Safety and efficacy of pyrotinib for HER-2-positive breast cancer in the neoadjuvant setting: A systematic review and meta-analysis

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Received November 3, 2023; Accepted February 16, 2024

DOI: 10.3892/ol.2024.14325

Abstract. As a novel tyrosine kinase inhibitor (TKI), pyrotinib can irreversibly block dual pan-ErbB receptors and has been used in the treatment of advanced or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, there are limited data on the use of pyrotinib in early breast cancer. Therefore, the present meta-analysis was conducted to evaluate the safety and efficacy of pyrotinib in the neoadjuvant setting for patients with early-stage or locally advanced HER2-positive breast cancer. Online databases (Pubmed, Web of Science, Embase and Cochrane Library) were comprehensively searched for eligible prospective clinical trials on August 17, 2023. The primary endpoint was the treatment-related adverse events (TRAEs), and the secondary endpoint was pathological complete response (pCR) rate. In total, seven trials with a total enrolment of 407 patients were included. A total of seven studies evaluated pyrotinib in combination with trastuzumab and chemotherapy in the neoadjuvant setting. The median age ranged from 47-50 years. The most common TRAEs were diarrhea [98% of patients; 95% confidence interval (CI): 92-100%], followed by anemia (71%; 95% CI: 55-89%), vomiting (69%; 95% CI: 55-82%), and leucopenia (66%; 95% CI: 35-91%). No treatment-related deaths occurred. The pooled pCR rate was 57% (95% CI: 47-68%). It was concluded that pyrotinib-containing neoadjuvant therapy could be an effective treatment strategy in patients with early-stage or locally advanced HER2-positive breast cancer; however, the management of adverse events should be a key consideration. The management of adverse events should be paid great attention to, during pyrotinib therapy, although pyrotinib-contained neoadjuvant therapy could be an effective treatment for patients with early-stage or locally advanced HER2-positive breast cancer. Head-to-head randomized clinical trials are warranted to further confirm the benefits and risks associated with pyrotinib therapy in patients with breast cancer.

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Key words: human epidermal growth factor receptor 2-positive breast cancer, meta-analysis, neoadjuvant therapy, pyrotinib, trastuzumab

Introduction

Breast cancer has overtaken lung cancer to become the most prevalent malignancy worldwide, according to the latest statistics (1). Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is one of the most invasive subtypes, accounting for 15-20% of all breast cancers (2). Beyond that, HER2-positive status is considered an independent prognostic factor and therapeutic target. In addition, anti-HER2 therapy has changed the treatment paradigm and altered the natural history of HER2-positive breast cancer (3,4).

For early-stage or locally advanced breast cancer, neoadjuvant therapy has emerged as the most effective method for decreasing advanced locoregional disease, which increases the chance of successful surgical resection and provides an opportunity for breast-preserving procedures in female patients (5). Moreover, response to neoadjuvant therapy provides prognostic information relevant to follow-up management. Neoadjuvant therapy with HER2-targeted agents has led to a considerable increase in the pathological complete response (pCR) rate in patients with HER2-positive breast cancer. Studies that combined dual anti-HER2 inhibition with conventional chemotherapy have shown improvements in survival compared with single-drug targeted combinations (6). Although a controversial surrogate for long-term survival, it is undeniable that pCR after neoadjuvant treatment correlates positively with DFS and OS, especially in triple-negative and HER2-positive subtypes (7).

Pyrotinib is an orally administered, small molecule, irreversible pan-ErbB receptor tyrosine kinase inhibitor (TKI) that can simultaneously target HER1/epidermal growth factor receptor (EGFR), HER2, and HER4 (8). In the PHENIX trial,

PHOEBE trial, and the study of Ma *et al* (9), 67-78.5% of patients in the respective pyrotinib group achieved an objective response. Furthermore, pyrotinib efficacy has been confirmed in patients with advanced HER2-positive breast cancer who progressed after trastuzumab and lapatinib treatment, as well as in those with brain metastases. Certainly, the treatment-related adverse events were inevitable, and the most common TRAEs caused by pyrotinib and capecitabine were diarrhea, hand-foot syndrome, vomiting, decreased white blood cell count, and decreased neutrophil count (9-14). Therefore, pyrotinib has been approved for use in combination with capecitabine in China for previously treated HER2-positive metastatic or advanced breast cancer patients (15).

