Effectiveness of second-line anti-HER2 treatment in HER2-positive metastatic breast cancer patients previously treated with trastuzumab: A real-world study

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Abstract

Objective: Several studies have demonstrated different benefits for patients whose disease progressed despite previous trastuzumab treatment. Due to limited real-world data, we evaluate the effectiveness of anti-human epidermal growth factor receptor 2 (HER2) therapy (lapatinib or trastuzumab) plus chemotherapy or chemotherapy alone in patients who were previously treated with trastuzumab-containing regimens and investigate factors associated with effectiveness. And we further show the effectiveness of the two anti-HER2 therapy groups.

Methods: A total of 342 HER2-positive metastatic breast cancer (MBC) patients whose disease progressed during prior anti-HER2 (trastuzumab) and standard chemotherapy therapy from Department of Breast Oncology, the Fifth Medical Center of Chinese PLA General Hospital, from August 2010 to December 2016 were included. Seventy-eight patients received standard chemotherapy only, 148 patients continued to receive trastuzumab and switched to other chemotherapy drugs, and 116 patients received tyrosine-kinase inhibitors (TKIs; lapatinib) and chemotherapy. The main outcome measures were progression-free survival (PFS), overall response rate (ORR), and clinical benefit rate (CBR). Subgroup analyses were conducted to identify patient characteristics associated with the greatest clinical benefit.

Results: After a median follow-up of 26.2 (range, 2.0–56.0) months, PFS significantly improved with anti-HER2 therapy compared with chemotherapy alone: median 6.0 months with lapatinib [95% confidence interval (95% CI), 4.53–7.47], 4.5 months with trastuzumab (95% CI, 3.99–5.01) vs. 3.0 months with chemotherapy alone (95% CI, 2.42–3.58); stratified hazard ratio (HR)=0.70, 95% CI, 0.60–0.81; P<0.0001. The ORR values were 33.6%, 25.0% and 12.8 %, respectively, the CBR values were 60.3%, 48.6% and 26.9%, respectively. The effectiveness of lapatinib group and trastuzumab group were further analyzed. In multivariate analysis, lapatinib group was associated with a longer PFS, after controlling other potential confounders (HR=0.68, 95% CI, 0.52–0.90; P=0.006).

Conclusions: The combination of TKIs and chemotherapy was effective in this cohort previously treated with trastuzumab treatment. Therefore, TKIs combined with chemotherapy is an option for Chinese HER2-positive MBC patients previously treated with trastuzumab treatment.

Keywords: Metastatic breast cancer; trastuzumab failure; second-line; real-world study

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Introduction

Trastuzumab was confirmed to provide significantly improved clinical benefits and formed the foundation of modern biotarget therapy in human epidermal growth factor receptor 2 (HER2)-positive breast cancer (1-4). However, most patients develop progressive disease during or after trastuzumab treatment (5-8), and additional intervention is often required.

The National Comprehensive Clinical Network (NCCN) guidelines (9) recommends trastuzumab emtansine (TDM1) as a preferred option for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have previously received a trastuzumab-based regimen (10). Other HER2-targeted treatments for HER2-positive MBC have expanded to include pertuzumab (11). However, in China, TDM1 and pertuzumab are unavailable.

Switching to the lapatinib-contained regimen is an option for patients with HER2-positive disease following progression on a trastuzumab-containing regimen according to NCCN panel. In preclinical studies, lapatinib was not cross-resistant with trastuzumab (12). The clinical activity of lapatinib-containing regimens has been demonstrated in women with HER2-positive breast cancer that progressed despite trastuzumab treatment (13-15). Several trials have demonstrated benefit of continuing trastuzumab therapy following disease progression on a trastuzumab-containing regimen (16-18). Therefore, the NCCN panel (9) recommends the continuation of a trastuzumab regimen and switching to other chemotherapy drugs for patients with HER2-positive disease following progression on a trastuzumab-containing regimen.

Although the NCCN panel recommends continuation of HER2 blockade for patients with HER2-positive MBC that progresses on first-line trastuzumab-containing regimens, in China, patients very commonly have inadequate funding for anti-HER2 treatment. Standard chemotherapy alone is also an option for patients whose disease progresses on a trastuzumab-containing regimen.

