Original Article

The efficacy of pyrotinib-based therapy in lapatinib-resistant metastatic *HER2*-positive breast cancer

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Background: Human epidermal growth factor receptor 2 (*HER2*)-positive breast cancer tends to metastasize and is associated with poor prognosis. Anti-*HER2* treatment combined with chemotherapy or endocrine therapy is often used for *HER2*-positive metastatic breast cancer (MBC). For later lines of therapy in *HER2*-positive MBC, there is no standard treatment. We investigated the efficacy of pyrotinib, a new irreversible tyrosine kinase inhibitor (TKI) targeting epidermal growth factor receptor, *HER2*, and *HER4*, in lapatinib-resistant *HER2*-positive MBC patients.

Methods: This is a retrospective observational study including lapatinib-resistant *HER2*-positive MBC patients who received pyrotinib-based treatment. We used the Kaplan-Meier method for the survival analyses.

Results: A total of 31 patients were included. Concurrent treatments included cytotoxic chemotherapy (29 patients, 93.6%), endocrine therapy (1 patient, 3.2%), and another targeted therapy (1 patient, 3.2%). The objective response rate (ORR) was 25.8% and the median progression-free survival in the study population was 4.5 months (95% CI: 3.1–5.9 months). The treatment-related adverse events (AEs) included diarrhea, neutropenia, vomiting, fatigue, and thrombocytopenia. Dose reduction to 320 mg was conducted in 19.4% of all cases due to severe AEs.

Conclusions: Pyrotinib-based treatment was effective and generally well tolerated in lapatinib-resistant *HER2*-positive MBC for later line treatment.

Keywords: Pyrotinib; lapatinib; tyrosine kinase inhibitor (TKI); human epidermal growth factor receptor 2-positive metastatic breast cancer (*HER2*-positive MBC)

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Introduction

Human epidermal growth factor receptor 2 (*HER2*) positivity and *HER2* gene amplification account for approximately 20% of all breast cancers (1). *HER2*-positive breast cancer tends to metastasize and is associated with poor prognosis. The overall survival (OS) of *HER2*-positive breast cancer has been prolonged since the use of anti-*HER2* targeted therapy. Chemotherapy and dual-blockade *HER2* targeted therapy with trastuzumab and pertuzumab is the standard first-line treatment for *HER2*-positive metastatic breast cancer (MBC) (2) due to its progression-free survival (PFS) and OS benefits. For the second-line treatment of *HER2*-positive MBC, ado-trastuzumab emtansine (T-DM1)-containing therapies are candidate regimens (3). T-DM1 is approved for MBC in China, but it's not covered by

medical insurance. Lapatinib, a tyrosine kinase inhibitor (TKI) targeting epidermal growth factor receptor and *HER2*, combined with chemotherapy is the recommended second-line anti-*HER2* treatment in China (3). For later lines of therapy in *HER2*-positive MBC, there is no standard treatment. Anti-*HER2* targeted therapy combined with chemotherapy, endocrine therapy, or another targeted therapy is usually used. Pyrotinib is a new TKI which could block epidermal growth factor receptor, *HER2*, and *HER4*. Thirty-eight patients were enrolled in the phase 1 study, who received in the 80- to 400-mg dose cohorts. The dose-limiting toxicity was grade 3 diarrhea, and the maximum tolerated dose was 400 mg. Pyrotinib was approved for *HER2*-positive MBC in mainland China in late 2018 based on its excellent efficacy, showing prolonged PFS and increased objective response rate (ORR) in a phase II study (4,5). A randomized, double-blind, placebo-controlled phase III study (PHENIX) showed that pyrotinib plus capecitabine had a significant increase in PFS for *HER2*-positive MBC after prior trastuzumab and taxanes (6). The PHOEBE study demonstrated that pyrotinib plus capecitabine had prolonged PFS compared with lapatinib and capecitabine in trastuzumab-treated TKI-untreated patients (7). Pyrotinib could block one more pathway, *HER4*, compared with lapatinib in terms of mechanism. However, the efficacy of pyrotinib in lapatinib-resistant patients is not reported in previous studies. Since pyrotinib can block the *HER4* pathway, which cannot be blocked by lapatinib, pyrotinib may be effective in lapatinib-resistant MBC patients. This study aimed to evaluate the effects of pyrotinib-containing treatment in lapatinib-resistant patients in the third or later line settings. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3965/rc).