Importantly, although several relevant early trials are underway, there is limited information on the use of pyrotinib in a neoadjuvant setting. Therefore, a meta-analysis was conducted to assess the safety and efficacy of pyrotinib in combination with trastuzumab and chemotherapy in stage I-III HER2-positive breast cancer.

Materials and methods

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16).

Search strategy. A systematic search was conducted using databases [PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com), Embase (https://www.embase.com/) and Cochrane Central (https://www.cochranelibrary.com/central/about-central)] to identify eligible studies. The last search date was August 17, 2023. The search terms included: i) pyrotinib, ii) trastuzumab and iii) breast cancer. Manual searches of reference lists in identified reviews were performed to identify additional eligible studies.

Outcomes. The primary outcome was treatment-related adverse events (TRAEs), including any Grade and ≥3 Grade TRAEs. The pCR rate was the secondary endpoint. pCR is defined as the absence of microscopically invasive residual tumor cells in the breast and axillary lymph nodes, with the possible presence of ductal carcinoma in situ (ypT0/Tis ypN0).

Study selection. Inclusion criteria were as follows: i) Participants: All patients had been newly diagnosed with early or local advanced (stage I-III) HER2-positive breast cancer; ii) Intervention: Patients were treated with pyrotinib-based dual-HER2 target neoadjuvant therapy; iii) Outcome: Detailed treatment-related data, such as TRAEs and/or pCR rate; iv) Study type: Prospective clinical trials published in English. Retrospective studies, preclinical studies, conference abstracts, case reports, reviews and commentaries, as well as articles published in languages other than English or without treatment data available were excluded.

Data extraction and quality assessment. The following data were extracted from included studies by two independent reviewers: Name of the first author, publication year, study design, sample size, median age, therapeutic strategy and toxicities. The quality of included randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool, and the quality of single-arm clinical trials was assessed according to the methodological index for non-randomized studies (17). The details of quality evaluation are shown in Fig. S1 and Table SI.

Statistical analysis and risk of bias. The incidence of TRAEs and pCR rates were analyzed using R software (version 4.2.1; The R Foundation) and RevMan 5.4 (The Cochrane Collaboration). For single-arm data, a random-effects model was applied to reduce the risk of bias. Relative risk was used for the dichotomous outcomes of subgroup analysis. Heterogeneity among the included studies was measured using the I^2 statistic. Based on the percentage of I^2, heterogeneity was defined as low level ($I^2 \leq 50\%$) and high level ($I^2 > 50\%$) (18). Egger's tests, funnel plots, and sensitivity analyses were used to evaluate publication bias.

Results

Eligible studies and basic characteristics. In total, 564 relevant records were identified, of which 91 records were from PubMed, 175 from Web of Science, 239 from Embase and 59 records from Cochrane Library. Overall, 242 duplicate records were excluded, and a further 274 records were excluded due to irrelevancy. A further sum of 41 articles were excluded in the following categories: Meeting abstracts (n=14); registered trials/no data (n=14); single target therapy (n=1); case report (n=3); retrospective studies (n=8); and non-English language (n=1). Finally, seven prospective studies were included that met all the selection criteria. A flow diagram detailing the present procedure is shown in Fig. 1 (19-25).

A total of seven prospective clinical trials with a combined total of 407 participants were included (382 patients in the safety analysis and 395 in the efficacy analysis). All studies were published between 2020-2023; details of each study are provided in Table I. The studies by Xuhong *et al* (22) and Shi *et al* (25), were reports from the same clinical trial (ChiCTR Identifier: ChiCTR1900022293) but presented different data. Patients in this clinical trial received a sequential anthracycline-taxane regimen, while patients in the five other studies received paclitaxel-based chemotherapy (23,24).

TRAEs. Overall, 382 patients across six studies (19-24) were included in the safety analysis. Details of TRAEs associated with pyrotinib combination therapy are shown in Table II. The pooled incidences of TRAEs (occurring in ≥40% patients) were: diarrhea [98%; 95% confidence interval (CI): 92-100%, P<0.01]; anemia (71%; 95% CI: 50-89%; P<0.01); vomiting (69%; 95% CI: 55-82%; P<0.01); leucopenia (66%; 95% CI: 35-91%; P<0.01); neutropenia (59%; 95% CI: 33-82%; P<0.01); nausea (59%; 95% CI: 38-77%; P<0.01); fatigue (58%; 95% CI: 34-81%; P<0.01); alanine transaminase (ALT) increased (42%; 95% CI: 31-54%; P<0.01); rash (42%; 95% CI: 21-64%; P<0.01). The aggregated incidence of Grade ≥3 TRAEs is displayed in Table III. Diarrhea, neutropenia and leucopenia were the most frequently reported Grade ≥3 TRAEs, with incidences of 44% (95% CI: 39-49%; P=0.82), 23% (95% CI: 10-39%;