Based on the currently available drugs in China (i.e., standard chemotherapy, trastuzumab, lapatinib), this retrospective analysis was conducted in a real-world population. It aimed to evaluate the effectiveness of HER2-target therapy plus chemotherapy or standard chemotherapy alone after disease progression in patients during trastuzumab treatment. We aimed to glean new information that could aid daily clinical practice.

Materials and methods

Study design and patients

Patients with HER2-positive MBC whose disease progressed despite previous trastuzumab-based therapy were treated with oral lapatinib (1,250 mg daily) plus chemotherapy, trastuzumab (6 mg/kg every 21 d following a loading dose of 8 mg/kg for cycle 1) plus chemotherapy, or chemotherapy only between August 2010 and December 2016 in Department of Breast Oncology, the Fifth Medical Center of Chinese PLA General Hospital. Data were retrospectively obtained from the patients’ medical charts. Forty-seven patients (31.8%) receiving trastuzumab in the trastuzumab group were from patient assistance program (PAP) (Founded by cancer foundation of China, PAP provide supports for low-income patients). Other patients are self-funding for lapatinib and trastuzumab in this study.

Eligibility criteria were as follows: 1) eligible patients were women >18 years of age with histologically or cytologically confirmed breast cancer; 2) patients must have had metastatic disease that progressed during their most recent treatment regimen containing trastuzumab; 3) HER2 gene amplification from tumors (primary or metastatic) was measured by fluorescence in situ hybridization, while HER2 overexpression was measured by immunohistochemistry (3+); 4) eligible patients had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) or bone-only disease; and 5) patients were required to have an Eastern Cooperative Oncology Group performance status ≤2; adequate hematologic, renal, and hepatic function; and a left ventricular ejection fraction (LVEF) of 50% or more that was sonographically confirmed. The study has been approved by the ethics committee of the Fifth Medical Center of Chinese PLA General Hospital.

Response and outcome

Effectiveness was assessed by progression-free survival (PFS), objective response rate (ORR), and clinical benefit rate (CBR). PFS was defined as the time from treatment initiation to progression or death. ORR was considered the percentage of complete response (CR) and partial response (PR). CBR was defined as the percentage of cases with CR, PR or stable disease for ≥24 weeks. Effectiveness was evaluated by computed tomography, magnetic resonance
imaging, bone scan, and physical examination every 6–8 weeks (two cycles) until disease progression occurred. Progression was assessed according to RECIST (version 1.1) criteria.

Statistical analysis

The log-rank test was used to compare differences between Kaplan-Meier curves for different treatment groups. Multivariate Cox regression analyses were used to estimate crude and adjusted hazard ratio (HR) and corresponding 95% confidence intervals (95% CIs) (19). Potential prognostic confounders adjusted in the model include age, hormone receptor status, number of metastatic sites, brain metastases, liver metastases, visceral metastases, duration of previous trastuzumab-containing. All other analyses were descriptive. All tests were two-sided at the 5% level of significance. Values of P<0.05 were considered statistically significant. The statistical analyses were conducted with available data using SAS software (Version 9.4; SAS Institute Inc., Cary, USA).

Results

Patient characteristics and treatment

Between August 2010 and December 2016, data were collected and censored to December 2016. A total of 342 HER2-positive MBC patients whose disease had progressed while on previous trastuzumab treatment. Patients were classified into three different groups by subsequent treatment: 78 (22.8%) received chemotherapy only, 148 (43.3%) continued to receive trastuzumab plus chemotherapy, and 116 (33.9%) received lapatinib plus chemotherapy. The demographic and baseline disease characteristics of the three treatment groups are shown in Table 1. Overall, most (n=246; 71.9%) of the 342 patients had visceral metastases and 156 (45.6%) had estrogen receptor-positive disease. And 24.4% (19/78) patients in the chemotherapy group had three or more metastatic sites, compared with 33 (22.3%) of 148 patients in the trastuzumab group and 35 (30.2%) of 116 patients in the lapatinib group. More patients (16.4%) in the lapatinib group had central nervous system (CNS) metastases. The

