Pertuzumab as second- or later-line therapy for human epidermal growth factor receptor 2-positive metastatic breast cancer: A clinical experience

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Received December 29, 2022; Accepted March 27, 2023

DOI: 10.3892/mco.2023.2648

Abstract. Trastuzumab and pertuzumab with taxane-based chemotherapy are considered the first-line standard therapy for human epidermal growth factor receptor 2 (*HER2*)-positive metastatic breast cancer (mBC). Pertuzumab is also a later-line therapy for mBC in Switzerland, although limited safety and efficacy data are available. The present study assessed the therapeutic regimens, toxicities and clinical outcomes after second- or later-line pertuzumab therapy in patients with mBC who did not receive pertuzumab as a first-line therapy. Physicians from nine major Swiss oncology centers retrospectively completed a questionnaire for each pertuzumab-naive patient who was treated with pertuzumab as a second- or later-line therapy. Of 35 patients with HER2-positive mBC (median age, 49 years; range, 35-87 years), 14 received pertuzumab as a second-line therapy, 6 as a third-line therapy, and 15 as a fourth- or later-line therapy. A total of 20 patients (57%) died during the study period. The median overall survival was 74.2 months (95% confidence interval, 47.6-139.8 months). Grade (G) 3/4 adverse events (AEs) were reported in 14% of patients, with only 1 patient discontinuing therapy due to pertuzumab-related toxicities. The most common AE was fatigue (overall, 46%; G3, 11%). Overall, congestive heart disease occurred in 14% of patients (G3, 6%), nausea in 14% of patients (all G1), and myelosuppression in 12% of patients (G3, 6%). In conclusion, the median overall survival of patients who underwent second- or later-line pertuzumab treatment was similar to that reported for patients who underwent first-line pertuzumab treatment, and the safety profile was acceptable. These data support the use of pertuzumab for second- or later-line therapy when it was not administered as first-line therapy.

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Key words: metastatic breast cancer, pertuzumab, trastuzumab, human epidermal growth factor receptor 2, second-line therapy, overall survival

Introduction

Breast cancer is a prevalent health concern affecting a significant number of women worldwide (1). Targeted therapies, such as trastuzumab, have been widely studied and shown to be effective in the treatment of HER2-positive breast cancer, leading to improved survival outcomes for patients (2). Despite advances in treatment, recurrence remains a significant challenge for patients with metastatic breast cancer (3). The human epidermal growth factor receptor 2 (*HER2*) proto-oncogene regulates cell growth, survival, and differentiation. *HER2* overexpression, commonly referred to as *HER2* positivity, is a poor prognostic sign in patients with breast cancer (2,4), and *HER2*-positive breast cancer accounts for 15-20% of annual breast cancer-associated deaths. The recurrence rate in HER2-positive metastatic breast cancer varies, but it is a significant factor affecting patient outcomes and prognosis.

Studies have shown that the recurrence rate in HER2-positive metastatic breast cancer ranges from 20-30% (3). However, the introduction of anti-*HER2* agents has revolutionized the standard of care for patients with *HER2*-positive breast cancer.

Pertuzumab is a recombinant human immunoglobulin G (IgG) monoclonal antibody that targets *HER2* and acts by blocking *HER2* dimerization with other *HER* family members including *HER1, HER3,* and *HER4* (5). Trastuzumab is another targeted therapy that binds similarly to *HER2*. However, while pertuzumab binds to subdomain II of the *HER2* extracellular domain epitope, trastuzumab binds to subdomain IV (6). Although these agents bind to different *HER2* epitopes, they have complementary mechanisms of action. The combined administration of trastuzumab and pertuzumab offers a more comprehensive blockade of the *HER2* signaling pathway and results in more antitumor activity (7).

The CLEOPATRA phase III trial demonstrated the efficacy of adding pertuzumab to trastuzumab-docetaxel combination therapy as a first-line agent in patients with *HER2*-positive metastatic breast cancer (mBC). The trial revealed that adding pertuzumab resulted in a significant improvement in overall survival (OS) compared with trastuzumab and docetaxel combined with a placebo (8,9). In addition, the toxicity profiles of patients receiving pertuzumab and those receiving placebo were similar and manageable. Based on the significantly improved OS in the CLEOPATRA trial, the combination of pertuzumab, trastuzumab, and docetaxel has become the standard of care for first-line therapy for patients with mBC. However, docetaxel is associated with significant toxicity. Therefore, several studies have reported that the combination of pertuzumab-trastuzumab with other chemotherapy agents, including weekly paclitaxel or nanoparticle albumin-bound (nab)-paclitaxel, is effective and more tolerable than regimens that include docetaxel (10-12). Therefore, the combination of pertuzumab-trastuzumab with either taxane- or vinorelbine-based chemotherapy agents is the new standard first-line therapy for patients with *HER2*-positive mBC.

