Real-World Evidence of Trastuzumab, Pertuzumab, and Docetaxel Combination as a First-Line Treatment for Korean Patients with HER2-Positive Metastatic Breast Cancer

Yong-Pyo Lee, Min-Sang Lee, HongSik Kim, Ji-Yeon Kim, Jin Seok Ahn, Young-Hyuck Im, Yeon Hee Park

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Purpose** Trastuzumab has markedly improved the survival outcomes of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and dual blockade of HER2 using trastuzumab and pertuzumab in combination with taxanes (THP) has become a standard of care for HER2-positive metastatic breast cancer (MBC) worldwide since the CLEOPATRA trial. We assessed the outcomes of THP as a first-line treatment for Korean HER2-positive MBC patients in the real-world setting.

**Materials and Methods** Between August 2008 and October 2020, we identified 228 HER2-positive MBC patients who received THP as a first-line palliative chemotherapy. We analyzed survival outcomes, efficacy, and adverse events of THP retrospectively.

**Results** After a median follow-up duration of 28.7 months, median overall survival and progression-free survival were 58.3 months (95% confidence interval [CI], 36.6 to 80.0) and 19.1 months (95% CI, 16.2 to 21.9), respectively. Better survival outcomes were observed in patients who received docetaxel for more than six cycles. Patients exposed to anti-HER2 directed therapies in a perioperative setting had poor survival outcomes. The overall response rate was 86.8% with a complete response (CR) rate of 17.7%. Among responders, 16.7% of patients sustained THP over 35 months and showed better survivals and higher CR rates. Adverse events were comparable to those reported in previous studies.

**Conclusion** In a real-world context, clinical outcomes of Korean HER2-positive MBC patients treated with THP were similar to those of patients in the CLEOPATRA trial. Much longer follow-up results would be warranted.

**Key words** Metastatic breast cancer, HER2 positive, Trastuzumab, Pertuzumab, Docetaxel

Introduction

Breast cancer (BC) is the most common cancer in women and the leading cause of cancer death worldwide [1]. Among all BC patients, approximately 15%-20% present with over-expression of human epidermal growth factor receptor 2 (HER2), which is characterized by a progressive nature and a poor clinical outcome [2,3]. Advances in HER2-targeted treatment strategies such as trastuzumab, a humanized monoclonal antibody that targets the extracellular domain of HER2 and inhibits proliferation [4], have improved the survival outcomes of patients with HER2-positive metastatic breast cancer (MBC) [5]. However, despite the use of trastuzumab, more effective treatment options and strategies are required to address disease progression. Pertuzumab, one of the new HER2 targeting agents, inhibits HER2 by a different mechanism than trastuzumab [6], and provides better anti-tumor activity than trastuzumab alone due to blockade of HER2 signaling when co-administered with trastuzumab [7]. The CLEOPATRA trial investigated the use of pertuzumab, trastuzumab and docetaxel (THP) as a first-line treatment for HER2-positive MBC patients and reported significantly prolonged survival outcomes with manageable toxicities [8-12]. Due to the findings of this pivotal trial, dual HER2 antibody therapy plus taxane has become the first-line standard of care for treating HER2-positive MBC patients, showing median overall survival (OS) close to 5 years.

Although clinical trials are the gold standard for demonstrating the efficacy of treatment, the outcomes of well-designed clinical trials might not reflect the real-world situation due to the careful selection of patients. Thus, analysis of real-world data is required to produce long-term efficacy data of treatments to compensate the weaknesses of clinical trials. In this retrospective study, we evaluated the efficacy and safety of THP treatment as a first-line palliative chemotherapy for Korean patients with HER2-positive MBC based on the single institution experience in the real-world context.
Materials and Methods

1. Patients and data collection
This is a retrospective study of HER2-positive MBC patients with treatment-naive for their metastatic disease. We identified patients who received THP as a first-line palliative chemotherapy and collected data retrospectively from medical records and laboratory results in the BC registry of single institution in Korea, Samsung Medical Center from August 2008 through October 2020. Demographic information and clinical characteristics were abstracted including age, date of diagnosis, confirmed pathology, initial cancer stage, hormone receptor status, type of perioperative treatment, and type of surgery. Patients received 6 mg/kg of trastuzumab (after an initial 8 mg/kg loading dose), 420 mg pertuzumab (after an initial 840 mg loading dose), plus 75 mg/m² of docetaxel every 3 weeks. In order to alleviate hypersensitivity and adverse events caused by docetaxel, each patient receiving docetaxel took 8 mg of dexamethasone 6 times over 3 days from the night before THP treatment to the next day. The treatment was continued until disease progression or occurrence of unacceptable toxicities. For patients who developed toxic effects that contraindicated docetaxel administration during THP treatment, we omitted docetaxel and maintained dual anti-HER2 directed therapy. HER2 overexpression was defined as either three-positive or two-positive on immunohistochemistry (IHC) test. For a two-positive IHC test result, HER2 status was confirmed through additional tests such as fluorescent in situ hybridization or silver in situ hybridization. In the in situ hybridization test, a positive HER2 gene amplification was defined as a HER2/centromere enumerator probe 17 ratio greater than 2.0.