Methods

Patients

This retrospective observational cohort study enrolled MBC patients from Ruijin Hospital Shanghai Jiaotong University School of Medicine in China between August 1, 2018 and September 30, 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ruijin Hospital Shanghai Jiaotong University School of Medicine (Ethic Committee Reference Number 2021178). As this retrospective study did not harm the rights and health of patients, and protected their privacy and personal information, the ethics committee waived the requirement to obtain informed consent. Participants were female patients with *HER2*-positive MBC receiving pyrotinib-containing therapy in Ruijin Hospital. The inclusion criteria were as follows: (I) patients with histologically confirmed *HER2*-positive MBC (3+ staining intensity by immunohistochemical analysis and/or *HER2* gene amplification by fluorescence *in situ* hybridization); (II) patients with adequate hematological, hepatic, and renal function; (III) prior disease progression during treatment with lapatinib; (IV) at least 1 measureable lesion according to the Response Evaluation Criteria in Solid Tumors guidelines (RECIST version 1.1). Routine clinical information was documented and collected from an electronic case record system by two physicians.

Treatment and dose adjustment

Patients were received the target treatment of pyrotinib (400 mg orally once daily). Combination treatment with cytotoxic drugs, anti-*HER2* drugs, or endocrine therapy drugs was determined according to patients' physical status and prior regimens used. Dose adjustment, dose interruption, and treatment discontinuation were decided by the physician according to the side-effects.

Outcome and safety assessments

Clinical follow-up was conducted weekly and radiographic examinations were conducted every 3 cycles of treatment (for pyrotinib combined with endocrine therapy, radiographic examinations were performed every 2 months). Tumor response assessments were made according to RECIST criteria (version 1.1) using radiological scans, including computed tomography (CT) or magnetic resonance imaging (MRI). Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, 4.0). AEs were collected from a patient self-reporting system and laboratory test results.

The primary endpoint was ORR, which was defined as the proportion of patients with complete response (CR) or partial response (PR). Secondary endpoints included PFS, clinical benefit rate (CBR), OS, and safety. PFS was defined as the time from starting pyrotinib treatment to the date of disease progression confirmed by CT/MRI scan or death of any cause, whichever occurred first. CBR was defined as the

Table 1 Patient characteristics

Variables	N	%
Age		
Mean ± standard deviation	55.9±10.4	
Menopausal status		
Premenopausal	8	74.2
Postmenopausal	23	25.8
ECOG PS		
0–1	21	67.7
2–3	10	32.3
ER		
Positive	9	29.0
Negative	22	71.0
De novo stage IV		
Yes	5	16.1
No	26	83.9
Visceral metastasis		
Yes	23	74.2
No	8	25.8
Liver metastasis		
Yes	9	29.0
No	22	71.0
Brain metastasis		
Yes	6	19.4
No	25	80.6
Trastuzumab use		
Adjuvant or neoadjuvant only	10	32.3
Palliative only	15	48.4
Adjuvant and palliative	6	19.4
Pertuzumab use		
Yes	1	3.2
No	30	96.8
T-DM1 use		
Yes	2	6.5
No	29	93.5
Lapatinib use		
Yes	31	100.0
No	0	0.0
Previous lines of palliative treatment		
Median [range]	3 [2–7]	
Combined treatment agent		
Vinorelbine	12	38.7
Capecitabine	8	25.8
Paclitaxel	4	12.9
Gemcitabine	3	9.7
Nab-paclitaxel	2	6.5
Letrozole	1	3.2
Trastuzumab	1	3.2

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; T-DM1, ado-trastuzumab emtansine.

proportion of patients with CR, PR, and stable disease (SD). OS was defined as the time period from starting pyrotinib treatment to the date of death of any cause.