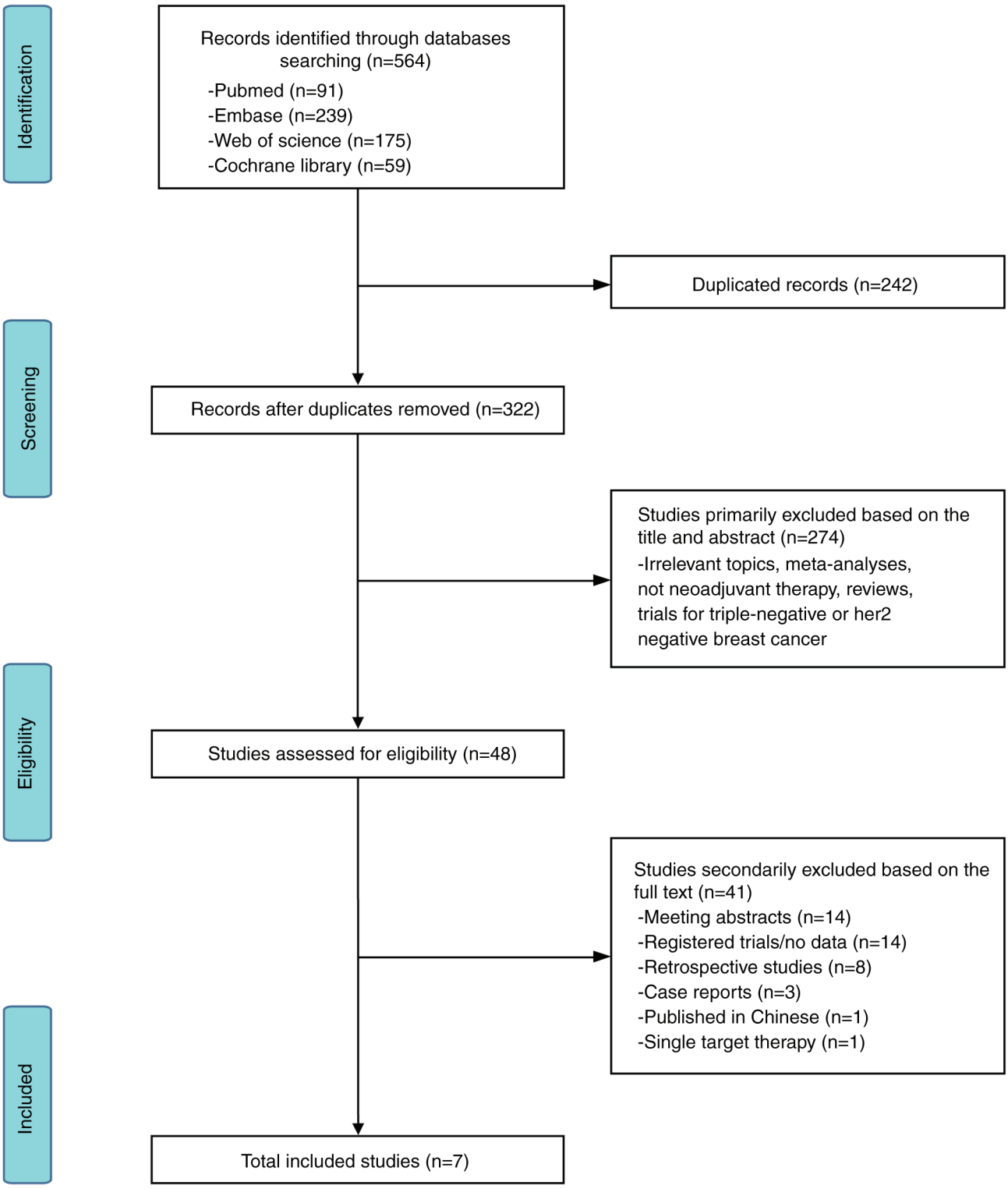

Figure 1. Flowchart of selecting the eligible studies.

P<0.01) and 20% (95% CI: 8-36%; P<0.01), respectively. No treatment-related deaths were reported.