In patients with *HER2*-positive mBC who have recurrence or disease progression following first-line therapy with pertuzumab-trastuzumab, physicians may choose to re-target the *HER2* receptor, though data regarding the safety and efficacy of this practice are relatively limited (9,13-15). Therefore, this retrospective, observational study involving physicians from major Swiss oncology centers aimed to assess the therapeutic regimens, toxicities, and clinical outcomes following second- or later-line pertuzumab therapy in patients with mBC who did not receive pertuzumab as a first-line chemotherapy agent.

Materials and methods

Data source. Patients with *HER2*-positive mBC who received second- or later-line pertuzumab therapy without having received pertuzumab as a first-line therapy at nine major Swiss oncology centers (Canton Hospital Winterthur, Med. Oncology, Winterthur, Switzerland; Department of Gynecology, Canton Hospital Baden, Baden; Switzerland; Canton Hospital Olten, Division of Internal Medicine, Olten, Switzerland; Tumor Center ZeTuP, Rapperswil; Canton Hospital Aarau, Aarau, Switzerland; Canton Hospital Muensterlingen, Münsterlingen; Switzerland; Oncology Private Practice Basel, Affiliate of the Department of Medical Oncology, University Hospital Basel, Basel; Switzerland; Medical University Clinic, Canton Hospital Baselland, Liestal; University of Basel, Basel, Switzerland) were retrospectively identified. The patients' demographic, clinical, and therapeutic data were extracted from the medical records. Physicians of these patients were asked to complete a questionnaire regarding treatment regimens, safety, and survival for each included patient. The questionnaire was previously developed by one of the authors with the support of a statistical team.

Table I. Patient characteristics (n=35).

Variables	No. (%)
Histological subtype	
Invasive ductal carcinoma	33 (94)
Invasive lobular carcinoma	2 (6)
Estrogen- and/or progesterone receptor-positive	24 (69)
Stage IV cancer at first diagnosis	17 (49)
Prior (neo)adjuvant chemotherapy	15 (43)
Prior trastuzumab	16 (46)
Metastatic sites	
Bone	22 (63)
Liver	15 (43)
Lymph nodes	15 (43)

Patient selection criteria. Pertuzumab-naive patients with *HER2*-positive mBC who had a relapse of mBC following first-line therapy between 2001 and 2016 and were subsequently treated with at least one dose of second- or later-line pertuzumab therapy were included in this study. Only female patients aged ≥18 years who were treated at one of the included Swiss oncology centers were included. All eligible patients had mBC with known *HER2*-positive status. The study end-date was September 12, 2017. Patients who were male, diagnosed or treated for another primary cancer during the study period, or enrolled in other clinical trials and those who had previously been administered pertuzumab as a first-line treatment were excluded.

Clinical study measures. The initial date of pertuzumab administration was defined as the index date. The primary endpoint was OS, calculated from the index date to death or the date of the last follow-up. Data regarding disease progression, adverse events (AEs), and co-administered treatments were retrieved from the medical records. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). The duration of pertuzumab therapy was defined as the time from the index date to the date of the last administration of pertuzumab, death, or the end of the study. Data of patients who were alive or lost to follow-up at the end of the study were censored.

Statistical analysis. Descriptive statistics were used to summarize patient demographics, clinical characteristics, treatment patterns, and AEs. Categorical variables are presented as

Table II. Chemotherapy regimens.

Regimen	All patients, n (%) (n=35)	Second-line, n (%) (n=14)	Third-line, n (%) (n=6)	Fourth- or later-line, n (%) (n=15)
Pertuzumab + trastuzumab + chemotherapy	29 (83)	12 (86)	5 (83)	12 (80)
Taxane	19 (54)	8 (57)	4 (67)	7 (47)
Vinorelbine	6 (17)	3 (21)	1 (17)	2 (13)
Gemcitabine	1 (3)	0 (0)	0 (0)	1 (7)
Carboplatin	1 (3)	0 (0)	0 (0)	1 (7)
Anthracycline	2 (6)	1 (7)	0 (0)	1 (7)
Pertuzumab + trastuzumab + endocrine therapy	1 (3)	1 (7)	0 (0)	0 (0)
Pertuzumab + trastuzumab alone	5 (14)	1 (7)	1 (17)	3 (20)

frequency and percentage, and continuous variables are presented as mean and standard deviation or median and range.

