

*Review*

Efficacy and Safety of Neoadjuvant Pyrotinib for Human Epidermal Receptor 2-Positive Breast Cancer: A Meta-Analysis

Xiaona Lin,¹ Xiao Liu,² Xiaohui Yang³ and Feng Sun¹

¹Department of Breast and Thyroid Surgery, Zibo Central Hospital, Zibo, Shandong, China

²Department of Ultrasound, Zibo Central Hospital, Zibo, Shandong, China

³Department of Anesthesia Surgery, Zibo Central Hospital, Zibo, Shandong, China

Neoadjuvant pyrotinib shows the potential to improve treatment response in human epidermal receptor 2 (HER2)-positive breast cancer patients, but relevant meta-analyses are scarce. This meta-analysis intended to explore the efficacy and safety of neoadjuvant pyrotinib for HER2-positive breast cancer patients. Studies comparing the efficacy and safety between HER2-positive breast cancer patients receiving pyrotinib-containing neoadjuvant treatment (pyrotinib group) and those receiving other neoadjuvant treatments (control group), were searched in EMBASE, Web of Science, Cochrane, PubMed, China National Knowledge Infrastructure, Wanfang, and SinoMed until December 2023. Six randomized controlled trials (RCTs) and 4 cohort studies were included. The pyrotinib group and control group contained 540 and 684 patients, respectively. Pathological complete response (pCR) was higher in the pyrotinib group than in the control group [relative risk (RR)=1.93; 95% confidence interval (CI) = 1.63-2.29; $P < 0.001$]. Similar results were discovered in subgroup analyses of RCTs (RR = 1.89; 95% CI = 1.49-2.40; $P < 0.001$) and cohort studies (RR = 1.98; 95% CI = 1.55-2.53; $P < 0.001$). The objective response rate (ORR) was also higher in the pyrotinib group than in the control group (RR = 1.14; 95% CI = 1.07-1.21; $P < 0.001$). Regarding adverse events, only the incidence of diarrhea was increased in the pyrotinib group versus the control group (RR = 1.97; 95% CI = 1.31-2.96; $P = 0.001$), while others were not different, including nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome, and alopecia (all $P > 0.05$). No publication bias existed, and sensitivity analysis suggested the satisfactory robustness of this meta-analysis. In conclusion, compared with other neoadjuvant treatments, pyrotinib-containing neoadjuvant treatment achieves a better treatment response with a good safety profile in HER2-positive breast cancer patients.

Keywords: breast cancer; efficacy; human epidermal receptor 2; neoadjuvant pyrotinib; safety

Tohoku J. Exp. Med., 2024 July, 263 (3), 175-184.

doi: 10.1620/tjem.2024.J026

Introduction

Breast cancer is one of the most commonly diagnosed cancers, with approximately 2.3 million new cases in 2020 worldwide (Sung et al. 2021). Human epidermal receptor 2 (HER2) is overexpressed in nearly 20% of breast cancer patients, which can be a target for treatment (Jackisch et al. 2017; Martinez-Saez and Prat 2021; Aapro et al. 2022). For HER2-positive breast cancer patients suitable for surgical resection, neoadjuvant therapy containing HER2-targeted agents (such as trastuzumab and pertuzumab) has become a

fundamental treatment strategy (Gianni et al. 2016; Korde et al. 2021; Loibl et al. 2021; Gunasekara et al. 2022). Unfortunately, a proportion of HER2-positive breast cancer patients cannot achieve pathological complete response (pCR) after neoadjuvant therapies, and the pCR rate is only approximately 30% to 50% (Denkert et al. 2018; Spring et al. 2020; Fazal et al. 2023). Moreover, unsatisfactory pCR is generally associated with a dismal prognosis in HER2-positive breast cancer patients (Broglio et al. 2016; Spring et al. 2020; Davey et al. 2022). Considering that rational combination therapy with other medications can potentially

Received February 6, 2024; revised and accepted April 16, 2024; J-STAGE Advance online publication April 25, 2024

Correspondence: Feng Sun, Department of Breast and Thyroid Surgery, Zibo Central Hospital, No. 54, Communist Youth League West Road, Zhangdian District, Zibo, Shandong 255000, China.

e-mail: sunfeng190219@163.com

©2024 Tohoku University Medical Press. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC-BY-NC-ND 4.0). Anyone may download, reuse, copy, reprint, or distribute the article without modifications or adaptations for non-profit purposes if they cite the original authors and source properly.

<https://creativecommons.org/licenses/by-nc-nd/4.0/>

overcome this obstacle, it is crucial to explore other novel neoadjuvant anti-HER2 agents to improve the clinical outcomes of HER2-positive breast cancer patients.

Pyrotinib is a novel, irreversible epidermal growth factor receptor (EGFR)/HER2 dual tyrosine kinase inhibitor for the treatment of HER2-positive breast cancer (Li et al. 2017; Singh et al. 2022; Qi et al. 2023). Compared with trastuzumab and pertuzumab, pyrotinib has several advantages, such as oral administration, the capacity to pass through the blood-brain barrier, multiple targets, and reduced cardiotoxicity (Qi et al. 2023). Notably, some previous meta-analyses indicated that pyrotinib was effective with manageable adverse events in HER2-positive metastatic breast cancer patients (Liao et al. 2021; Hu et al. 2023; Yuan et al. 2023). In addition, several clinical studies investigated the efficacy and safety of neoadjuvant pyrotinib in HER2-positive breast cancer patients (Mao et al. 2022; Yin et al. 2022; Tian et al. 2023; Wang et al. 2023). For instance, one previous study reported that pyrotinib-containing neoadjuvant treatment achieved a pCR rate of 69.81% in HER2-positive breast cancer patients, and the most common grade 3-4 adverse events were diarrhea, leukopenia, and neutropenia (Yin et al. 2022). In addition, pyrotinib-containing neoadjuvant treatment achieved a higher pCR rate than other neoadjuvant treatments [43.8% versus (vs.) 25.0%], while it also induced a higher incidence of diarrhea and hand-foot syndrome in HER2-positive breast cancer patients (Zheng et al. 2021). However, relevant meta-analyses regarding the potential of neoadjuvant pyrotinib for the treatment of HER2-positive breast cancer are scarce, which restricts its clinical application.

Accordingly, this meta-analysis aimed to investigate the efficacy and safety of neoadjuvant pyrotinib in HER2-positive breast cancer patients.

Methods

Study searching

This meta-analysis referred to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Hutton et al. 2015) and focused on the treatment efficacy and safety of pyrotinib as a neoadjuvant therapy for HER2-positive breast cancer. The databases used for study searching were EMBASE, Web of Science, Cochrane Library, PubMed, China National Knowledge Infrastructure (CNKI), Wanfang, and SinoMed. The retrieval date was up to December 2023. The keywords used for the search were pyrotinib, neoadjuvant, neoadjuvant, breast cancer, and breast neoplasms. To include as much of the relevant literature as possible, the references of eligible studies were also screened.

