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Review Article

Pyrotinib: A promising Tyrosine Kinase Inhibitor for treating Breast Cancer

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Abstract

Globally breast cancer is the second leading cause of mortality in women. The past two decades have seen tremendous progress in understanding and treating the disease, leading to more efficient and less toxic regimens. Anti-HER2 cancer drugs, particularly for metastatic breast cancer (MBC), are key for effective treatment. Lapatinib and neratinib are Food and Drug Administration (FDA) approved, while pyrotinib, a novel and potentially safer HER2-targeted drug, shows promise in treating HER2-positive MBC. Phase I and II trials demonstrated pyrotinib's safety and efficacy, particularly when combined with capecitabine. Compared to lapatinib, pyrotinib achieved significantly higher overall response rates and prolonged progression-free survival (PFS) in patients with HER2-positive MBC previously treated with standard therapies. Notably, pyrotinib also exhibited anti-tumor activity against brain metastases, a common challenge in HER2-positive MBC. In addition to performing well, pyrotinib is more tolerable, with manageable side effects, than the standard treatment, like trastuzumab. While conditionally approved in China, further research is needed to fully establish pyrotinib's safety and efficacy profile. Ongoing phase IV trials in China and a phase I trial in the USA are crucial steps. Overall, pyrotinib offers a promising new option for HER2-positive breast cancer treatment, potentially with a better safety and efficacy profile than existing drugs.

Keywords: Pyrotinib, HER2-positive breast cancer, clinical trial, anti-tumor, novel cancer treatment

1. Introduction

Gastric carcinoma Trastuzumab revolutionized HER2-positive breast cancer treatment, but lapatinib, a small molecule and predecessor of pyrotinib, proved to be less effective. Also, T-DM1, an antibody-drug conjugate further positioned small molecules like lapatinib for later treatment stages. However, novel small-molecule drugs, like Pyrotinib, are emerging as promising options with improved efficacy compared to lapatinib. Researchers are exploring using pyrotinib earlier in the treatment course and potentially during the perioperative period to potentially suppress brain metastasis recurrence (Yamashita 2020). Pyrotinib, also known as SHR1258, is a new generation of anti-HER2 therapeutic target drugs developed by Jiangsu Hengrui Pharma (Xuhong et al. 2019). It received conditional approval from the Chinese State Drug Administration based on its positive results in a phase II trial (Blair 2018). The molecular formula of pyrotinib is $C_{32}H_{31}ClN_6O_3$, while its molecular weight is to be 583.1 g/mol (Pharmacompass 2018).

A pharmacokinetic study of pyrotinib identified 24 metabolites, including 16 phase I and 8 phase II metabolites. Pyrotinib was absorbed in 1 hour,

peaked at 4 hours, and exhibited slow elimination. The covalently bound pyrotinib dissociated from the human plasma protein, metabolized by oxidation, was excreted via fecal clearance (main excretion route) (Meng et al. 2019). The principal human metabolites (M1, M2, and M5) were confirmed via synthetic references. CYP3A4 played a key role in pyrotinib biotransformation, emphasizing the need to assess potential CYP3A-mediated drug interactions in humans (Zhu et al. 2016).

It is an orally bioavailable, dual kinase inhibitor of the epidermal growth factor receptor (EGFR or HER-1) and the human epidermal growth factor receptor 2 (ErbB2 or HER-2). Following drug administration, pyrotinib binds to and inhibits EGFR and HER2, potentially inhibiting tumor growth, as well as angiogenesis, and tumor regression in EGFR/HER2-expressing tumor cells. The up-regulation of *EGFR* and *HER2* (tyrosine kinases) in various tumor cell types plays a major role in tumor cell proliferation and tumor vascularization (Pharmacompass 2018). Notably, Small molecule drugs, due to their ability to cross the blood-brain barrier, hold promise for treating brain metastases, a challenge with antibody therapies (Yamashita 2020).

