Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first line treatment in patients with HER2 positive metastatic breast cancer (PHILA): randomised, double blind, multicentre, phase 3 trial

Fei Ma,[1] Min Yan,[2] Wei Li,[3] Quchang Ouyang,[4] Zhongsheng Tong,[5] Yuee Teng,[6] Yongsheng Wang,[7] Shusen Wang,[8] Cuizhi Geng,[9] Ting Luo,[10] Jincai Zhong,[11] Qingyuan Zhang,[12] Qiang Liu,[13] Xiaohua Zeng,[14] Tao Sun,[15] Qinguo Mo,[16] Hu Liu,[17] Ying Cheng,[18] Jing Cheng,[19] Xiaojia Wang,[20] Jianyun Nie,[21] Jin Yang,[22] Xinhong Wu,[23] Xinshuai Wang,[24] Huiping Li,[25] Changsheng Ye,[26] Fangli Dong,[27] Shuchao Wu,[27] Xiaoyu Zhu,[27] Binghe Xu,[1] on behalf of the PHILA Investigators

For numbered affiliations see end of the article

Correspondence to: B Xu
xubinghe@medmail.com.cn
(ORCID 0000-0003-4195-337X)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;383:e076065
http://dx.doi.org/10.1136/bmj-2023-076065

Accepted: 28 September 2023

ABSTRACT

OBJECTIVE

To assess the efficacy and safety of pyrotinib (an irreversible pan-HER (human epidermal growth factor receptor) inhibitor), trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel for untreated HER2 positive metastatic breast cancer.

DESIGN

Randomised, double blind, placebo controlled, multicentre, phase 3 trial.

SETTING

40 centres in China between 6 May 2019 and 17 January 2022.

PARTICIPANTS

590 female patients (median age 52 (interquartile range 46-58) years) with untreated HER2 positive metastatic breast cancer.

INTERVENTIONS

Eligible patients were randomised 1:1 to receive either oral pyrotinib (400 mg once daily) or placebo, both combined with intravenous trastuzumab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles) and docetaxel (75 mg/m^2) on day 1 of each 21 day cycle. Randomisation was stratified by treatment history of trastuzumab in the (neo)adjuvant setting and hormone receptor status. Patients, investigators, and the sponsor's study team were masked to treatment assignment.

MAIN OUTCOME MEASURES

The primary endpoint was progression-free survival as assessed by the investigator.

RESULTS

Of the 590 randomised patients, 297 received pyrotinib, trastuzumab, and docetaxel treatment (pyrotinib group), and 293 received placebo, trastuzumab, and docetaxel treatment (placebo group). At data cut-off on 25 May 2022, the median follow-up was 15.5 months. The median progression-free survival according to the investigator was significantly longer in the pyrotinib group than in the placebo group (24.3 (95% confidence interval 19.1 to 33.0) months versus 10.4 (9.3 to 12.3) months; hazard ratio 0.41 (95% confidence interval 0.32 to 0.53); one sided P<0.001). Treatment related adverse events of grade 3 or higher were reported in 267 (90%) of the 297 patients in the pyrotinib group and 224 (76%) of the 293 patients in the placebo group. No treatment related deaths occurred in the pyrotinib group, and one (<1%; diabetic hyperosmolar coma) treatment related death occurred in the placebo group. Survival and toxicities are still under assessment with longer follow-up.

CONCLUSIONS

Pyrotinib, trastuzumab, and docetaxel showed superiority by significantly improving progression-free survival compared with placebo, trastuzumab, and docetaxel in patients with untreated HER2 positive metastatic breast cancer. The toxicity was manageable. The findings support this dual anti-HER2 regimen as an alternative first line treatment option in this patient population.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03863223.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of dual anti-HER2 components with complementary mechanisms of action can provide more comprehensive blockade of HER2 signalling than either agent alone

The standard of care for untreated patients with HER2 positive metastatic breast cancer is pertuzumab plus trastuzumab and docetaxel

Pyrotinib has shown promising antitumor activity and a manageable safety profile in HER2 positive metastatic breast cancer

WHAT THIS STUDY ADDS

Pyrotinib with trastuzumab, and docetaxel represents a novel first line therapy for patients with HER2 positive metastatic breast cancer

Pyrotinib plus trastuzumab and docetaxel significantly improved progression-free survival versus placebo with trastuzumab and docetaxel

This study is the first to show the progression-free survival benefits of dual HER2 inhibition using a monoclonal antibody and a small molecule tyrosine kinase inhibitor in this setting

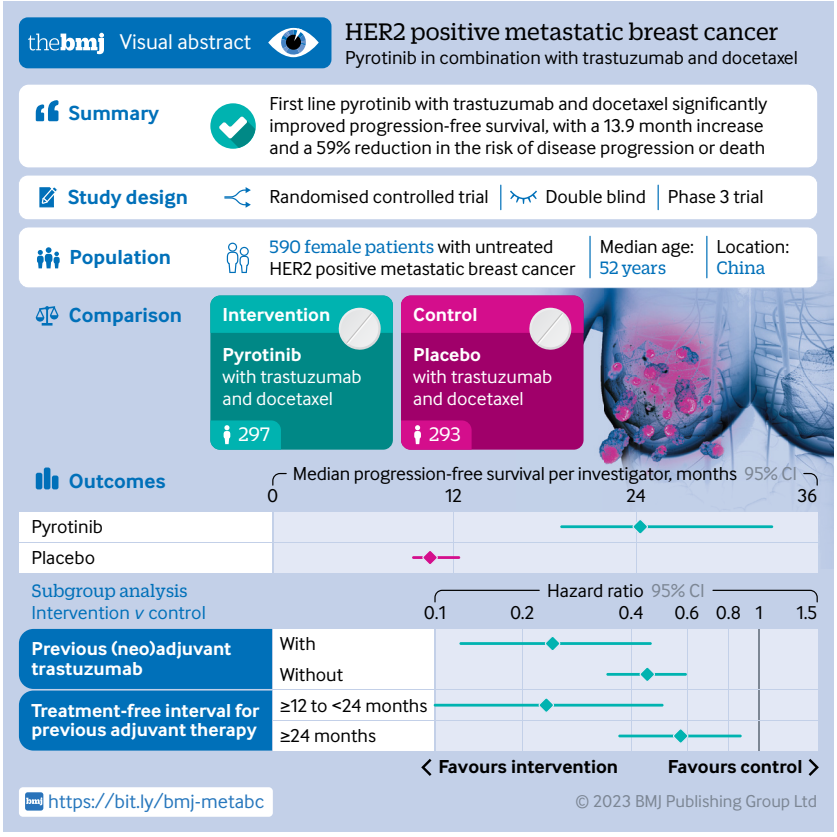
Introduction

Over-expression or gene amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of all breast cancers, and the HER2 positive phenotype is associated with a more aggressive disease and an unfavourable prognosis.[1 2]

The development of multiple anti-HER2 agents with various mechanisms of action has significantly improved the clinical outcomes of patients with HER2 positive breast cancer.

