

Pyrotinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (PERSIST): A multicenter phase II trial

Reviewed Preprint

v1 • December 9, 2024

Not revised

Feilin Cao , Zhaosheng Ma, Zenggui Wu, Weizhu Wu, Ouchen Wang, Binbin Cui, Xiaotao Zhu, Jing Hao, Xiaochun Ji, Zhanwen Li, Deyou Tao, Qingjing Feng, Wei Lin, Dongbo Shi, Jingde Shu, Jichun Zhou, Shifen Huang

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China • Department of Thyroid and Breast Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo, China • Department of Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China • Department of Thyroid and Breast Surgery, Jinhua Municipal Central Hospital, Jinhua, China • Department of Thyroid and Breast Surgery, Yiwu Central Hospital, Jinhua, China • Department of Breast Surgery, Ningbo Women & Children's Hospital, Ningbo, China • Department of Breast Surgery, Yiwu Maternity and Children Hospital, Jinhua, China • Department of Surgical Oncology, Quzhou People's Hospital, Quzhou, China • Department of Breast Surgery, The First Affiliated Hospital of Ningbo University, Ningbo, China • Department of Surgical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

 https://en.wikipedia.org/wiki/Open_access

 Copyright information

eLife Assessment

This study provides **valuable** insights into the efficacy and safety of pyrotinib as an extended adjuvant therapy following trastuzumab-based treatment in patients with high-risk HER2-positive breast cancer. The strength of evidence is **solid**, supported by the multicenter phase II trial design, which included a substantial number of patients across 23 centers in China. However, the single-arm study design without a control group limits the ability to draw definitive conclusions about the comparative effectiveness of pyrotinib.

<https://doi.org/10.7554/eLife.101724.1.sa2>

Abstract

Background

Approximately one-third of patients with HER2-positive breast cancer experienced recurrence within 10 years after receiving 1 year of adjuvant trastuzumab. The ExteNET study showed that 1 year of extended adjuvant neratinib after trastuzumab-based adjuvant therapy could reduce invasive disease-free survival (iDFS) events compared with placebo. This study investigated the efficacy and safety of pyrotinib, an irreversible pan-HER receptor tyrosine kinase inhibitor, after trastuzumab-based adjuvant therapy in patients with high-risk, HER2-positive early or locally advanced breast cancer.

Methods

This multicenter phase II trial was conducted at 23 centers in China. After enrollment, patients received 1 year of extended adjuvant pyrotinib (400 mg/day), which should be initiated within 6 months after the completion of 1-year adjuvant therapy (trastuzumab alone or plus pertuzumab). The primary endpoint was 2-year iDFS rate.

Results

Between January 2019 and February 2022, 141 eligible women were enrolled and treated. As of October 10, 2022, the median follow-up was 24 (interquartile range, 18.0-34.0) months. The 2-year iDFS rate was 94.59% (95% CI: 88.97-97.38) in all patients, 94.90% (95% CI: 86.97-98.06) in patients who completed 1-year treatment, 90.32% (95% CI: 72.93-96.77) in patients who completed only 6-month treatment, 96.74% (95% CI: 87.57-99.18) in the hormone receptor-positive subgroup, 92.77% (95% CI: 83.48-96.93) in the hormone receptor-negative subgroup, 96.88% (95% CI: 79.82-99.55) in the lymph node-negative subgroup, 93.85% (95% CI: 86.81-97.20) in the lymph node-positive subgroup, 97.30% (95% CI: 82.32-99.61) in patients with adjuvant trastuzumab plus pertuzumab, and 93.48% (95% CI: 86.06-97.02) in patients with adjuvant trastuzumab. The most common adverse events were diarrhea (79.4%), fatigue (36.9%), lymphocyte count decreased (36.9%), nausea (33.3%), and hand-foot syndrome (33.3%).

Conclusion

Extended adjuvant pyrotinib administrated after trastuzumab-based adjuvant therapy showed promising efficacy in patients with high-risk HER2-positive breast cancer. The follow-up is ongoing to determine the long-term benefit.

Background

Worldwide, breast cancer is the most commonly diagnosed malignancy in women. Approximately 15-20% of breast cancer cases are characterized by the overexpression of human epidermal growth factor receptor 2 (HER2) (1, 2). Over the past 20 years, with the emergence of HER2-targeted agents, it has been proved that the addition of 1-year trastuzumab to adjuvant chemotherapy significantly reduces the recurrence rate and prolongs survival in patients with HER2-positive breast cancer (3-5). However, the phase III HERA study found that, despite receiving 1 year of adjuvant trastuzumab, 31% of patients with HER2-positive breast cancer experienced recurrence within 10 years (4). In addition, the phase III APHINITY study reported a 12% recurrence rate in HER2-positive breast cancer patients with node-positive disease after receiving 1 year of adjuvant trastuzumab, pertuzumab and chemotherapy with a median follow-up of 74 months (6). Consequently, novel treatment approaches are warranted to extend the time to recurrence.

Currently, the efficacy of extended adjuvant therapy has only been investigated in the phase III ExteNET study. The results showed that 1 year of neratinib after trastuzumab-based adjuvant therapy significantly improved invasive disease-free survival (iDFS) in women with HER2-positive

breast cancer. However, the iDFS benefit did not translate into overall survival benefit in the intention-to-treat population after 8-year follow-up, except for patients with hormone receptor (HR)-positive disease ([7](#)–[9](#)).

Pyrotinib is an oral irreversible pan-HER receptor tyrosine kinase inhibitor (TKI), targeting epidermal growth factor receptor, HER2, and HER4 ([10](#)–[12](#)). For patients with HER2-positive metastatic breast cancer, improved survival outcomes were shown in the pyrotinib group when compared with the control group in the phase III PHOEBE and PHILA studies ([13](#), [14](#)). Additionally, results from the phase III PHEDRA trial demonstrated clinical benefits of pyrotinib plus trastuzumab and docetaxel for patients with HER2-positive early or locally advanced breast cancer in the neoadjuvant setting ([15](#)).