Statistical analysis

Median PFS (mPFS) were calculated by the Kaplan-Meier method and subgroup comparisons were evaluated by the log-rank test. The median follow-up time was calculated by the reverse Kaplan-Meier method. The stepwise Cox regression model was used to analyze the correlations between factors and PFS. All statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

Between August 1, 2018 and September 30, 2020, a total of 31 patients were enrolled in this study. Among these patients, the mean age was 55.9 (range, 31 to 69) years. The baseline characteristics are summarized in *Table 1*. Six patients (19.4%) had brain metastasis. All patients were heavily treated MBC, and they all had prior trastuzumab-containing therapy, with 32.3% of patients treated in the adjuvant or neoadjuvant setting (2 patients received neoadjuvant treatment), 15% of patients treated in the palliative setting, and the remaining

Table 2 Radiological response at first assessment

Response	N	%
Clinical benefit response	21	67.7
Objective response	8	25.8
PR	8	25.8
SD	13	41.9
Progressive disease	10	32.3

PR, partial response; SD, stable disease.

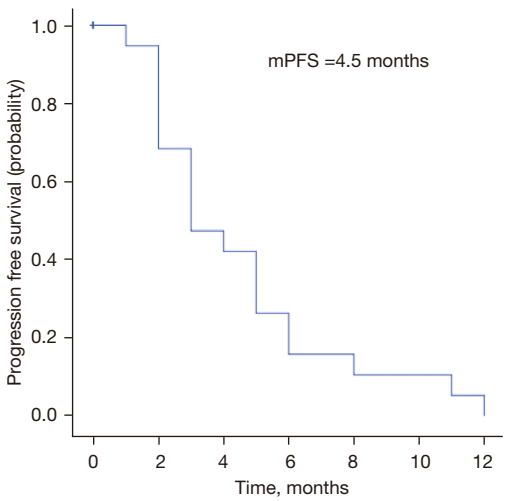

Figure 1 Kaplan-Meier plot of PFS of pyrotinib-based treatment in lapatinib-resistant patients. PFS, progression-free survival; mPFS, median PFS.

19.4% of patients treated in both the adjuvant and palliative settings. All patients had prior lapatinib-containing therapy. One patient had prior pertuzumab-containing therapy, and 2 patients had prior T-DM1 treatment. The median number of previous lines of anti-*HER2* treatment was 3 (range, 2–7) lines. Twenty-nine of the 31 patients (93.5%) concurrently received cytotoxic drugs. Of these, 12 patients (38.7%) received vinorelbine, 8 patients (25.8%) received capecitabine, 4 patients (12.9%) received paclitaxel, 3 patients (9.7%) received gemcitabine, and 2 patients (6.5%) received nab-paclitaxel. One patient concurrently received letrozole, and another patient concurrently received trastuzumab.

Efficacy

As of November 2020, the median follow-up duration

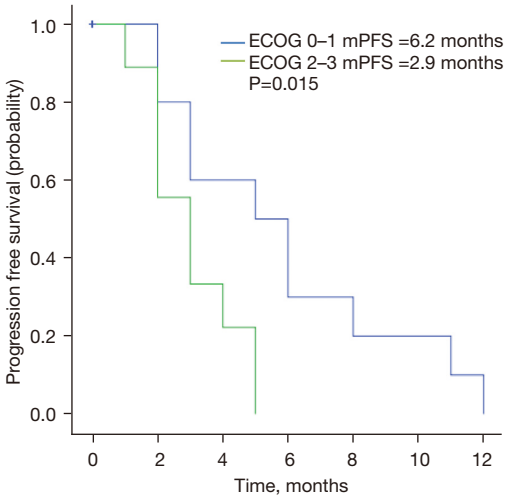

Figure 2 Kaplan-Meier plot of PFS for patients with ECOG PS 0–1 and ECOG PS 2–3. PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; mPFS, median PFS.