Clinical evidence has shown that the use of dual anti-HER2 components directed at HER2 with complementary mechanisms of action can provide a more comprehensive blockade of HER2 signalling than the use of either agent alone.[3-7] In the first line setting of patients with HER2 positive metastatic breast cancer, the CLEOPATRA study showed that the combination of two anti-HER2 monoclonal antibodies that bind at different extracellular subdomains of HER2, pertuzumab and trastuzumab, with docetaxel led to significantly longer median progression-free survival (hazard ratio 0.69) and overall survival (hazard ratio 0.69) than trastuzumab and docetaxel alone.[5 8-11] This pertuzumab based therapy is now the standard of care for this population.

Pyrotinib is a small molecule, irreversible, pan-HER receptor tyrosine kinase inhibitor that targets epidermal growth factor receptor and HER2, as well as HER4.[12] The irreversible nature of pyrotinib may sustain its inhibition of HER signalling and facilitate the maintenance of its anti-tumour activity over the reversible epidermal growth factor receptor/HER2 targeted tyrosine kinase inhibitors.[12] Pyrotinib, as monotherapy and in combination with capecitabine, has shown promising anti-tumour activity and manageable safety profiles in HER2 positive metastatic breast cancer.[13-19] Pyrotinib plus capecitabine has been approved for clinical use as a second line treatment for HER2 positive metastatic breast cancer in China. In this context, we did the phase 3 PHILA study to assess the efficacy and safety of the dual anti-HER2 components of pyrotinib, trastuzumab, and docetaxel, compared with placebo, trastuzumab, and docetaxel, as first line treatment for patients with HER2 positive metastatic breast cancer.



Methods

Patients and trial oversight

The PHILA study was a randomised, double blind, multicentre, phase 3 trial conducted at 40 centres in China. Eligible patients were biological females aged 18 to 75 years, had histologically confirmed HER2 positive (immunohistochemistry 3+ or in situ hybridisation positive) recurrent or metastatic breast cancer, were naive to systemic anti-tumour treatment for recurrent or metastatic disease, had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had adequate organ function. We excluded patients with a history of anti-HER2 treatment (other than trastuzumab in the (neo) adjuvant setting), a disease-free interval of less than 12 months from the completion of the (neo)adjuvant treatment, central nervous system metastases, or other malignancies.

Randomisation and interventions

We randomly assigned patients (1:1) to receive either oral pyrotinib (400 mg once daily) or a placebo, combined with intravenous trastuzumab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles) and docetaxel (75 mg/m^2) on day 1 of each 21 day cycle. Treatment was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or investigator's decision. We recommended that patients receive at least six cycles of docetaxel. Loperamide hydrochloride (up to 16 mg/day) was allowed for secondary prevention of and intervention for diarrhoea during the treatment period of pyrotinib or placebo.

We used a centralised interactive web response system for randomisation. The stratification factors were treatment history of trastuzumab in the (neo) adjuvant setting (yes versus no) and hormone receptor status (oestrogen receptor and/or progesterone receptor positive versus oestrogen receptor and progesterone receptor negative). Treatment assignments were masked for patients, investigators, and sponsor. Dose reductions stepwise from 400 mg to 320 mg to 240 mg of pyrotinib were permitted to manage toxicities. A dose reduction of trastuzumab was allowed only when the decline in body weight was greater than 10%. The dose of docetaxel was permitted to be reduced to a minimum of 60 mg/m^2. Interruptions in treatment with pyrotinib/placebo, trastuzumab, or docetaxel were allowed, and detailed guidelines for dose interruption and modification are available in the protocol (web appendix 1).

Assessments

Tumour assessments by computed tomography or magnetic resonance imaging were conducted at baseline, every nine weeks for the initial 18 months, and every 12 weeks thereafter. Treatment interruptions did not affect the protocol pre-specified time points of tumour imaging examination. Tumour responses were evaluated by both investigators and an independent review committee according to RECIST version 1.1. Laboratory assessments, 12 lead electrocardiographs, and monitoring of vital signs were conducted each cycle, and echocardiography was done every 12 weeks. Adverse events were assessed throughout treatment until 28 days after the last dose and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03.

Outcomes

The primary endpoint was progression-free survival (the time from randomisation to the first documented radiographic progression or to death due to any cause, whichever occurred first) as assessed by the investigator. The secondary endpoints were progression-free survival as assessed by the independent review committee, overall survival, objective response rate, duration of response, clinical benefit rate, and safety.

Statistical analysis

Assuming a median progression-free survival of 12.5 months with trastuzumab and docetaxel, 410 progression-free survival events would provide 80% power to detect a median progression-free survival of 16.5 months with the treatment of pyrotinib, trastuzumab, and docetaxel. This assumed a superiority of 4.0 months in median progression-free survival, a hazard ratio of 0.76 for progression or death, and a one sided significance level of 0.025. Considering a dropout rate of approximately 15%, we planned to enrol a total of 590 patients. We did a pre-specified interim analysis of progression-free survival when approximately 67% (275 events) of the expected events had occurred.

As of 25 May 2022, 277 progression-free survival events had occurred, accounting for 68% of the expected events. Based on the observed number of progressions or deaths, the threshold of the one sided α level for the interim analysis of progression-free survival was 0.0064, determined according to the Lan-DeMets (O'Brien-Fleming) α spending function. The independent data monitoring committee reported that the efficacy boundaries for progression-free survival had been crossed, which indicated that the difference in progression-free survival between the pyrotinib group and the control group had achieved statistical significance as predefined. Survival and toxicities are still under assessment with longer follow-up.