| Table 1 Baseline patient characteristics by treatment group |
|-------------------------------------------------------------|
| Variables | Group A (N=78) | Group B (N=148) | Group C (N=116) | P |
| Age (year) [median (range)] | 44.5 (23–67) | 47.0 (24–75) | 43.5 (26–68) | 0.3451 |
| Hormone receptor status | | | | 0.1979 |
| Positive | 41 (52.6) | 69 (46.6) | 46 (39.7) | | |
| Negative | 37 (47.4) | 79 (53.4) | 70 (60.3) | | |
| Number of metastatic sites | | | | 0.4316 |
| 1 | 27 (34.6) | 56 (37.8) | 41 (35.3) | | |
| 2 | 32 (40.0) | 59 (39.9) | 40 (34.5) | | |
| 3 | 14 (17.9) | 20 (13.5) | 21 (18.1) | | |
| ≥4 | 5 (6.4) | 13 (8.8) | 14 (12.1) | | |
| Visceral metastases | 55 (70.5) | 105 (70.9) | 86 (74.1) | 0.8071 |
| CNS | 8 (10.3) | 10 (6.8) | 19 (16.4) | 0.0434 |
| Liver | 26 (33.3) | 51 (34.5) | 46 (39.7) | 0.5868 |
| Chemotherapy of the trial* | | | | |
| Capecitabine | 25 (32.1) | 58 (39.2) | 97 (83.6) | <0.0001 |
| Vinorelbine | 20 (25.6) | 49 (33.1) | 9 (7.8) | <0.0001 |
| Taxane | 24 (30.8) | 33 (22.3) | 9 (7.8) | <0.0001 |
| Gemcitabine | 17 (21.8) | 13 (8.8) | 1 (0.9) | <0.0001 |
| Others | 12 (15.4) | 4 (2.7) | 1 (0.9) | <0.0001 |

Group A, chemotherapy-only group; Group B, trastuzumab combination group; Group C, lapatinib combination group; CNS, central nervous system; *, Totals exceed 100% because patients could have received more than one treatment.
drugs of chemotherapy were unbalanced among the three groups, and more capecitabine in the lapatinib group.

**Effectiveness**

At a median follow-up of 26.2 (range, 2.0–56.0) months, a total of 325 PFS events (77 in the chemotherapy-only arm, 143 in the trastuzumab arm, and 105 in the lapatinib arm) were reported of the 342 enrolled patients. Patients receiving anti-HER2 therapy experienced significantly improved PFS compared to those receiving chemotherapy alone (HR=0.70, 95% CI, 0.60–0.81; P<0.0001; Figure 1). The median PFS was 4.5 months for the trastuzumab combination group, 6.0 months for the lapatinib combination group, and 3.0 months for the chemotherapy-only arm. The ORR was 12.8% in the chemotherapy-only group, 25.0% in the trastuzumab group, and 33.6% in the lapatinib group. The CBR values of the three groups were 31.3%, 48.6% and 63.8%, respectively (Table 2).

**Anti-HER2 therapy subgroup analysis**

We further showed the subgroup analyses of lapatinib group and trastuzumab group. The improved PFS benefit associated with lapatinib was consistent across some of the clinically important subgroups, such as duration of previous trastuzumab-containing regimen ≥6 months compared with the trastuzumab combination regimen (8.0 months vs. 5.0 months; stratified HR=0.60, 95% CI, 0.38–0.96; P=0.033; Figure 2A). For patients with a duration of previous trastuzumab-containing regimen <6 months, the median PFS of the lapatinib combination group and trastuzumab combination group was not significantly different (5.4 months vs. 5.0 months; stratified HR=0.80, 95% CI, 0.59–1.09; P=0.160; Figure 2B). PFS associated with the two groups was demonstrated across subgroups, including those defined by age, hormone receptor status, visceral involvement, and duration of previous trastuzumab-containing (Figure 3).

In multiple analysis, after controlling other potential confounders, treating with lapatinib (HR=0.68, 95% CI, 0.52–0.90) and duration of previous trastuzumab-containing regimen ≥6 months (HR=0.78, 95% CI, 0.64–0.96) remain statistically significant (Table 3).