PCR rate. To calculate the overall pCR rate for pyrotinib in neoadjuvant settings, the pCR values for 395 patients across six studies (19-21,23-25) were pooled. The proportion of participants who achieved pCR was 57% (95% CI: 47-68%; P<0.01) (Fig. 2A). Moreover, the association between pCR rate and hormone receptor (HR) status was evaluated. The results of the present study revealed that the pooled pCR rate for patients with HR negative status (estrogen receptor and progesterone receptor negative) and HR positive status (estrogen receptor and/or progesterone receptor positive) was 72% (95% CI: 59-83%; P=0.02) and 46% (95% CI: 33-59%, P<0.01), respectively (Fig. 2B and C). HR negative status was associated with a significantly higher pCR rate than HR

Table I. Basic characteristics and treatment schedules of eligible studies.

Author(s), year	Design	Number of patients	Median age (range)	Pyrotinib	Trastuzumab	Chemotherapy	Cycles	Median duration of therapy (range)	(Refs.)
Xuhong *et al*, 2020	Single arm, prospective study	20	47.5 (30-66)	400 mg once daily	8 mg/kg first load followed by 6 mg/kg on day 1, for cycles 5 to 8	Epirubicin: 100 mg/ m^2 on day 1, for cycles 1 to 4; cyclophosphamide: 600 mg/m^2 on day 1, for cycles 1 to 4; docetaxel: 100 mg/m^2 on day 1, for cycles 5 to 8	Eight 21-day cycles	5.7 (5.3-6.1) months	(22)
Zhong *et al*, 2022	Single arm, prospective study	21	48 (28-57)	400 mg once daily	4 mg/kg loading dose, followed by 2 mg/kg once a week	Nab-paclitaxel: 125 mg/m^2 on days 1, 8 and 15	Four 21-day cycles	2.7 (2.6-3.1) months	(19)
Liu *et al*, 2022	Single arm, prospective study	74	50 (31-64)	400 mg once daily	8 mg/kg loading dose and 6 mg/kg maintenance dose on day 1	Docetaxel: 75 mg/m^2 on day 1; carboplatin: 6 mg/ml/min on day 1	Six 21-day cycles	NR	(21)
Yin *et al*, 2022	Single arm, prospective study	53	47 (26-66)	400 mg once daily	4 mg/kg loading dose and 2 mg/kg maintenance once a week	Paclitaxel: 80 mg/m^2 on days 1, 8, 15 and 22; cisplatin: 25 mg/m^2 on days 1, 8 and 15	Four 28-day cycle	NR	(20)
Shi *et al*, 2023	Single arm, prospective study	45	48 (NR)	400 mg once daily	8 mg/kg first load followed by 6 mg/kg on day 1, for cycles 5 to 8	Epirubicin: 100 mg/m^2 on day 1, for cycles 1 to 4; cyclophosphamide: 600 mg/m^2 on day 1, for cycles 1 to 4; docetaxel: 100 mg/m^2 on day 1, for cycles 5 to 8	Eight 21-day cycles	NR	(25)

Table I. Continued.

Author(s), year	Design	Number of patients	Median age (range)	Pyrotinib	Trastuzumab	Chemotherapy	Cycles	Median duration of therapy (range)	(Refs.)
Wu *et al*, 2022	Randomized, prospective study	178	50 (43-55)	400 mg once daily	8 mg/kg loading dose and 6 mg/kg maintenance dose on day 1	Docetaxel: 100 mg/m^2 on day 1	Four 21-day cycles	NR	(24)
Ding *et al*, 2023	Randomized, prospective study	36	53 (31-69)	400 mg once daily	8 mg/kg first load followed by 6 mg/kg on day 1, for cycles 5 to 8	Docetaxel: 75 mg/m^2 on day 1; carboplatin: 6 mg/ml/min on day 1	Six 21-day cycles	NR	(23)

NR, not reported.

positive status [relative risk (RR)=1.57; 95% CI: 1.24-1.98; P=0.0002] (Fig. 3A).

In addition to hormonal status, there are other factors that may influence patient outcomes. Therefore, a subgroup analysis was performed which revealed that early nodal stage (RR=1.24; 95% CI: 0.92-1.69; P=0.16; Fig. 3B), early clinical stage (RR=1.45; 95% CI: 1.00-2.09; P=0.05; Fig. 3C) and early clinical tumor stage (RR=1.50; 95% CI: 1.16-1.93, P=0.002; Fig. 3D) were associated with a higher pCR rate.