2. Breast Cancer Pathophysiology

Physiologically, HER2 activation leads to a cascade of phosphorylation events involving Grb2, SOS, RAS, Raf, MEK, and ultimately ERK. Activated ERK enters the nucleus and triggers gene expression for various cellular processes, including cell growth and survival.

Furthermore, when HER2 forms a complex with HER3, it triggers the PI3K pathway. This pathway leads to the production of PIP3, which activates AKT. Activated AKT regulates various cellular processes through the phosphorylation of other proteins. Additionally, HER2 can indirectly activate AKT by inhibiting PTEN, a natural inhibitor of the PI3K pathway (Maadi et al. 2021).

However, breast cancer cells often have an overabundance of HER2 receptors on their surface. This is referred to as HER2 overexpression or amplification. Unlike other HER family members, HER2 itself lacks a known activating ligand. However, it excels at partnering with other ligand-bound HER receptors to form dimers. These HER2-containing dimers are particularly stable and potent compared to single-receptor activation. This dimerization triggers a cascade of phosphorylation events within the cell, activating crucial downstream pathways like MAPK and PI3K/AKT. These pathways regulate cell growth, proliferation, survival, and migration. HER2 overexpression biases the formation of these potent signaling dimers, leading to uncontrolled cell growth in breast cancer. Consequently, the strong and prolonged signaling triggered by HER2-containing dimers contributes to oncogenic transformation. This, essentially, means normal cells are converted into cancer cells with uncontrolled growth and survival (Yarden 2001).

Deciphering HER2's role in breast cancer has led to the development of targeted therapies. For instance, anti-HER2 antibodies, like trastuzumab, are designed to bind to the HER2 receptor on the cell surface. This can either block its interaction with other HER family members or trigger its degradation through cellular processes (Yarden 2001).

3. HER2-positive Breast Cancer: Deciding Between Pyrotinib and Antibodies

(Li et al. 2017) explained that both pyrotinib and antibodies, like trastuzumab, target the HER2 receptor but have different mechanisms of action. Trastuzumab works by binding to the extracellular domain of the HER2 receptor on

the surface of cancer cells. This blocks HER2 from interacting with other growth factors, essentially inhibiting signaling pathways that promote cancer cell growth and survival. On the other hand, pyrotinib is a small-molecule TKI that binds to the intracellular domain of the HER2 receptor, specifically targeting the ATP binding pocket of the kinase domain. This binding inhibits the enzymatic activity of HER2, preventing it from transmitting signals that promote cancer cell growth and survival.

The fundamental distance is that trastuzumab acts like a "blocker" on the outside of the cell, whereas pyrotinib acts like an "inhibitor" within the cell, targeting a different part of the HER2 protein**.** This difference in mechanism of action can potentially lead to advantages and disadvantages for each drug.

Pyrotinib may be effective against HER2 mutations that render trastuzumab ineffective. However, pyrotinib may have more off-target effects due to targeting the kinase domain, which can be present in other proteins (Li et al. 2017).

A study evaluated pyrotinib, alone or with trastuzumab, to treat HER2-positive metastatic colorectal cancer (mCRC) that has not responded well to other treatments. For this purpose, they enrolled 32 patients with HER2+, RAS wild-type mCRC who had already received at least one standard chemotherapy treatment. The findings revealed that the median PFS was 5.7 months for all patients. A significant portion of patients (34.4%) showed tumor shrinkage (ORR), and disease control (including stable disease) was achieved in 87.5%. Notably, the combination of pyrotinib and trastuzumab appeared to be more effective than pyrotinib alone, with a longer median PFS (8.6 vs. 5.5 months) and a higher ORR (50% vs. 25%). This study suggests pyrotinib, with or without trastuzumab, shows promise for treating HER2-positive mCRC that has not responded well to other treatments. Importantly, the side effects seemed manageable (Zhou et al. 2024).

In clinical studies, when compared to the other two tyrosine kinase inhibitors (TKIs) namely, lapatinib, and neratinib, pyrotinib demonstrated decent levels of drug tolerance, safety, and efficacy, though its efficacy needs to be confirmed by further research (Xuhong et al. 2019).