was 11.4 months. The radiological response at the first assessment is shown in *Table 2*. No patient achieved CR, while 8 patients (25.8%) achieved PR. The ORR was 25.8%. Thirteen patients (41.9%) achieved SD for a CBR of 67.7%. The mPFS in the study population was 4.5 months (95% CI: 3.1–5.9 months; *Figure 1*). Twelve patients were still in treatment and the mOS was not achieved by the time of this study. Physical status [Eastern Cooperative Oncology Group (ECOG) 0–1 *vs.* 2–3] was significantly correlated with PFS (6.2 *vs.* 2.9 months, P=0.015) (*Figure 2*). No significant associations were found between PFS and liver metastasis (yes *vs.* no) (*Figure 3*) or brain metastasis (yes *vs.* no) (*Figure 4*).

Safety

The AEs are shown in *Table 3*. The most common grade 3–4 AEs were diarrhea (19.4%), neutropenia (9.7%), and vomiting (6.5%). Dose reduction to 320 mg was conducted in 19.4% of all cases due to severe AEs mentioned above. No significant association was found between PFS and dose reduction (yes *vs.* no) (*Figure 5*).

Discussion

The progress of anti-*HER2* therapy has significantly improved the survival of patients with *HER2*-positive

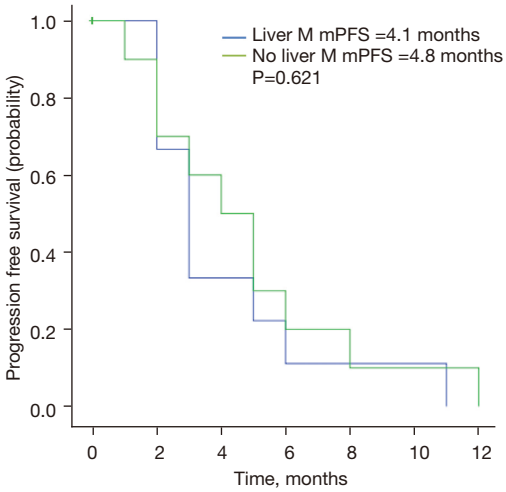

Figure 3 Kaplan-Meier plot of PFS for patients with and without liver metastasis. PFS, progression-free survival; M, metastasis; mPFS, median PFS.

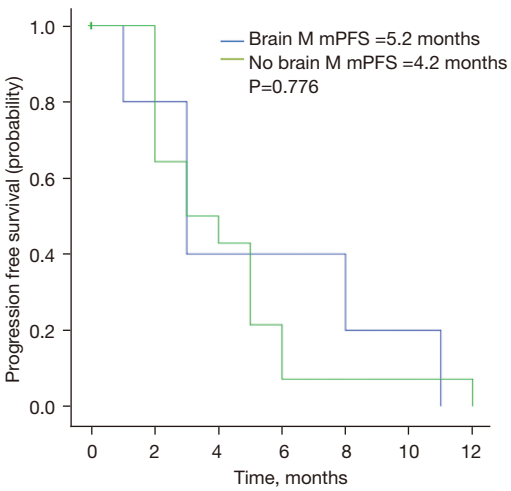

Figure 4 Kaplan-Meier plot of PFS for patients with and without brain metastasis. PFS, progression-free survival; M, metastasis; mPFS, median PFS.

Table 3 AEs

AEs	Any grade (%)	Grade 3–4 (%)
Diarrhea	81.6	19.4
Vomiting	61.3	6.5
Fatigue	48.4	0.0
Neutropenia	71.0	9.7
Thrombocytopenia	12.9	0.0

AEs, adverse events.