Study inclusion criteria

The inclusion criteria were a) comparing efficacy or safety with or without pyrotinib as neoadjuvant therapy for HER2-positive breast cancer; b) reporting at least one index

of interest, which included the pCR rate, objective response rate (ORR), and adverse events; and c) reporting a population older than 18 years. The exclusion criteria were a) focusing on pyrotinib for metastatic breast cancer; b) single-arm studies; c) case reports, reviews, or meta-analyses; and d) reporting irrelevant or unextractable data.

Study assessment

Data collection and quality assessment were completed strictly. The first author, year, study design, sample size, age, treatment, pyrotinib dose, and outcomes were retrieved. The adverse events that were reported in 3 or more studies were pooled and analyzed, as they were not the same in different studies. The Cochrane Collaboration tool and Newcastle-Ottawa Scale were used to evaluate the quality of randomized controlled trials (RCTs) and cohorts, respectively (Lundh and Gotzsche 2008; Wells et al. 2000).

Statistical analysis

Stata V.14.0 (Stata Corp., College Station, Texas, USA) was utilized. Heterogeneity was evaluated using I^2 and P values (Higgins et al. 2003). If neoadjuvant therapy included pyrotinib, then HER2-positive breast cancer patients were defined as the pyrotinib group. Otherwise, patients were defined as the control group. The results were described as the relative risk (RR) [95% confidence interval (CI)]. If I^2 was greater than 50.0% and P was less than 0.05, heterogeneity was deemed to exist, and a random effects model was chosen; otherwise, a fixed effects model was chosen. The sensitivity analysis was completed by omitting the studies one by one and repeating the analyses. Publication bias was considered present if the P value of Begg's test or Egger's test was less than 0.05.

Results

Study screening procedure

A total of 226 studies were screened from the databases, including 41 studies from the Web of Science, 25 studies from PubMed, 38 studies from the Cochrane Library, 67 studies from EMBASE, 28 studies from CNKI, 10 studies from SinoMed, and 17 studies from Wanfang. Moreover, 1 reference of each eligible study was also screened. Subsequently, 124 duplicated studies were excluded, and the titles and abstracts of the remaining 103 records were screened. Then, 92 studies were further excluded, including 39 studies with irrelevant topics, 25 studies with irrelevant data, 17 single-arm studies, 7 case reports, and 4 reviews or meta-analyses. After that, 11 studies were assessed based on full texts, and 1 study was excluded for irrelevant data. Ultimately, 10 studies were included and analyzed (Fig. 1).

Characteristics of the included studies

The 10 screened studies included 1,224 HER2-positive breast cancer patients, and the publication years of the included studies ranged from 2021 to 2023 (Ding et al.

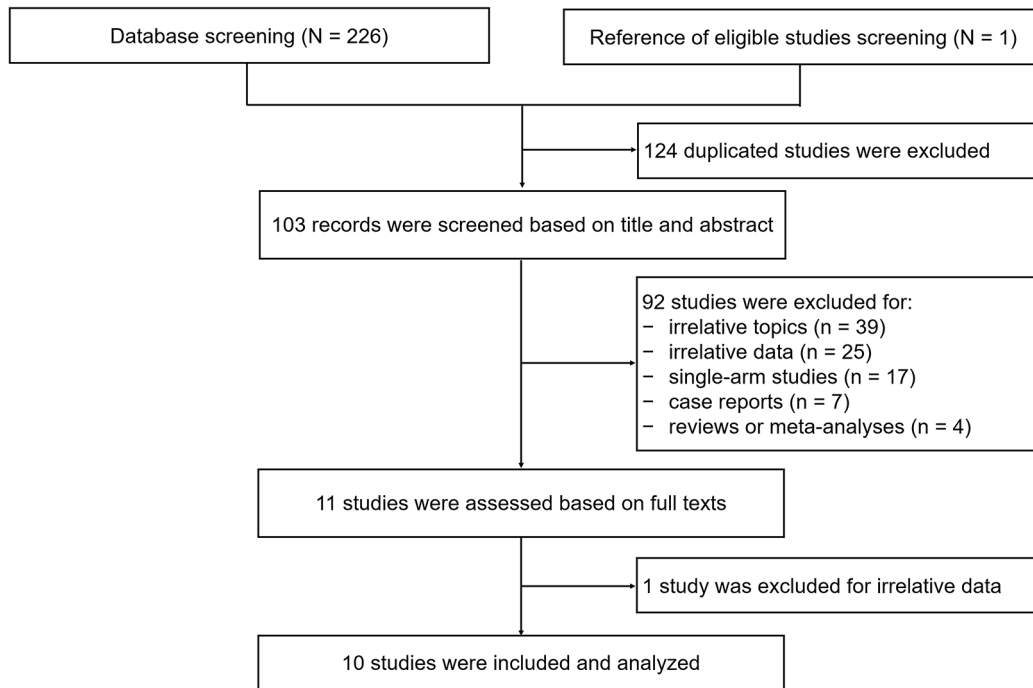


Fig. 1. Study screening.

2021; Li et al. 2021b; Yu et al. 2021; Zheng et al. 2021; Tang and Huang 2022; Wu et al. 2022; Zhang et al. 2022; Zhu et al. 2022; Ding et al. 2023; Fu et al. 2023). There were 6 RCTs and 4 cohort studies. The dose of pyrotinib was 320 mg in Zheng et al. (2021) and Tang and Huang (2022), and it was 400 mg in other studies. The efficacy indices included pCR and ORR, and the safety indices included diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome, and alopecia. However, the safety indices of Ding et al. (2021), Yu et al. (2021), Zhang et al. (2022), Zhu et al. (2022), and Fu et al. (2023) were not reported. The specific features of the screened studies are shown in Table 1.

Comparison of treatment efficacy between the pyrotinib and control groups

A total of 9 studies reported pCR, and heterogeneity did not exist among these studies ($I^2 = 0.0\%$, $P = 0.976$). The fixed effect model suggested that pCR was increased in the pyrotinib group vs. the control group [RR (95% CI): 1.93 (1.63, 2.29), actual value: 50.1% vs. 28.6%, $P < 0.001$] (Fig. 2). Subgroup analysis for pCR was conducted based on study designs. A total of 5 RCTs reported pCR, and heterogeneity did not exist among these RCTs ($I^2 = 0.0\%$, $P = 0.999$). The fixed effect model disclosed that pCR was elevated in the pyrotinib group vs. the control group [RR (95% CI): 1.89 (1.49, 2.40), actual value: 48.0% vs. 25.7%, $P < 0.001$] (Fig. 3A). Four cohort studies reported pCR, and there was no heterogeneity ($I^2 = 0.0\%$, $P = 0.534$). The fixed effect model suggested that pCR was increased in the pyrotinib group vs. the control group [RR (95% CI): 1.98

(1.55, 2.53), actual value: 52.8% vs. 30.7%, $P < 0.001$] (Fig. 3B).