2. Statistical analysis
OS was defined as the time from the initiation of THP treatment to the date of death from any cause and was censored at the date of last available follow-up. Progression-free survival (PFS) was measured from the initiation of THP treatment to progression or death from any cause, and was censored at the date of last available follow-up. The primary objective of this study was to evaluate survival outcomes, including median OS and PFS. Secondary objectives were to assess treatment efficacy by objective response rate (ORR), safety profiles of THP, and clinical outcomes of subsequent treatment after progression. ORR was defined as the proportion of patients who achieved a complete response (CR) or partial response as their best responses obtained during THP treatment. Response evaluation to treatment was assessed in patients with measurable lesions according to the Response Evaluation Criteria in Solid Tumors [13] using computed tomography and magnetic resonance imaging.

| Characteristic                          | No. (%) |
|----------------------------------------|---------|
| No. of patients                        | 228     |
| Age (yr)                               |         |
| Median (range)                         | 60 (26-78) |
| ≤ 40                                   | 14 (6.1)  |
| > 40 and ≤ 50                          | 64 (28.0) |
| > 50 and ≤ 60                          | 82 (35.9) |
| > 60                                   | 68 (29.8) |
| Menopausal status                      |         |
| Pre-menopause                          | 113 (49.5) |
| Post-menopause                         | 107 (46.9) |
| Unknown                                | 8 (3.5)  |
| Hormone receptor status                |         |
| ER positive and/or PR positive         | 124 (54.3) |
| ER negative and PR negative            | 94 (41.2)  |
| Unknown                                | 10 (4.3)  |
| De novo metastatic breast cancer       | 123 (53.9) |
| Relapsed metastatic breast cancer      | 105 (46.0) |
| Curative surgery                       | 96/105 (91.4) |
| Progression during neoadjuvant treatment | 6/105 (5.7)  |
| Unknown for surgery                    | 3/105 (2.8) |
| Perioperative chemotherapy             | 83 (86.4) |
| Neoadjuvant chemotherapy               | 29      |
| TCHP → Surgery → Herceptin            | 2       |
| AC followed by TH → Surgery           | 25      |
| → Herceptin                            |         |
| AC followed by T → Surgery             | 2       |
| Adjuvant treatment                     | 54      |
| AC followed by TH                      | 32      |
| TCH                                    | 5       |
| AC followed by T                       | 7       |
| FAC                                    | 5       |
| HTx. only                              | 5       |

(Continued to the next page)
Events, ver. 5.0 [14]. For statistical analyses, demographics and patient characteristics were summarized by descriptive statistics, and the chi-square test was used for comparison of characteristics. The Kaplan-Meier method was used for univariate analysis of survival outcomes, and the log-rank test was used for comparisons. All data were analyzed using the Statistical Package for Social Sciences software ver. 24.0 (IBM Corp., Armonk, NY).

**Results**

1. **Patient characteristics**

We analyzed a total of 228 patients with MBC who received THP as a first-line palliative chemotherapy. Baseline characteristics of the patients are shown in Table 1. Median age at the time of THP treatment was 60 years (range, 26 to 78 years). Among 228 patients, 123 patients (53.9%) had *de novo* stage IV disease and 105 patients (46.0%) had relapsed MBC. Of the patients with recurrent disease, 96 patients (91.4%) underwent curative surgery, and six of nine patients

| AC, adriamycin, cyclophosphamide; ER, estrogen receptor; FAC, fluorouracil, doxorubicin, cyclophosphamide; HTx, hormone therapy; PR, progesterone receptor; TCH, docetaxel, carboplatin, trastuzumab; TCHP, docetaxel, carboplatin, trastuzumab, pertuzumab; TH, docetaxel, trastuzumab; THP, docetaxel, trastuzumab, pertuzumab. |  |

