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Tyrosine kinase inhibitors and human epidermal growth factor receptor-2 positive breast cancer

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Abstract

The body of evidence investigating human epidermal growth factor receptor-2 (HER2) directed therapy in patients with breast cancer (BC) has been growing within the last decade. Recently, the use of tyrosine kinase inhibitors (TKIs) has been of particular interest in the treatment of human malignancies. This literature commentary is intended to highlight the most recent findings associated with the widely-studied TKI agents and their clinical significance in improving the outcomes of HER2 positive BC.

Key Words: Human epidermal growth factor receptor-2 positive breast cancer; Tyrosine kinase inhibitors; Lapatinib; Pyrotinib; Tucatinib; Trastuzumab

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Core Tip: Newly published randomized controlled trials within the past two years have provided compelling evidence on the use of tyrosine kinase inhibitors (TKIs) such as Lapatinib, Pyrotinib, Neratinib, Tucatinib, Ruxolitinib, and Afatinib. Several of these agents were found to offer better outcomes in terms of progression-free survival when combined with other agents. While some TKIs, namely Lapatinib, and Neratinib, are supported with a large amount of data than others, the medical literature still lacks substantial evidence to draw a clinical conclusion that could modify/add to the present recommendations in human epidermal growth factor receptor-2 positive breast cancer treatment guidelines.

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INTRODUCTION

In 2022, breast cancer (BC) has been the most common cause of cancer-related mortality in women in the United States[1]. Amongst all confirmed BC cases, human epidermal growth factor receptor-2 (HER2) positive BC is estimated to comprise around 15%-20%[2]. Thus, the emergence of HER2-directed therapy, namely, humanized monoclonal antibodies (mAbs), has transformed the path of BC outcomes. The first agent, Trastuzumab, was approved by the United States Food and Drug Administration (FDA) in the past two decades and has revolutionized the treatment modalities[3]. Soon after the approval of other mAbs such as Pertuzumab, and ado-Trastuzumab emtansine, several tyrosine kinase inhibitors (TKIs) have also been approved as targeted therapies[4]. **Figure 1** illustrates various TKIs and their targets. Within the last two years (2021 and 2022), significant additions to the literature were made on the use of TKIs in HER2 positive BC. This commentary aims to highlight the most recent findings published in the literature up to this date. Furthermore, since all TKIs, (*e.g.*, Lapatinib, Neratinib, Pyrotinib, and Tucatinib) can be used to treat both early stages and metastatic BC (mBC), either in combination or as monotherapy, their addition to hospital formularies can be of benefit from a pharmacoeconomic perspective[5]. The summary highlighting the ongoing and completed/terminated clinical trials on TKIs in HER2 positive BC patients is given in **Table 1**.

In a recent phase III randomized controlled trials, dual HER2 blockade with Lapatinib, Trastuzumab, and an aromatase inhibitor (AI) was found to be superior compared to a single HER2 blockade with AI plus Lapatinib alone or Trastuzumab alone in terms of progression-free survival (PFS) in postmenopausal women [hazard ratio: 0.62 (95%CI: 0.45-0.88); $P = 0.0063$][6]. However, this trial was intended to offer an alternative regimen for patients not receiving chemotherapy, a scenario typically followed when chemotherapy is contraindicated[6]. Nevertheless, the question of whether dual blockade with Lapatinib + Trastuzumab combination can be superior to first-line chemotherapy in terms of PFS remained unanswered.

Conversely, in another phase III trial, Pyrotinib + Capecitabine combination was found to yield longer PFS [12.5 mo (95%CI: 9.7-not reached)] as compared to the arm receiving Lapatinib + Capecitabine treatment [6.8 mo (5.4-8.1); hazard ratio 0.39 (95%CI: 0.27-0.56); one-sided $P < 0.0001$][7]. However, unlike the above-mentioned trial, the patient population in this trial was comprised of mBC patients.