A survival analysis was performed using the Kaplan-Meier methodology, using the LIFETEST procedure. All statistical analyses were performed using SPSS 17.0 statistical software.

Results

Patient characteristics. Overall, 35 female patients (median age: 49 years; range: 35-87 years) with *HER2*-positive mBC were included in the study. The clinicopathological characteristics of the patients are summarized in Table I. Overall, 33 patients (94%) had invasive ductal carcinoma and two (6%) had invasive lobular carcinoma. Twenty-four patients (69%) had ER-positive or PR-positive tumors, 17 (49%) had stage IV cancer, and five (14%) had stage III cancer at diagnosis. Sixteen patients (46%) received trastuzumab therapy prior to pertuzumab therapy. The most common metastatic sites were the bone (n=22; 63%), liver (n=15; 43%), and lymph nodes (n=14; 43%).

Ten patients (29%) underwent primary breast-conserving procedures and 16 (46%) underwent ablative (mastectomy) procedures. Thirteen patients (37%) underwent radiotherapy and 15 (43%) underwent chemotherapy.

Treatments. A total of 14 patients (40%) received pertuzumab as a second-line agent, six (17%) as a third-line agent, and 15 (43%) as a fourth- or later-line agent (Table II).

The median duration of pertuzumab administration was 6 months (range: 2-60 months). The median duration of pertuzumab therapy was 5.5 months (range: 2-30 months) for patients who received pertuzumab as a second-line agent (n=24), 6 months (range: 2-60 months) for patients who received pertuzumab as a third-line agent (n=6), and 11 months (range: 2-40 months) for patients who received pertuzumab as a fourth- or later-line agent (n=15).

Most patients (n=29; 83%) received a combination of pertuzumab-trastuzumab with another chemotherapeutic agent, including taxane (n=19; 54%), vinorelbine (n=6; 17%), anthracyclines (n=2; 6%), and gemcitabine and carboplatin (n=1; 3%). Among the remaining six patients, one (3%) was administered pertuzumab-trastuzumab with endocrine therapy and five (14%) were administered pertuzumab-trastuzumab alone.

Pertuzumab was discontinued mainly due to disease progression (n=23; 66%) and toxicity (n=5; 14%) (Fig. 1). However, pertuzumab-associated toxicities were noted in one patient (3%).

Safety outcomes. G3 toxicities were reported in five patients (14%) (Table III). No patients had G4 toxicities. The most commonly-recorded AE was fatigue (overall: n=16, 46%; G3: n=4, 11%), followed by congestive heart failure (overall: n=5, 14%; G3: n=2, 6%), nausea (overall: n=5, 14%; G3: n=0), and myelosuppression (overall: n=4, 11%; G3: n=2, 6%).

Overall survival. At the final follow-up, 20 patients (57%) had died. The median OS was 74.2 months (95% confidence interval: 47.6-139.8 months) (Fig. 2).

Discussion

HER2-positive breast cancer has been linked to more aggressive tumor behavior and poorer outcomes than *HER2*-negative breast cancer (16). However, the use of trastuzumab significantly improves the OS in patients with advanced *HER2*-positive breast cancer. Several new chemotherapeutic agents are currently being developed or are undergoing clinical investigation, including trastuzumab-emtansine, trastuzumab-deruxtecan, neratinib, and tucatinib. Most patients with mBC experience disease progression following first-line treatment (17-21). The continuation of trastuzumab administration in patients who experience disease progression has been associated with improvement in the time to progression without an increased risk of treatment-related toxicity (22). In 2010, a phase II trial conducted by Baselga *et al* (23) revealed that patients with mBC who experienced disease progression during prior trastuzumab therapy tolerated and responded well to the addition of pertuzumab to their therapeutic regimen. Combining pertuzumab-trastuzumab with taxane-based chemotherapy has become the new standard first-line therapy for patients with *HER2*-positive mBC based on the findings of the CLEOPATRA trial (9). The combination of pertuzumab-trastuzumab with vinorelbine-based chemotherapy is as effective as and less toxic than the combination with taxane-based therapy (10). However, as a second-line treatment, the administration of pertuzumab-trastuzumab

Table III. Adverse events.