In the present PERSIST study, our objective was to assess the efficacy and safety of administering extended adjuvant pyrotinib treatment following trastuzumab-based adjuvant therapy in patients with high-risk, HER2-positive early or locally advanced breast cancer. This report presents the efficacy and safety results with a median follow-up of 2 years, while longer follow-up is still ongoing.

Methods

Study design and participants

This multicenter, single-arm, investigator-initiated, phase II exploratory study was conducted at 23 sites in China. The study protocol was approved by the institutional ethics committee of Taizhou Hospital of Zhejiang Province and all other participating centers, and the trial was performed in accordance with the 2013 Declaration of Helsinki. This trial was registered at ClinicalTrials.gov (NCT05880927). Written informed consent was obtained from all patients before study enrollment.

Participants were eligible if they were women aged 18–75 years with high-risk, HER2-positive (immunohistochemistry 3+, or 2+ with gene amplification by fluorescence in situ hybridization) early or locally advanced invasive breast cancer; had previously completed 1 year of adjuvant therapy with either trastuzumab or trastuzumab plus pertuzumab within 6 months before enrollment; had an Eastern Cooperative Oncology Group performance status of 0 or 1; had known HR status; and had adequate bone marrow, hepatic, renal and cardiac functions.

High-risk patients were defined as those meeting one of the following criteria: N stage ≥ 1 ; T stage ≥ 2 ; absence of pathological complete response (pCR) after neoadjuvant therapy; presence of pCR after neoadjuvant therapy but with tumor size ≥ 5 cm or N stage ≥ 2 ; tumor size < 2 cm but with high Ki-67 level or histologic grade 3. Clinical and pathological stage was assessed according to the eighth edition of American Joint Committee on Cancer tumor-node-metastasis staging system. The expression of Ki-67 was categorized as low ($< 20\%$) and high ($\geq 20\%$) based on the ratio of positive cells to all tumor cells in 10 high-power fields.

The main exclusion criteria were bilateral breast cancer, inflammatory breast cancer, previous participation in other clinical trials involving anticancer therapy, allergies to the drug components in this protocol, history of immunodeficiency diseases, inability to swallow, and pregnancy or lactation.

Procedure

Pyrotinib 400 mg was administered orally once daily within 6 months of completing trastuzumab-based adjuvant therapy. Concurrent adjuvant endocrine therapy for HR-positive disease was recommended.

Treatment duration was 12 months unless intolerable adverse events, disease recurrence, death, or consent withdrawal occurred.

Outcomes and assessment

The primary endpoint was iDFS rate at 2 years. IDFS was defined as time from the initiation of pyrotinib treatment to invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause. The secondary endpoint was safety profile, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Patients were followed every 3 months for the first 2 years. The follow-up assessments included physical examination, Eastern Cooperative Oncology Group performance status, complete blood count, blood chemistry analysis, 12-lead electro-cardiogram, recording of adverse events, concomitant medications, and ultrasound. Computed tomography and bone scans may be conducted if clinically indicated.

Statistical analysis

Based on the previous ExteNET trial (16 [link](#)), the 2-year iDFS rate was assumed as 91% in the present study. To restrain the width of 2-sided 95% confidence interval (CI) to no more than 0.1, 126 patients were required. Considering a dropout rate of 10%, a total of 140 participants were recruited.

Continuous data were presented as median (range or interquartile range), while categorical data were presented as frequency (percentage). IDFS was estimated using the Kaplan-Meier method, and the corresponding 95% CI was estimated using the Brookmeyer-Crowley method. Efficacy analysis was performed in the full analysis set, which included all patients who received at least one dose of study drug. Safety analysis was performed in the safety set, defined as all patients who received at least one dose of the study drug and underwent at least one safety assessment.

Results

Baseline characteristics

Between January 2019 and February 2022, a total of 141 eligible women were enrolled in the study and received pyrotinib. All these patients were included in the full analysis set and safety set. The median age was 50 years (range, 25-72). Of the 141 patients, 107 (75.9%) patients had node-positive disease, and 64 (45.4%) had HR-positive disease. Detailed baseline characteristics are summarized in **Table 1** [link](#).

In terms of treatment duration, 11 patients discontinued their treatment due to adverse events, while 38 patients had a treatment duration of less than or equal to 6 months due to the COVID-19 pandemic or personal reasons. A total of 92 and 31 patients completed 1-year and 6-month treatment of extended adjuvant pyrotinib, respectively (**Figure 1** [link](#)).

Efficacy

As of October 10, 2022, the median follow-up duration was 24 (interquartile range, 18.0-34.0) months. Of the 141 patients, seven patients experienced iDFS events, including one local recurrence, three brain metastases, two lung metastases, and one death due to distant metastasis. The 2-year iDFS rate was 94.59% (95% CI: 88.97-97.38; **Figure 2** [link](#)).

Table 1.

Baseline characteristics of patients in the full analysis set

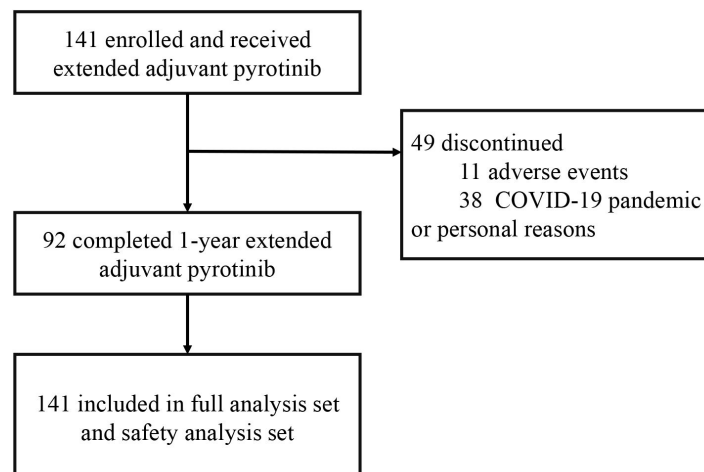
Variables	All (n=141)
Age (years), median (range)	50 (25-72)
T stage, n (%)	
T1	43 (30.5%)
T2	83 (58.9%)
T3	11 (7.8%)
T4	2 (1.4%)
Unable to determine	2 (1.4%)
Nodal status, n (%)	
Negative	34 (24.1%)
1-3 positive nodes	49 (34.8%)
>3 positive nodes	58 (41.1%)
Hormone receptor status, n (%)	
Negative (ER and PR negative)	77 (54.6%)
Positive (ER positive, PR positive, or both)	64 (45.4%)
Ki-67, n (%)	
≥20%	119 (84.4%)
<20%	22 (15.6%)
Previous neoadjuvant therapy, n (%)	26 (17.7%)
Previous adjuvant therapy, n (%)	
Trastuzumab	92 (65.2%)
Trastuzumab plus pertuzumab	49 (34.8%)

ER, estrogen receptor; PR, progesterone receptor.