A total of 6 studies reported ORR, and heterogeneity did not exist ($I^2 = 0.0\%$, $P = 0.831$). The fixed effect model indicated that ORR was elevated in the pyrotinib group vs. the control group [RR (95% CI): 1.14 (1.07, 1.21), actual value: 87.3% vs. 75.3%, $P < 0.001$] (Fig. 4).

Comparison of safety between the pyrotinib and control groups

Diarrhea was recorded in 5 studies, and heterogeneity existed among these studies ($I^2 = 91.9\%$, $P < 0.001$). The random effect model suggested that the incidence of diarrhea was increased in the pyrotinib group compared with the control group [RR (95% CI): 1.97 (1.31, 2.96), actual value: 94.8% vs. 49.5%, $P = 0.001$] (Fig. 5A).

Five studies reported nausea and vomiting, and heterogeneity existed among these studies ($I^2 = 93.8\%$, $P < 0.001$). The random effect model revealed that the incidence of nausea and vomiting did not differ between the two groups [RR (95% CI): 1.26 (0.85, 1.88), actual value: 70.9% vs. 45.0%, $P = 0.253$] (Fig. 5B).

Four studies reported leukopenia, and there was no heterogeneity among the studies ($I^2 = 0.0\%$, $P = 0.976$). The fixed effect model indicated that the incidence of leukopenia did not differ between the two groups [RR (95% CI): 1.02 (0.86, 1.20), actual value: 45.7% vs. 44.1%, $P = 0.830$] (Fig. 5C).

Thrombocytopenia was recorded in 4 studies, and there was no heterogeneity among these studies ($I^2 = 0.0\%$, $P = 0.832$). The fixed effect model revealed that the inci-

Table 1. Information on the included studies.

No.	First author	Year	Study design	Sample size		Age		Treatment		Pyrotinib dose (mg)	Efficacy indices	Safety indices
				Pyrotinib	Control	Pyrotinib	Control	Pyrotinib	Control			
1	Ding et al.	2021	RCT	21	30	NR	NR	TCbH+Py	TCbH	400	pCR, ORR	NR
2	Li et al.	2021b	Cohorts	63	53	48 (26-71)	52 (33-65)	EC-T/TCb/T+H+Py	EC-T/TCb/T+H	400	pCR, ORR	Diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome
3	Yu et al.	2021	Cohorts	26	10	NR	NR	TCbH+Py	TCbH	400	pCR	NR
4	Zheng et al.	2021	RCT	16	16	31.7 ± 3.5	32.4 ± 3.9	TCbH+Py	TCbH	320	pCR	Diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome, alopecia
5	Tang and Huang	2022	RCT	50	50	50.7 ± 9.5	50.7 ± 8.9	TAC+Py	TAC	320	ORR	Diarrhea, nausea and vomiting, thrombocytopenia, alopecia
6	Wu et al.	2022	RCT	178	177	50 (43, 55)	50 (44, 55)	TH+Py	TH	400	pCR, ORR	Diarrhea, nausea and vomiting, leukopenia, alopecia
7	Zhang et al.	2022	RCT	40	16	NR	NR	EC-TH Py	EC-TH	400	pCR, ORR	NR
8	Zhu et al.	2022	Cohorts	63	284	≥ 50 years, 28 (44.4%)	≥ 50 years, 123 (43.3%)	TCbH+Py	TCbH	400	pCR	NR
9	Ding et al.	2023	RCT	36	33	51 (31, 69)	54 (35, 68)	TCbH+Py	TCbH	400	pCR, ORR	Diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome
10	Fu et al.	2023	Cohorts	47	15	≥ 50 years, 26 (55.3%)	≥ 50 years, 8 (53.3%)	EC-T/TCb+H+Py	EC-T/TCb+H	400	pCR	NR

Age was shown with mean ± standard deviation, median (quartile 25th, quartile 75th), median (minimum-maximum), or number (percentage).

Py, pyrotinib; RCT, randomized controlled trial; NR, not reported; T, paclitaxel/docetaxel; Cb, carboplatin; H, trastuzumab; A, doxorubicin; C, cyclophosphamide; E, epirubicin; pCR, pathological complete response; ORR, objective response rate.

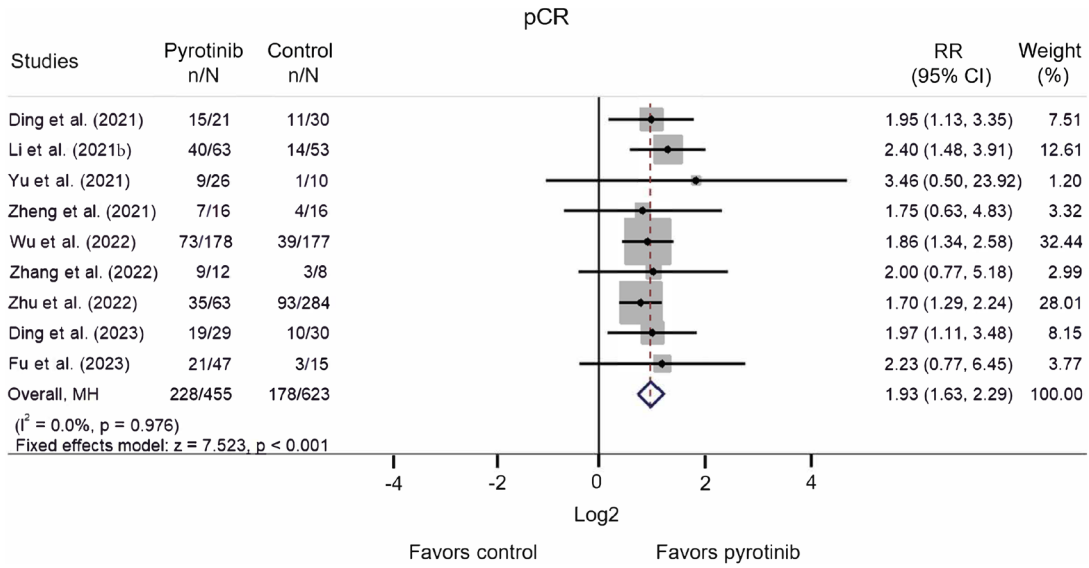
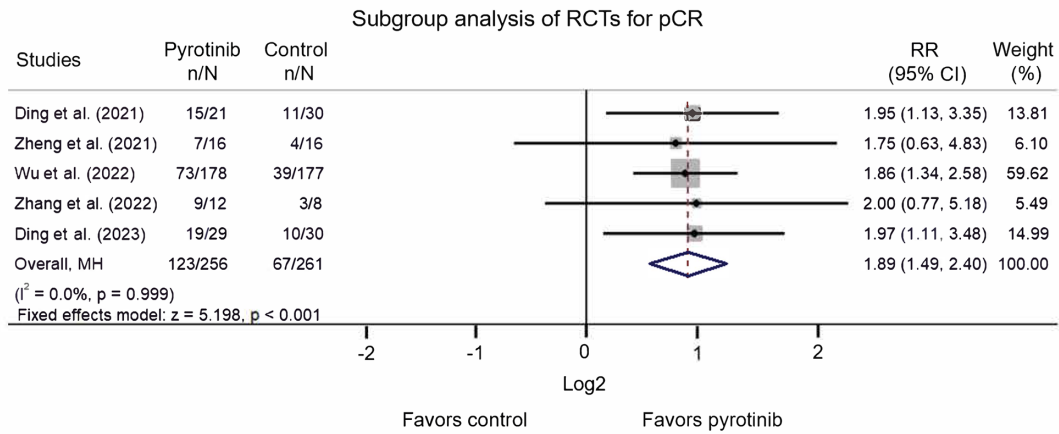