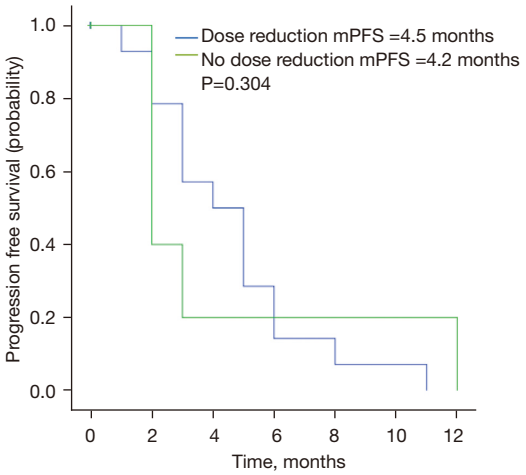

Figure 5 Kaplan-Meier plot of PFS for patients with and without dose reduction. PFS, progression-free survival; mPFS, median PFS.

MBC. Patients progressing on anti-*HER2* therapy should be offered additional anti-*HER2* therapy with subsequent cytotoxic or endocrine treatment, since it is beneficial to continue blocking the *HER2* pathway. The choice of the anti-*HER2* agent will depend on the specific anti-*HER2* therapy previously administered, country-specific availabilityand the time to progression (8). Pertuzumab, lapatinib, and T-DM1 are candidate regimens commonly recommended for failure of trastuzumab in *HER2*-positive MBC. T-DM1 could be considered for patients with *HER2*-positive MBC who have previously received trastuzumab and lapatinib for its favourable benefit than traditional combinations of chemotherapy (9,10). However, T-DM1 has already been approved for MBC in mainland China in 2021, but it's not covered by medical insurance.

Neratinib is an irreversible *ErbB* receptor TKI. The mPFS of 8.8 months in the NALA trial and the mPFS of 12.9 months in the NEfERT-T trial suggests its promising anti-*HER2* efficacy (11,12). Furthermore, the TBCRC022 trial showed that neratinib plus capecitabine had a mPFS of 3.1 months, an intracranial ORR of 33%, and an extracranial ORR of 43% in lapatinib-treated patients, demonstrating the efficacy of neratinib in lapatinib-treated patients (13).

Pyrotinib, serving as a TKI, directly blocks the intracellular domain and inhibits downstream pathway activation. Thus, it has the potential to overcome the drug resistance caused by traditional anti-*HER2* drugs. Due to the limitations of drug selection, pyrotinib, with its novel

anti-*HER2* efficacy, has become a key approved regimen for treating *HER2*-positive MBC in trastuzumab-resistant patients in China. The results of this study demonstrated that pyrotinib-containing therapy achieved a mPFS of 4.5 months and an ORR of 25.8% in HER2-positive MBC. Compared to the mPFS of 11.1 months and the ORR of 68.5% achieved in the PHENIX study, the data in this study were less promising (6). The apparent difference was the patient characteristics between the 2 studies. The patients included in the PHENIX study had disease progression during or after treatment with trastuzumab plus no more than 2 lines of chemotherapy. The PHENIX study excluded patients previously treated with lapatinib. All patients in our study were heavily treated and failed in lapatinib-containing therapy. The patients in this study were recognized to be an anti-*HER2* treatment refractory population.

One Chinese study reported the efficacy of pyrotinib-containing treatment in HER2-positive MBC lapatinib-naïve and lapatinib-treated patients. The mPFS was 5.4 months and the ORR was 23.2% for lapatinib-treated patients (14). The results in our study were comparable to the results of the lapatinib-treated subgroup. Thus, our results provide evidence in favor of the use of pyrotinib-containing therapy after failure of lapatinib-containing therapy. The number of patient samples in this study is too small, and a large sample study should be added in further study. Another limitation of this study was that few patients were treated with pertuzumab and T-DM1 before enrollment.