Tumors were assessed as being ER or PR positive with a threshold of 1%.

Figure 1.

Study flowchart.



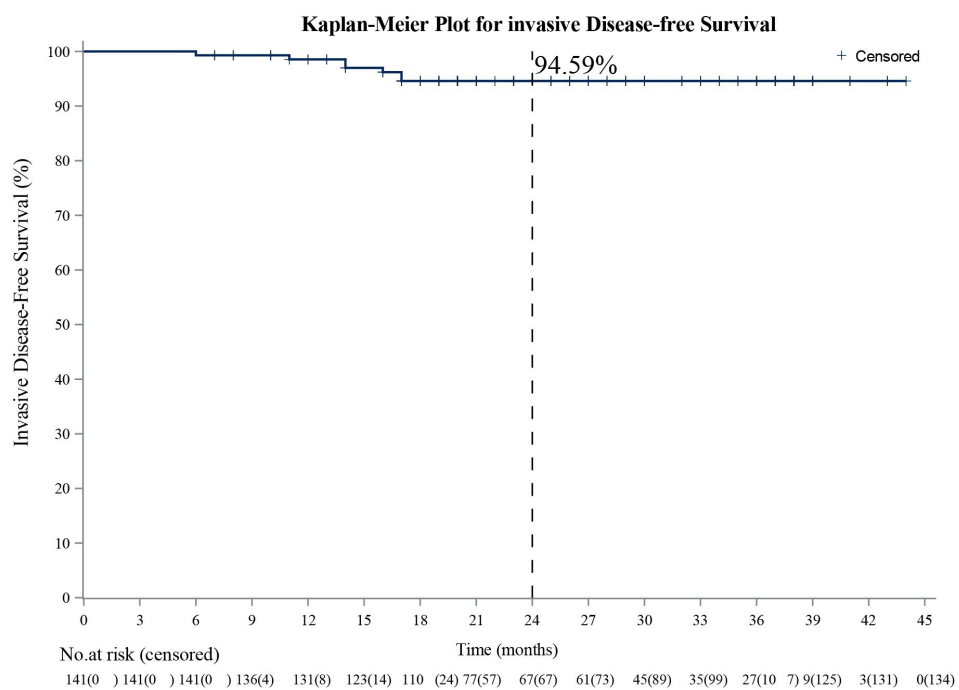


Figure 2.

Invasive disease-free survival in the full analysis set.

Subgroup analyses showed that the 2-year iDFS rate was 94.90% (95% CI: 86.97-98.06) in the 1-year treatment subgroup and 90.32% (95% CI: 72.93-96.77) in the 6-month treatment subgroup (**Figure 3A**). Concerning HR status, the 2-year iDFS rate was 96.74% (95% CI: 87.57-99.18) in patients with HR-positive breast cancer and 92.77% (95% CI: 83.48-96.93) in patients with HR-negative breast cancer (**Figure 3B**). In terms of lymph node status, the 2-year iDFS rate was 96.88% (95% CI: 79.82-99.55) in patients with lymph node-negative breast cancer and 93.85% (95% CI: 86.81-97.20) in patients with lymph node-positive breast cancer (**Figure 3C**). Regarding trastuzumab-based adjuvant regimen, the 2-year iDFS rate was 97.30% (95% CI: 82.32-99.61) in patients who received adjuvant trastuzumab plus pertuzumab, and 93.48% (95% CI: 86.06-97.02) in patients who received adjuvant trastuzumab (**Figure 3D**).

Safety

The most frequently reported treatment-emergent adverse event was diarrhea (112 [79.4%]), followed by fatigue (52 [36.9%]), lymphocyte count decreased (52 [36.9%]), nausea (47 [33.3%]), and hand-foot syndrome (47 [33.3%]). Forty-three patients (30.5%) experienced grade 3 diarrhea, while no grade 4 or higher adverse events was reported (**Table 2**). Treatment discontinuation occurred in 11 (7.8%) patients, due to grade 3 diarrhea (n=8), grade 3 hand-foot syndrome (n=1), and intolerance (n=2). In addition, 16 patients had dose reduction because of adverse events.

Discussion

To the best of our knowledge, this multicenter phase II study is the first prospective study to explore the efficacy and safety of extended adjuvant pyrotinib after trastuzumab-based adjuvant therapy in patients with high-risk HER2-positive breast cancer. Furthermore, while the ExteNET study only included patients who received neoadjuvant or adjuvant trastuzumab, over one-third of the patients in our study had received dual anti-HER2 blockade with trastuzumab and pertuzumab, making it more clinically applicable to current clinical practice (17). In China, pertuzumab was approved for the treatment of HER2-positive breast cancer in the adjuvant setting in 2018, and has been covered by medical insurance since 2020. The PERSIST study started in 2019, thus the proportion of eligible patients who received trastuzumab and pertuzumab in our study was relatively high.

Currently, only neratinib has been approved by Food and Drug Administration in the extended adjuvant setting for patients with HER2-positive early or locally advanced breast cancer. In the 2023 National Comprehensive Cancer Network guidelines, it has been recommended for the treatment of high-risk, HR-positive, HER2-positive breast cancer (18). In the ExteNET study, 1-year neratinib treatment after adjuvant trastuzumab significantly improved iDFS in patients with HER2-positive breast cancer, with a 2-year iDFS rate of 93.9% in the neratinib group and 91.6% in the placebo group (9, 16). In our study, the 2-year iDFS rate was 94.59%, comparable to that in the ExteNET study.