**Toxicity**

Safety analysis was conducted on 88 patients in the lapatinib group and 118 patients in the trastuzumab group.

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**Figure 1** Kaplan-Meier estimates of locally assessed progression-free survival in the full analysis set (Log-rank, P<0.0001). Group B vs. A: HR=0.66 (0.50–0.88), P=0.0037; Group C vs. A: HR=0.49 (0.36–0.66), P<0.0001. Group A, chemotherapy-only group; Group B, trastuzumab combination group; Group C, lapatinib combination group; HR, hazard ratio.

**Table 2** Efficacy outcomes by treatment group

| Outcomes          | Group A (N=78) | Group B (N=148) | Group C (N=116) | P         |
|-------------------|---------------|-----------------|-----------------|-----------|
| CR                | 0 (0)         | 2 (1.4)         | 4 (3.4)         |           |
| PR                | 10 (12.8)     | 35 (23.6)       | 35 (30.2)       |           |
| SD                | 50 (64.1)     | 93 (62.8)       | 66 (56.9)       |           |
| SD ≥6 months      | 11 (14.1)     | 35 (23.6)       | 31 (26.7)       |           |
| PD                | 18 (23.1)     | 18 (12.2)       | 11 (9.5)        |           |
| ORR               | 10 (12.8)     | 37 (25.0)       | 39 (33.6)       | 0.0047    |
| CBR               | 21 (26.9)     | 72 (48.6)       | 70 (60.3)       | 0.0013    |

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, overall response rate, ORR=CR+PR; CBR, clinical benefit rate, CBR=CR+PR +SD ≥6 months.
Lapatinib group was associated with higher proportions of diarrhea, hand-foot syndrome, vomiting, whereas trastuzumab was associated with higher proportions of neutropenia, anemia, and thrombocytopenia (Table 4). Two

Figure 2 Kaplan-Meier estimates of locally assessed progression-free survival with that of patients who had disease control time of previous trastuzumab-containing ≥6 months (A) (HR=0.60, 95% CI, 0.38–0.96; Log-rank P=0.033) and disease control time of previous trastuzumab-containing <6 months (B) (HR=0.80, 95% CI, 0.59–1.09; Log-rank P=0.160). HR, hazard ratio; 95% CI, 95% confidence interval.

Figure 3 Subgroup analysis of progression-free survival (PFS). Data from primary PFS analysis were analyzed. *, Derived from the Cox proportional hazards model. Hormone receptor status: estrogen receptor (ER)- and/or progesterone receptor (PR)-positive vs. ER-negative and PR-negative. HR, hazard ratio; 95% CI, 95% confidence interval.
patients (2.3%) in the lapatinib group and 3 patients (2.5%) in the trastuzumab group, respectively, had a decrease of LVEF to less than 50% and at least 10 percentage points below the baseline value. No therapy-related death occurred.

**Discussion**

The clinical trial unquestionably remains a powerful tool for accumulating scientific evidence about the safety and efficacy of a medical product. However, clinical trials often include specific populations within specialized environments that differ from real clinical settings (20). Real-world studies offer the potential to supplement knowledge gaps and address questions that cannot be solved by clinical trials (21). To our knowledge, Hammerman’s (22) research groups have compared the OS of trastuzumab beyond progression with lapatinib for patients previously received trastuzumab treatment. However, OS may be affected by the use of subsequent-line therapies, which makes it difficult to assess the impact of only one treatment on survival. The focus of our work is on PFS and response associated from patients treated with HER2-targeted therapy in this setting from real-world sources, which is very different from Hammerman’s work, and this is also the major contribution of our work. This study was designed to evaluate the effectiveness outcomes of the three regimens under non-controlled real-life conditions with an unselected population of patients with HER2-positive MBC and experienced disease progression while on previous trastuzumab treatment.

In this cohort of 342 MBC patients, we showed that an anti-HER2 therapy regimen significantly improved PFS compared with the chemotherapy group and the benefit was observed in ORR and CBR. The findings correspond with the NCCN panel recommendation of the continuation of HER2 blockade for patients with HER2-positive MBC that progresses on first-line trastuzumab-containing regimens.