The incidence of brain metastasis is higher in the *HER2*-positive breast cancer subtype than other subtypes. Radiotherapy is a common treatment, and anti-*HER2* small molecule TKIs have been used due to their ability to penetrate the blood brain barrier. The subgroup of 31 patients with brain metastasis receiving pyrotinib and capecitabine in the PHENIX trial had a mPFS of 6.9 months, and the patients with brain metastasis in the PHENIX study did not receive prior lapatinib-containing therapy. In the TBCRC022 trial, the subgroup of lapatinib-treated patients with brain metastasis receiving neratinib plus capecitabine had a mPFS of 3.1 months. In our study, there were only 6 brain metastasis patients, with a mPFS of 5.2 months. The results of our study suggest that pyrotinib-containing therapy may be an optimal treatment for *HER2*-positive MBC with brain metastasis after failure of lapatinib-containing therapy. The limitation of the small sample size of our study should be taken into consideration, and studies with a larger sample size are needed to confirm the results.

The pyrotinib-related AEs were generally tolerated, including diarrhea, neutropenia, vomiting, fatigue, and thrombocytopenia, among others. Diarrhea was the most common AE. The incidence of diarrhea observed in our study was similar to that of previous studies. It was controllable with loperamide treatment in 80% of patients. Neutropenia occurred in 71% of patients, which was higher than in the PHENIX study, probably because a larger proportion of patients in our study had received anti-*HER2* therapy in combination with more than 2 lines of cytotoxic drugs before enrollment. Hand-foot syndrome in our study was less common than in the PHENIX study, as 74.2% of patients were not treated in combination with capecitabine. Pyrotinib in combination with cytotoxic drugs other than capecitabine also showed a good safety profile. And a long-term safety analysis should be reported after longer follow-up.

Conclusions

In conclusion, this study demonstrated the promising efficacy of pyrotinib-containing therapy for lapatinib-treated *HER2*-positive MBC in the third or later line settings. Pyrotinib-containing therapy was a safe treatment option with tolerable and controllable side effects. Prospective randomized controlled clinical studies with large sample sizes are needed to further investigate the role of pyrotinib in previously heavily-treated *HER2*-positive MBC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3965/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3965/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3965/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ruijin Hospital Shanghai Jiaotong University School of Medicine (Ethic Committee Reference Number 2021178). As this retrospective study did not harm the rights and health of patients, and protected their privacy and personal information, the ethics committee waived the requirement to obtain informed consent.

References

1. Onitilo AA, Engel JM, Greenlee RT, et al. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009;7:4-13.
2. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724-34.
3. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
4. Ma F, Li Q, Chen S, et al. Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol 2017;35:3105-12.
5. Ma F, Ouyang Q, Li W, et al. Pyrotinib or Lapatinib Combined With Capecitabine in HER2-Positive Metastatic Breast Cancer With Prior Taxanes, Anthracyclines, and/or Trastuzumab: A Randomized, Phase II Study. J Clin Oncol 2019;37:2610-9.
6. Yan M, Bian L, Hu X, et al. Pyrotinib plus capecitabine for human epidermal growth factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes (PHENIX): a randomized, double-blind, placebo-controlled phase 3 study. Transl Breast Cancer Res 2020;1:13.
7. Xu B, Yan M, Ma F, et al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:351-60.
8. Untch M, Würstlein R, Marschner N, et al. 4th International Consensus Conference on Advanced Breast Cancer (ABC4), Lisbon, November 4, 2017 : ABC4 Consensus: Assessment by a Panel of German Experts. Geburtshilfe Frauenheilkd 2018;78:469-80.
9. Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689-99.
10. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol 2017;18:743-54.
11. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020;38:3138-49.
12. Awada A, Colomer R, Inoue K, et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial. JAMA Oncol 2016;2:1557-64.
13. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol 2019;37:1081-9.
14. Lin Y, Lin M, Zhang J, et al. Real-World Data of Pyrotinib-Based Therapy in Metastatic HER2-Positive Breast Cancer: Promising Efficacy in Lapatinib-Treated Patients and in Brain Metastasis. Cancer Res Treat 2020;52:1059-66.

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