In terms of subgroup analyses, the HR-positive group seemed to show a numerically higher 2-year iDFS rate than the HR-negative group (96.74% vs. 92.77%). Consistently, similar results were observed in the ExteNET study. The underlying mechanism may involve cross-talk between HR and HER2 pathways (19, 20). Preclinical studies have shown that in estrogen receptor+/HER2+ cell lines, neratinib treatment also suppresses the activity of estrogen reporter (21). In the present study, adjuvant endocrine therapy was recommended for patients with HR-positive disease when treated with pyrotinib, which may generate synergistic effects (22, 23). Regarding duration of treatment, the results showed that the 2-year iDFS rate was numerically higher with 1-year pyrotinib treatment (94.90%) versus 6-month pyrotinib treatment (90.32%). In the adjuvant setting, a phase III PHARE trial compared 1-year adjuvant trastuzumab with 6-month

Figure 3.

Invasive disease-free survival in subgroups. (A) Treatment duration of pyrotinib (1 year vs. 6 months). (B) Hormone receptor status (positive vs. negative). (C) Node status (positive vs. negative). (D) Adjuvant regimen before extended adjuvant pyrotinib (trastuzumab vs. trastuzumab plus pertuzumab).

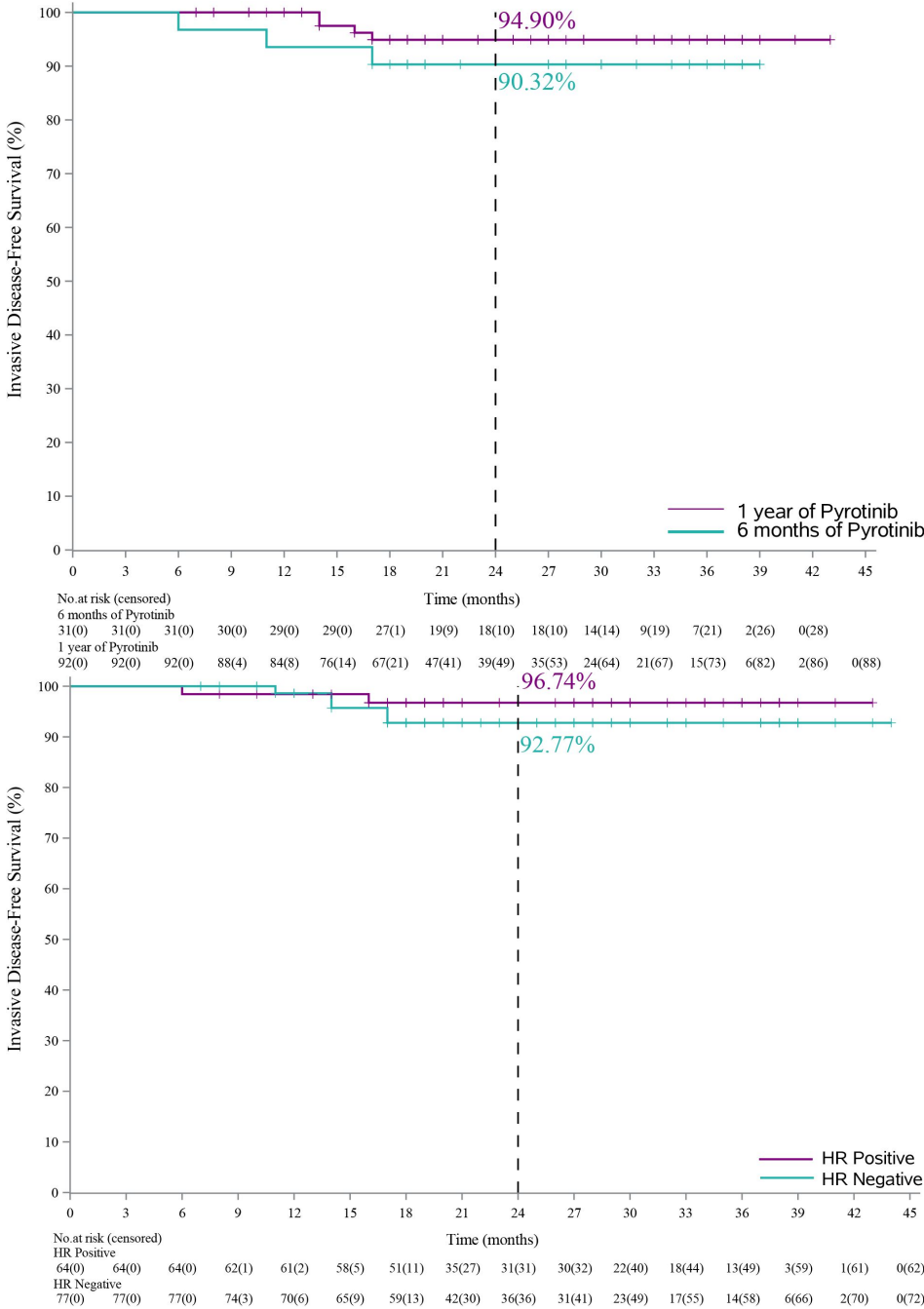
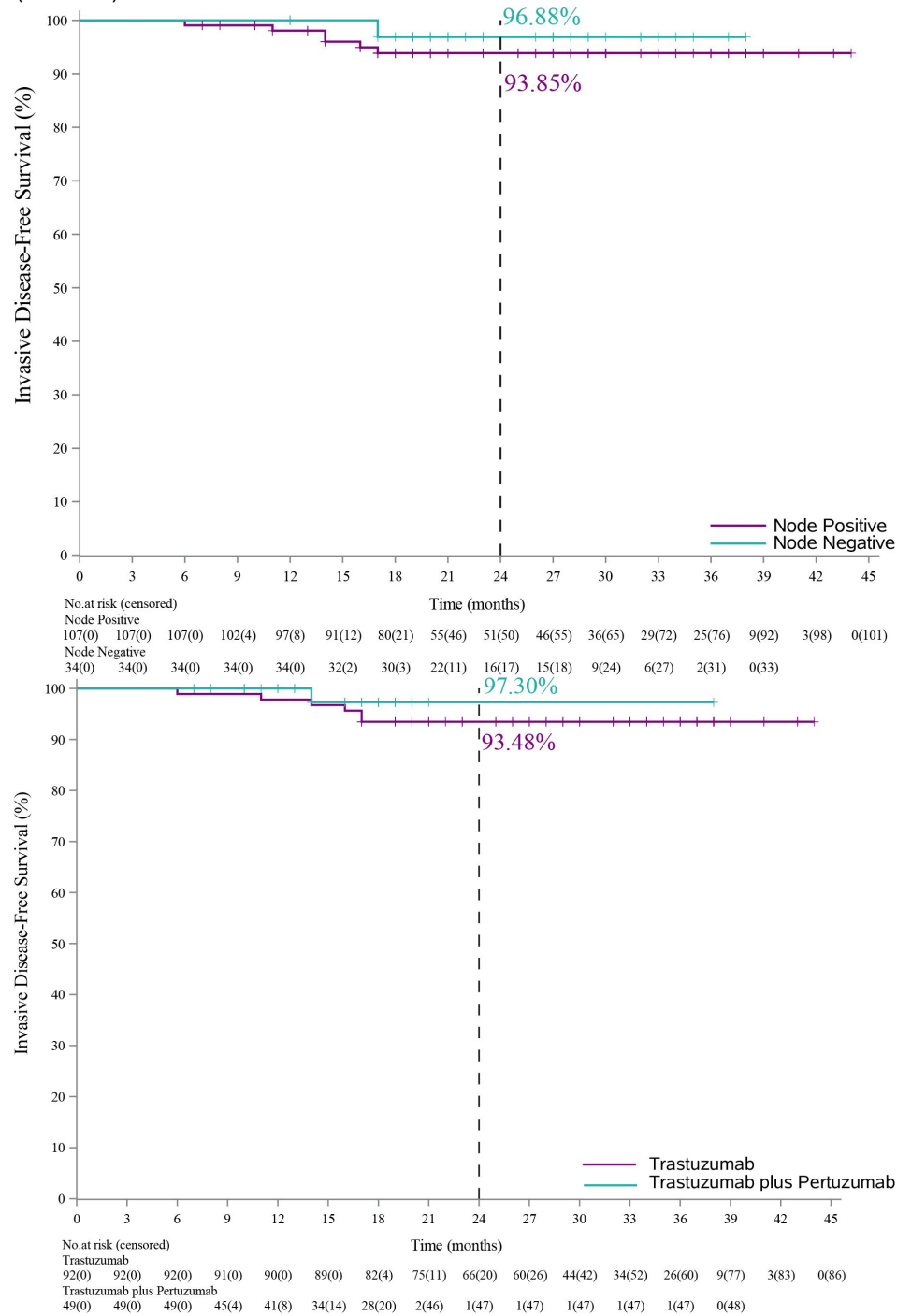