The subanalysis demonstrated that lapatinib plus chemotherapy improved PFS compared with trastuzumab plus chemotherapy, a result that is in accordance with those of previous studies that assessed the ability of lapatinib to overcome the mechanism that induces trastuzumab resistance in preclinical and clinical studies (12,15,23).

### Table 3 Subgroup analysis of progression-free survival, multivariate Cox regression analysis

| Variables                                                   | HR   | 95% CI       | P   |
|--------------------------------------------------------------|------|--------------|-----|
| Lapatinib group vs. trastuzumab group                        | 0.68 | 0.52–0.90    | 0.006 |
| Age ≥45 years vs. <45 years                                  | 1.09 | 0.84–1.42    | 0.517 |
| Hormone receptor status positive vs. negative                | 1.24 | 0.96–1.60    | 0.101 |
| No. of metastatic sites ≤2 vs. >2                            | 1.10 | 0.80–1.52    | 0.560 |
| Brain metastases (yes vs. no)                               | 0.91 | 0.67–1.24    | 0.544 |
| Liver metastases (yes vs. no)                               | 1.23 | 0.91–1.66    | 0.188 |
| Visceral metastases (yes vs. no)                            | 1.12 | 0.81–1.56    | 0.500 |
| Duration of previous trastuzumab-containing regimen ≥6 months vs. <6 months first-line vs. second and third line | 0.78 | 0.64–0.96    | 0.048 |

HR, hazard ratio; 95% CI, 95% confidence interval.

### Table 4 Most common treatment-related adverse events*

| Adverse events          | Lapatinib group (N=88) | Trastuzumab group (N=118) |
|-------------------------|------------------------|---------------------------|
|                         | Events of any grade | Events of grade 3–4 | Events of any grade | Events of grade 3–4 |
| Diarrhea                | 63 (71.6) | 14 (15.9) | 42 (35.6) | 2 (1.7) |
| Hand-foot syndrome      | 42 (47.7) | 15 (17.0) | 8 (6.8) | 1 (0.8) |
| Vomiting                | 22 (25.0) | 4 (4.5) | 19 (16.1) | 2 (1.7) |
| Neutropenia             | 15 (17.0) | 5 (5.7) | 31 (26.3) | 9 (7.6) |
| Anemia                  | 9 (10.2) | 1 (1.1) | 27 (22.9) | 2 (1.7) |
| Thrombocytopenia        | 7 (8.0) | 1 (1.1) | 18 (15.3) | 3 (2.5) |

* Safety analysis was conducted on 88 patients in the lapatinib group and 118 patients in the trastuzumab group.
Moreover, our previous study (24) showed that after the patients developed trastuzumab resistance, the PFS of patients receiving the lapatinib regimen was significantly longer compared with the patients receiving the trastuzumab regimen (6.0 vs. 4.5 months, respectively; P=0.006).

NCCN guidelines list several therapeutic options for anti-HER2 therapy in patients who experienced disease progression while on previous trastuzumab treatment (9). These include switching to the lapatinib-contained regimen, continuously administering trastuzumab and switching to other chemotherapy drugs, terminating chemotherapy and applying trastuzumab plus lapatinib dual-targeted therapy, and the administration of TDM1. However, TDM1 is unavailable in China, the patient subgroup suitable for dual-targeted therapy is limited, and anti-HER2 targeted therapy is expensive. The anti-HER2 therapy (i.e. lapatinib or trastuzumab) plus a chemotherapy regimen or the use of chemotherapy alone remains the most likely option for most Chinese patients who experienced disease progression while on prior trastuzumab treatment.

In China, patients very commonly have inadequate funding for medical treatment. Therefore, TDM1 or the widespread combined use of two targeted drugs to treat HER2-positive breast cancer patients who experienced disease progression on previous trastuzumab treatment is unrealistic. Our study accurately reflected the true clinical use of treatment in a heterogeneous population of breast cancer patients across China, suggesting that switching to lapatinib plus chemotherapy will result in a significantly longer PFS than treatment with trastuzumab plus chemotherapy. Furthermore, subgroup analyses were conducted to identify the characteristics of patients deriving the greatest clinical benefit from these regimens. In addition, we can see that the toxicity of lapatinib group is manageable. These data will improve the effectiveness of salvage treatments for patients and ensure that patients maximally benefit from treatment.