**Table 1.** Continued

| Characteristic | No. (%) |
|----------------|---------|
| Disease-free interval (mo) | 96 |
| Median (range) | 38.5 (6.5-1,387.5) |
| > 6 and ≤ 12 | 5/96 (5.2) |
| > 12 and ≤ 24 | 23/96 (23.9) |
| > 24 | 64/96 (66.6) |
| Non-available | 4/96 (4.1) |

**Site of metastasis at the time of THP treatment**

| Site of metastasis | No. (%)|
|-------------------|---------|
| Visceral metastasis | 78 (34.2) |
| Bone metastasis | 51 (22.3) |
| Brain metastasis | 6 (2.6) |

![Graph A](https://via.placeholder.com/150)

**Fig. 1.** OS (A) and PFS (B) after THP treatment. OS according to the number of docetaxel administrations (C) and exposure to trastuzumab prior to THP treatment (D). CI, confidence interval; OS, overall survival; PFS, progression-free survival; THP, docetaxel, trastuzumab, pertuzumab.
did not receive curative surgical treatment due to progressive disease during neoadjuvant chemotherapy. The treatment history of the remaining three patients was confirmed before THP treatment, but it was uncertain whether they were treated surgically. Of the 96 patients who underwent curative surgery, 83 (86.4%, 83/96) patients received perioperative treatment, including chemotherapy, radiotherapy, or hormonal therapy. While receiving perioperative treatment, a total of 67 patients, including three who did not undergo surgery due to progressive disease during neoadjuvant treatment, were exposed to anti-HER2 directed therapies (two patients received trastuzumab plus pertuzumab, 62 patients received trastuzumab alone). Most patients (n=208, 91.2%) received more than six cycles of docetaxel. At the time of diagnosis of MBC, visceral metastasis was presented in one-third of patients (78/228), and bone metastasis was presented in approximately 20% of patients (51/228). In contrast, only six patients (2.6%) had brain metastasis.

2. Survival outcomes of THP as a first-line treatment

For a median follow-up duration of 28.7 months (range, 0.7 to 143.5 months), median OS and PFS in our study were 58.3 months (95% confidence interval [CI], 36.6 to 80.0) and 19.1 months (95% CI, 16.2 to 21.9), respectively (Fig. 1A and B). In subgroup analysis, there was no difference in survival outcomes according to age, menstrual condition, status of hormonal receptor expression, or metastatic site. Patients who received docetaxel for more than six cycles along with anti-HER2 directed therapies had significantly improved survivals than patients who received less than six cycles of docetaxel (p < 0.001) (Fig. 1C). In our study, patients unexposed to anti-HER2 directed therapies prior to THP treatment (trastuzumab–non-exposed patients) had better survival outcomes than those patients already exposed (trastuzumab-exposed patients) (p=0.043) (Fig. 1D). Survival analysis did not reveal any significant difference between de novo MBC patients and relapsed MBC patients (S1A Fig.).

### Table 2. Response rate of patients of first-line THP treatment with measurable lesions

| Best response     | No. (%) (n=220) |
|-------------------|-----------------|
| Complete response | 39 (17.7)       |
| Partial response  | 152 (69.0)      |
| Overall response  | 191 (86.8)      |
| Stable disease    | 25 (11.3)       |
| Progressive disease| 4 (1.8)        |

THP, docetaxel, trastuzumab, pertuzumab.
3. Response to THP treatment and safety outcomes

In 220 patients with measurable lesions, ORR was 86.8% (191/220) with a 17.7% CR rate (39/220) (Table 2). Median number of THP cycles was 19 (range, 2 to 88). After co-administration of docetaxel for a median of nine cycles (range, 1 to 28), we continued to use trastuzumab and pertuzumab as maintenance therapy with omission of docetaxel. The median duration of response who achieved objective response was 21.3 months (95% CI, 15.1 to 27.5) and 93.1% of responders (178/191) received docetaxel for more than six cycles. Among responders, 32 (16.7%) were long-term responders, defined as patients who sustained THP over 35 months. In our study, long-term responders had better survival outcomes and higher CR rates than non–long-term responders, and more long-term responders were observed in trastuzumab–non-exposed patients than other patient groups (Fig. 2, S2 Table). During THP treatment, 118 patients (51.7%) experienced any kind of neutropenia, and 63 patients (27.6%) experienced grade 3 or 4 neutropenia. In the neutropenic period, about 10% of patients had febrile events (21/228), and of patients who had febrile neutropenia, 11 patients had actual bacteremia. In addition to hematopoietic adverse events, patients who underwent THP therapy suffered from non-hematopoietic adverse events, including diarrhea, nausea, vomiting, and mucositis (Table 3). Among patients who suffered from any grade of peripheral neuropathy (n=62, 27.1%), 8.7% of patients had high-grade neuropathy and required interventions such as medications, dose reduction (n=20), or cessation of docetaxel (n=12). Sixty deaths were reported among all enrolled patients; however, there was no death events related to THP treatment.