Fig. 2. Forest plot of pCR.

A



B

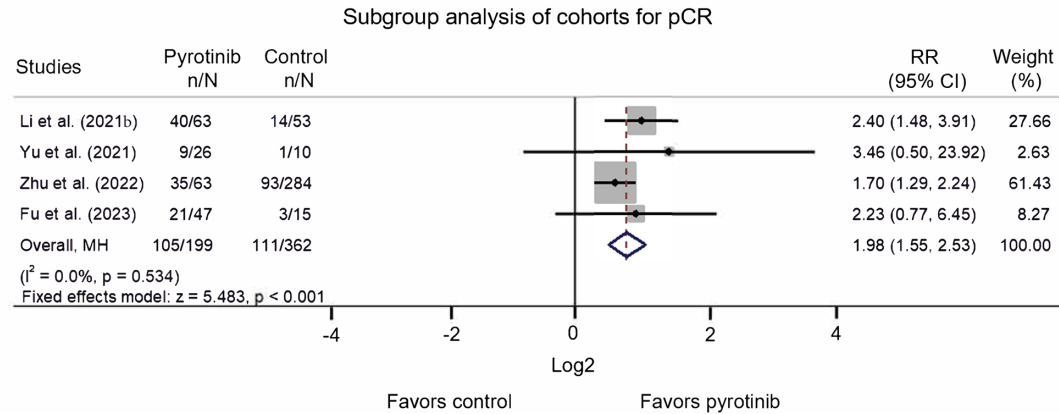


Fig. 3. Subgroup analysis for pCR based on study designs.
Subgroup analysis for pCR in RCTs (A) and cohort studies (B).

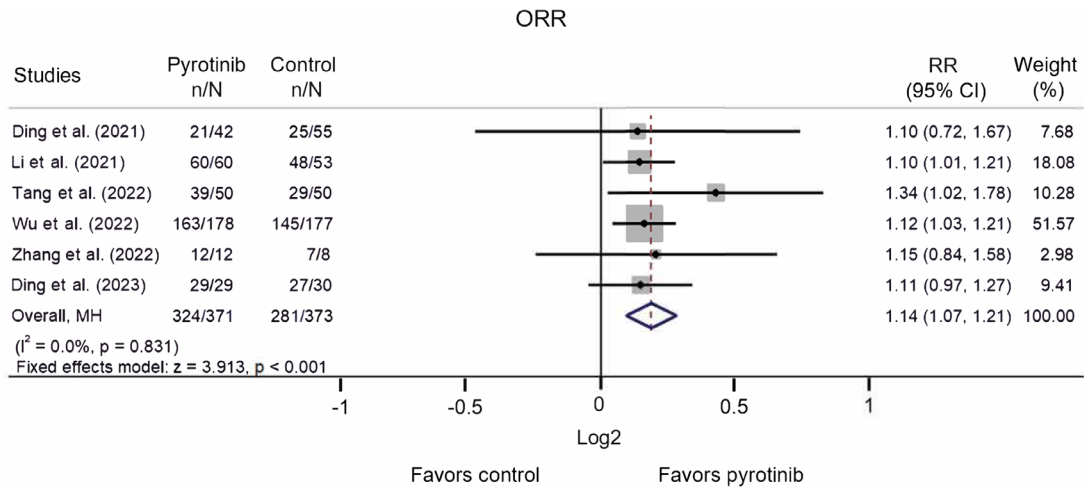


Fig. 4. Forest plot of ORR.