4. Clinical Studies on Pyrotinib

4.1. Phase I Studies

A phase I and clinical trial about pyrotinib in patients with HER2-positive metastatic breast carcinoma have been completed. This was a single-center, open-label study conducted in China to determine the safety, efficacy, pharmacokinetics, and biomarkers of pyrotinib, sponsored by Jiangsu HengRui Medicine Co., Ltd. The eligibility criteria stated that patients should be between 18 and 70 years of age, with a histologic or cytologic diagnosis of HER2-positive metastatic breast carcinoma, had a performance status of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale, and had adequate bone marrow and organ function. However, subjects with a history of treatment with small molecular anti-HER2 TKIs were excluded. Subsequently, thirty-eight female patients were enrolled, after fulfilling the inclusion criteria. The patients were administered pyrotinib continuously, orally, once per day. Planned dose escalation was 80, 160, 240, 320, 400, and 480 mg. The study found that a continuous once-daily dose of pyrotinib was well tolerated and demonstrated significant antitumor activity and the maximum tolerated dose was 400 mg. However, diarrhea was a dose-limiting toxicity. The promising antitumor activity and acceptable tolerability of pyrotinib warranted further assessment in a phase II study (clinicaltrial.gov ID NCT01937689) (Ma et al. 2017).

The LORDSHIPS, a single-center, open-label, dose-finding phase Ib study, explored the safety and efficacy of a novel oral triplet combination (dalpiciclib, pyrotinib, letrozole) in postmenopausal females with HER2-positive, HR-positive unresectable, relapsed, or metastatic breast cancer (MBC), by using a 3 + 3 design. The inclusion criteria were that the patients must have received ≤1 line of systemic chemotherapy for metastatic stage, ≤1 line of HER2 targeted therapy, and ≤1 line of endocrine therapy. Additionally, the subjects must have at least one extra-cranial measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, an ECOG status of 0-1, and adequate bone marrow and organ function. The exclusion criteria included untreated central nervous system metastases, any prior treatment with CDK4/6 inhibitor, or proven primary resistance to letrozole or anastrozole. 15 participants were split into 3 cohorts. The Dose combination of 2.5mg letrozole, 320mg pyrotinib, and 125mg dalpiciclib was identified as potent. However, dose-limiting toxicities occurred in three patients, with notable grade 3-4 adverse events. Notably, the median PFS was 11.3 months, suggesting potential efficacy. These findings guide further development, particularly in the first-line HER2-positive breast cancer setting (ClinicalTrials.gov ID NCT03772353) (Zhang, Meng, et al. 2022).

4.2. Phase II Studies

One of the significant studies for pyrotinib in phase II trials PERMEATE was a multicenter, single-arm, and two-cohort trial. One notable aspect of this trial was that it delved into the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive MBC. Since these patients are at a higher risk of developing brain metastases. Cohort A included 59 patients who had radiotherapy-naive HER2-positive brain metastases, while cohort B included 19 subjects with progressive disease after radiotherapy, with an ECOG performance status of 0-2. The recruits received 400 mg pyrotinib orally once daily, and 1000 mg/m^2 capecitabine orally, twice daily for 14 days, followed by 7 days off every 3 weeks till disease progression or unacceptable toxicity. The study found that the intracranial objective response rate in cohort A was 74.6%, while in cohort B, it was 42.1%. The study is ongoing, but recruitment is complete. Furthermore, the most common grade 3 adverse event was diarrhea, occurring in 24% of patients in cohort A and 21% in cohort B. However, serious adverse events related to treatment were observed in 3% of patients in cohort A and 16% in cohort B. Notably, no treatment-related deaths occurred during the study. Importantly, the majority of patients in both cohorts had previous exposure to trastuzumab (ClinicalTrials.gov NCT03691051) (Yan et al. 2022).