Sensitivity analysis. The sensitivity analysis of the present study revealed that the arbitrary deletion of a study had little effect on the final pooled outcome, indicating that the results of this data analysis are reliable (Fig. S2A-F).

Risk of publication bias. As demonstrated in Figs. S2-S4 and Table SII, the presence of asymmetric funnel plots indicated a potential publication bias. However, the asymmetry in the funnel plots could also be attributed to other factors, such as genuine heterogeneity among the studies. Furthermore, no significant publication bias was detected with Egger's test for both the incidence of TRAEs and the pooled pCR rate (P>0.05).

Discussion

Monoclonal antibodies (mABs), small molecule TKIs, and antibody-drug conjugates are being increasingly adopted in clinical practice, which has enriched the treatment options for patients and helped to overcome the problem of therapeutic resistance. Studies have confirmed that small-molecule TKIs, such as lapatinib, can also be an effective neoadjuvant treatment strategy (26). A network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer reported that the combination of dual-targeted therapy (trastuzumab plus pertuzumab) and neoadjuvant chemotherapy showed the highest efficacy (27). The pCR rates for patients who received this neoadjuvant therapy ranged from 39.3-66.2% (28-31). However, pyrotinib was not included in the analyses because it had just been approved at the time, and there were no available RCTs. In the present study, a meta-analysis to explore the potential of pyrotinib as neoadjuvant therapy for HER2-positive breast cancer was performed, the results of which may provide useful, informative data for treatment decision-making in clinical practice. Currently, most prospective studies on the combination of pyrotinib and trastuzumab in neoadjuvant therapy are either single-arm studies or RCTs comparing it with a placebo. In the present study, the efficacy of pyrotinib was assessed by analyzing the pooled pCR rate. The pCR rates for patients who received neoadjuvant chemotherapy with the dual-target treatment based on pyrotinib ranged from 41 to 73.58%. While a direct comparison with trastuzumab plus pertuzumab is not feasible, the data suggested that the efficacy of pyrotinib-based dual-targeted therapy is comparable to the current standard treatment (trastuzumab plus pertuzumab).

Pyrotinib acts by competitively binding to the HER2 intracellular kinase domain, effectively inhibiting the activation of downstream signaling pathways. However,

Table II. Treatment-related adverse events (any grades) occurred in patients who received neoadjuvant therapy.

Adverse events	Number of studies	Incidence, %	95% CI, %	P-value
Diarrhea	6	98	92-100	<0.01
Leucopenia	5	66	35-91	<0.01
Vomiting	6	69	55-82	<0.01
Anemia	5	71	50-89	<0.01
Neutropenia	5	59	33-82	<0.01
Fatigue	6	58	34-81	<0.01
Nausea	6	59	38-77	<0.01
ALT increased	6	42	31-54	<0.01
Rash	4	42	21-64	<0.01
AST increased	6	35	23-48	<0.01
Creatinine increased	4	26	17-38	0.05

ALT, alanine transaminase; AST, aspartate transaminase.

Table III. Treatment-related adverse events (≥3 grades) occurred in patients who received neoadjuvant therapy.

Adverse events	Number of studies	Incidence, %	95% CI, %	P-value
Diarrhea	6	44	39-49	0.82
Leucopenia	5	20	8-36	<0.01
Vomiting	6	5	0-12	<0.01
Anemia	5	6	0-21	<0.01
Neutropenia	5	23	10-39	<0.01
Fatigue	6	1	0-3	0.05
Nausea	6	0	0-1	0.91
ALT increased	6	2	1-4	0.23
Rash	4	0	0-1	0.94
AST increased	6	1	0-2	0.81
Creatinine increased	4	1	0-3	0.66

ALT, alanine transaminase; AST, aspartate transaminase.

EGFR and HER2 are also expressed in healthy cells. Consequently, up to 96% of patients with diarrhea treated with second-generation TKIs are assumed to have direct mucosal atrophy and injury caused by the inhibition of ErbB signaling within the intestinal epithelia (32,33). The results from the analysis of the present study revealed that gastrointestinal reactions, as well as myelosuppression, are the most common adverse events of any Grade and also Grade ≥3, which was consistent with other retrospective studies (34-37). It is worth noting that nearly half of the participants in the present analysis experienced Grade 3 diarrhea, with a significantly higher incidence compared with capecitabine combination therapy in advanced or metastatic breast cancer. However, diarrhea (any Grade or Grade ≥3) mainly occurred during cycles 1-2 of treatment, and was generally reversible with appropriate drugs and dose reduction. It is likely that the severity and incidence of diarrhea will increase when TKIs are used in combination with chemotherapy; therefore, clinicians should pay attention to published guidelines on the treatment of diarrhea when managing patients in practice (38).