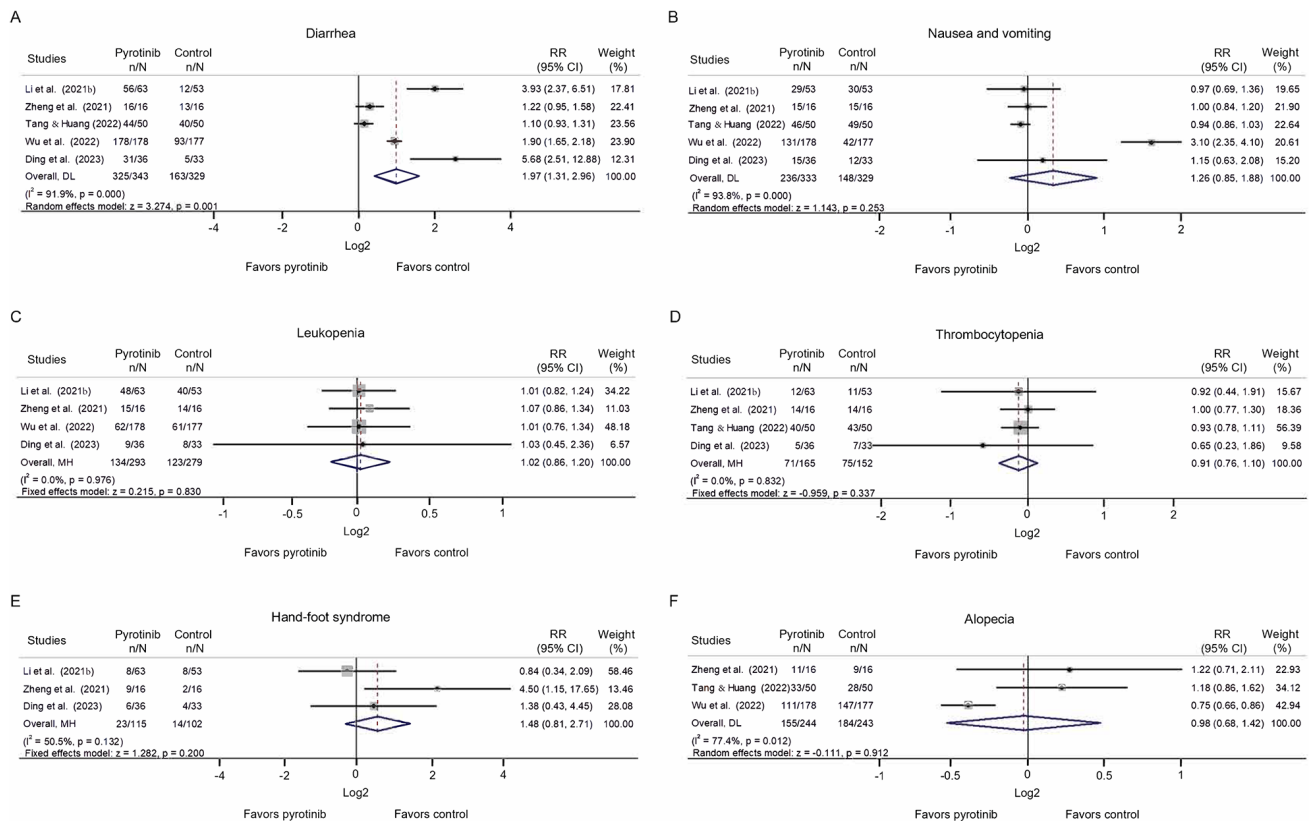


Fig. 5. Forest plot of adverse events. Forest plot of diarrhea (A), nausea and vomiting (B), leukopenia (C), thrombocytopenia (D), hand-foot syndrome (E), and alopecia (F).

dence of thrombocytopenia did not differ between the two groups [RR (95% CI): 0.91 (0.76, 1.10), actual value: 43.0% vs. 49.3%, $P = 0.337$] (Fig. 5D).

Three studies reported on hand-foot syndrome, and no heterogeneity existed among the studies ($I^2 = 50.5\%$, $P = 0.132$). The fixed effect model suggested that the incidence

of hand-foot syndrome did not differ between the two groups [RR (95% CI): 1.48 (0.81, 2.71), actual value: 20.0% vs. 13.7%, $P = 0.200$] (Fig. 5E).

Alopecia was recorded in 3 studies, and heterogeneity existed among these studies ($I^2 = 77.4\%$, $P = 0.012$). According to the random effect model, the incidence of alo-

Table 2. Quality assessment for RCTs by Cochrane Collaboration’s tool.

Studies	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ding et al. (2021)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Zheng et al. (2021)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Tang and Huang (2022)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Wu et al. (2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhang et al. (2022)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Ding et al. (2023)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

RCTs, randomized controlled trials.

Table 3. Quality assessment for cohorts by the Newcastle-Ottawa Scale criteria.

Studies	Selection	Comparability	Outcome	Total score
Li et al. (2021b)	4	2	3	9
Yu et al. (2021)	4	1	2	7
Zhu et al. (2022)	4	2	3	9
Fu et al. (2023)	4	2	2	8

pecia did not differ between the two groups [RR (95% CI): 0.98 (0.68, 1.42), actual value: 63.5% vs. 75.7%, $P = 0.912$] (Fig. 5F).

Quality assessment

According to the Cochrane Collaboration’s tool, both Zheng et al. (2021) and Tang and Huang (2022) were assessed as having a high risk of performance bias and detection bias. Notably, the risks of selection bias, attrition bias, reporting bias, and other biases were low in all 6 RCTs (Table 2). The Newcastle-Ottawa Scale criteria were applied to assess the quality of cohort studies. The total score ranged from 7 to 9, which suggested that the risk of bias was low among the 4 studies (Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis revealed that omitting Li et al. (2021b) would affect the results of hand-foot syndrome. Apart from that, omitting any single study did not affect the results of pooled analyses, which suggested the stability of this meta-analysis (Supplementary Table S1). No publication bias existed in the results for pCR, ORR, diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome, or alopecia (all $P > 0.05$) (Supplementary Table S2).

Discussion

Although HER2-targeted therapy with trastuzumab and pertuzumab remains the standard neoadjuvant treatment for HER2-positive breast cancer patients, pyrotinib enriches treatment options for these patients (Jagosky and Tan 2021; Korde et al. 2021; Qi et al. 2023). Currently,

several clinical studies reported that neoadjuvant pyrotinib improved treatment responses compared to other neoadjuvant treatments in HER2-positive breast cancer patients (Li et al. 2021b; Wu et al. 2022; Zhu et al. 2022; Ding et al. 2023). In this meta-analysis, it was found that the pCR rate and ORR were increased by pyrotinib-containing neoadjuvant treatment compared to other neoadjuvant treatments in HER2-positive breast cancer patients. We speculated that the potential reasons might be that: (1) monoclonal antibodies, such as trastuzumab, act by binding to the extracellular domain of HER2, suppressing downstream pathways and thereby inhibiting tumor progression (Nielsen et al. 2009; Swain et al. 2023). However, pyrotinib exerted anti-tumor effects by binding to the adenosine triphosphate binding site of the intracellular kinase domain of HER1, HER2, and HER4, resulting in the inhibition of tyrosine kinase phosphorylation subsequently obstructing the activation of several pathways (such as the mitogen-activated protein kinase and phosphoinositide 3-kinase/protein kinase B pathways) (Nielsen et al. 2009; Xuhong et al. 2019). Therefore, pyrotinib had a different mechanism from trastuzumab, which might further enhance its antitumor effect, thereby improving the treatment response to neoadjuvant treatment. (2) Pyrotinib might also assist in sensitizing resistant breast cancer cells to HER2 antibody therapies, which further improved the treatment response to neoadjuvant treatment (Derakhshani et al. 2020; Singla and Munshi 2020). (3) Pyrotinib might have synergistic effects with chemotherapies, such as doxorubicin, which inhibited breast cancer cell proliferation, migration, and invasion, thereby improving the treatment response to neoadjuvant treatment (Wang et al. 2021). Taken together, pyrotinib-containing neoadjuvant treatment enhanced the treatment response in HER2-positive breast cancer patients. Moreover, our further subgroup analyses for pCR suggested that the beneficial effect of neoadjuvant pyrotinib on pCR was not affected by the study design.

Tyrosine kinase inhibitors often induce gastrointestinal adverse reactions, and diarrhea is the most frequent adverse event caused by pyrotinib in HER2-positive breast cancer patients (Schlam and Swain 2021; Fang et al. 2022; Mao et al. 2022; Yin et al. 2022; Shyam Sunder et al. 2023).