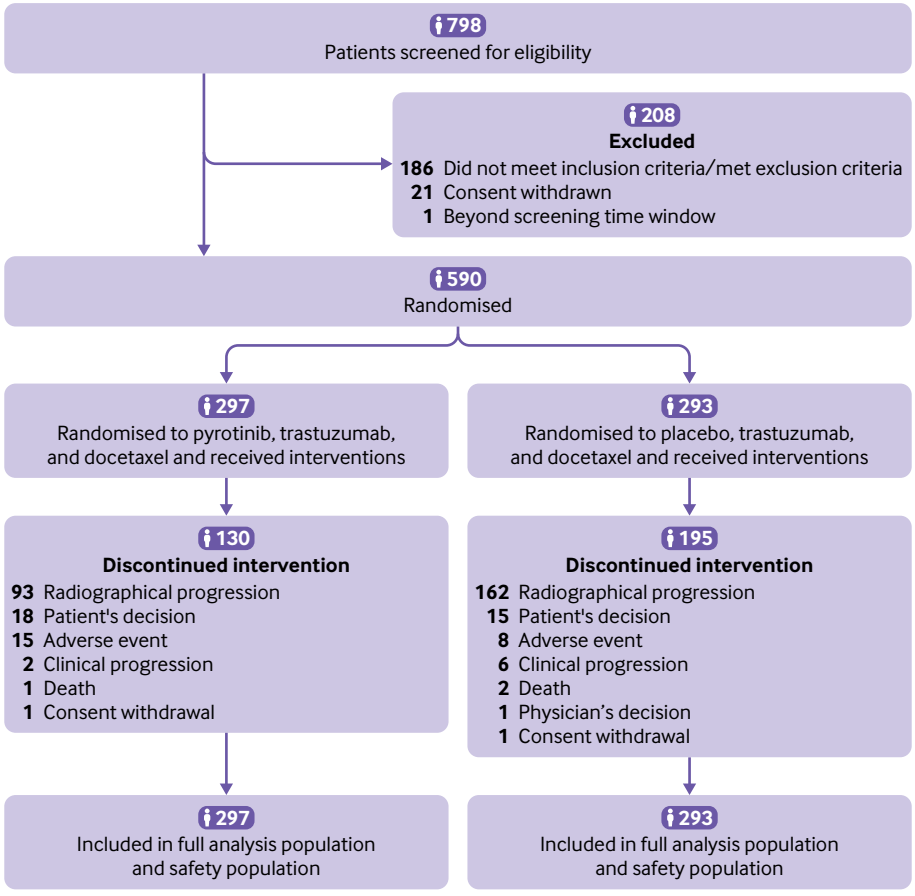


Fig 1 | Trial profile

Table 1 | Baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristics	Pyrotinib group (n=297)	Placebo group (n=293)
Age, years:		
Median (IQR)	52 (46-58)	52 (46-57)
<65	267 (90)	263 (90)
≥65	30 (10)	30 (10)
ECOG performance status:		
0	164 (55)	155 (53)
1	133 (45)	138 (47)
Visceral metastases:		
Yes	219 (74)	223 (76)
Liver	109 (37)	116 (40)
Lung	137 (46)	137 (47)
No	78 (26)	70 (24)
Hormone receptor status:		
ER positive, PR positive, or both	172 (58)	169 (58)
ER negative and PR negative	125 (42)	124 (42)
HER2 status (IHC)*:		
1+/2+	61 (21)	53 (18)
3+	236 (79)	240 (82)
HER2 status (FISH)*:		
Positive	95 (32)	91 (31)
Negative	2 (1)	0
Undetermined	200 (67)	202 (69)
Previous neoadjuvant or adjuvant systemic therapy:		
Yes	148 (50)	153 (52)
Endocrine therapy	80 (27)	86 (29)
Taxane	123 (41)	124 (42)
Anthracycline	122 (41)	129 (44)
Trastuzumab	46 (15)	42 (14)
No	149 (50)	140 (48)
Treatment-free interval with previous adjuvant therapy:		
≥12 to <24 months	30 (10)	38 (13)
≥24 months	99 (33)	100 (34)
Unknown†	168 (57)	155 (53)

ECOG=Eastern Cooperative Oncology Group; ER=oestrogen receptor; FISH=fluorescence in situ hybridisation; IHC=immunohistochemistry; IQR=interquartile range; PR=progesterone receptor.
*HER2 status was assessed at each site according to 2013 American Society of Clinical Oncology/College of American Pathologists guidelines.
†These patients had stage IV disease on initial diagnosis, so treatment-free interval data were unavailable.

We assessed treatment efficacy endpoints, including progression-free survival, overall survival, objective response rate, duration of response, and clinical benefit rate, in the full analysis set comprising all randomised patients. We assessed safety in a safety set that included all randomised patients who received at least one dose of study drugs. We used the Kaplan-Meier method to estimate time-to-event endpoints and the Brookmeyer-Crowley method to calculate their corresponding 95% confidence intervals.[20] We assessed between group differences in progression-free and overall survival by using a stratified log-rank test, and we used the stratified Cox proportional hazards model to calculate hazard ratios and corresponding 95% confidence intervals. We compared proportions of overall responses and clinical benefits between groups by using the Cochran-Mantel-Haenszel method with stratification factors and used the Wald method to estimate the 95% confidence interval. We did subgroup analysis for progression-free survival by using the unstratified Cox proportional hazards model. We used SAS, version 9.4 or above, for all statistical analyses.

Patient and public involvement

Participants were aware of the purpose and content of this trial during recruitment, although they were not involved in the initial design of the trial. Considering the confidentiality of clinical data, patients did not participate in the subsequent statistical analysis or writing of the manuscript. However, the results were communicated to patients who expressed an interest during clinic visits.

Results

Patients

Between 6 May 2019 and 17 January 2022, 798 patients from 40 study centres (supplementary table S1) were screened and 590 eligible patients were randomly assigned to study treatment, of whom 297 were assigned to the pyrotinib, trastuzumab, and docetaxel group (pyrotinib group) and 293 to the placebo, trastuzumab, and docetaxel group (placebo group). All patients received at least one dose of treatment and were included in the full analysis set and safety set (fig 1). The baseline characteristics of the two study groups were generally similar (table 1).

At the data cut-off for this interim analysis, the median follow-up was 15.5 months overall—15.8 (interquartile range 10.3-22.8) months in the pyrotinib group and 14.9 (9.7-22.5) months in the placebo group. A total of 167 (56%) patients in the pyrotinib group and 98 (33%) patients in the placebo group remained in treatment. The primary reason for treatment discontinuation in both groups was radiological progression (93 (31%) and 162 (55%) in the pyrotinib and placebo groups, respectively).

Efficacy

Disease progressions or deaths (assessed by the investigator) were reported in 99 (33%) of the 297 patients in the pyrotinib group and 178 (61%) of 293 patients in the placebo group. Pyrotinib, trastuzumab, and docetaxel significantly improved progression-free survival in comparison with placebo, trastuzumab, and docetaxel (24.3 (95% confidence interval 19.1 to 33.0) months versus 10.4 (9.3 to 12.3) months; hazard ratio 0.41 (95% confidence interval 0.32 to 0.53); stratified one sided P<0.001) (fig 2, top). The estimated progression-free survival rate at 12 months and 24 months was 74.3% (95% confidence interval 68.1% to 79.5%) and 50.3% (41.9% to 58.1%) in the pyrotinib group and 44.0% (37.5% to 50.3%) and 16.6% (10.7% to 23.7%) in the placebo group.