In an open-label, multicenter, randomized phase II study, the efficacy and tolerability of pyrotinib were compared with lapatinib in combination with capecitabine for Chinese women with HER2-positive MBC. The trial involved 128 patients previously treated with taxanes, anthracyclines, and/or trastuzumab. Pyrotinib demonstrated a significantly higher overall response rate (78.5%) and prolonged PFS (18.1 months) compared to lapatinib (57.1% and 7.0 months, respectively). Moreover, common grade 3 to 4 adverse events included hand-foot syndrome, diarrhea, and decreased neutrophil count (Ma et al. 2019).

4.3. Phase III Studies

In a double-blinded, multicenter, randomized phase III trial, Chinese patients with HER2+ MBC, previously treated with taxanes and trastuzumab, were recruited. In this study, participants were randomized (2:1) to receive 400 mg pyrotinib or placebo once daily with capecitabine. The findings indicated a

significant improvement with pyrotinib plus capecitabine (median PFS: 11.1 months) compared to placebo plus capecitabine (median PFS: 4.1 months). Notably, patients progressing on placebo received subsequent pyrotinib, showing a 38 % response rate and a median PFS of 5.5 months. The most common treatment-related ≥ grade 3 adverse events included diarrhea (30.8%) and hand-foot syndrome (15.7%). The study concluded that in the case of HER2+ MBC that was previously treated with taxanes and trastuzumab, pyrotinib plus capecitabine exhibited significantly better PFS. Moreover, pyrotinib monotherapy showed anti-tumour activity (ClinicalTrial.gov ID NCT02973737) (Jiang et al. 2019)

5. Optimizing Treatment Strategies: Exploring Pyrotinib in HER2-positive Breast Cancer

Numerous studies, in addition to clinical trials, explore the efficacy and potential of pyrotinib. Notably, pyrotinib is reported to be effective as a monotherapy, in combination, as well as adjuvant therapy. Following are some studies furnishing the therapeutic benefits of pyrotinib in breast cancer treatment:

5.1. Pyrotinib as Monotherapy

a) To evaluate how pyrotinib performs in real-world clinical practice for HER2-positive advanced breast cancer (ABC), 171 patients who received pyrotinib treatment between 2017 and 2020 were enrolled in a study. The results indicated that median PFS was 12.0 months overall, whereas, objective response rate (ORR) - meaning tumor shrinkage - was 45.1%. Moreover, clinical benefit rate (CBR) - including complete/partial response and stable disease - was 81.5%. Furthermore, patients who received pyrotinib as first-line treatment, or had not received lapatinib before showed a significantly longer PFS. Notably, a median PFS of 5.0 months was observed for patients who received pyrotinib after other treatments (cross-line treatment). All patients experienced side effects, with diarrhea being the most common (Zhang, Li, et al. 2022)

b) A multicenter real-world study included 172 patients with HER2-positive MBC who received pyrotinib as part of their treatment outside of a clinical trial setting (real-world data). Many patients had received prior treatments, including lapatinib and some had brain metastases. The median PFS was 8.83 months. Patients who received pyrotinib as the first line had a significantly longer PFS compared to those who received it later. Overall response rate (complete or partial response) was good, with over 60% of patients achieving some level of tumor shrinkage. Besides diarrhea, anemia, and leukopenia, there were no major side effects (Yin et al. 2023)

c) Another real-world study was done in China for long-term outcome analysis of pyrotinib in patients With HER2-Positive MBC and brain metastases. For this purpose, researchers looked at the medical records of 239 patients with MBC, who had received pyrotinib treatment between June 2018 and June 2022. Median PFS varied depending on when pyrotinib was given (as first-line, second-line, etc.) but ranged from 8 to 14 months. Interestingly, prior treatment with other HER2-targeted drugs did not significantly affect PFS. Furthermore, for the 61 patients with brain metastasis, the median PFS was 7.5 months, with a median CNS-PFS (central nervous system progression-free survival) of 11.17 months, and a median OS of 21.27 months. It is noteworthy that patients, with brain metastasis, who received radiotherapy along with pyrotinib had a longer OS than those who did not (almost 34 months vs. 20 months, although this difference wasn't statistically significant) (Liang et al. 2023).