According to a previous study, the incidence of diarrhea was 88.89% in HER2-positive breast cancer patients receiving pyrotinib-containing neoadjuvant treatment, which was higher than that in patients receiving other neoadjuvant treatments (Li et al. 2021b). In this meta-analysis, it was discovered that the incidence of diarrhea was increased by pyrotinib-containing neoadjuvant treatment compared to other neoadjuvant treatments in HER2-positive breast cancer patients. We speculated that the following potential reasons might explain this difference: (1) Pyrotinib might cause a metabolic imbalance in gut microorganisms, which would contribute to the occurrence of diarrhea (Lai et al. 2023). (2) Pyrotinib might disrupt the negative regulation of chloride secretion by ErbB, which resulted in the occurrence of diarrhea (Van Sebille et al. 2015). (3) Pyrotinib would activate the basolateral membrane potassium channels and apical membrane chloride channels in the intestinal epithelia, which further induced diarrhea (Duan et al. 2019). Although pyrotinib frequently induced diarrhea, this adverse event could be managed by antidiarrheal agents, such as loperamide (Fang et al. 2022). In addition, previous studies also indicated that most diarrhea induced by neoadjuvant pyrotinib was mild (Mao et al. 2022; Wu et al. 2022; Liu et al. 2023; Tian et al. 2023). Therefore, this meta-analysis suggested that the benefit of neoadjuvant pyrotinib in improving treatment response might outweigh its risk of developing diarrhea in HER2-positive breast cancer patients. Apart from diarrhea, other adverse events, including nausea and vomiting, leukopenia, thrombocytopenia, hand-foot syndrome, and alopecia, were not different between pyrotinib-containing neoadjuvant treatment and other neoadjuvant treatments in HER2-positive breast cancer patients. The findings of this meta-analysis suggested that neoadjuvant pyrotinib is a safe and manageable treatment option for HER2-positive breast cancer patients.

According to previous meta-analyses, pyrotinib had the potential to treat HER2-positive metastatic breast cancer patients (Liao et al. 2021; Hu et al. 2023; Yuan et al. 2023). These previous meta-analyses concluded that pyrotinib-containing treatment improved treatment response and survival with manageable adverse events in HER2-positive metastatic breast cancer patients (Liao et al. 2021; Hu et al. 2023; Yuan et al. 2023). However, relevant meta-analyses that focus on neoadjuvant pyrotinib are scarce. Inspired by this, this meta-analysis included 10 studies and revealed the satisfactory efficacy and safety of neoadjuvant pyrotinib in HER2-positive breast cancer patients. However, it should be clarified that although the risk of bias was low and the stability of this meta-analysis was generally good, more evidence is needed to validate the findings of this meta-analysis. Notably, neoadjuvant pertuzumab combined with trastuzumab achieves a higher pCR rate compared to trastuzumab alone in HER2-positive breast cancer patients (Loibl and Gianni 2017). Therefore, it might be meaningful to conduct an analysis comparing efficacy and safety of neoadjuvant pyrotinib combined with pertuzumab and trastu-

zumab versus neoadjuvant pertuzumab combined with trastuzumab in HER2-positive breast cancer patients. Additionally, some previous studies reported that pyrotinib-containing regimens improved the survival profiles compared to other regimens that did not contain pyrotinib in HER2-positive metastatic breast cancer patients (Li et al. 2021a; Xu et al. 2021; Ma et al. 2022; Ma et al. 2023). However, since the survival data are immature in HER2-positive breast cancer patients receiving neoadjuvant regimens, pCR is generally served as a study endpoint (Spring et al. 2020). Therefore, studies with long follow-ups are required to explore the effect of neoadjuvant pyrotinib on survival profiles in HER2-positive breast cancer patients.

Limitations could not be omitted in this meta-analysis. (1) Further studies should explore the effect of neoadjuvant pyrotinib on survival profiles in HER2-positive breast cancer patients. (2) The neoadjuvant regimens used differed among the included studies, which may have affected the results of this meta-analysis. (3) Selection bias and information bias were unavoidable among the 4 cohort studies; thus, more RCTs should be conducted to determine the benefit of neoadjuvant pyrotinib in HER2-positive breast cancer patients.

Our meta-analysis concludes that pyrotinib-containing neoadjuvant treatment enhances the treatment response with controllable adverse events compared to other neoadjuvant treatments in HER2-positive breast cancer patients. The findings of this meta-analysis may provide evidence that pyrotinib could be considered an optional neoadjuvant regimen for HER2-positive breast cancer patients.

Conflict of Interest

The authors declare no conflict of interest.

References

- Aapro, M., Cardoso, F., Curigliano, G., Eniu, A., Gligorov, J., Harbeck, N., Mueller, A., Pagani, O., Paluch-Shimon, S., Senkus, E., Thurlimann, B. & Zaman, K. (2022) Current challenges and unmet needs in treating patients with human epidermal growth factor receptor 2-positive advanced breast cancer. *Breast*, **66**, 145-156.
- Broglio, K.R., Quintana, M., Foster, M., Olinger, M., McGlothlin, A., Berry, S.M., Boileau, J.F., Brezden-Masley, C., Chia, S., Dent, S., Gelmon, K., Paterson, A., Rayson, D. & Berry, D.A. (2016) Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. *JAMA Oncol.*, **2**, 751-760.
- Davey, M.G., Browne, F., Miller, N., Lowery, A.J. & Kerin, M.J. (2022) Pathological complete response as a surrogate to improved survival in human epidermal growth factor receptor-2-positive breast cancer: systematic review and meta-analysis. *BJS Open*, **6**, zrac028.
- Denkert, C., von Minckwitz, G., Darb-Esfahani, S., Lederer, B., Heppner, B.I., Weber, K.E., Budczies, J., Huober, J., Klauschen, F., Furlanetto, J., Schmitt, W.D., Blohmer, J.U., Karn, T., Pfitzner, B.M., Kummel, S., et al. (2018) Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol.*, **19**, 40-50.
- Derakhshani, A., Rezaei, Z., Safarpour, H., Sabri, M., Mir, A.,