Results of subgroup analysis of progression-free survival were generally consistent with those for all patients (fig 3). Progression-free survival benefits with pyrotinib, trastuzumab, and docetaxel were apparent in patients with previous (neo)adjuvant trastuzumab (hazard ratio 0.23, 0.12 to 0.46; supplementary figure S1A), those without previous (neo)adjuvant trastuzumab (0.45, 0.34 to 0.59; supplementary figure S1B), those who had a treatment-free interval of ≥12 to <24 months for previous adjuvant therapy (0.22, 0.10 to 0.50; supplementary figure S2A), and those who had

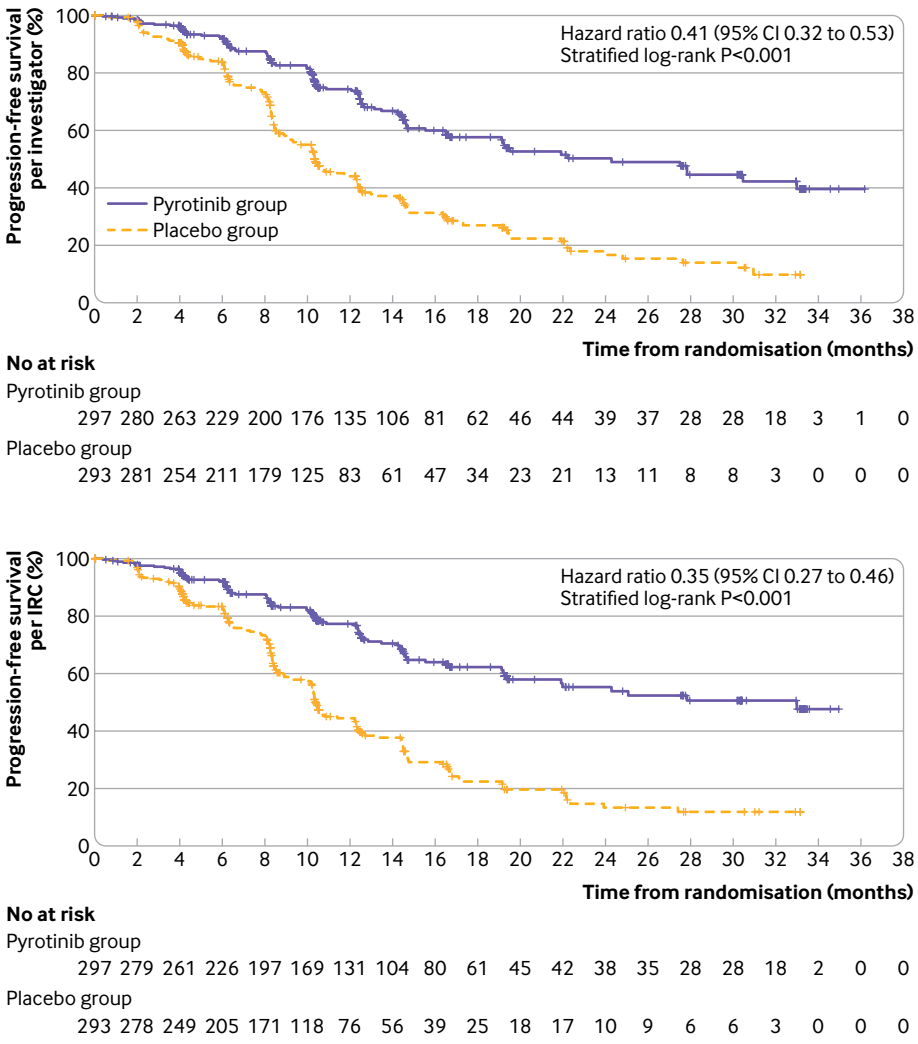


Fig 2 | Progression-free survival. Top: Kaplan-Meier curve of progression-free survival as assessed by investigator. Bottom: Kaplan-Meier curve of progression-free survival as assessed by independent review committee (IRC). Tick marks indicate censored individuals

a treatment-free interval of ≥24 months for previous adjuvant therapy (0.57, 0.37 to 0.87; supplementary figure S2B).

Objective responses were achieved in 246 (83%, 95% confidence interval 78% to 87%) of the 297 patients in the pyrotinib group and 207 (71%, 65% to 76%) of the 293 patients in the placebo group (difference 12.2%, 95% confidence interval 5.4% to 18.9%; stratified one sided P<0.001) (table 2). The proportion of patients with clinical benefits was 87% (259/297; 83% to 91%) in the pyrotinib group and 80% (233/293; 74% to 84%) in the placebo group. The median duration of response was 25.9 (95% confidence interval 17.3 to not reached) months in the pyrotinib group and 9.5 (8.3 to 10.6) months in the placebo group.

The efficacy results assessed by the independent review committee were generally consistent with the findings assessed by the investigator. Independent review committee assessed progression-free survival showed consistent improvement with pyrotinib, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel (33.0 (19.4 to not reached) months versus 10.4 (10.2 to 12.2) months; hazard ratio 0.35 (0.27 to 0.46); one sided P<0.001) (fig 2, bottom). The proportion of patients who achieved objective responses was 88% (262/297; 84% to 92%) in the pyrotinib group and 73% (213/293; 67% to 78%) in the placebo group (difference 15.5%, 9.2% to 21.8%; stratified one sided P<0.001) (table 2). The clinical benefit rate in each group was 89% (263/297; 84% to 92%) and 82% (239/293; 77% to 86%), respectively. The median duration of response was not reached (20.0 months to not reached) in the pyrotinib group and 10.3 (8.3 to 12.3) months in the placebo group.

Only 30 (10%) of the 297 patients in the pyrotinib group and 31 (11%) of the 293 patients in the placebo group died. The median overall survival data in both groups were immature.