Along similar lines, when Neratinib + Capecitabine (N + C) treatment was compared to Lapatinib + Capecitabine (L + C) combination, N + C resulted in longer PFS (Median PFS = 7 mo compared to 5.4 mo; $P = 0.0011$)[8]. Besides, the duration of response (DoR) in N + C *vs* L + C was 11.1 mo *vs* 4.2 mo ($P < 0.0001$), and time to intervention for central nervous system (CNS) illness was 27.9% *vs* 33.8% ($P = 0.039$) in Asian patients with mBC who had previously received at least two HER2-directed regimens[8]. The effectiveness and safety profiles of the N + C combination in the Asian group matched those of the general population. The studies indicated that Neratinib may provide further advantages for HER2+ mBC patients treated with Trastuzumab-only regimens for their metastatic illnesses such as CNS[8].

With the scarcity of published evidence comparing the efficacy of Tucatinib to other TKIs, the question of whether it offers additional PFS benefit was investigated through one network meta-analysis[9]. The data demonstrated that the combination of Tucatinib + Trastuzumab + Capecitabine is regarded as the most effective option in improving both overall survival (OS) and PFS ($P = 0.003$ and $P < 0.0001$). With OS, the choices of Trastuzumab emtansine ($P < 0.004$) and Pertuzumab + Trastuzumab + Capecitabine ($P = 0.011$) are comparatively superior. On the other hand, Neratinib and Lapatinib resulted in greater improvement in PFS ($P = 0.001$) when combined with Capecitabine[9].

However, despite the promising efficacy of Tucatinib over other TKIs, it was associated with increased levels of serum creatinine, which was concerning regarding its effect on renal function. However, the increase in serum creatinine level was found to be attributed to the inhibition of tubular secretion of creatinine[10]. Importantly, one study evaluated the use of Tucatinib *vs* placebo when both were combined with Trastuzumab and Capecitabine. It was concluded that Tucatinib can significantly improve OS (9.1 mo longer in the Tucatinib group) and delay the progression of brain metastasis [hazard ratio, 0.55 (95%CI: 0.36-0.85)][11].

Of note, within the last two years, no additional data regarding Afatinib's use in HER2 positive BC was published. Notably, only one study reported the benefits of Afatinib but the subjects included were not limited to BC, and those included BC patients were not HER2 positive[12]. Thus, there is no significant update regarding Afatinib's role in HER2 positive BC treatment.

Table 1 Main ongoing and completed phase 3 trials evaluating tyrosine kinase inhibitors with HER2+ breast cancer