Adverse events	All grades, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Fatigue	16 (46)	7 (20)	5 (14)	4 (11)	0 (0)
Congestive heart disease	5 (14)	1 (3)	2 (6)	2 (6)	0 (0)
Nausea	5 (14)	5 (14)	0 (0)	0 (0)	0 (0)
Myelosuppression	4 (11)	1 (3)	1 (3)	2 (6)	0 (0)
Diarrhea	3 (9)	3 (9)	0 (0)	0 (0)	0 (0)
Vomiting	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)
Mucositis	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)

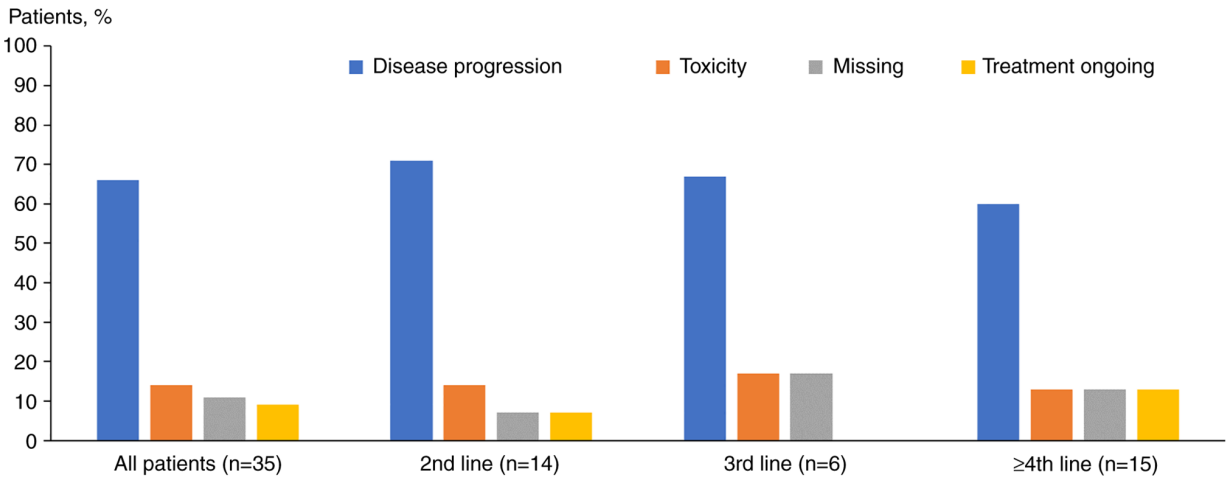

Figure 1. Treatment discontinuation indications.

combined with capecitabine was not superior to the combination of soletrastuzumab and capecitabine (24).

In the CLEOPATRA trial, the median OS was significantly higher in patients who received pertuzumab compared to patients who received placebo (9). These previous results are consistent with the results of this study. In this study, the first dose of later-line pertuzumab was administered on the OS index date, rather than on the first treatment date for mBC. Therefore, these results may reflect a patient selection bias.

As in the CLEOPATRA trial, chemotherapy accounted for most of the AEs reported in this study. Symptoms that developed during pertuzumab therapy in this study did not differ from those reported in previous studies. The addition of pertuzumab to the patients' therapeutic regimens did not increase cardiac toxicity in this study.

The pertuzumab-trastuzumab combination has a higher anti-cancer activity than either drug alone (7,25). The combination therapy has been reported as effective against advanced breast cancer following disease progression (8) and for patients receiving neoadjuvant therapy. Pertuzumab, trastuzumab, and docetaxel have been associated with higher complete response rates in pathological samples than trastuzumab-docetaxel, pertuzumab-docetaxel, or pertuzumab-trastuzumab combinations (25). The combination of pertuzumab-trastuzumab and chemotherapy has been approved for the neoadjuvant treatment of *HER2*-positive early breast cancer with a high risk of recurrence by the Food and Drug Administration in the United States and the Swiss Medic in Switzerland (26). Therefore, an increasing number of patients with metastatic *HER2*-positive breast cancer will be pretreated with pertuzumab in the future.

More clinical uses of combination therapy are currently being investigated. A randomized phase III trial (Detect V/CHEVENDO; NCT02344472) comparing the safety and efficacy of the pertuzumab-trastuzumab combination with either endocrine therapy or chemotherapy is being conducted in patients with hormone receptor-positive and *HER2*-positive mBC. *HER2*-/neu-targeted combinations may help patients avoid potential chemotherapy-related toxicities while achieving high efficacy, which will improve the patients' quality of life (9,27-29).

This study has several limitations, including its retrospective nature and small sample size. In addition, the OS outcomes may have been overestimated as the index date for the OS calculation was much later in the disease course in this study compared to that in previous studies. This difference may have resulted in a patient selection bias toward favorable prognosis factors (long-term response in first-line therapy), similar to the bias in a previous study regarding trastuzumab-deruxtecan (19). However, the remarkably long OS observed in this study warrants further prospective investigations of the use of pertuzumab in later-line regimens.