Safety

The median duration of exposure to pyrotinib and placebo was 11.1 (interquartile range 6.2-16.9) months and 8.6 (5.6-12.7) months, respectively. The median number of treatment cycles of trastuzumab was 15.0 (interquartile range 9.0-24.0) and 12.0 (8.0-18.0) in each group, and the median number for docetaxel

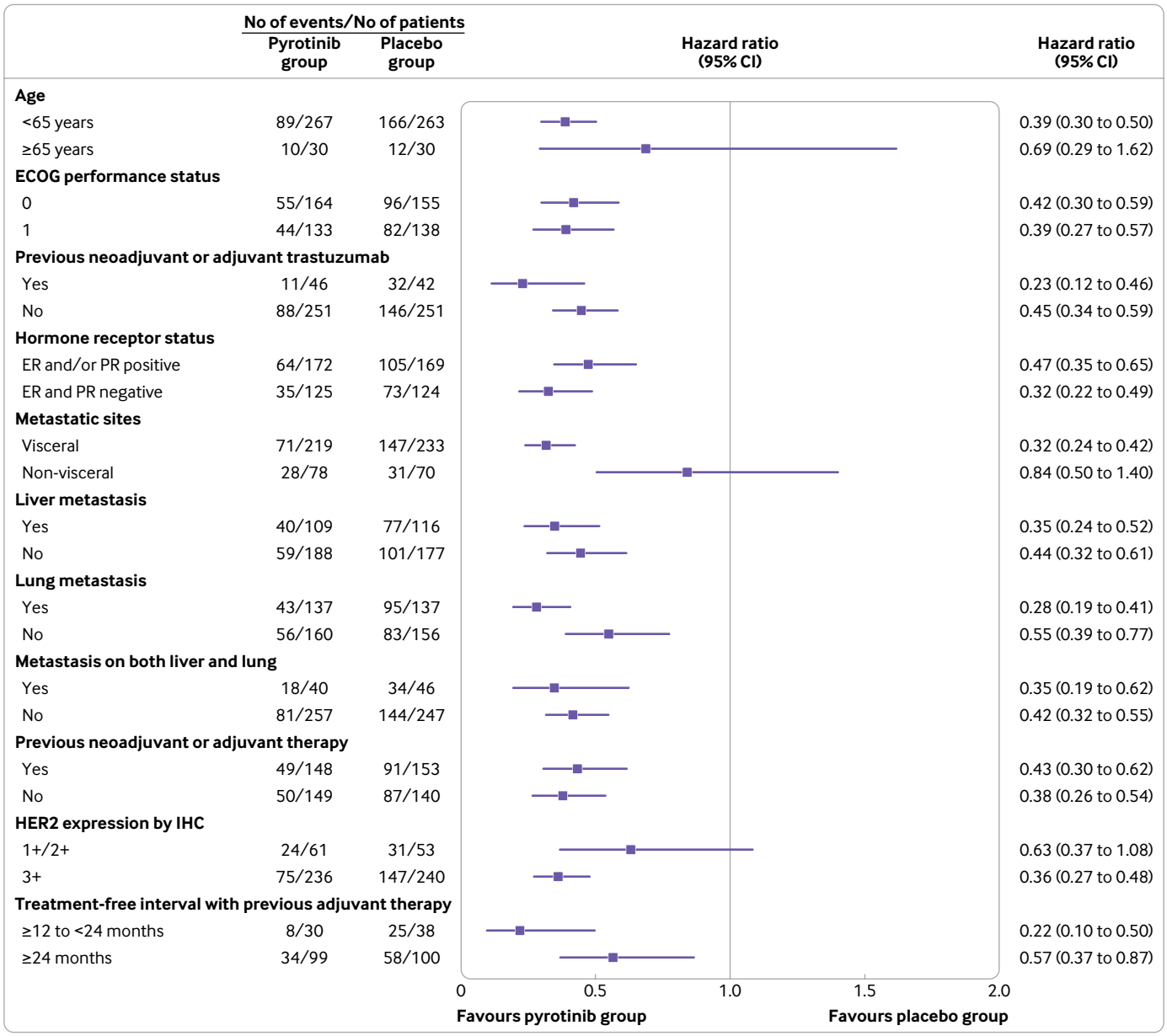


Fig 3 | Subgroup analyses of progression-free survival. Forest plot shows progression-free survival as assessed by investigator. Hazard ratios are from unstratified analyses. ECOG=Eastern Cooperative Oncology Group; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PR=progesterone receptor

was 8.0 (6.0-9.0) and 8.0 (6.0-10.0), respectively. The duration of treatment interruption for each treatment component is presented in supplementary table S2.

The overall incidence of treatment related adverse events was 100% (297/297) in patients in the pyrotinib group and 100% (292/293) in patients in the placebo group (table 3). Grade 3 or above treatment related adverse events were reported in 267 (90%) of the 297 patients in the pyrotinib group and 224 (76%) of the 293 patients in the placebo group, with decreased neutrophil count (63% *v* 65%), decreased white blood cell count (53% *v* 51%), and diarrhoea (46% *v* 3%) being the most frequently reported adverse events. A total of 74 (25%) patients in the pyrotinib group and 18 (6%) patients in the placebo group had treatment related serious adverse events; those with a frequency of ≥3% were diarrhoea (5% *v* 0), increased alanine aminotransferase (3% *v* <1%), and febrile neutropenia (3% *v* 2%) (supplementary table S3).

Treatment related adverse events leading to a dose reduction of any treatment component were reported in 77 (26%) of the 297 patients in the pyrotinib group and 9 (3%) of the 293 patients in the placebo group. Treatment interruptions of any treatment component owing to treatment related toxicities occurred in 168 (57%) and 71 (24%) in the two study groups, respectively. Thirty nine (13%) patients in the pyrotinib group and 21 (7%) patients in the placebo group discontinued treatment with any component as a result of treatment related adverse events (supplementary table S4). No treatment related deaths occurred in the pyrotinib group, and one (<1%; diabetic hyperosmolar

Table 2 | Tumour responses. Values are numbers (percentages) unless stated otherwise

	Investigator assessed		IRC assessed	
Response	Pyrotinib group (n=297)	Placebo group (n=293)	Pyrotinib group (n=297)	Placebo group (n=293)
Best overall response*:				
Complete response	19 (6)	8 (3)	13 (4)	6 (2)
Partial response	227 (76)	199 (68)	249 (84)	207 (71)
Stable disease	31 (10)	63 (22)	15 (5)	54 (18)
Progression disease	8 (3)	16 (5)	7 (2)	18 (6)
Not assessable	12 (4)	7 (2)	13 (4)	8 (3)
Objective response—No (%, 95% CI)	246 (83%, 78% to 87%)	207 (71%, 65% to 76%)	262 (88%, 84% to 92%)	213 (73%, 67% to 78%)
Clinical benefit—No (%, 95% CI)	259 (87%, 83% to 91%)	233 (80%, 74% to 84%)	263 (89%, 84% to 92%)	239 (82%, 77% to 86%)
Median (95% CI) duration of response, months	25.9 (17.3 to NR)	9.5 (8.3 to 10.6)	NR (20.0 to NR)	10.3 (8.3 to 12.3)

CI=confidence interval; IRC=independent review committee; NR=not reached.
*Tumour responses were evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1.

coma) treatment related death occurred in the placebo group.