5.2. Pyrotinib as an Adjuvant

a) (Xuhong et al. 2020) investigated pyrotinib for treating HER2-positive breast cancer before surgery (neoadjuvant therapy). It was the first study of its kind to look at pyrotinib, combined with a specific chemotherapy regimen (epirubicin, cyclophosphamide, docetaxel) and trastuzumab for HER2-positive breast cancer before surgery. The treatment seemed effective, 73.7% of patients achieved a complete pathological response (tpCR), meaning no sign of cancer cells in the breast tissue after treatment. All the patients had some tumor shrinkage (objective response rate). The treatment was well-tolerated; however, the most common side effects were diarrhea and leukopenia, but no severe side effects occurred (Xuhong et al. 2020).

b) Similar to the previous study, a Phase II clinical trial used pyrotinib for treating HER2-positive breast cancer before surgery as a neoadjuvant therapy. The patients received pyrotinib followed by a combination of epirubicin/cyclophosphamide and then docetaxel/trastuzumab. The treatment appeared effective as 73.7% of patients achieved a tpCR. Notably, all the patients showed some tumor shrinkage, with manageable side effects like diarrhea, and leukocytopenia (Xuhong et al. 2020).

c) This study compares the effectiveness and safety of pyrotinib with trastuzumab to pertuzumab, both used in combination with neoadjuvant therapy for HER2-positive breast cancer. Group I: Pyrotinib + Trastuzumab, Group II: Pertuzumab + Trastuzumab (existing treatment), and Control Group: Trastuzumab alone with chemotherapy (standard care). The 166 patients with HER2-positive breast cancer received neoadjuvant therapy and surgery. The results indicated that Group I (pyrotinib) had a tpCR rate of 63.49%, similar to Group II (pertuzumab) at 54.00%. Both groups achieved a 100% objective response rate (tumor shrinkage). Diarrhea was the most common side effect in the pyrotinib group (88.89%), with some cases being severe (grade 3). In conclusion, pyrotinib with trastuzumab appears to be as effective as pertuzumab with trastuzumab in neoadjuvant therapy for HER2-positive breast cancer (Li et al. 2017).

d) Another study measured the effectiveness and safety of a new drug combination for HER2-positive breast cancer treatment before surgery (neoadjuvant therapy). In this study, pyrotinib was combined with trastuzumab and chemotherapy. Researchers looked at the medical records of 38 patients with HER2-positive breast cancer who received this combination therapy. The percentage of patients with complete disappearance of tumors (complete response) increased throughout treatment (0% to 100%). A significant majority of patients (over 75%) showed tumor shrinkage (objective response) after 4 cycles. Over half (52.6%) of patients achieved tpCR**.** The treatment was generally well-tolerated, with diarrhea being the most common side effect (Yibo Chen 2024)

e) A promising new clinical trial (PILHLE-001) evaluated the effectiveness and safety of a drug combination for treating HR-positive/HER2-low (IHC 2+/FISH negative) early breast cancer (EBC), responding poorly to traditional treatments. The study investigated a combination of pyrotinib with chemotherapy before surgery. The main measure of success was the percentage of patients who achieved a complete or near-complete disappearance of cancer cells (RCB 0/I rate). Over half (54.2%) of patients achieved RCB 0/I. Other positive outcomes included a high rate of breast-conserving surgery (BCS) and a good overall response rate (ORR). Side effects were mostly mild or moderate (grade 1 or 2), while serious side effects (grade 3) occurred in some patients,

with diarrhea being the most common. There were no treatment-related deaths (Gong et al. 2024).

f) Pyrotinib was investigated as a neoadjuvant therapy, in combination, with trastuzumab-based therapy in a real-world setting for treating early-stage HER2-positive breast cancer before surgery. The study included 23 patients with early-stage HER2-positive breast cancer, who received pyrotinib, trastuzumab, and one of two standard chemotherapy regimens. A notable 52.2% of patients achieved tpCR, meeting the study's success criteria. Similar to previous studies, diarrhea, leukopenia, and anemia, were the commonly reported side effects, but there were no treatment-related deaths (Zhou and Wang 2024).

g) A meta-analysis confirmed that pyrotinib holds promise for treating early-stage HER2-positive breast cancer, but with some caveats. The literature search gave a promising tpCR rate of 57%. Whereas, diarrhea remained the most common side effect, affecting nearly all patients (98%). However, the meta-analysis looked at data from a relatively small number of patients (407) across seven studies (Ma et al. 2024).