4. Efficacy of subsequent treatment after THP treatment

In our study, 131 patients (57.4%) who received first-line THP had progressive disease and excluding five patients who died or refused further treatment, 126 patients underwent subsequent treatment. Most patients received trastuzumab emtansine (T-DM1) (72.2%, 91/126) while other patients received capecitabine plus lapatinib (17.4%, 22/126) or conventional chemotherapy with anthracycline plus cyclophosphamide (6.3%, 8/126) as second-line treatments (S3 Table). Median OS and PFS of T-DM1 were 30.3 months (95% CI, 25.2 to 35.3) and 9.9 months (95% CI, 7.0 to 12.8), respectively (S4A and S4B Fig.). Among patients who received second-line T-DM1 therapy, 57.4% showed disease progression and underwent several salvage-line chemotherapies. In our study, 15 (11.9%, 15/126) patients who had progressive disease after THP treatment participated in clinical trials. Although there was no significant difference in survivals between the clinical trial group and the conventional chemotherapy group, the survival curve for the group of patients enrolled in clinical trials plateaued over time (S1D Fig.).

Discussion

We analyzed the real-world, single-center data from patients who underwent combination treatment with trastuzumab, pertuzumab, and docetaxel as a first-line chemotherapy for HER2-positive MBC. Survival outcomes in this study were comparable to those of previous ones, including several studies using real-world data [12,15-17]. In addition, in terms of ORR, our results were similar or better than those reported previously along with a higher CR rate of 17.9% [8,15]. Although safety outcomes in our study were consistent with those of previous studies, it should be considered that evaluation of toxicities was quite limited by the retrospective nature of this study. Although the proportion of long-term responders was smaller than that of the CLEOPATRA study

---

Table 3. Adverse events of THP treatment

| Grade 1-2 | Grade 3 | Grade 4 |
|-----------|---------|---------|
| **Hematopoietic adverse events** | | |
| Neutropenia | 55 (24.1) | 28 (12.2) | 35 (15.3) |
| Febrile neutropenia | - | 21 (9.2) | - |
| **Non-hematopoietic adverse events** | | |
| Diarrhea | 37 (16.2) | - | 8 (3.5) |
| Nausea | 126 (55.2) | 45 (19.7) | |
| Vomiting | 105 (46.0) | 31 (13.5) | |
| Mucositis | 118 (51.7) | 35 (15.3) | |
| Peripheral neuropathy | 62 (27.1) | 20 (8.7) | |
| Any kind of bacteremia | - | 11 (4.8) | - |

THP, docetaxel, trastuzumab, pertuzumab.
(14.0% vs. 29.6%, respectively) [12], long-term responders in our study showed higher CR rates than non–long-term responders (43.8% vs. 16.3%) (Fig. 2B), which was associated with better survival outcomes (median OS, 80.5 months vs. 49.5 months) (Fig. 2A), consistent with the findings of Wong et al. [18]. Furthermore, approximately 70% of patients who experienced progressive disease after first-line THP received T-DM1 as a second-line treatment. In this patient population, we performed survival analysis as a secondary objective. Survival outcomes including OS and PFS were similar to those of the EMILIA trial, which demonstrated the efficacy of T-DM1 as a secondary treatment (S4A and S4B Fig.) [19,20]. Analysis of adverse events of T-DM1 was beyond the scope of this study. Thus, we demonstrated the efficacy of T-DM1 as a subsequent treatment after THP in a real-world context.