Our study was retrospective and its groups were not prospectively randomized; therefore, it was subject to limitations including lack of some clinical characteristics such as performance status, TNM staging, and other baseline characteristics, and possible selection bias. And the retrospective study using secondary data, multiple testing might increase the risk of type I error while using 0.05 as statistical significance level. In addition, indications for treatment were based on physicians’ discretion and not specified. Thus, the sample size must be further expanded in a multicenter study.

Despite these limitations, our study is important for at least two reasons. First, it offers first-hand real-world data of the effectiveness of anti-HER2 in combination with chemotherapy and chemotherapy in Chinese patients, which can be important for clinical oncologists and provide supplementary data for the coming registration clinical trials in China. Second, exploratory analysis provides clues for the selection of patients who are likely to benefit more from TKI treatment.

**Conclusions**

Based on the currently available drugs in China, lapatinib plus chemotherapy significantly prolonged PFS compared with trastuzumab combined with chemotherapy as well as chemotherapy alone in patients with HER2-positive MBC who were previously treated with trastuzumab. Currently, the results show that patients who were available to lapatinib, had the longest PFS estimates of all of the observed patients in this study. We still need to expand the sample sizes from a multicenter study to support our conclusion.

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**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**References**

1. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320-68.
2. Pathmanathan N, Provan PJ, Mahajan H, et al. Characteristics of HER2-positive breast cancer diagnosed following the introduction of universal HER2 testing. Breast 2012;21:724-9.
3. Slamon D, Eiermann W, Robert N, et al. Adjuvant
trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.

4. Guo J, Li Q, Zhang P, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer: a real-world retrospective study in Chinese patients. Chin J Cancer Res 2019;31:759-70.

5. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol 2013;24(suppl 6):vi7-23.

6. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32:3744-52.

7. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017;389:1195-205.

8. Lambertini M, Pondé NF, Solinas C, et al. Adjuvant trastuzumab: a 10-year overview of its benefit. Expert Rev Anticancer Ther 2017;17:61-74.

9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology-Breast Cancer, version 2. Available online: https://www.nccn.org/professionals/physician_gls/default.aspx#bone.

10. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.

11. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.

12. Ritter CA, Perez-Torres M, Rinehart C, et al. Human breast cancer cells selected for resistance to trastuzumab in vivo overexpress epidermal growth factor receptor and ErbB ligands and remain dependent on the ErbB receptor network. Clin Cancer Res 2007;13:4909-19.

13. Segovia-Mendoza M, González-González ME, Barrera D, et al. Efficacy and mechanism of action of the tyrosine kinase inhibitors gefitinib, lapatinib and neratinib in the treatment of HER2-positive breast cancer: Preclinical and clinical evidence. Am J Cancer Res 2015;5:2531-61.

14. Madden R, Kosari S, Peterson GM, et al. Lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer: A systematic review. Int J Clin Pharmacol Ther 2018;56:72-80.

15. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008;112:533-43.

16. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2014;2014:CD006242.

17. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006.

18. Takano T, Tsurutani J, Takahashi M, et al. A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP. Breast 2018;40:67-75.

19. Andersen PK, Gill RD. Cox’s regression model for counting processes: a large sample study. Ann Statist 1982;10:1100-20.

20. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence — what is it and what can it tell us? N Engl J Med 2016;375:2293-7.

21. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014;110:551-5.

22. Hammerman A, Greenberg-Dotan S, Feldhamer I, et al. Second-line treatment of Her2-positive metastatic breast cancer: trastuzumab beyond progression or lapatinib? A population based cohort study. PLoS One 2015;10:e0138229.

23. Lyu H, Yang XH, Edgerton SM, et al. The erbB3- and IGF-1 receptor-initiated signaling pathways exhibit distinct effects on lapatinib sensitivity against trastuzumab-resistant breast cancer cells. Oncotarget.
24. Bian L, Wang T, Zhang S, et al. Trastuzumab plus capecitabine vs. lapatinib plus capecitabine in patients with trastuzumab resistance and taxane-pretreated metastatic breast cancer. Tumour Biol 2013;34:3153-8.