5.3. Pyrotinib in Combination Therapy

a) A nonrandomized Phase II trial provided the combination therapy for breast cancer with brain metastases. The trial aimed to assess whether adding radiotherapy to a drug combination (pyrotinib and capecitabine) improves survival for patients with ERBB2-positive breast cancer that has metastasized to the brain, conducted in 40 women. The study concluded that 75% of patients had no progression of their brain tumors after 1 year. Whereas, Median central nervous system PFS was 18 months without their brain tumors growing. In addition, side effects were manageable, with diarrhea being the most common serious side effect. This treatment combination shows the potential to be a new option for this aggressive cancer (Yang et al. 2024).

b) To synergize the effects of pyrotinib in treating HER2-positive breast cancer, researchers studied the combined effects of pyrotinib with chrysin, a natural compound. The findings unveiled that combining pyrotinib with chrysin significantly increased apoptosis and reduced tumor growth compared to pyrotinib alone. This effect seems to be due to increased stress on the endoplasmic reticulum (ER) in cancer cells, leading to a process called autophagy. Interestingly, the combination also increased the breakdown of the G6PD protein, crucial for cancer cell survival. This breakdown is regulated by another protein, ZBTB16, whose activity is in turn controlled by a microRNA molecule (miR-16-5p). Blocking miR-16-5p further enhanced the effectiveness of the pyrotinib-chrysin combination (Luo et al. 2024).

c) Brain metastasis is a common problem for patients with this type of breast cancer. Pyrotinib seems effective in such cases, but more real-world data is needed. For this purpose, researchers looked at the medical records of 101 patients with HER2-positive metastatic breast cancer and brain metastasis, who received pyrotinib treatment in hospitals across China's Shandong region. The treatment showed promising results as the median PFS was 11 months overall. Prior treatment with pertuzumab + trastuzumab and a lower number of brain metastases were linked to longer PFS. Notably, radiotherapy for brain metastasis, especially when combined with pyrotinib, significantly improved PFS. The overall response rate (tumor shrinkage) was 42.6%, and the disease control rate was 88.1%. However, diarrhea was the most common side effect (Huang et al. 2024).

d) To see if combining pyrotinib with vinorelbine is an effective and safe second-line treatment for cancer, a study included 39 patients with HER2-positive MBC who had already received treatment with trastuzumab (Herceptin) and other medications. During the trial, all patients received pyrotinib daily along with vinorelbine given either intravenously or orally on specific days of a 21-day cycle. The median PFS was 6.4 months. Many patients (43.6%) showed tumor shrinkage (ORR), and 84.6%. disease control (including stable disease) was achieved. The most common severe (grade 3/4) side effects were diarrhea, decreased white blood cell counts, and vomiting, but these appeared manageable. Moreover, patients who had not received prior pertuzumab treatment had a longer PFS (Jiang et al. 2024).

e) A study looked at data from 333 patients with HER2+ MBC who received pyrotinib plus trastuzumab (Herceptin) (PyroH) or pertuzumab plus trastuzumab (HP) with chemotherapy between 2017 and 2022. The outcomes indicated that when not used with taxane chemotherapy, PyroH showed a longer PFS than HP. PyroH also showed a numerically longer PFS in patients with brain metastases, although not statistically significant. Importantly, both treatments were tolerable, but PyroH had a higher rate of severe (grade 3/4) diarrhea compared to HP (34.3% vs. 3.0%). However, the side effects were generally well-tolerated. PyroH seems to be as effective (comparable) as HP in the second-line or later treatment setting and for patients with brain metastases. PyroH might also be more effective than HP without taxane chemotherapy (Li et al. 2021).