In our study, trastuzumab-exposed patients had poorer survival outcomes with significantly fewer long-term responders than trastuzumab–non-exposed patients (Fig. 2C). In a past study, Uncu et al. [21] demonstrated clinical benefits through continuous HER2 blocking treatment with trastuzumab in patients receiving several anti-HER2 treatments. In addition, in patients exposed to trastuzumab as (neo)-adjuvant treatment, the efficacy of re-treatment with trastuzumab in relapse had been proved [22,23]. In contrast, a study conducted by Rier et al. [24] suggested that palliative anti-HER2 treatment in a group of patients treated with HER2 blockade therapy before and after surgery had reduced efficacy. Although few studies have directly compared the efficacy of first exposure versus re-challenge for trastuzumab, several studies had shown the efficacy of continued blockade of the HER2 pathway through other mechanisms in patients with recurrent or progressive disease treated with trastuzumab as an adjuvant or a palliative treatment [20,25]. Given that the use of anti-HER2 directed therapies for HER2-positive MBC patients is inevitable in subsequent treatment, it is important to distinguish between patients who will benefit from continued use of trastuzumab and those who require different HER2 blockade strategies, and it is important to determine the proper duration of maintenance anti-HER2 directed therapy in future studies.

According to recent studies, the proportion of de novo stage IV BC has increased to the extent that it accounts for more than 50% of MBC [18,26]. Although de novo stage IV BC accounted for more than 50% of BCs in this study, there were no survival benefits of de novo BC compared to recurrent BC in contrast to the previous study [26]. Furthermore, when we performed survival analysis of three patient groups: a de novo stage IV group, a trastuzumab–non-exposed relapsed group, and a trastuzumab-exposed relapsed group, there was no significant difference in OS between the de novo stage IV group and the trastuzumab–non-exposed group (80.5 months [95% CI, 40.7 to 12.2] vs. 86.2 months [95% CI, not available (NA) to NA], p=0.360). However, the trastuzumab-exposed group had an OS of 46.6 months (95% CI, 36.8 to 56.0), which was lower than that of the other groups. There were more patients with no evidence of disease or long-term responders in the trastuzumab–non-exposed relapsed patient group than in the trastuzumab-exposed relapsed patient group. Other than that, there were no significant differences in overall response or duration of response to THP or subsequent treatment after THP. Considering the significant difference in OS upon trastuzumab exposure in patients with recurrent MBC (S1E Fig.), anti-HER2 agent use may have decreased efficacy following reuse. Therefore, when considering continuing anti-HER2 directed therapy after disease progression, it is necessary to consider the possibility of decreased efficacy in patients pre-exposed to anti-HER2 directed agents.

Taxanes, including paclitaxel and docetaxel, are commonly used standard therapeutic options for (neo)-adjuvant and palliative treatment of MBC [27,28]. Despite the benefits, limited doses of docetaxel are often given because of dose-dependent persistent peripheral neuropathy [29]. In this study, patients were divided into three groups according to the number of docetaxel doses: less than six, six to nine, and more than nine. Most patients (91.2%) received six or more cycles of docetaxel based on the initial CLEOPATRA trial design (median cycles of docetaxel in the THP group and control group were eight in the CLEOPATRA trial) [11]. The leading cause of fewer than six cycles of docetaxel administration was unmanageable adverse events including anaphylaxis or infusion-related syndrome. Administration of docetaxel for more than six cycles had survival benefits in our study, but more than nine cycles of docetaxel treatment was not associated with better survivals (S1B and S1C Fig.), rather concerning severe toxicities including neutropenia (p < 0.001) and high-grade peripheral neuropathy (p=0.004). Although the optimal doses and cycles of docetaxel have not been established yet, at least six cycles of docetaxel administration are necessary to improve long-term survival outcomes.

Innovative HER2-targeted therapeutics such as trastuzumab deruxtecan, tucatinib, and margetuximab have recently been demonstrated to be effective against advanced HER2-positive BC [30-32], therefore better clinical outcomes are expected for HER2-positive MBC in the near future. Our single center-based retrospective study demonstrated that THP combination treatment of Korean patients with HER2-positive MBC is an effective first-line palliative chemotherapy with a good safety profile in the real-world context, consistent with the findings of the CLEOPATRA trial.
Electronic Supplementary Material
Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement
This study was approved by the institutional review board of Samsung Medical Center (IRB No. 2021-07-192) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study. We used only anonymized information from patients’ medical charts. All research was carried out in accordance with relevant guidelines and regulations.

Author Contributions
Conceived and designed the analysis: Lee YP, Park YH.
Collected the data: Lee YP, Lee MS, Kim H, Kim JY, Ahn JS, Im YH.
Performed the analysis: Lee YP, Lee MS, Kim H, Kim JY, Ahn JS, Im YH, Park YH.
Wrote the paper: Lee YP, Park YH.