Supplementary table S5 summarises data on diarrhoea of any cause. Grade 3 diarrhoea occurred mainly during the first cycle of treatment (36% (107/297) in the pyrotinib group versus 1% (2/293) in the placebo group) and substantially decreased in cycle 2 (20% *v* 1%) and after that. No grade 4 or 5 diarrhoea occurred. The median time to the onset of grade 3 diarrhoea was 8 (interquartile range 6.0-15.0) days in the pyrotinib group and 71 (23.0-178.0) days in the placebo group. The median duration of grade 3 diarrhoea was 1.0 (1.0-1.0) day in both groups, and the median cumulative duration was 3.0 (2.0-6.0) days and 1.0 (1.0-2.0) days in each group, respectively. No patients discontinued study treatment owing to grade 3 diarrhoea in either group.

Discussion

Pyrotinib, trastuzumab, and docetaxel significantly prolonged progression-free survival compared with placebo, trastuzumab, and docetaxel in untreated patients with HER2 positive metastatic breast cancer (24.3 *v* 10.4 months; hazard ratio 0.41; stratified one sided P<0.001), which met the criteria for statistical significance in the pre-specified interim analysis of progression-free survival. The adverse events were manageable. To our knowledge, this is the first phase 3 study to show benefits in progression-free survival from dual HER2 inhibition with the use of a monoclonal antibody plus a small molecule tyrosine kinase inhibitor in the first line setting of HER2 positive metastatic breast cancer.

Comparison with other studies

The median progression-free survival with the current standard of care pertuzumab, trastuzumab, and docetaxel was 18.7 months.[8 10] In our PHILA study, the progression-free survival with pyrotinib, trastuzumab, and docetaxel, as assessed by the investigator (24.3 months) and the independent review committee (33.0 months), both exceeded two years, indicating

Table 3 | Treatment related adverse events. Values are numbers (percentages)

	Pyrotinib group (n=297)		Placebo group (n=293)	
Treatment related adverse events*	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Any	297 (100)	267 (90)	292 (100)	224 (76)
Diarrhoea	293 (99)	138 (46)	154 (53)	9 (3)
White blood cell count decreased	250 (84)	158 (53)	250 (85)	149 (51)
Neutrophil count decreased	233 (78)	186 (63)	246 (84)	191 (65)
Anaemia	225 (76)	26 (9)	140 (48)	7 (2)
Vomiting	187 (63)	25 (8)	43 (15)	4 (1)
Weight decreased	172 (58)	22 (7)	24 (8)	1 (<1)
Nausea	128 (43)	3 (1)	55 (19)	1 (<1)
Hypokalaemia	125 (42)	41 (14)	27 (9)	3 (1)
Aspartate aminotransferase increased	122 (41)	8 (3)	115 (39)	1 (<1)
Alanine aminotransferase increased	116 (39)	12 (4)	118 (40)	5 (2)
Alopecia	115 (39)	0	140 (48)	0
Blood creatinine increased	107 (36)	1 (<1)	14 (5)	0
Asthenia	96 (32)	2 (1)	75 (26)	1 (<1)
Decreased appetite	93 (31)	12 (4)	36 (12)	0
Hypoalbuminaemia	74 (25)	0	59 (20)	0
Hypertriglyceridaemia	68 (23)	7 (2)	86 (29)	6 (2)
Rash	51 (17)	1 (<1)	28 (10)	0
γ-glutamyltransferase increased	50 (17)	0	40 (14)	4 (1)
Hypocalcaemia	49 (16)	3 (1)	21 (7)	0
Hypercholesterolaemia	29 (10)	0	61 (21)	0

*Treatment related adverse events occurring in 15% or more of patients in either group are listed. Events are shown in descending order of frequency in pyrotinib group. Adverse events were classified according to Medical Dictionary for Regulatory Activities, version 24.0, and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

the promising dual HER2 inhibition activity with the use of an intracellular small molecule in combination with an extracellular antibody. Subgroup data showed a consistent trend towards progression-free survival benefits with pyrotinib, trastuzumab, and docetaxel therapy compared with placebo, trastuzumab, and docetaxel therapy in all analysed subgroups, including several subgroups associated with a high risk of progression or death, such as visceral metastasis, liver metastasis, lung metastasis, or metastasis in both the liver and lung.

In the CLEOPATRA study, the progression-free survival benefit of pertuzumab, trastuzumab, and docetaxel compared with trastuzumab and docetaxel was lower in patients who had received previous trastuzumab in a (neo)adjuvant setting (16.9 *v* 10.4 months; hazard ratio 0.62) than in those who had not received previous trastuzumab (21.6 *v* 12.6 months; hazard ratio 0.60).[5] However, in this PHILA study, greater progression-free survival benefit with pyrotinib, trastuzumab, and docetaxel was achieved in patients with previous (neo) adjuvant trastuzumab (not reached versus 9.3 months; hazard ratio 0.23) than in those without previous (neo) adjuvant trastuzumab (21.9 *v* 10.4 months; hazard ratio 0.45). The PANDORA trial of pyrotinib plus docetaxel in patients with untreated HER2 positive metastatic breast cancer showed a similar result to the PHILA study; that is, the median progression-free survival of patients with previous trastuzumab was longer than that of patients without previous trastuzumab (20.8 *v* 14.8 months).[21] In addition, previous retrospective studies showed that for patients who had developed drug resistance to monoclonal antibodies, subsequent treatment with small molecule tyrosine kinase inhibitor could provide better efficacy than continuing to be treated with antibodies.[6 7 22 23] These findings indicate that not only might the combination of monoclonal antibody and small molecule tyrosine kinase inhibitor, which have complementary mechanisms of action, be synergistic or additive but the intracellular small molecule tyrosine kinase inhibitor may also be able to overcome the secondary drug resistance caused by the deletion or mutation of extracellular monoclonal antibody binding sites.[23] Patients with previous trastuzumab history may develop drug resistance or may not be sensitive to trastuzumab; they may be the preferred subpopulation to use a combination of monoclonal antibody and small molecule tyrosine kinase inhibitor.[6 7 22 23] Further investigations are warranted to validate these data and explore the underlying mechanism of this combination strategy.

The safety profile in this study was generally consistent with the known adverse events of pyrotinib based therapies.[15 16 18] Diarrhoea was the most common adverse event with HER2 targeted drugs.[24] In this study, although the incidence of diarrhoea in the pyrotinib group was higher than that in the placebo group, most diarrhoea events were of grade 1 or 2. Grade 3 diarrhoea occurred mainly during the first cycle of treatment and decreased dramatically in the second cycle. No grade 4 or 5 diarrhoea occurred. Diarrhoea was generally manageable, and loperamide hydrochloride was recommended for secondary prevention and treatment of diarrhoea to alleviate symptoms.[25-27] The high frequency of grade 3 or higher treatment related adverse events was primarily due to the frequent occurrence of treatment related haematological adverse events in both groups, which were mainly attributed to docetaxel and masked the grade 3 adverse events caused by pyrotinib. The docetaxel induced haematological adverse events can be effectively managed through the use of leukopoietic agents. After discontinuation of docetaxel, the incidence of haematological toxicities in both groups markedly decreased.