Figure 3. (continued)



Events, n (%)	All (n=141)	
	Any grade	Grade 3
Diarrhea	112 (79.4%)	43 (30.5%)
Fatigue	52 (36.9%)	0
Lymphocyte count decreased	52 (36.9%)	0
Nausea	47 (33.3%)	0
Hand-foot syndrome	47 (33.3%)	1 (0.7%)
Hyperuricemia	33 (23.4%)	0
White blood cell count decreased	26 (18.4%)	0
Dizziness	26 (18.4%)	0
Anemia	24 (17.0%)	0
Vomiting	22 (15.6%)	0
Headache	19 (13.5%)	0
Creatinine increased	17 (12.1%)	0
Neutrophil count decreased	16 (11.3%)	0

Table 2.

Treatment-emergent adverse events occurring in at least 10% of the patients.

treatment, and the non-inferiority was not achieved for disease-free survival. Therefore, 1-year adjuvant trastuzumab remained the standard treatment (24 [↗](#)). Further studies are warranted to find the optimal duration of extended adjuvant pyrotinib.

Adjuvant treatment regimens before extended adjuvant treatment may also be associated with iDFS. In the present study, the 2-year iDFS rate was 93.48% and 97.30% in the trastuzumab subgroup and trastuzumab plus pertuzumab subgroup, respectively. The APHINITY study demonstrated a significantly improved iDFS with adjuvant trastuzumab plus pertuzumab than with adjuvant trastuzumab alone (25 [↗](#)). Therefore, the iDFS benefits may last and affect the results in the extended adjuvant period.

None of the patients in the PERSIST study received trastuzumab emtansine (T-DM1), which is now a standard of care for HER2-positive patients with residual cancer after neoadjuvant therapy based on the phase III KATHERINE trial (26 [↗](#)). Since T-DM1 was approved in China in 2020 and was not covered by medical insurance until 2023, it has not been widely used in clinical practice. Recently, a real-world study showed that patients with metastatic breast cancer could benefit from pyrotinib-based therapy after T-DM1 treatment (27 [↗](#)). Therefore, patients with high-risk breast cancer may also benefit from extended adjuvant pyrotinib after being treated with T-DM1 in the adjuvant setting, which needs further investigation.

Regarding adverse events, diarrhea was the major safety concern in the present study, leading to treatment discontinuation in eight patients. This adverse event as well as vomiting and nausea are TKI-related common adverse events. The underlying mechanisms of these adverse events are not clear yet, and the mainstream hypothesis is that the growth and healing of epithelial cells in gastrointestinal tract are inhibited by TKIs (28 [↗](#), 29 [↗](#)). In the present study, 43 (30.5%) patients experienced grade 3 diarrhea, which were consistent with previous studies of pyrotinib (11 [↗](#), 30 [↗](#)). Noteworthy, primary prophylaxis was not mandatory in this PERSIST trial. Currently, loperamide hydrochloride has been found to significantly alleviate symptoms of diarrhea and reduce diarrhea-related treatment discontinuation. It has been recommended for patients treated with pyrotinib (31 [↗](#)). In the PANDORA trial of pyrotinib plus docetaxel, the incidence of diarrhea was significantly lower in the loperamide prophylaxis group (8.9%) compared with the non-prophylaxis group (38.2%) (32 [↗](#)). In the CONTROL trial, all cohorts that received loperamide prophylaxis and the dose escalation cohort of neratinib exhibited lower grade 3 diarrhea rates and fewer instances of diarrhea-related treatment discontinuation compared with ExteNET (33 [↗](#)). The above two studies indicated that pyrotinib-related diarrhea could be controlled with prophylaxis or dose modification.