ORCID iDs
Yong-Pyo Lee: https://orcid.org/0000-0002-6153-9742
Yeon Hee Park: https://orcid.org/0000-0003-4156-9212

Conflicts of Interest
Park YH reports grants from AstraZeneca, Pfizer, Eisai, Roche, Daiichi-Sankyo, Eli Lilly, Novartis, Hammi, Merck and Alteogen. All other authors declare no competing interests.

References
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14:320–68.
3. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235:177-82.
4. Hudis CA. Trastuzumab: mechanism of action and use in clinical practice. N Engl J Med. 2007;357:39-51.
5. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-92.
6. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009;9:463-75.
7. Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoe flight KP, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. Cancer Res. 2008;68:5878-87.
8. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2011;366:109-19.
9. Swain SM, Ewer MS, Cortes J, Amadori D, Miles D, Knott A, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist. 2013;18:257-64.
10. Swain SM, Kim SB, Cortes J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013;14:461-71.
11. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372:724-34.
12. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:519-30.
13. Schwartz LH, Litiere S, de Vries E, Ford R, Gwyther S, Mandrekas S, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132-7.
14. U.S. Departement of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [Internet]. Washington, DC: U.S. Departement of Health and Human Services; 2017 [cited 2019 Feb 26]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
15. Takahashi M, Ohtani S, Nagai SE, Takashima S, Yamaguchi M, Tsuneizumi M, et al. The efficacy and safety of pertuzumab plus trastuzumab and docetaxel as a first-line therapy in Japanese patients with inoperable or recurrent HER2-positive breast cancer: the COMACHI study. Breast Cancer Res Treat. 2021;185:125-34.
16. Gamucci T, Pizzuti L, Natoli C, Mentuccia L, Sperduti I, Barba M, et al. A multicenter RETrospective observational study of first-line treatment with PERtuzumab, trastuzumab and taxanes for advanced HER2 positive breast cancer patients. RePer Study. Cancer Biol Ther. 2019;20:192-200.
17. Ramagopalan SV, Pisoni R, Rathore LS, Ray J, Sammon C.
Association of pertuzumab, trastuzumab, and docetaxel combination therapy with overall survival in patients with metastatic breast cancer. JAMA Netw Open. 2021;4:e2027764.

18. Wong Y, Raghavendra AS, Hatzis C, Irizarry JP, Vega T, Horowitz N, et al. Long-term survival of de novo stage IV human epidermal growth receptor 2 (HER2) positive breast cancers treated with HER2-targeted therapy. Oncologist. 2019;24:313-8.

19. Dieras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:732-42.

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

21. Uncu D, Bayoglu IV, Arslan UY, Kucukoner M, Artac M, Koca D, et al. Efficacy of trastuzumab-based therapy after disease progression on lapatinib based therapy in heavily pretreated HER2-positive metastatic breast cancer patients. J Clin Oncol. 2014;32(15 Suppl):e11586.

22. Lang I, Bell R, Feng FY, Lopez RI, Jassem J, Semiglazov V, et al. Trastuzumab retreatment after relapse on adjuvant trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer: final results of the Retreatment after HERceptin Adjuvant trial. Clin Oncol (R Coll Radiol). 2014;26:81-9.

23. Xu B, Hu XC, Zheng H, Wang X, Zhang Q, Cui S, et al. Outcomes of re-treatment with first-line trastuzumab plus taxane in patients (pts) with metastatic breast cancer (mBC) who relapsed after (neo)adjuvant trastuzumab: a prospective multicenter study. J Clin Oncol. 2016;34(15 Suppl):e12068.

24. Rier HN, Levin MD, van Rosmalen J, Bos M, Drooger JC, de Jong P, et al. First-line palliative HER2-targeted therapy in HER2-positive metastatic breast cancer is less effective after previous adjuvant trastuzumab-based therapy. Oncologist. 2017;22:901-9.

25. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617-28.

26. Tripathy D, Bruuskay A, Cobleigh M, Jahanzeb M, Kaufman PA, Mason G, et al. De novo versus recurrent HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from the SystHERs Registry. Oncologist. 2020;25:e214-22.

27. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. Breast Cancer (Auckl). 2012;6:159-71.

28. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352:2302-13.

29. Stubblefield MD, McNeely ML, Alfano CM, Mayer DK. A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. Cancer. 2012;118:2250-60.

30. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610-21.

31. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382:597-609.

32. Rugo HS, Im SA, Cardoso F, Cortes J, Curigliano G, Musolin A, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2021;7:573-84.