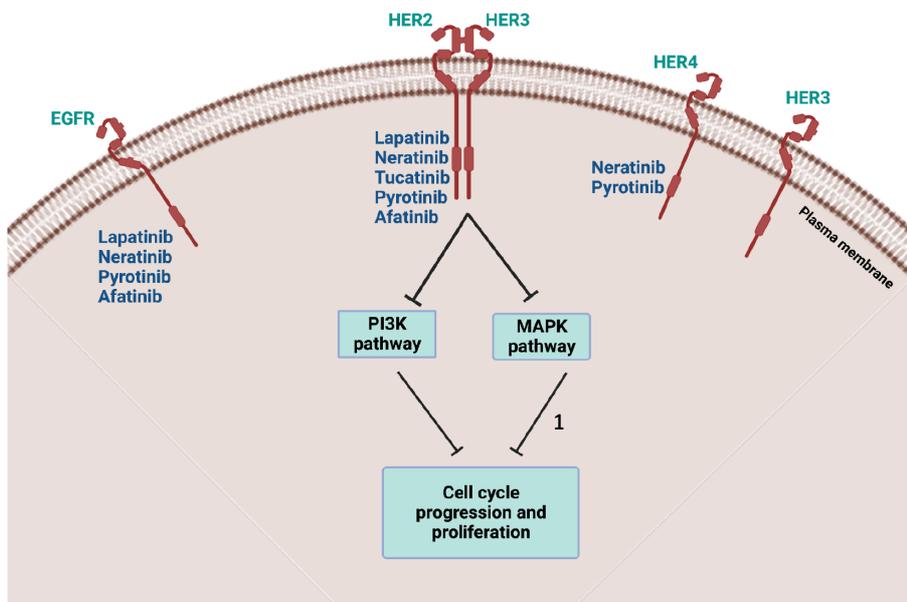
Study title	Conditions	Interventions	Outcome measures	NCT number
Pyrotinib rechallenge in HER2-positive metastatic breast cancer pretreated with Pyrotinib and Trastuzumab	HER2-positive breast cancer, metastatic breast cancer	Trastuzumab plus chemotherapy; Trastuzumab in combination with Pyrotinib plus chemotherapy	PFS, ORR, AEs	NCT05346861 [14]
A study of Pyrotinib plus Capecitabine in patients with HER2+ metastatic breast cancer	HER2 positive metastatic breast cancer	Pyrotinib, Capecitabine	PFS, ORR, AEs, SAEs, DoR, CBR, OS	NCT02973737 [15]
A randomized controlled trial of HER2 positive breast cancer patients treated with Lapatinib vs herceptin	HER2-positive breast cancer	Lapatinib/Herceptin	DFS, OS	NCT03085368 [16]
Tykerb evaluation after chemotherapy (TEACH): Lapatinib versus placebo in women with early-stage breast cancer	Neoplasms, breast	Lapatinib	This clinical trial has several outcomes measures to be evaluated including DFS, OS, MDFS	NCT00374322 [17]
Neo alto (neoadjuvant Lapatinib and/or Trastuzumab treatment optimization) study	Neoplasms, breast	Lapatinib, Trastuzumab, Paclitaxel	This clinical trial has several outcomes measures to be evaluated including OS, Par with pCR at the ToS, OR at the ToS	NCT00553358 [18]
Lapatinib in combination with Trastuzumab versus Lapatinib monotherapy in subjects with HER2-positive metastatic breast cancer	Neoplasms, breast	Lapatinib, Trastuzumab	PFS, OS, OR, CBR, TTR, DR, change from baseline in FACT-B scores at week 4, week 12, week 16, week 24, and conclusion or withdrawal from study	NCT00320385 [19]
Paclitaxel with/ without GW572016 (Lapatinib) as first line therapy for women with advanced or metastatic breast cancer	Neoplasms, breast	Paclitaxel, GW572016 (Lapatinib)	This clinical trial has several outcomes measures to be evaluated including PFS, OS, DoR	NCT00075270 [20]
Continued HER2 suppression with Lapatinib plus Trastuzumab vs Trastuzumab alone (terminated)	Cancer	Lapatinib, Trastuzumab	PFS, OS, Best overall response, CBR (CR, PR or SD \geq 24 wk), AE	NCT00968968 [21]

PFS: Progression-free survival; ORR: overall response rate; AEs: Adverse events; SAE; serious adverse events; DoR: Duration of response; OS: Overall survival; CBR: Clinical benefit rate; MDFS; Modified disease-free survival; Par: Number of participants; TTR: Time in the therapeutic range; DR: Duration of response; pCR: Pathological complete response; DFS: Disease-free Survival; FACT-B: Functional assessment of cancer therapy-breast cancer; OR: Overall response; ToS: Time of surgery; NCT: National clinical trial.

With Ruxolitinib, a class of the Janus kinase inhibitors, the first and only study performed so far with a Trastuzumab combination indicated that the tolerability data is appealing[12]. However, there was no difference in the PFS than that of Trastuzumab alone in mBC patients as compared to the historical control[13]. To draw a more robust conclusion regarding Ruxolitinib and explore its implications with TKIs, more interventional studies are warranted with larger power using randomized and prospective designs since these aspects are lacking in Ruxolitinib studies.

CONCLUSION

In conclusion, while the body of evidence currently available in the literature is still insufficient to offer recommendations in the treatment guidelines of HER2 positive BC, the existing studies concluding the benefits of TKIs promise hope for patients resistant to conventional first- and second-line treatments.



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Figure 1 Schematic representation of TKIs targeting EGFR and various HER family receptors, leading to the inhibition of downstream PI3K and MAPK pathway, resulting in the regulation of cell cycle progression and proliferation. ¹The sign denotes inhibition. The authors would like to acknowledge Biorender.com software that was used to create Figure 1.

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