treatment (days) = (last dose date of pyrotinib/placebo - first dose date of pyrotinib/placebo + 1).

Dose intensity of docetaxel (mg/3 weeks) = cumulative dose of docetaxel (mg)/(planned duration of treatment/21 days). For docetaxel, planned duration of treatment = (last dose date of docetaxel + 20 - first dose date of docetaxel + 1).

Relative dose intensity of pyrotinib (%) = 100 × [dose intensity of pyrotinib (mg/day)/ 400 (mg/day)].

Relative dose intensity of docetaxel (%) = 100 × [dose intensity of docetaxel (mg/3 weeks)/ 75 (mg/m^2/3 weeks)/baseline body surface area (m^2)].

In addition, the number of subjects with dose reduction of pyrotinib, the number of subjects and events with dose interruption, the number of subjects and events with dose interruption of trastuzumab and drug holidays, the number of subjects and events with dose modification of docetaxel, the number of subjects and events with dose interruption and drug holidays will be summarized using descriptive statistics.

Study drug exposure will be listed, including the start and end dates of study treatment, duration of exposure, and number of treatment cycles. Study drug interruption and dose modification will also be listed, including details of dose interruptions/modifications and start and end dates of interruptions/modifications.

5.5.2. Adverse events

AEs (defined in Section 4.2.1) will be summarized by actual group using frequency and percentage, including:

- All TEAEs (overview, summarized by SOC and PT, summarized by SOC, PT, and CTCAE grade)
- All TRAEs (overview, summarized by SOC and PT, summarized by SOC, PT, and CTCAE grade)
- All treatment-emergent SAEs (summarized by SOC and PT)
- All treatment-emergent treatment-related SAEs (summarized by SOC and PT)

- CTCAE Grade ≥ 3 TEAEs
- CTCAE Grade ≥ 3 TRAEs
- TEAEs with an incidence of ≥ 10%
- TRAEs with an incidence of ≥ 10%
- TEAEs leading to discontinuation of any study drug
- TRAEs leading to discontinuation of any study drug
- TEAEs leading to treatment discontinuation, dose reduction, and dose interruption of study drugs
- TRAEs leading to treatment discontinuation, dose reduction, and dose interruption of study drugs
- TEAEs leading to death
- TRAEs leading to death

For the same system organ class (SOC) and/or preferred term (PT), multiple occurrences of the same event in one subject will be counted only once. For the same AE (same SOC and PT) reported in one subject multiple times but varying in CTCAE grade, the worst grade will be counted. The incidence of an AE will be calculated based on the number of subjects experiencing the AE, instead of the number of AE episodes.

AEs will be ordered by descending incidence of SOC (treatment group), and by descending incidence of PT within each SOC (treatment group). If the incidence of ≥ 2 PTs is equal, the AEs will be ordered alphabetically. If there is no AE under a SOC or PT, the analysis will not be conducted.

For treatment-emergent AESIs, if "Yes" is ticked for the question "AESI or Not" on the AE page of the eCRF, the number and percentage of subjects will be summarized by SOC, PT, and CTCAE grade. In addition, TEAEs with PTs coded as potential drug-induced liver injury, diarrhea, neutrophil count decreased, and white blood cell count decreased according to MedDRA V24.0 will be summarized using descriptive statistics. The number and percentage of subjects with potential drug-induced liver injury will be summarized by PT and CTCAE grade. Diarrhea, neutrophil count decreased, and white blood cell count decreased will be summarized and analyzed by groups. If applicable, the number and percentage of subjects with at least one selected AE will be summarized. If applicable, the time to the first onset of event (days), duration of a event (days), cumulative duration of event (days), number of events will be summarized using mean, standard deviation, median, maximum, minimum, and quartiles (Q_1 and

Q_3). The number and percentage of subjects will be summarized by CTCAE grade and action taken for the study drugs, respectively.

Time to the first onset of event (days) = date of first onset of event - date of first dose + 1;

Duration of a event (days) = end date of event - onset date of event + 1;

Cumulative duration of event (days) = latest end date of event - earliest onset date of event + 1 - number of event-free days during the period.

The number and percentage of subjects with the highest CTCAE grade will be summarized by cycle. The definition of cycle is as follows:

In the combined administration of pyrotinib/placebo, trastuzumab, and docetaxel, the cycle is defined according to the cycle of intravenous administration. Specifically, the start date of the cycle is the earlier date of either the docetaxel dose date or trastuzumab dose date in the same cycle, and the end date is the earlier date of either docetaxel dose date or trastuzumab dose date in the next cycle - 1 day. If pyrotinib/placebo is used alone, that is, docetaxel and trastuzumab are permanently discontinued but the administration of pyrotinib/placebo is continued, then for three-agent combination stage, the end date of the last cycle is the start date of this cycle + 20 days, and subsequent cycles are calculated in a fixed period of 21 days.