6. Pyrotinib vs. Trastuzumab: A Comparative Analysis of Adverse Effects and Efficacy across Trial Phases

A review of the Clinical trials registry (clinicaltrials.gov) and randomized controlled trials (RCTs) compared treatment regimens with and without trastuzumab, including 18000 patients. In conclusion, trastuzumab was linked to 25 side effects, including pain, fatigue, skin problems, infections, diarrhea, and heart problems (Jackson, Finikarides, and Freeman 2022). In addition, the real-world risk of severe cardiotoxicity from trastuzumab use wasn't well-established. The researchers conducted a meta-analysis of 58 studies from major medical databases for relevant studies (1996-2014). The analysis mainly focused on the frequency of severe cardiotoxicity within 3 years of starting trastuzumab. It included patients with overall, early breast cancer, and MBC. They found that around 3% of patients experienced severe cardiotoxicity. In the case of MBC, the risk was slightly higher and further increased if trastuzumab was used beyond first-line therapy. Furthermore, the study found that RCTs generally reported lower cardiotoxicity rates compared to observational studies (closer to real-world scenarios) (Mantarro et al. 2016). A study published in The New England Journal of Medicine compared trastuzumab to observation following adjuvant chemotherapy. It reported that severe cardiotoxicity developed in 0.5% of patients receiving trastuzumab (Piccart-Gebhart et al. 2005). However, a retrospective study revealed that among 179 patients, 78 cases of trastuzumab-induced cardiotoxicity (44%, 95% CI 37% to 51%) and four cases of heart failure (2%, 95% CI 0% to 4%) were reported. 14 patients stopped trastuzumab as a result of cardiotoxicity. None of the cardiac risk factors or concomitant cardiovascular medications altered the risk of TIC (Farolfi et al. 2013).

If one looks at real-world clinical practice regarding pyrotinib, it shows that all patients experienced side effects, with diarrhea being

the most common (Zhang, Li, et al. 2022) Another multicenter real-world study found that besides diarrhea, anemia, and leukopenia, there were no major side effects (Yin et al. 2023). Lastly, encouraging results with better PFS and manageable side effects were reported by another real-world study (Liang et al. 2023).

7. Potential Indications of Pyrotinib

In addition to treating HER2-positive breast cancer, pyrotinib showed promise in treating the rare form of breast cancer patients with synchronous contralateral axillary lymph node metastasis (CAM), which lacks published treatment guidelines. In a case study, a 47-year-old woman diagnosed with HER-2 positive breast cancer with regional lymph node metastasis and trastuzumab resistance, was successfully treated with pyrotinib, with a PFS of over 27 months (Yuan et al. 2021). Furthermore, a retrospective study revealed that not only pyrotinib exhibited good efficacy and safety in patients with HER-2 positive breast cancer but also in HER-2 positive/mutation solid tumors (Qian et al. 2020).

In a prospective, multicenter, phase I study, pyrotinib demonstrated great anti-tumor activity in preclinical studies of gastric cancer. The combination of pyrotinib and docetaxel produced this effect with an acceptable level of side effects. (ClinicalTrials.gov, NCT02378389) (Liu et al. 2023). Similarly, in a single-arm, open-label phase 1 dose-escalation (1a) and expansion (1b) study investigated camrelizumab, an anti-PD-1 antibody, plus pyrotinib and chemotherapy as first-line treatment for advanced HER2-positive gastric and gastroesophageal junction (G/GEJ) adenocarcinoma. Among 27 patients who received pyrotinib, two patients (7.4%) achieved a confirmed complete response, and 19 patients (70.4%) achieved a confirmed partial response, resulting in a confirmed ORR of 77.8% (95% CI: 57.7–91.4). Therefore, pyrotinib, and camrelizumab, combined with chemotherapy had a promising activity in the first-line treatment of advanced HER2-positive G/GEJ cancer (Trial ID: ChiCTR2000029717) (Li et al. 2023).