Regarding the generalisability of the combination of pyrotinib, trastuzumab, and docetaxel to populations outside China, we propose that the efficacy of this combination therapy may generally remain consistent across different racial groups of patients with HER2 positive metastatic breast cancer, on the basis of several pieces of evidence. Firstly, the molecular characteristics of HER2 positive advanced breast cancer in the global population and the Chinese population show certain similarities in their genomic profiles.[28] Secondly, the efficacy and safety of various therapies for HER2 positive advanced breast cancer, including anti-HER2 antibodies (such as pertuzumab)[5 8-11] and small molecules (such as lapatinib[18 29] and neratinib[30 31]), are generally consistent between the global population and the Chinese population. Furthermore, the pharmacokinetic characteristics of pyrotinib were found to be consistent in Chinese and US participants (data on file, Hengrui). These pieces of evidence potentially support the extrapolation of the results from the PHILA study to other populations with HER2 positive metastatic breast cancer, but this hypothesis needs further validation in subsequent studies.

Limitations of study

This study has several limitations. Firstly, at the time of design of this study in 2018, pertuzumab, trastuzumab, and docetaxel had not been approved in the first line setting in China; therefore, the control group did not receive the pertuzumab-trastuzumab combination therapy. Secondly, only 15% of the patients used trastuzumab as adjuvant treatment, and none used pertuzumab in the adjuvant setting. Thirdly, the assessments of HER2 status were not centrally confirmed, as 40 study centres were involved in this trial. Fourthly, the overall survival data are immature and require further follow-up. However, US Food and Drug Administration guidelines and several studies support that progression-free survival can represent a direct clinical benefit and can serve as a primary endpoint for drug approval in advanced or metastatic breast cancer.[32-36]

Conclusions

Pyrotinib, trastuzumab, and docetaxel conferred a statistically significant improvement in progression-

free survival compared with placebo, trastuzumab, and docetaxel in women with HER2 positive metastatic breast cancer in the first line setting. This combination treatment was also associated with a manageable safety profile. The results of this study show that pyrotinib, trastuzumab, and docetaxel constitute a novel first line therapy for patients with untreated HER2 positive metastatic breast cancer, as well as an alternative strategy to the current treatment landscape in this patient population. Based on the data from this phase 3 PHILA study, the combination of pyrotinib with trastuzumab and docetaxel was granted approval by the China National Medical Products Administration as a first line treatment for HER2 positive advanced breast cancer in April 2023, and this marks the third approved indication for pyrotinib in China.

AUTHOR AFFILIATIONS

[1]Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

[3]Department of Oncology, The First Hospital of Jilin University, Changchun, China

[4]Breast Internal Medicine Department, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

[5]Department of Breast Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

[6]Department of Breast Internal Medicine, The First Hospital of China Medical University, Shenyang, China

[7]Breast Surgery, Shandong Cancer Hospital and Institute, Jinan, China

[8]Department of Internal Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

[9]Breast Center, The Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital, Shijiazhuang, China

[10]Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China

[11]Medical Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

[12]Ward One of Mammary Department, Harbin Medical University Cancer Hospital, Harbin, China

[13]Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

[14]Breast Cancer Center, Affiliated Cancer Hospital of Chongqing University, Chongqing, China

[15]Breast Internal Medicine Department, Liaoning Cancer Hospital & Institute, Shenyang, China

[16]Breast Surgery, Guangxi Medical University Affiliated Tumor Hospital, Nanning, China

[17]Department of Medical Oncology, The First Affiliated Hospital of USTC West District, Hefei, China

[18]Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, China

[19]Oncology Center Breast Department, Union Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

[20]Breast Medicine, Zhejiang Cancer Hospital, Hangzhou, China

[21]Breast Surgery, Yunnan Cancer Hospital, Kunming, China

[22]Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[23]Department of Breast Oncology, Hubei Cancer Hospital, Wuhan, China

[24]Department of Medical Oncology, Henan Key Laboratory of Cancer Epigenetics, Cancer Hospital, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang, China

[25]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Breast Oncology, Peking University Cancer Hospital and Institute, Beijing, China

[26]Department of Breast, Southern Medical University Nanfang Hospital, Guangzhou, China

[27]Jiangsu Hengrui Pharmaceuticals Co, Ltd, Shanghai, China

We thank the patients, their families, the investigators, the site staff, and the trial teams. We also thank Jiaman Lin (Hengrui) for doing the literature search and Kaijing Zhao (Hengrui) for providing pharmacokinetic data during the revision process. Medical writing assistance was provided by Tengfei Zhang (medical writer at Hengrui) according to Good Publication Practice Guidelines.

Contributors: BX and XZ contributed to the study design, supervision, and administrative, technical, or material support. All co-authors contributed to the acquisition, analysis, or interpretation of data. FD did the statistical analysis. BX and XZ drafted the manuscript. All authors contributed to revision of the manuscript and approved the final draft. FM and MY contributed equally to this work. BX is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by Jiangsu Hengrui Pharmaceuticals and partly supported by the CAMS Innovation Fund for Medical Sciences (CIFMS; 2021-I2M-1-014). This trial was designed by the authors in collaboration with Jiangsu Hengrui Pharmaceuticals. The authors and Jiangsu Hengrui Pharmaceuticals were involved in data collection, analysis, and interpretation and guaranteed the accuracy and completeness of the data, the writing of the report, and the decision to submit the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: BX has served as advisor or consultant for Novartis and Roche and as a speaker or a member of a speakers' bureau for AstraZeneca, Pfizer, Roche, and Eisai; JN has received research grants from Hengrui, Sanofi, Qilu, Junshi, Zhengdatianqing, Boan, Maiwei, Novartis, and Xuanzhu; FD, SW, and XZ are employed by Jiangsu Hengrui Pharmaceuticals; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the ethics committee of each study centre (supplementary table S1) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent.