There are several limitations in the present study. Firstly, our study was a single-arm study without control group. Secondly, patients who received T-DM1 therapy in the adjuvant setting were not enrolled. Thirdly, 27.0% of patients did not complete 1-year extended adjuvant pyrotinib due to COVID-19 pandemic or personal reasons. Finally, the follow-up time was short. A phase III clinical trial (NCT03980054) of extended adjuvant pyrotinib in patients with high-risk HER2-positive breast cancer is ongoing, which will further demonstrate the efficacy of extended adjuvant TKI and bring new hope for patients with high-risk HER2-positive breast cancer.

Conclusions

Our study suggests the potential of extended adjuvant pyrotinib in patients with high-risk HER2-positive early or locally advanced breast cancer after trastuzumab-based adjuvant therapy. The follow-up is ongoing to determine the long-term benefit of extended adjuvant pyrotinib.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

We thank all the patients who participated in this trial and their families, as well as the investigators and staff. We thank Yan Luo (Department of Medical Affairs, Jiangsu Hengrui Pharmaceuticals Co., Ltd.) for data interpretation and Yunning Yang (Department of Medical Affairs, Jiangsu Hengrui Pharmaceuticals Co., Ltd.) for medical writing assistance according to Good Publication Practice Guidelines.

Additional information

Author contributions

Huiqiang Huang: Conceptualization (Equal); Resources (Equal); Visualization (Equal); Zhaosheng Ma: Conceptualization (Equal); Investigation (Equal); Writing – original draft (Equal); Zenggui Wu: Investigation (Equal); Methodology (Equal); Writing – original draft (Equal); Weizhu Wu: Formal analysis (Equal); Methodology (Equal); Software (Equal); Writing – original draft (Equal); Ouchen Wang: Methodology (Equal); Resources (Equal); Writing – review & editing (Equal); Binbin Cui: Investigation (Equal); Project administration (Equal); Software (Equal); Xiaotao Zhu: Investigation (Equal); Resources (Equal); Writing – original draft (Equal); Jing Hao: Investigation (Equal); Writing – original draft (Equal); Writing – review & editing (Equal); Xiaochun Ji: Conceptualization (Equal); Supervision (Equal); Zhanwen Li: Methodology (Equal); Project administration (Equal); Resources (Equal); Deyou Tao: Software (Equal); Validation (Equal); Qingjing Feng: Methodology (Equal); Supervision (Equal); Validation (Equal); Writing – original draft (Equal); Wei Lin: Methodology (Equal); Supervision (Equal); Writing – original draft (Equal); Writing – review & editing (Equal); Dongbo Shi: Supervision (Equal); Validation (Equal); Visualization (Equal); Writing – original draft (Equal); Writing – review & editing (Equal); Jingde Shu: Software (Equal); Writing – review & editing (Equal); Jichun Zhou: Methodology (Equal); Supervision (Equal); Validation (Equal); Writing – review & editing (Equal); Shifen Huang: Resources (Equal); Writing – review & editing (Equal)

Funding

None.

Conflict of interest statement

The authors declare no conflict of interests.

Ethics approval and consent to participate

The study protocol was approved by the institutional ethics committee of Taizhou Hospital of Zhejiang Province and all other participating centers, and the trial was performed in accordance with the 2013 Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical trial registration number

This trial was registered at ClinicalTrials.gov (NCT05880927).

References

- 1 Siegel R, Ma J, Zou Z, Jemal A (2014) **Cancer statistics, 2014** *CA: a Cancer Journal For Clinicians* **64** <https://doi.org/10.3322/caac.21208>
- 2 Loibl S, Gianni L (2017) **Her2-positive breast cancer** *Lancet (London, England)* **389**:2415–2429 [https://doi.org/10.1016/S0140-6736\(16\)32417-5](https://doi.org/10.1016/S0140-6736(16)32417-5)
- 3 Perez EA *et al.* (2014) **Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: Planned joint analysis of overall survival from nsabp b-31 and ncctg n9831** *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* **32**:3744–3752 <https://doi.org/10.1200/JCO.2014.55.5730>
- 4 Cameron D *et al.* (2017) **11 years' follow-up of trastuzumab after adjuvant chemotherapy in her2-positive early breast cancer: Final analysis of the herceptin adjuvant (hera) trial** *Lancet (London, England)* **389**:1195–1205 [https://doi.org/10.1016/S0140-6736\(16\)32616-2](https://doi.org/10.1016/S0140-6736(16)32616-2)
- 5 Wolff AC *et al.* (2013) **Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of american pathologists clinical practice guideline update** *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* **31**:3997–4013 <https://doi.org/10.1200/JCO.2013.50.9984>
- 6 Piccart M *et al.* (2021) **Adjuvant pertuzumab and trastuzumab in early her2-positive breast cancer in the aphinity trial: 6 years' follow-up** *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* **39**:1448–1457 <https://doi.org/10.1200/JCO.20.01204>
- 7 Holmes FA *et al.* (2023) **Overall survival with neratinib after trastuzumab-based adjuvant therapy in her2-positive breast cancer (extenet): A randomised, double-blind, placebo-controlled, phase 3 trial** *European Journal of Cancer (Oxford, England : 1990)* **184** <https://doi.org/10.1016/j.ejca.2023.02.002>
- 8 Lüftner D, Tesch H, Schmidt M, Hartkopf AD, Streicher S, Resch A, Genovese L, Rosé C, Valenti R, Harbeck N (2021) **Neratinib as extended adjuvant therapy in patients with copositive early breast cancer: German health technology assessment-driven analyses from the extenet study** *European Journal of Cancer (Oxford, England : 1990)* **150** <https://doi.org/10.1016/j.ejca.2021.03.045>
- 9 Martin M *et al.* (2017) **Neratinib after trastuzumab-based adjuvant therapy in her2-positive breast cancer (extenet): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial** *The Lancet Oncology* **18**:1688–1700
- 10 Blair HA (2018) **Pyrotinib: First global approval** *Drugs* **78**:1751–1755 <https://doi.org/10.1007/s40265-018-0997-0>
- 11 Ma F *et al.* (2019) **Pyrotinib or lapatinib combined with capecitabine in her2-positive metastatic breast cancer with prior taxanes, anthracyclines, and/or trastuzumab: A randomized, phase ii study** *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* **37**:2610–2619 <https://doi.org/10.1200/JCO.19.00108>

