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Efficacy of cross-line therapy with anti-HER2 TKI in HER2-positive MBC: a multicenter real-world study

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Objective

Human epidermal growth factor receptor (HER2)-targeted tyrosine kinase inhibitors (TKIs) have transformed the treatment landscape for HER2-positive metastatic breast cancer (MBC). Previous studies demonstrated the robust antitumor activity of TKIs in both first-line and later-line settings. Nevertheless, the benefits of maintaining TKI-based regimens after resistance remain uncertain. Based on real-world data, this study **comprehensively assessed the clinical value of cross-line TKI application and investigated key factors influencing efficacy**, aiming to provide insights for TKI administration in the advanced stage.

Methods

This real-world study consecutively enrolled HER2-positive MBC patients receiving TKI-based regimens at 3 institutions (including the National Cancer Center, China) from October 2014 to April 2024. **Inclusion criteria included patients who received at least two lines of TKI-based therapy in the advanced settings.** Patients receiving cross-line TKI therapy not due to disease progression and with incomplete clinical records were excluded. The primary endpoint was progression-free survival (PFS).

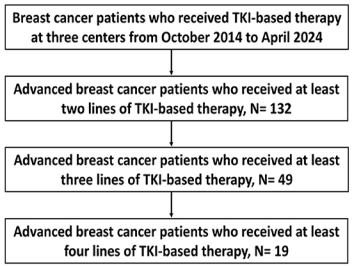


Figure 1. Flowchart of the study.

Results

1. A total of 132 patients with HER2-positive metastatic breast cancer who received two or more lines of TKI-based regimens were enrolled, with 49 receiving three lines and 19 receiving four lines of TKI therapy.
2. The median age of all patients was 52 years. In patients receiving two lines of TKI therapy (N = 132), **second-line PFS (PFS2) was significantly shorter than first-line (median PFS (mPFS): 5.5 vs. 9.0 months**; hazard ratio (HR) 2.048; 95% confidence interval (CI) 1.588 - 2.640; $P < 0.001$).
3. Multivariate Cox regression analysis identified **PFS1 ≥ 6 months as an independent predictor of prolonged PFS2** (HR 0.492; 95% CI 0.333 - 0.728; $P < 0.001$).
4. Among patients receiving TKI as the sole HER2-targeted agent (TKI with/without chemotherapy or endocrine therapy) (N = 70), **the addition of chemotherapy in the second-line setting was associated with a significantly longer PFS2** compared to chemotherapy-free regimens (mPFS: 6.4 vs. 2.2 months; HR 0.404; 95% CI 0.208 - 0.787; $P = 0.005$).
5. Similarly, **patients who switched to a different TKI agent experienced a longer PFS2** than those who continued the original TKI regimen (mPFS: 6.8 vs. 4.5 months; HR 0.581; 95% CI 0.356 - 0.948; $P = 0.025$).
6. Importantly, **patients who switched from lapatinib to pyrotinib had a significantly longer PFS2** compared to those who continued pyrotinib in the second-line setting (mPFS: 7.0 vs. 4.1 months, HR 0.523, 95%CI 0.298 - 0.917, $P < 0.001$).
7. Further analysis of patients receiving three lines of TKI therapy (N = 49) showed that **PFS3 was shorter than PFS2 and PFS1** (mPFS: 4.1, 6.2, and 9.1 months, respectively; $P < 0.001$, P for trend < 0.0001).
8. Notably, patients with high HER2 expression (immunohistochemistry 3+ vs. 2+ and fluorescence in situ hybridization positive, HR 0.282; 95% CI 0.117 - 0.680; $P = 0.005$) and PFS1 > 9.1 months (HR 0.549; 95% CI 0.306 - 0.988; $P = 0.045$) were associated with markedly longer PFS3.
9. In the second- and third-line TKI settings, PFS did not significantly differ between regimens using TKI as the sole anti-HER2 agent and those combining TKI with another anti-HER2 agent (antibody or antibody-drug conjugate) ($P > 0.05$).

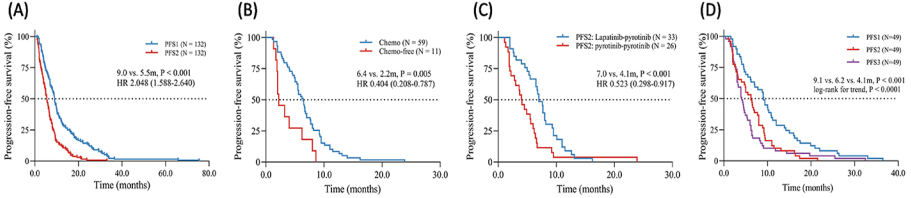


Figure 2. Kaplan-Meier analysis of progression-free survival in HER2-positive advanced breast cancer patients receiving TKI plus antibody therapy. (A) PFS1 and PFS2 of patients who had received at least two lines of TKI-based therapy. (B) PFS2 stratified by concomitant chemotherapy in patients receiving TKI as . (the sole anti-HER2 agent in the first and second TKI-based settings. (C) PFS2 in patients treated with one of two distinct TKI sequences: lapatinib followed by pyrotinib, or pyrotinib in both lines, as the exclusive anti-HER2 therapy. (D) PFS1, PFS2, and PFS3 of patients who had received at least three lines of TKI-based therapy.

Conclusions

This study indicated **that cross-line anti-HER2 TKI therapy confers sustained PFS benefits in HER2-positive MBC**. Notably, **patients with longer frontline PFS and those who switched TKI agents exhibited superior survival outcomes in subsequent treatment lines**. Further prospective studies are warranted to confirm these findings.

Univariate analysis of PFS2	P value	HR	95% CI
Age (≥40 vs. <40)	0.081	1.499	0.952-2.360
HR status (Positive vs. Negative)	0.207	1.276	0.874-1.864
HER2 status (3+ vs.2+)	0.586	0.882	0.561-1.387
Number of PFS1 lines (≥Third line ≤Second line)	0.826	0.960	0.666-1.384
PFS1 duration (≥6 months vs. <6 months)	< 0.001	0.492	0.333-0.728
Number of PFS2 lines (≥Fifth line vs. ≤Fourth line)	0.150	1.313	0.906-1.904
Anti-HER2 therapy in the second TKI setting (Dual-target vs. Single-target)	0.229	0.799	0.555-1.151
Visceral metastasis (Yes vs. No)	0.754	0.941	0.641-1.380
Bone metastasis (Yes vs. No)	0.916	1.020	0.703-1.482
Lymph node metastasis (Yes vs. No)	0.625	1.095	0.760-1.578
Brain metastasis (Yes vs. No)	0.248	0.743	0.449-1.230
New metastases after PFS1 (Yes vs. No)	0.789	1.077	0.627-1.848
Type of TKI-2 agent compared to TKI-1 (Different vs. Same)	0.144	0.772	0.546-1.092
Multivariate analysis of PFS2	**P value**	**HR**	**95% CI**
Age (≥40 vs. <40)	0.114	-	-
PFS1 duration (≥6 months vs. <6 months)	<0.001	0.492	0.333-0.728
Number of PFS2 lines (≥Fifth line vs. ≤Fourth line)	0.233	-	-
Type of TKI-2 agent compared to TKI-1 (Different vs. Same)	0.200	-	-

Table 1. Cox proportional hazards regression analysis for progression-free survival in the second anti-HER2 TKI setting.

Founding and Disclosure
The authors have no conflicts of interest to declare.

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