Association of Pertuzumab, Trastuzumab, and Docetaxel Combination Therapy With Overall Survival in Patients With Metastatic Breast Cancer

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Introduction

In 2012, the combination of pertuzumab, trastuzumab, and docetaxel was approved by the US Food and Drug Administration for the treatment of patients with ERBB2 (formerly HER2)-positive metastatic breast cancer (MBC) who have not received prior anti-ERBB2 therapy or chemotherapy. The approval was based on data from the phase 3 pertuzumab, trastuzumab, and docetaxel for ERBB2-positive metastatic breast cancer (CLEOPATRA) trial. End-of-study results have confirmed the long-term benefit of this combination in the trial population; however, there has been limited analysis of its real-world effectiveness. To fill this evidence gap, we undertook a retrospective cohort study within the Flatiron Health electronic health record–derived database to assess the effectiveness of pertuzumab, trastuzumab, and docetaxel treatment of ERBB2-positive MBC in real-world US patients.

Methods

The Flatiron Health database includes information from more than 265 cancer clinics across the United States. Research with the database was approved by the Copernicus Group Institutional Review Board, which waived informed consent because all data were deidentified. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline

Table. Patient Demographic and Clinical Characteristics

| Characteristic                        | No. (%) | Flatiron Health cohort | CLEOPATRA trial |
|---------------------------------------|---------|------------------------|-----------------|
|                                       |         | All patients (N = 546) | Trial eligible (n = 211) | |
| Age at treatment initiation, median (IQR), y | 59 (50-66) | 58 (49.5-65.5) | 54 (22-82) |
| Female                                | 541 (99.1) | 210 (99.5) | 402 (100) |
| Race/ethnicity                        |         |                       |                 |
| White                                 | 329 (60.3) | 121 (57.3) | 245 (60.9) |
| Asian                                 | 13 (2.4) | 7 (3.3) | 128 (31.8) |
| Black or African American             | 87 (15.9) | 42 (19.9) | 10 (2.5) |
| Hispanic or Latino                    | 3 (0.5) | 0 | |
| Missing/other                         | 114 (20.9) | 41 (19.4) | 19 (4.7) |
| ECOG                                  |         |                       |                 |
| 0                                     | 166 (30.4) | 128 (60.7) | 274 (68.2) |
| 1                                     | 112 (20.5) | 83 (39.3) | 125 (31.1) |
| 2                                     | 30 (5.5) | 0 | 3 (0.7) |
| 3                                     | 6 (1.1) | 0 | 0 |
| 4                                     | 0 | 0 | 0 |
| Missing                               | 232 (42.5) | 0 | 0 |
| Site of disease involvement           |         |                       |                 |
| Visceral                              | 347 (63.6) | 131 (62.1) | 314 (78.1) |
| Nonvisceral                           | 197 (36.1) | 78 (37.0) | 88 (21.9) |

(continued)
Table. Patient Demographic and Clinical Characteristics* (continued)

| Characteristic | Flatiron Health cohort | | |
|----------------|------------------------|------------------------|------------------------|
| | All patients (N = 546) | Trial eligible (n = 211) | CLEOPATRA trial (n = 402) |
| Site of metastasesf | | | |
| Brain/CNS | 38 (7.0) | 0 | 0 |
| Bone | 311 (57.0) | 114 (54.0) | NA |
| Liver | 212 (39.8) | 83 (39.3) | NA |
| Lung | 186 (34.1) | 76 (36.0) | NA |
| Hormonal receptor status | | | |
| ER positive or PR positive | 333 (61.0) | 128 (60.7) | 189 (47.0) |
| ER negative and PR negative | 169 (31.0) | 67 (31.8) | 212 (52.7) |
| Unknown | 44 (8.1) | 16 (7.6) | 1 (0.2) |
| No. of metastatic sites | | | |
| 1 | 252 (46.2) | 104 (49.3) | NA |
| 2 | 151 (27.7) | 58 (27.5) | NA |
| ≥3 | 141 (25.8) | 47 (22.3) | NA |
| Missing | 2 (0.4) | 2 (0.9) | | |
| Cancer stage at initial disease diagnosis | | | |
| I | 45 (8.2) | 18 (8.5) | NA |
| II | 90 (16.5) | 29 (13.7) | NA |
| III | 97 (17.8) | 28 (13.3) | NA |
| IV | 294 (53.8) | 128 (60.7) | NA |
| Not documented | 20 (3.7) | 8 (3.8) | NA |
| Any other cancer in the 5 y before MBC diagnosis | 89 (16.3) | 0 | NA |
| Presence of a nononcologic comorbidity from Charlson Comorbidity Index ever before MBC diagnosis | 23 (4.2) | 0 | NA |
| Clinical practice | | | |
| Academic | 23 (4.2) | 4 (1.9) | NA |
| Community | 523 (95.8) | 207 (98.1) | NA |

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IQR, interquartile range; MBC, metastatic breast cancer; NA, not available; PR, progesterone receptor.