Furthermore, dual-HER2 targeted therapy has also given effective antitumor effect in patients with HER2-positive colorectal cancer, who received pyrotinib and trastuzumab after the unsuccessful second-line treatment. The results were encouraging; after a median follow-up of 11.2 months, median PFS and OS were 7.53 and 16.8 months, respectively. The RAS/BRAF wild-type patients had prolonged survival (PFS: 7.53 vs. 1.63 months, P = .02; OS: NR vs.4.13 months, P = .001) compared with RAS/BRAF mutant patients. (Clinical Trial.gov, NCT04960943, and is ongoing) (Chang et al. 2022).

In a study, pyrotinib was studied as a possible therapeutic agent for the treatment of Parkinson's disease. In this study, mutations in the *PINK1* gene, found on the outer membrane of healthy mitochondria, were linked to early-onset Parkinson's disease. *PINK1* acts as a quality control system, targeting and eliminating dysfunctional mitochondria through a process called mitophagy. The researchers identified kinase inhibitors, like pyrotinib, appeared to bind selectively to the mutant form of *PINK1* (Pawar et al. 2023).

Moreover, for treating brain metastases, pyrotinib outperformed lapatinib and neratinib. Pyrotinib treatment resulted in fewer new brain metastases compared to the placebo group (Yamashita 2020, Yang et al. 2024).

8. Future Directions and Conclusion

While the FDA has approved lapatinib and neratinib, the Chinese State Drug Administration has green-lit pyrotinib in HER2 targeted treatment of breast cancer. A series of

clinical trials involving pyrotinib, some of those mentioned in this article, have shown promise, particularly in MBC. In addition to pyrotinib being an effective anti-tumor drug as monotherapy, discovering a potent combination of it with currently available HER2 targeted drugs, AKT inhibitors, CDK4/6 inhibitors, or PD1/PDL1 antibodies, may also discover effective therapy for HER2 positive breast cancer. Pyrotinib's mode of action is slightly different from that of trastuzumab and studies are proving their combination to be more potent. Moreover, pyrotinib may fill the treatment gaps left by trastuzumab resistance. In addition, pyrotinib has demonstrated efficacy in combination with phytocompounds, like chrysin. This may expand therapeutic options if explored thoroughly. Furthermore, a pharmacoeconomic evaluation of pyrotinib + capecitabine versus lapatinib + capecitabine, based on China's specific economic context, suggested that using pyrotinib + capecitabine for second-line treatment of HER2+ advanced breast cancer is more cost-effective than lapatinib + capecitabine (Wang and Chen 2022). Moreover, a plethora of studies indicated that pyrotinib works better as an adjuvant or in combination with other anti-cancer drugs, as compared to its monotherapeutic application. Furthermore, a comparative analysis of pyrotinib and trastuzumab paints the former in a more favorable light than the letter; however, a continuous assessment is needed given the novelty of pyrotinib. To consolidate these findings, a wide-scale replication of clinical studies for pyrotinib is required, in a diverse population. In a study, approved by the institutional ethics board of Guangdong Hospital of Traditional Chinese Medicine (No. ZF2020-274-01), pyrotinib-associated side effects are being studied and managed for treatment optimization (Fang et al. 2022). Notably, pyrotinib is in phase IV of trials in China (ChiCTR1800020217, ChiCTR1900021819, and ChiCTR1800020449), while entering Phase I in the USA (ClinicalTrials.gov ID NCT02500199). The results indicate that pyrotinib holds potential and further tests and trials are needed to establish its efficacy.

Conflict of Interest

The authors declare that they have no competing interests.

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Data Availability

All the raw data related to this study is available with the authors.

Authors Contributions

NS conceptualized and organized the study, QR and AQK did the literature search and analysis, NS and HHB wrote the initial manuscript, NS wrote the final manuscript, and supervised the project.

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NA

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