Of note, it was discovered that the incidence of ALT increased, aspartate transaminase increased, leukopenia and neutropenia were similar between the pyrotinib group and the placebo group in the studies by Wu *et al* (24) and Ding *et al* (23), suggesting that these TRAEs are not significantly related to the addition of pyrotinib, and could be reversed in most patients after symptomatic and prophylactic therapy. It was suggested that drug-related cardiotoxicity should also be closely monitored in clinical practice since anthracycline is associated with cardiotoxicity, especially when given in combination with trastuzumab (39). Small-molecule TKIs are less cardiotoxic compared with mABs (40). It was confirmed that no increased risk of cardiac insufficiency with concomitant pyrotinib and trastuzumab or anthracycline in previous studies (20,22-24). The incidence of other TRAEs caused by pyrotinib-contained neoadjuvant therapy, such as anemia, vomiting, fatigue and creatinine increase was <10%.

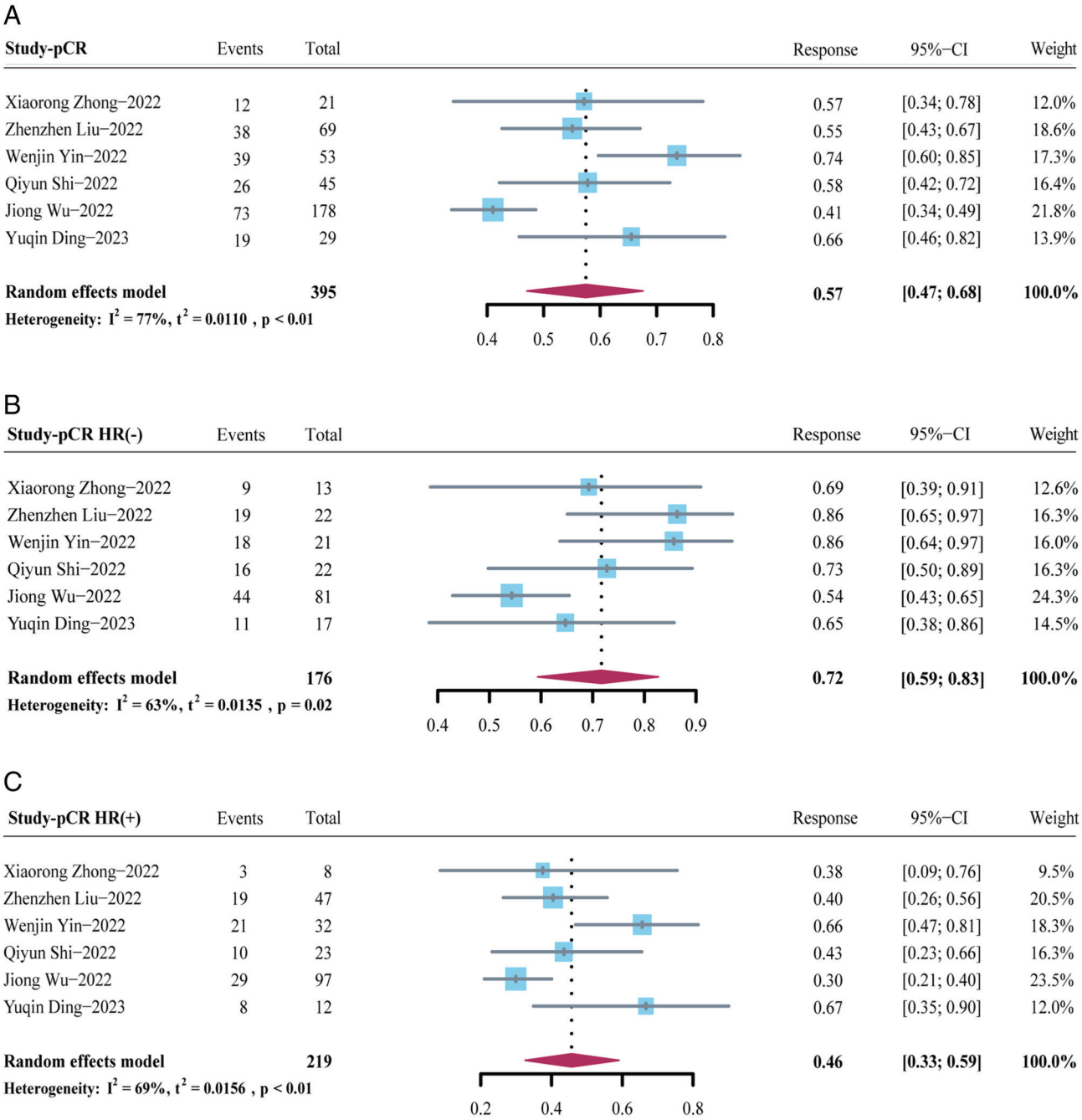

Figure 2. Forest plot about the pooled rate of pCR (A) in total population, (B) in patients with HR-negative and (C) in patients with HR-positive. pCR, pathological complete response; HR, hormone receptor; CI, confidence interval.

Overall, 207 out of 395 patients who received pyrotinib-containing neoadjuvant therapy achieved pCR (defined as the proportion of patients who achieved a complete response or partial response), and the objective response rate was close to 100% across all five studies. Real-world studies have confirmed the activity of pyrotinib in the neoadjuvant setting (34-37). Owing to discrepancies in inclusion criteria, drug dosage and duration of therapy, optimal dosing of pyrotinib in combination with chemotherapy remains unknown and must be further explored in future research. However, several trails published to date have demonstrated that standard neoadjuvant chemotherapy with anthracyclines or paclitaxel plus pyrotinib was well tolerated and effective.

Of note, patients with HR-negative status were more likely to achieve pCR than HR-positive positive (72 vs. 46%, respectively). This is likely due to the high dependence of HR-negative tumors on the HER2 gene for growth and proliferation. Tumors with HR-positive status also rely on the estrogen receptor pathway, and blocking HER2 alone is not sufficient to achieve a potent antitumor effect (36). Despite this, it was identified that pCR was positively associated with long-term outcomes regardless of HR status. PIK3CA mutations are common in breast cancer, and ~20-25% of patients with HER2-positive breast cancer have this mutation. PIK3CA has emerged as a major cause of resistance to HER2-targeted therapy and is associated with a lower pCR rate and poor