- 12 Guan X *et al.* (2023) **Survival benefit and biomarker analysis of pyrotinib or pyrotinib plus capecitabine for patients with her2-positive metastatic breast cancer: A pooled analysis of two phase i studies** *Biomarker Research* **11** <https://doi.org/10.1186/s40364-023-00453-0>
- 13 Xu B *et al.* (2021) **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** *The Lancet Oncology* **22**:351–360 [https://doi.org/10.1016/S1470-2045\(20\)30702-6](https://doi.org/10.1016/S1470-2045(20)30702-6)
- 14 Ma F, Yan M, Li W, Ouyang Q, Tong Z, Teng Y, et al. (2023) **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** *BMJ (Clinical Research ed)* **383** <https://doi.org/10.1136/bmj.p2665>
- 15 Wu J *et al.* (2022) **Neoadjuvant pyrotinib, trastuzumab, and docetaxel for her2-positive breast cancer (phedra): A double-blind, randomized phase 3 trial** *BMC Medicine* **20** <https://doi.org/10.1186/s12916-022-02708-3>
- 16 Chan A *et al.* (2016) **Neratinib after trastuzumab-based adjuvant therapy in patients with her2-positive breast cancer (extenet): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial** *The Lancet Oncology* **17**:367–377 [https://doi.org/10.1016/S1470-2045\(15\)00551-3](https://doi.org/10.1016/S1470-2045(15)00551-3)
- 17 Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, Senn HJ, Winer EP, Gnant M (2021) **Customizing local and systemic therapies for women with early breast cancer: The st. Gallen international consensus guidelines for treatment of early breast cancer 2021** *Annals of Oncology : Official Journal of the European Society For Medical Oncology* **32**:1216–1235 <https://doi.org/10.1016/j.annonc.2021.06.023>
- 18 Bevers TB *et al.* (2023) **Nccn guidelines® insights: Breast cancer screening and diagnosis, version 1.2023** *Journal of the National Comprehensive Cancer Network : JNCCN* **21**:900–909 <https://doi.org/10.6004/jnccn.2023.0046>
- 19 Nahta R, O'Regan RM (2012) **Therapeutic implications of estrogen receptor signaling in her2-positive breast cancers** *Breast Cancer Research and Treatment* **135**:39–48 <https://doi.org/10.1007/s10549-012-2067-8>
- 20 Pegram M, Jackisch C, Johnston SRD (2023) **Estrogen/her2 receptor crosstalk in breast cancer: Combination therapies to improve outcomes for patients with hormone receptor-positive/her2-positive breast cancer** *NPJ Breast Cancer* **9** <https://doi.org/10.1038/s41523-023-00533-2>
- 21 Sudhan DR *et al.* (2019) **Extended adjuvant therapy with neratinib plus fulvestrant blocks er/her2 crosstalk and maintains complete responses of er+/her2+ breast cancers: Implications to the extenet trial** *Clinical Cancer Research : an Official Journal of the American Association For Cancer Research* **25**:771–783 <https://doi.org/10.1158/1078-0432.CCR-18-1131>
- 22 Hu Z-Y *et al.* (2023) **Pyrotinib in combination with letrozole for hormone receptor-positive, human epidermal growth factor receptor 2-positive metastatic breast cancer (pleherm): A multicenter, single-arm, phase ii trial** *BMC Medicine* **21** <https://doi.org/10.1186/s12916-023-02943-2>

- 23 Zhang J, Meng Y, Wang B, Wang L, Cao J, Tao Z, Li T, Yao W, Hu X (2022) **Dalpiciclib combined with pyrotinib and letrozole in women with her2-positive, hormone receptor-positive metastatic breast cancer (lordships): A phase ib study** *Frontiers In Oncology* **12** <https://doi.org/10.3389/fonc.2022.775081>
- 24 Pivot X *et al.* (2019) **6 months versus 12 months of adjuvant trastuzumab in early breast cancer (phare): Final analysis of a multicentre, open-label, phase 3 randomised trial** *Lancet (London, England)* **393**:2591–2598 [https://doi.org/10.1016/S0140-6736\(19\)30653-1](https://doi.org/10.1016/S0140-6736(19)30653-1)
- 25 von Minckwitz G *et al.* (2017) **Adjuvant pertuzumab and trastuzumab in early her2-positive breast cancer** *The New England journal of medicine* **377**:122–131 <https://doi.org/10.1056/NEJMoa1703643>
- 26 von Minckwitz G *et al.* (2019) **Trastuzumab emtansine for residual invasive her2-positive breast cancer** *The New England Journal of Medicine* **380**:617–628 <https://doi.org/10.1056/NEJMoa1814017>
- 27 Liang X, Gui X, Yan Y, Di L, Liu X, Li H, Song G (2024) **Long-term outcome analysis of pyrotinib in patients with her2-positive metastatic breast cancer and brain metastasis: A real-world study** *The Oncologist* **29**:e198–e205 <https://doi.org/10.1093/oncolo/oyad228>
- 28 Shyam Sunder S, Sharma UC, Pokhare S (2023) **Adverse effects of tyrosine kinase inhibitors in cancer therapy: Pathophysiology, mechanisms and clinical management** *Signal Transduction and Targeted Therapy* **8** <https://doi.org/10.1038/s41392-023-01469-6>
- 29 Secombe KR, Van Seville YZA, Mayo BJ, Collier JK, Gibson RJ, Bowen JM (2020) **Diarrhea induced by small molecule tyrosine kinase inhibitors compared with chemotherapy: Potential role of the microbiome** *Integrative Cancer Therapies* **19** <https://doi.org/10.1177/1534735420928493>
- 30 Guan X, Ma F, Li Q, Chen S, Fan Y, Wang J, Luo Y, Zhang P, Li Q, Xu B (2023) **Pyrotinib plus capecitabine could significantly improve overall survival in her2-positive metastatic breast cancer** *Signal Transduction and Targeted Therapy* **8** <https://doi.org/10.1038/s41392-023-01322-w>
- 31 Fang C, Wen J, Kang M, Zhang Y, Chen Q, Ren L (2022) **Incidence and management of pyrotinib-associated diarrhea in her2-positive advanced breast cancer patients** *Annals of Palliative Medicine* **11**:210–216 <https://doi.org/10.21037/apm-21-3978>
- 32 Zheng Y *et al.* (2023) **Pyrotinib plus docetaxel as first-line treatment for her2-positive metastatic breast cancer: The pandora phase ii trial** *Nature Communications* **14** <https://doi.org/10.1038/s41467-023-44140-y>
- 33 Barcenas CH *et al.* (2020) **Improved tolerability of neratinib in patients with her2-positive early-stage breast cancer: The control trial** *Annals of oncology : official journal of the European Society for Medical Oncology* **31**:1223–1230