- Sanati, M.A., Vahidian, F., Gholamiyan Moghadam, A., Aghadokht, A., Hajiasgharzadeh, K. & Baradaran, B. (2020) Overcoming trastuzumab resistance in HER2-positive breast cancer using combination therapy. *J. Cell. Physiol.*, **235**, 3142-3156.
- Ding, X., Mo, W., Xie, X., Wang, O., Ding, Y., Zhao, S., He, X., Feng, W., Zou, D. & Yang, H. (2021) Pyrotinib as neoadjuvant therapy for HER2⁺ breast cancer: A multicenter, randomized, controlled, phase II trial. *J. Clin. Oncol.*, **39**, 574-574.
- Ding, Y., Mo, W., Xie, X., Wang, O., He, X., Zhao, S., Gu, X., Liang, C., Qin, C., Ding, K., Yang, H. & Ding, X. (2023) Neoadjuvant Pyrotinib plus Trastuzumab, Docetaxel, and Carboplatin in Early or Locally Advanced Human Epidermal Receptor 2-Positive Breast Cancer in China: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial. *Oncol. Res. Treat.*, **46**, 303-311.
- Duan, T., Cil, O., Thiagarajah, J.R. & Verkman, A.S. (2019) Intestinal epithelial potassium channels and CFTR chloride channels activated in ErbB tyrosine kinase inhibitor diarrhea. *JCI Insight*, **4**, e126444.
- 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. *Ann. Palliat. Med.*, **11**, 210-216.
- Fazal, F., Bashir, M.N., Adil, M.L., Tanveer, U., Ahmed, M., Chaudhry, T.Z., Ijaz, A.A. & Haider, M. (2023) Pathologic Complete Response Achieved in Early-Stage HER2-Positive Breast Cancer After Neoadjuvant Therapy With Trastuzumab and Chemotherapy vs. Trastuzumab, Chemotherapy, and Pertuzumab: A Systematic Review and Meta-Analysis of Clinical Trials. *Cureus*, **15**, e39780.
- Fu, C.B., Han, H., Lin, S.G. & Xu, C.S. (2023) A retrospective clinical study of pyrotinib in combination with trastuzumab and pertuzumab in neoadjuvant therapy for HER-2 positive breast cancer. *Chin. J. Clin. Oncol.*, **50**, 882-887.
- Gianni, L., Pienkowski, T., Im, Y.H., Tseng, L.M., Liu, M.C., Lluch, A., Staroslawska, E., de la Haba-Rodriguez, J., Im, S. A., Pedrini, J.L., Poirier, B., Morandi, P., Semiglazov, V., Srimuninnimit, V., Bianchi, G.V., et al. (2016) 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.*, **17**, 791-800.
- Gunasekara, A.D.M., Anothaisintawee, T., Youngkong, S., Ha, N.T., McKay, G.J., Attia, J. & Thakkinian, A. (2022) Neoadjuvant Treatment with HER2-Targeted Therapies in HER2-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis. *Cancers (Basel)*, **14**, 523.
- Higgins, J.P., Thompson, S.G., Deeks, J.J. & Altman, D.G. (2003) Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-560.
- Hu, W., Yang, J., Zhang, Z., Xu, D. & Li, N. (2023) Pyrotinib for HER2-positive metastatic breast cancer: a systematic review and meta-analysis. *Transl. Cancer Res.*, **12**, 247-256.
- Hutton, B., Salanti, G., Caldwell, D.M., Chaimani, A., Schmid, C.H., Cameron, C., Ioannidis, J.P., Straus, S., Thorlund, K., Jansen, J.P., Mulrow, C., Catala-Lopez, F., Gotsche, P.C., Dickersin, K., Boutron, I., et al. (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann. Intern. Med.*, **162**, 777-784.
- Jackisch, C., Lammers, P. & Jacobs, I. (2017) Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars. *Breast*, **32**, 199-216.
- Jagosky, M. & Tan, A.R. (2021) Combination of Pertuzumab and Trastuzumab in the Treatment of HER2-Positive Early Breast Cancer: A Review of the Emerging Clinical Data. *Breast Cancer (Dove Med Press)*, **13**, 393-407.
- Korde, L.A., Somerfield, M.R., Carey, L.A., Crews, J.R., Denduluri, N., Hwang, E.S., Khan, S.A., Loibl, S., Morris, E.A., Perez, A., Regan, M.M., Spears, P.A., Sudheendra, P.K., Symmans, W.F., Yung, R.L., et al. (2021) Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J. Clin. Oncol.*, **39**, 1485-1505.
- Lai, J., Zhuo, X., Yin, K., Jiang, F., Liu, L., Xu, X., Liu, H., Wang, J., Zhao, J., Xu, W., Yang, S., Guo, H., Yuan, X., Lin, X., Qi, F., et al. (2023) Potential mechanism of pyrotinib-induced diarrhea was explored by gut microbiome and ileum metabolomics. *Anticancer Drugs*, **34**, 747-762.
- Li, C., Bian, X., Liu, Z., Wang, X., Song, X., Zhao, W., Liu, Y. & Yu, Z. (2021a) Effectiveness and safety of pyrotinib-based therapy in patients with HER2-positive metastatic breast cancer: A real-world retrospective study. *Cancer Med.*, **10**, 8352-8364.
- Li, Q., Wang, Y., Zhu, M., Gu, Y. & Tang, Y. (2021b) Clinical observation of neoadjuvant chemotherapy with pyrotinib plus trastuzumab in HER2-positive breast cancer: a cohort study. *Gland Surg.*, **10**, 3389-3402.
- Li, X., Yang, C., Wan, H., Zhang, G., Feng, J., Zhang, L., Chen, X., Zhong, D., Lou, L., Tao, W. & Zhang, L. (2017) 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.*, **110**, 51-61.
- Liao, H., Huang, W., Liu, Y., Pei, W. & Li, H. (2021) Efficacy and Safety of Pyrotinib Versus T-DM1 in HER2⁺ Metastatic Breast Cancer Patients Pre-Treated With Trastuzumab and a Taxane: A Bayesian Network Meta-Analysis. *Front. Oncol.*, **11**, 608781.
- Liu, L., Zhu, M., Wang, Y., Li, M. & Gu, Y. (2023) Neoadjuvant pyrotinib plus trastuzumab and chemotherapy for HER2-positive breast cancer: a prospective cohort study. *World J. Surg. Oncol.*, **21**, 389.
- Loibl, S. & Gianni, L. (2017) HER2-positive breast cancer. *Lancet*, **389**, 2415-2429.
- Loibl, S., Poortmans, P., Morrow, M., Denkert, C. & Curigliano, G. (2021) Breast cancer. *Lancet*, **397**, 1750-1769.
- Lundh, A. & Gotsche, P.C. (2008) Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. *BMC Med. Res. Methodol.*, **8**, 22.
- Ma, F., Yan, M., Li, W., Ouyang, Q., Tong, Z., Teng, Y., Wang, Y., Wang, S., Geng, C., Luo, T., Zhong, J., Zhang, Q., Liu, Q., Zeng, X., Sun, T., 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*, **383**, e076065.
- Ma, X., Li, Y., Li, L., Gao, C., Liu, D., Li, H., Zhao, Z. & Zhao, B. (2022) Pyrotinib-based treatments in HER2-positive breast cancer patients with brain metastases. *Ann. Med.*, **54**, 3085-3095.
- Mao, X., Lv, P., Gong, Y., Wu, X., Tang, P., Wang, S., Zhang, D., You, W., Wang, O., Zhou, J., Li, J. & Jin, F. (2022) Pyrotinib-Containing Neoadjuvant Therapy in Patients With HER2-Positive Breast Cancer: A Multicenter Retrospective Analysis. *Front. Oncol.*, **12**, 855512.
- Martinez-Saez, O. & Prat, A. (2021) Current and Future Management of HER2-Positive Metastatic Breast Cancer. *JCO Oncol. Pract.*, **17**, 594-604.
- Nielsen, D.L., Andersson, M. & Kamby, C. (2009) HER2-targeted therapy in breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. *Cancer Treat. Rev.*, **35**, 121-136.
- Qi, X., Shi, Q., Xuhong, J., Zhang, Y. & Jiang, J. (2023) Pyrotinib-based therapeutic approaches for HER2-positive breast cancer: the time is now. *Breast Cancer Res.*, **25**, 113.
- Schlam, I. & Swain, S.M. (2021) HER2-positive breast cancer and