Data sharing: Reasonable requests for data sharing should be made to the corresponding author and will be handled in line with the data access and sharing policy of the Human Genetic Resource Administration of China.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Participating sites were informed of the results. The results can be communicated to study participants who express an interest during clinic visits. Dissemination to the public will be achieved through media outreach.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-12. doi:10.1126/science.2470152

2 Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;14:320-68. doi:10.1634/theoncologist.2008-0230

3 Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25-32. doi:10.1016/S1470-2045(11)70336-9

4 Baselga J, Bradbury I, Eidtmann H, et al, NeoALTTO Study Team. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012;379:633-40. doi:10.1016/S0140-6736(11)61847-3
5 Baselga J, Cortés J, Kim SB, et al, CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366:109-19. doi:10.1056/NEJMoa1113216
6 Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol* 2012;30:2585-92. doi:10.1200/JCO.2011.35.6725
7 Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med* 2020;382:597-609. doi:10.1056/NEJMoa1914609
8 Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013;14:461-71. doi:10.1016/S1470-2045(13)70130-X
9 Swain SM, Baselga J, Kim SB, et al, CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-34. doi:10.1056/NEJMoa1413513
10 Swain SM, Miles D, Kim SB, et al, CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:519-30. doi:10.1016/S1470-2045(19)30863-0
11 Xu B, Li W, Zhang Q, et al. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (PUFFIN): a phase III, randomized, double-blind, placebo-controlled study. *Breast Cancer Res Treat* 2020;182:689-97. doi:10.1007/s10549-020-05728-w
12 Li X, Yang C, Wan H, et al. Discovery and development of pyrotinib: A novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor with favorable safety profiles for the treatment of breast cancer. *Eur J Pharm Sci* 2017;110:51-61. doi:10.1016/j.ejps.2017.01.021
13 Ma F, Li Q, Chen S, et al. Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *J Clin Oncol* 2017;35:3105-12. doi:10.1200/JCO.2016.69.6179
14 Gourd E. Pyrotinib shows activity in metastatic breast cancer. *Lancet Oncol* 2017;18:e643. doi:10.1016/S1470-2045(17)30755-6
15 Li Q, Guan X, Chen S, et al. Safety, Efficacy, and Biomarker Analysis of Pyrotinib in Combination with Capecitabine in HER2-Positive Metastatic Breast Cancer Patients: A Phase I Clinical Trial. *Clin Cancer Res* 2019;25:5212-20. doi:10.1158/1078-0432.CCR-18-4173
16 Ma F, Ouyang Q, Li W, et al. Pyrotinib or Lapatinib Combined With Capecitabine in HER2-Positive Metastatic Breast Cancer With Prior Taxanes, Anthracyclines, and/or Trastuzumab: A Randomized, Phase II Study. *J Clin Oncol* 2019;37:2610-9. doi:10.1200/JCO.19.00108
17 Gourd E. Pyrotinib versus lapatinib in HER2-positive breast cancer. *Lancet Oncol* 2019;20:e562. doi:10.1016/S1470-2045(19)30568-6
18 Xu B, Yan M, Ma F, et al, PHOEBE Investigators. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol* 2021;22:351-60. doi:10.1016/S1470-2045(20)30702-6
19 Blair HA. Pyrotinib: First Global Approval. *Drugs* 2018;78:1751-5. doi:10.1007/s40265-018-0997-0
20 Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. *Biometrics* 1982;38:29-41. doi:10.2307/2530286.
21 Wang X, Huang J. 239P Pyrotinib in combination with docetaxel as first-line treatment for HER2-positive metastatic breast cancer (PANDORA): A single-arm, multicenter phase II trial. *Ann Oncol* 2022;33:S646-7. doi:10.1016/j.annonc.2022.07.278.
22 Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010;28:1124-30. doi:10.1200/JCO.2008.21.4437
23 Wynn CS, Tang SC. Anti-HER2 therapy in metastatic breast cancer: many choices and future directions. *Cancer Metastasis Rev* 2022;41:193-209. doi:10.1007/s10555-022-10021-x
24 Li J. Diarrhea With HER2-Targeted Agents in Cancer Patients: A Systematic Review and Meta-Analysis. *J Clin Pharmacol* 2019;59:935-46. doi:10.1002/jcph.1382
25 Kruse ML, Kang IM, Bagegni NA, et al. Management of Diarrhea in Patients with HER2-Positive Breast Cancer Treated with Neratinib: A Case Series and Summary of the Literature. *Oncol Ther* 2022;10:279-89. doi:10.1007/s40487-021-00178-w
26 Swain SM, Schneeweiss A, Gianni L, et al. Incidence and management of diarrhea in patients with HER2-positive breast cancer treated with pertuzumab. *Ann Oncol* 2017;28:761-8. doi:10.1093/annonc/mdw695
27 Fang C, Wen J, Kang M, Zhang Y, Chen Q, Ren L. Incidence and management of pyrotinib-associated diarrhea in HER2-positive advanced breast cancer patients. *Ann Palliat Med* 2022;11:210-6. doi:10.21037/apm-21-3978
28 Zhang G, Wang Y, Chen B, et al. Characterization of frequently mutated cancer genes in Chinese breast tumors: a comparison of Chinese and TCGA cohorts. *Ann Transl Med* 2019;7:179. doi:10.21037/atm.2019.04.23
29 Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733-43. doi:10.1056/NEJMoa064320
30 Saura C, Oliveira M, Feng YH, et al, NALA Investigators. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol* 2020;38:3138-49. doi:10.1200/JCO.20.00147
31 Xu B, Kim S-B, Inoue K, et al. Abstract P5-21-17: Efficacy, safety and tolerability of neratinib-based therapy in patients from Asia with metastatic HER2+ breast cancer and other solid tumors: A pooled analysis of 6 clinical trials. *Cancer Res* 2018;78(4_Supplement):P5-21-17. doi:10.1158/1538-7445.SABCS17-P5-21-17.
32 Hurvitz SA. Evolving options for the treatment of metastatic breast cancer: progression-free survival as an endpoint. *Cancer Treat Rev* 2011;37:495-504. doi:10.1016/j.ctrv.2011.01.002
33 Hirai T, Nemoto A, Ito Y, Matsuura M. Meta-analyses on progression-free survival as a surrogate endpoint for overall survival in triple-negative breast cancer. *Breast Cancer Res Treat* 2020;181:189-98. doi:10.1007/s10549-020-05615-4
34 Kaklamani VG. Clinical Implications of the Progression-Free Survival Endpoint for Treatment of Hormone Receptor-Positive Advanced Breast Cancer. *Oncologist* 2016;21:922-30. doi:10.1634/theoncologist.2015-0366
35 Forsythe A, Chandiwana D, Barth J, et al. Is progression-free survival a more relevant endpoint than overall survival in first-line HR+/HER2- metastatic breast cancer?*Cancer Manag Res* 2018;10:1015-25. doi:10.2147/CMAR.S162714
36 Miksad RA, Zietemann V, Gothe R, et al. Progression-free survival as a surrogate endpoint in advanced breast cancer. *Int J Technol Assess Health Care* 2008;24:371-83. doi:10.1017/S0266462308080495

Web appendix: Protocol
Web appendix: Supplementary tables and figures