See Section 5.1.6.2 and Section 5.1.6.3 for imputation rules for missing onset and resolve dates of AEs.

All AEs (including but not limited to causality with study drugs, leading to withdrawal from study, and action taken for study drugs), SAEs, death, etc. will be listed.

5.5.3. Laboratory evaluations

If applicable, the laboratory test results and their changes from baseline will be summarized by visits. Shift tables will be provided, summarizing changes from baseline to post-baseline in terms of clinical significance of various test items (normal/abnormal without clinical significance/abnormal with clinical significance, using the worst post-baseline result, including unscheduled visit examinations). All laboratory evaluations will be listed by subject ID, with the clinical significance indicated (with or without).

5.5.4. Vital signs

The results and their changes from baseline will be summarized by visits.

In addition, a detailed listing of vital signs will also be provided. The listing will include at least name of visit, date of measurement, various vital sign measurements, etc.

5.5.5. 12-Lead ECG

The results obtained at various time points and their changes from baseline will be summarized by visits.

Shift tables will be provided, summarizing changes from baseline to post-baseline in terms of worst clinical significance (including unscheduled visit examinations). Clinical significance includes normal, abnormal without clinical significance, and abnormal with clinical significance.

For the maximum post-baseline QTcF interval, the number and percentage of subjects will be summarized according to Appendix 1.2.

A detailed listing of 12-Lead ECG results will be provided.

5.5.6. ECOG PS

The highest ECOG PS at baseline and post-baseline will be summarized. All ECOG PS will be reported in the form of listing.

5.5.7. Physical examination

Data of physical examination will be listed.

5.5.8. Other safety measures

For left ventricular ejection fraction (LVEF), the results at each time point and their changes from baseline will be summarized by visits. For echocardiography, shift tables will be provided, summarizing changes from baseline to post-baseline in terms of worst clinical significance (including unscheduled visit examinations). The decrease of LVEF from baseline will be summarized according to Appendix 1.3. Echocardiography results will be listed.

5.6. Exploratory Analysis

5.6.1. Immunogenicity

Not applicable.

5.6.2. Quality of life index

Not applicable.

5.6.3. Biomarker

Not applicable.

5.7. Pharmacokinetics and Pharmacodynamics

PK analysis will be performed based on the subjects with at least one evaluable PK concentration data in the SS.

The plasma concentration of pyrotinib will be summarized by scheduled blood sampling time points using descriptive statistics (N, arithmetic mean, standard deviation, coefficient of variation, geometric mean, geometric coefficient of variation, median, minimum, maximum, etc.). The plasma concentration of pyrotinib at each blood sampling time point will be listed.

There are no pharmacodynamic data in this study.

6. INTERIM ANALYSIS

According to the protocol, an interim efficacy analysis is planned for the primary endpoint investigator-assessed PFS and the interim analysis will be conducted when 67% of PFS events (about 275 events) are collected. The Lan-DeMets (O'Brien-Fleming) α spending function will be used in the interim analysis to control the overall type I error rate to not exceed 0.025 (one-sided), and the superiority boundaries determined by the O'Brien-Fleming method are as follows:

Table 2. Boundaries and nominal significance levels for the planned interim and final analyses of PFS

Analysis Time Point	Number of PFS Events	Boundary Z-Value (Corresponding HR)	One-Sided Nominal Significance Level
Interim	275 (67%)	-2.500 (HR=0.74)	0.0062
Final	410	-1.994(HR=0.82)	0.0231

Note: HR = Hazard ratio; PFS = Progression-free survival.

The boundaries will be adjusted according to the specific number of events in the interim analysis and the Lan-DeMets (O'Brien Fleming) α spending function. The interim analysis will allow the study to be terminated early due to superior results. The unblinded interim analysis will be completed by independent statisticians and their programming team. The results of the unblinded interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study based on the results.

The actual interim analysis is planned to be based on the data collected until 25 May, 2022. It is estimated that as of 25 May, 2022 when the data screenshot is taken, 277 PFS events (investigator-assessed) will actually be collected, accounting for about 67.6% of the prespecified total number of events. Based on the 277 events, the efficacy of the treatment group will be judged superior to that of the control group if a one-sided p value of ≤ 0.0064 is obtained from the stratified log-rank test.

7. REFERENCES

[1]. Jennison, C., and Turnbull, B. W. (2000). Group Sequential Methods with Applications to Clinical Trials. New York: Chapman & Hall.