- tyrosine kinase inhibitors: the time is now. *NPJ Breast Cancer*, **7**, 56.
- Shyam Sunder, S., Sharma, U.C. & Pokharel, S. (2023) Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Signal Transduct. Target. Ther.*, **8**, 262.
- Singh, D.D., Lee, H.J. & Yadav, D.K. (2022) Clinical updates on tyrosine kinase inhibitors in HER2-positive breast cancer. *Front. Pharmacol.*, **13**, 1089066.
- Singla, H. & Munshi, A. (2020) HER2 Tyrosine Kinase Inhibitors in the Sensitization to Cancers Resistant to HER2 Antibodies. *Crit. Rev. Oncog.*, **25**, 241-250.
- Spring, L.M., Fell, G., Arfe, A., Sharma, C., Greenup, R., Reynolds, K.L., Smith, B.L., Alexander, B., Moy, B., Isakoff, S.J., Parmigiani, G., Trippa, L. & Bardia, A. (2020) Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. *Clin. Cancer Res.*, **26**, 2838-2848.
- Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.*, **71**, 209-249.
- Swain, S.M., Shastry, M. & Hamilton, E. (2023) Targeting HER2-positive breast cancer: advances and future directions. *Nat. Rev. Drug Discov.*, **22**, 101-126.
- Tang, D.Y. & Huang, J.Y. (2022) Effect of Pyrotinib Combined with TAC Chemotherapy on Disease Control and Expression of IGF-1 and EGFR Protein in Locally Advanced HER2 Positive Breast Cancer. *Medical Innovation of China*, **19**, 078-082.
- Tian, C., Wang, M., Liu, H., Liu, J., Xu, M. & Ma, L. (2023) Efficacy and safety of neoadjuvant pyrotinib plus docetaxel/liposomal doxorubicin/cyclophosphamide for HER2-positive breast cancer. *Ir. J. Med. Sci.*, **192**, 1041-1049.
- Van Sebillie, Y.Z., Gibson, R.J., Wardill, H.R. & Bowen, J.M. (2015) ErbB small molecule tyrosine kinase inhibitor (TKI) induced diarrhoea: Chloride secretion as a mechanistic hypothesis. *Cancer Treat. Rev.*, **41**, 646-652.
- Wang, C., Deng, S., Chen, J., Xu, X., Hu, X., Kong, D., Liang, G., Yuan, X., Li, Y. & Wang, X. (2021) The Synergistic Effects of Pyrotinib Combined With Adriamycin on HER2-Positive Breast Cancer. *Front. Oncol.*, **11**, 616443.
- Wang, H., Cao, H. & Guo, Z. (2023) Efficacy, toxicity and prognostic factors of pyrotinib-involved neoadjuvant therapy in HER2-positive breast cancer: A retrospective study. *Oncol. Lett.*, **26**, 314.
- Wells, G.A., Shea, B., Connell, O.D., Peterson, J., Welch, V., Losos, M. & Tugwell, P. (2000) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses
http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
[Accessed: April 2, 2024].
- Wu, J., Jiang, Z., Liu, Z., Yang, B., Yang, H., Tang, J., Wang, K., Liu, Y., Wang, H., Fu, P., Zhang, S., Liu, Q., Wang, S., Huang, J., Wang, C., et al. (2022) Neoadjuvant pyrotinib, trastuzumab, and docetaxel for HER2-positive breast cancer (PHEDRA): a double-blind, randomized phase 3 trial. *BMC Med.*, **20**, 498.
- Xu, B., Yan, M., Ma, F., Hu, X., Feng, J., Ouyang, Q., Tong, Z., Li, H., Zhang, Q., Sun, T., Wang, X., Yin, Y., Cheng, Y., Li, W., Gu, Y., 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. *Lancet Oncol.*, **22**, 351-360.
- Xuhong, J.C., Qi, X.W., Zhang, Y. & Jiang, J. (2019) Mechanism, safety and efficacy of three tyrosine kinase inhibitors lapatinib, neratinib and pyrotinib in HER2-positive breast cancer. *Am. J. Cancer Res.*, **9**, 2103-2119.
- Yin, W., Wang, Y., Wu, Z., Ye, Y., Zhou, L., Xu, S., Lin, Y., Du, Y., Yan, T., Yang, F., Zhang, J., Liu, Q. & Lu, J. (2022) Neoadjuvant Trastuzumab and Pyrotinib for Locally Advanced HER2-Positive Breast Cancer (NeoATP): Primary Analysis of a Phase II Study. *Clin. Cancer Res.*, **28**, 3677-3685.
- Yu, Z.G., Xiong, B., Yang, Z., Kong, L., Wang, F. & Wang, Y. (2021) The addition of pyrotinib in early or locally advanced HER2-positive breast cancer patients with no response to two cycles of neoadjuvant therapy: A prospective, multicenter study. *Ann. Oncol.*, **32**, S428.
- Yuan, Y., Liu, X., Cai, Y. & Li, W. (2023) Pyrotinib versus lapatinib therapy for HER2 positive metastatic breast cancer patients after first-line treatment failure: A meta-analysis and systematic review. *PLoS One*, **18**, e0279775.
- Zhang, X., Zhang, S., Li, Z., Niu, F., Cai, H., Li, X., Han, M., Huang, R. & Liu, Y. (2022) Pyrotinib combined with EC-TH neoadjuvant therapy for patients with HER2-positive breast cancer: A multicenter, randomized, phase II, open-label trial, **40**, e12604-e12604.
- Zheng, X.X., Zhang, X.X., Wu, J., Gu, S.C., Jiang, X.L., Shi, X.H., Yuan, M., Lu, B.L., Qiu, X., Bai, J.Y., Yang, P. & Guan, X.Q. (2021) Efficacy and safety of pyrotinib combined with TCbH regimen in treatment of young patients with locally advanced HER-2 positive breast cancer at first diagnosis. *Chinese Journal of General Surgery*, **30**, 1304-1310.
- Zhu, J., Jiao, D., Wang, C., Lu, Z., Chen, X., Li, L., Sun, X., Qin, L., Guo, X., Zhang, C., Qiao, J., Yan, M., Cui, S. & Liu, Z. (2022) Neoadjuvant Efficacy of Three Targeted Therapy Strategies for HER2-Positive Breast Cancer Based on the Same Chemotherapy Regimen. *Cancers (Basel)*, **14**, 4508.

Supplementary Files

Please find supplementary file(s);
<https://doi.org/10.1620/tjem.2024.J026>