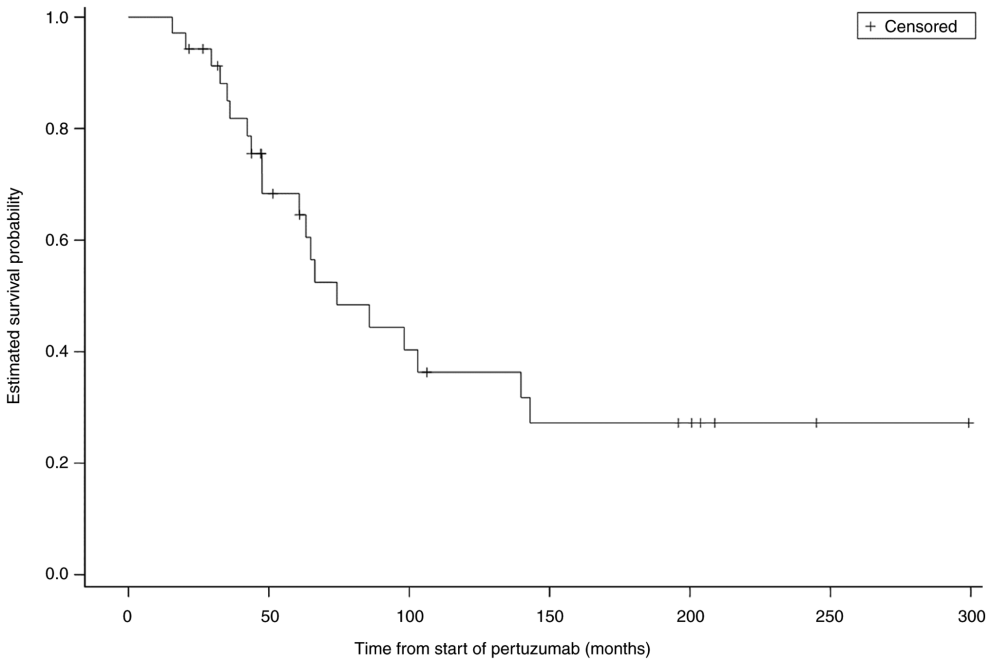

Figure 2. Overall survival.

In conclusion, the use of trastuzumab has been shown to significantly improve overall survival in patients with advanced HER2-positive breast cancer. The pertuzumab-trastuzumab combination has been approved for the neoadjuvant treatment of high-risk HER2-positive early breast cancer and has been shown to have a higher anti-cancer activity than either drug alone. This study investigates the use of pertuzumab in later-line treatment regimens for metastatic HER2-positive breast cancer. The median OS and safety profile of second- or later-line pertuzumab therapy are consistent with those reported for the first-line use of pertuzumab. These results indicate that the combination of pertuzumab and trastuzumab may have a positive impact on overall survival in later-line regimens for patients with metastatic HER2-positive breast cancer. However, due to its retrospective nature and small sample size, further prospective investigations are warranted to confirm these findings.

Acknowledgements

The authors would like to thank Professor Liwei Wang (State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China) for his support in editing the manuscript. Roche Pharma (Switzerland) provided administrative support for the analysis.

Funding

The study was funded by F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EB, CMS, AM, CL, CUN, DK, AS, CT, DT and MV conducted the research. EB, ELGM and MV wrote and revised the manuscript. EB and ELGM interpreted the data, and prepared the figures and tables. CMS, AM, CL, CUN, DK, AS, CT and DT analyzed the data. MV supervised and managed the research activity. EB and MV confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective, observational questionnaire was conducted according to the Declaration of Helsinki and local legislation. Ethics approval was not required for the present study as retrospective questionnaire-based studies on records do not require formal approval.

Patient consent for publication

Not applicable.

Competing interests

AM: Honoraria: Roche Switzerland, Novartis, Pfizer, Amgen, and Tesaro; Consulting/advisory role: Roche Switzerland, Novartis, AstraZeneca, Pfizer, and Amgen; Expert testimony: Roche Switzerland; CL: Honoraria: Pfizer and AstraZeneca; Consulting/advisory role: Pfizer and AstraZeneca; AS: Honoraria: Amgen, Roche, Pfizer, MSD, BMS, Lilly, Celgene, and Merck; CT: Consulting/advisory role: Celgene, Amgen, and Janssen; Research funding: Celgene. DT: Honoraria: Roche; Consulting/advisory role: Roche; MV: Honoraria: Roche, Novartis, and Pfizer; Consulting/advisory role: Roche,

Novartis, and Pfizer; Research funding: Roche. EB was supported by Krebsliga Schweiz, BIL KFS 4261-08-2017. All other authors declare that they have no competing interests.

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