[2]. Public Workshop: Oncology Clinical Trials in the presence of non-proportional hazards. 2018. https://healthpolicy.duke.edu/sites/default/files/atoms/files/oncology_trials_workshop_meeting_summary_0.pdf.

[3]. Knezevic, A., and Patil, S. (2020). Combination weighted log-rank tests for survival analysis with non-proportional hazards. SAS Global Forum 2020.

8. APPENDICES

Appendix 1.1. Key SAS Code

SAS code for PFS analysis

Kaplan-Meier method and stratified log-rank test:

```
Proc lifetest data=dataset;
   Time aval*cnsr(1);
   Strata strata1 strata2/group=TREATMENT;
Run;
```

The stratified Cox proportional hazards model analysis method:

```
Proc phreg data=dataset;
   Class TREATMENT (ref='2');        /***1 = treatment group, 2 = control group*****/
   Model aval*cnsr(1)= TREATMENT/ties=discrete;
   Hazardratio TREATMENT /diff = ref;
   Strata strata1 strata2;
Run;
```

Calculation of the two-sided repeated confidence interval (RCI) of the hazard ratio of PFS between groups analyzed at the interim and final analyses using the Jennison & Turnbull method (1984, 1989):

```
/* Step1: using the stratified Cox proportional hazards model */
   proc phreg data=dataset;
     class TREATMENT (ref='2');      /***1 = treatment group, 2 = control group*****/
      model aval*cnsr(1)= TREATMENT /ties=discrete;
      strata strata1 strata2;
      ods output CensoredSummary=CesSum_Cox    parameterestimates=Parms_Cox;
   run;
```

```
data Parms_Cox;
    set Parms_Cox;
    if Parameter=upcase("TREATMENT");
        id=1;
    keep Parameter Estimate StdErr id;
run;

/* Step2: calculation of boundaries for interim analysis */
/*%let Total_event_plan=410; *prespecified number of events for final analysis in the protocol;*/
/*%let IA_event_actual =XXX; *actual number of collected events for interim analysis;*/
/*%let alpha=0.025;*one-sided;*/
data quantile_alphaIA;
   fra=&IA_event_actual/&Total_event_plan;
   qnorm_alpha=probit(1-&alpha/2)/sqrt(fra);
   alphaIA=2-2*cdf("Normal",qnorm_alpha);
   Q_alphaIA=probit(1-alphaIA);
   id=1;
run;

/*Step 3: calculation of RCI of hazard ratio for interim analysis */
data RCI;
   merge Parms_Cox quantile_alphaIA;
   by id;
   HREstimate=exp(Estimate);
   lower_bound=exp(Estimate-Q_alphaIA*StdErr);
   upper_bound=exp(Estimate+Q_alphaIA*StdErr);
   keep Parameter HREstimate lower_bound upper_bound;
run;
```

SAS code for ORR analysis

Calculation of rate of difference in ORR and 95% CI:

```
Proc freq data= dataset;
   Tables TREATMENT*aval / riskdiff (method = wald);
Run;
```

Stratified CMH test for ORR difference between groups:

```
Proc freq data=dataset;
   Tables strata1* strata2* TREATMENT*aval/CMH;
Run;
```

strata1: prior neoadjuvant/adjuvant therapy: with or without trastuzumab, strata2: ER/PR status: positive or negative.

TREATMENT refers to the study group, 1: treatment group, 2: control group.

1: censored; 0: event.

Appendix 1.2. Statistical Rules for the Maximum QTcF Interval after Baseline

QTcF (ms)	450 ≤ maximum QTcF interval ≤ 480
	480 < maximum QTcF interval ≤ 500
	Maximum QTcF interval > 500
	Maximum QTcF interval ≥ 480 or increase > 60 from baseline

Appendix 1.3. Summary of Decrease of LVEF

Decrease	**Pyrotinib Combined with Trastuzumab and Docetaxel (N = xxx)**	**Placebo Combined with Trastuzumab and Docetaxel (N = xxx)**
Decrease from baseline by < 10% or value ≥ 50%, n (%)		
Decrease from baseline by ≥ 10%, n (%)		
Value < 50%, n (%)		
Decrease from baseline by ≥ 10% and value < 50%, n (%)		
Time (days) of first occurrence of decrease from baseline by ≥ 10% and value < 50%		
Number of subjects		
Median		
Q1, Q3		
Min, Max		
Time (days) of subsequent recovery* of decrease from baseline by ≥ 10% and value < 50%		
Number of subjects (Recovered)		
Median		
Q1, Q3		
Min, Max		

N is the number of subjects in each group. The percentage is calculated using N as the denominator and only when the numerator is not 0. n is the number of subjects in a particular category.

*Recovery is defined as the first occurrence of LVEF ≥ 50% in subsequent assessments.