Author information

Feilin Cao*

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China
ORCID iD: [0009-0002-5083-1462](https://orcid.org/0009-0002-5083-1462)

For correspondence: drcfl@126.com

*These authors contributed equally to this work and should be considered co-first authors.

Zhaosheng Ma*

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China

*These authors contributed equally to this work and should be considered co-first authors.

Zenggui Wu*

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China

*These authors contributed equally to this work and should be considered co-first authors.

Weizhu Wu

Department of Thyroid and Breast Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo, China

Ouchen Wang

Department of Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Binbin Cui&

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China

&These authors contributed equally to this work and should be considered co-fourth authors.

Xiaotao Zhu&

Department of Thyroid and Breast Surgery, Jinhua Municipal Central Hospital, Jinhua, China

&These authors contributed equally to this work and should be considered co-fourth authors.

Jing Hao^

Department of Thyroid and Breast Surgery, Yiwu Central Hospital, Jinhua, China

^These authors contributed equally to this work and should be considered co-fifth authors.

Xiaochun Ji[^]

Department of Thyroid and Breast Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo, China

[^]These authors contributed equally to this work and should be considered co-fifth authors.

Zhanwen Li[^]

Department of Breast Surgery, Ningbo Women & Children's Hospital, Ningbo, China

[^]These authors contributed equally to this work and should be considered co-fifth authors.

Deyou Tao

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China

Qingjing Feng[£]

Department of Breast Surgery, Yiwu Maternity and Children Hospital, Jinhua, China

[£]These authors contributed equally to this work and should be considered co-seventh authors.

Wei Lin[£]

Department of Surgical Oncology, Quzhou People's Hospital, Quzhou, China

[£]These authors contributed equally to this work and should be considered co-seventh authors.

Dongbo Shi[£]

Department of Breast Surgery, The First Affiliated Hospital of Ningbo University, Ningbo, China

[£]These authors contributed equally to this work and should be considered co-seventh authors.

Jingde Shu[£]

Department of Surgical Oncology, Quzhou People's Hospital, Quzhou, China

[£]These authors contributed equally to this work and should be considered co-seventh authors.

Jichun Zhou

Department of Surgical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

Shifen Huang

Department of Thyroid and Breast Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Taizhou, China

Editors

Reviewing Editor

Yu Zhao

Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Senior Editor

Caigang Liu

Shengjing Hospital of China Medical University, Shenyang, China

Reviewer #1 (Public review):

Summary:

This study introduces a novel therapeutic strategy for patients with high-risk HER2-positive breast cancer and demonstrates that the incorporation of pyrotinib into adjuvant trastuzumab therapy can improve invasive disease-free survival.

Strengths:

The study features robust logic and high-quality data. Data from 141 patients across 23 centers were analyzed, thereby effectively mitigating regional biases and endowing the research findings with high applicability.

Weaknesses:

- (1) Introduction and Discussion: Update the literature regarding the efficacy of pyrotinib combined with trastuzumab in treating HER2-positive advanced breast cancer.
- (2) Did all the data have a normal distribution? Expand the description of statistical analysis.
- (3) The novelty and innovative potential of your manuscript compared to the published literature should be described in more detail in the abstract and discussion section.
- (4) Figure legend should provide a bit more detail about what readers should focus on.
- (5) P-values should be clarified for the analysis.
- (6) The order (A, B, and C) in Figure 3 should be labeled in the upper left corner of the Figure.

<https://doi.org/10.7554/eLife.101724.1.sa1>

Reviewer #2 (Public review):

In this manuscript, Cao et al. evaluated the efficacy and safety of 12 months pyrotinib after trastuzumab-based adjuvant therapy in patients with high-risk, HER2-positive early or locally advanced breast cancer. Notably, the 2-year iDFS rate reached 94.59% (95% CI: 88.97-97.38) in all patients, and 94.90% (95% CI: 86.97-98.06) in patients who completed 1-year treatment of pyrotinib. This is an interesting and uplifting results, given that in ExteNET study, the 2-year iDFS rate was 93.9% (95% CI 92.4-95.2) in the 1-year neratinib group, and the 5-year iDFS survival was 90.2%, and 1-year treatment of neratinib in ExteNET study did not translate into OS benefit after 8-year follow-up. In this case, readers will be eagerly anticipating the long-term follow-up results of the current PERSIST study, as well as the results of the phase III clinical trial (NCT03980054).

I have the following comments:

(1) The introduction of the differences between pyrotinib and neratinib in terms of mechanism, efficacy, resistance, etc. is supposed to be included in the text so that authors could better highlight the clinical significance of the current trial.

(2) Please make sure that a total of 141 patients were enrolled in the study, 38 patients had a treatment duration of less than or equal to 6 months, and a total of 92 and 31 patients completed 1-year and 6-month treatment of extended adjuvant pyrotinib, respectively, which means 7 patients had a treatment duration of fewer than 6 months.

(3) The previous surgery history should be provided, and how many patients received lumpectomy, and mastectomy.

<https://doi.org/10.7554/eLife.101724.1.sa0>