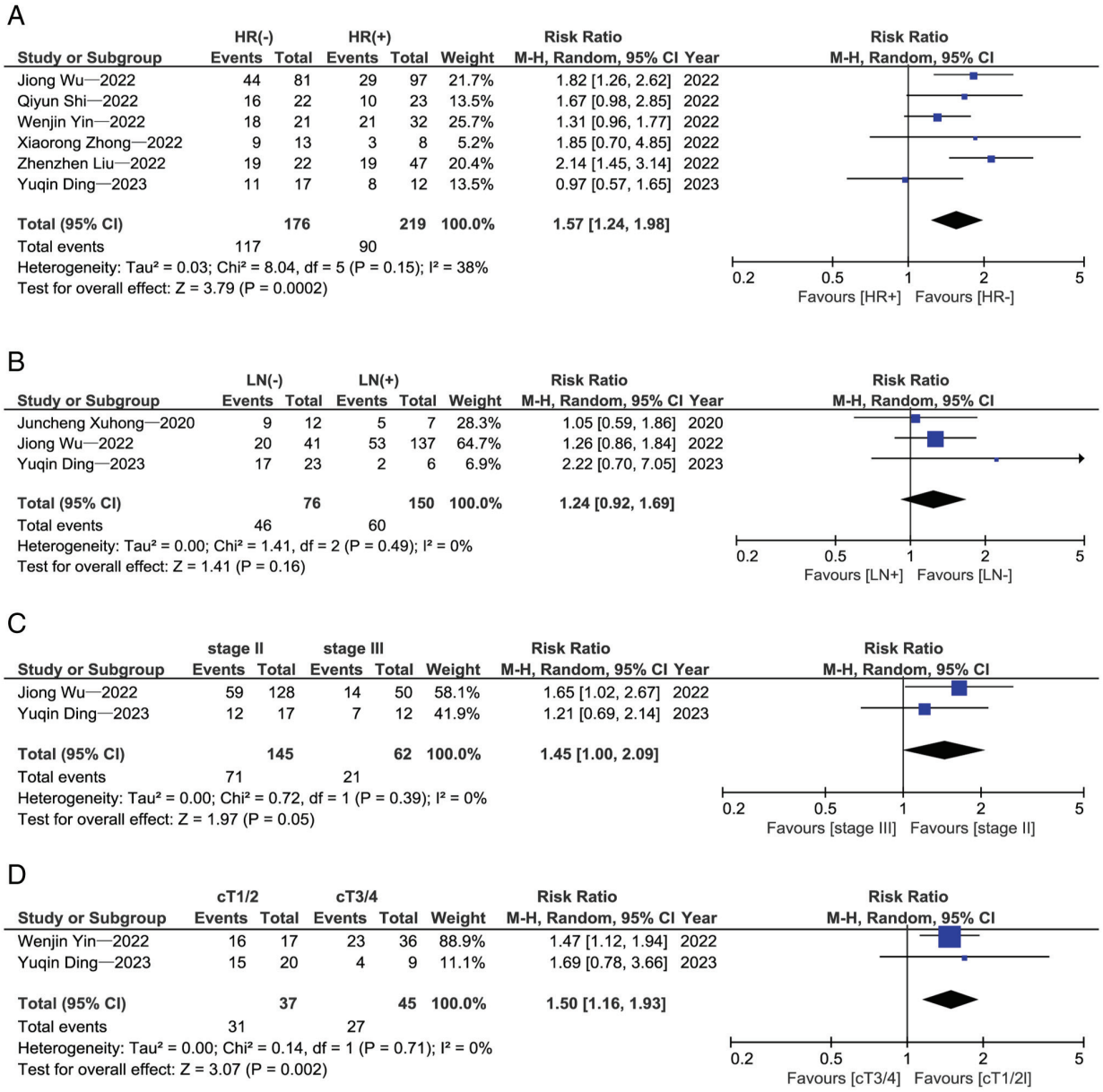

Figure 3. Subgroup analysis: Meta-analysis of pCR (A) in patients with HR negative and HR positive, (B) in patients with LN-negative and LN-positive, (C) in patients with clinical stage II and clinical stage III and (D) in patients with clinical tumor stage 1/2 and clinical tumor stage 3/4. pCR, pathological complete response; HR, hormone receptor; LN, lymph node; CI, confidence interval.

prognosis (41-43). In the NeoATP trial, ~24% (n=13) of patients with HER2-positive breast cancer had PIK3CA mutations, and their pCR rate after neoadjuvant therapy was not significantly different from that of wild-type patients (76.92 vs. 72.50%, respectively; P=0.753). However, this is in contradiction with the results reported in a number of studies (25,44).

In the past, numerous research analyses on pyrotinib in patients with advanced HER2-positive breast cancer have been published (14,45). However, the present study represents the first investigation into the safety and efficacy of pyrotinib in neoadjuvant therapy for HER2-positive breast cancer patients, to the best of the authors' knowledge. Additionally, in the present research, the relationships between tumor staging, hormone status, PIK3CA mutations and treatment efficacy were explored. Certainly, there are several limitations to the analysis of the present study. Firstly, some of the included studies were single-arm, phase II trials with small patient populations and no control arm. Secondly, each trial used different regimens and doses of neoadjuvant chemotherapy, and it was not possible to estimate the impact of different chemotherapy strategies on the incidence and severity of adverse events, which may have led to bias in the results of the present study. Finally, included clinical trials were carried out in recent years and had a short follow-up time; therefore, time followed-up, mature survival data were not available. In spite of these limitations, both pooled data and individual data from each trial demonstrated the efficacy and safety of pyrotinib for neoadjuvant therapy in patients with HER-2 positive breast cancer.

In conclusion, the results of the present meta-analysis, affirmed that pyrotinib plus trastuzumab is a relatively tolerable and effective dual-HER2 blockade regimen for patients

with HER2-positive breast cancer in the neoadjuvant setting, whether in combination with paclitaxel- or anthracycline-based chemotherapies. However, given the notable incidence of adverse events in the analysis of the present study, proactive management of toxicities and regular laboratory examination are essential for patients on combination therapy, with particular vigilance required for the development of severe diarrhea, leukopenia, and neutropenia. Importantly, most adverse events are reversible with drug reduction or symptomatic treatment. In the future, more relevant clinical RCTs will be required to verify the conclusions of the analysis of the present study. In addition, additional studies are needed to identify the optimal combination therapies, patient population, dosage and treatment cycles with pyrotinib-containing neoadjuvant therapy in clinical practice.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

QM conceptualized the present study. BCW and BW developed methodology. QM and BCW extracted data. QM, BCW, BW, GW, XZ and YW performed formal analysis. QM wrote the original draft. BCW and BW wrote, reviewed and edited the manuscript. QM, BW and BCW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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