* Data on metastasis site were unavailable for 2 patients.

b Self-reported race/ethnicity.

c For patients who self-identified as not belonging to any of the other races/ethnicities.

d The maximum ECOG value recorded between MBC diagnosis date and the start of first-line treatment was used. For ECOG values, 0 represents fully active, able to carry out all pre-disease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work); 2, ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3, capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4, completely disabled; cannot carry on any self-care, totally confined to bed or chair.

* Visceral disease was defined in the Flatiron Health cohort as lung, liver, or brain metastasis.

† Site metastasis was recorded in the same month as the MBC diagnosis.

Figure. Kaplan-Meier Estimates of Overall Survival

Survival function estimates from Flatiron Health (FH) data are shown for all patients and trial-eligible patients, respectively. Survival function estimates for the CLEOPATRA trial population are displayed with a dashed gray line, and shaded areas represent 95% CIs. NR indicates not reached.

* Digitized overall survival.

b Sensitivity analysis, which included patients for whom Eastern Cooperative Oncology Group performance status was missing.
for cohort studies was followed. For this study, data from January 1, 2011, through October 31, 2020, were included for patients with an International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, Tenth Revision (ICD-10) diagnosis of breast cancer, documentation confirming MBC and a positive \textit{ERBB2} test result, who received pertuzumab, trastuzumab, and docetaxel combination therapy after their MBC diagnosis as first-line therapy for MBC. Patients were excluded if they were younger than 18 years at the time of treatment initiation, had fewer than 2 clinic encounters after treatment initiation, or had a gap of more than 90 days between the diagnosis of MBC and initiation of the collection of structured data.

Baseline patient demographic and clinical characteristics were summarized using descriptive statistics, and the Kaplan-Meier method was used to evaluate overall survival (OS). The Kaplan-Meier curve for OS from the CLEOPATRA trial was digitized, and individual patient-level survival times were estimated using the Guyot algorithm to allow for comparison with the Flatiron Health cohort using log-rank tests.\textsuperscript{1,3}

Sensitivity analyses were performed excluding patients who did not meet key inclusion criteria of the CLEOPATRA clinical trial: patients with Eastern Cooperative Oncology Group performance status greater than 1 (with or without missing values), brain metastases, and a history of comorbidities included in the Charlson comorbidity index.\textsuperscript{4}

Analyses were performed using Python 3.8 series programming language (Python Software Foundation), with Bonferroni-corrected, 2-sided \( P < .05 \) considered statistically significant.

### Results

In total, 546 patients with \textit{ERBB2}-positive MBC received combined pertuzumab, trastuzumab, and docetaxel therapy. Of these, 541 (99.1\%) were women, 329 (60.3\%) were White, and their median age at treatment initiation was 59 (interquartile range, 50-66) years. The Flatiron Health cohort differed in some patient characteristics from that of the CLEOPATRA trial (Table). The median follow-up for the cohort was 45.3 months (95\% CI, 40.6-48.0 months) and median OS was 48.6 months (95\% CI, 41.4-53.9 months). Overall survival did not differ from that in the CLEOPATRA trial (Figure; digitized OS, 56.4 months; 95\% CI, 51.0-71.9 months; log-rank test, \( P = .05 \)). In the sensitivity analysis excluding trial-ineligible patients (leaving 211 patients), survival did not differ from that in the CLEOPATRA trial (median OS, 55.6 months; 95\% CI, 46.7-82.4 months; log-rank test \( P > .99 \)).

### Discussion

Overall survival in this real-world cohort of \textit{ERBB2}-positive patients with MBC who were treated with pertuzumab, trastuzumab, and docetaxel combination therapy was similar to that demonstrated in the CLEOPATRA trial. The findings are comparable with recent real-world studies from Singapore (median, 51.5 [95\% CI, 35.8-60.0] after median follow-up of 20.6 months\textsuperscript{5}) and Italy (3-year overall survival, 72.2\% after median follow-up of 21 months\textsuperscript{6}).

Limitations of electronic health records are well documented and include incomplete information on some variables, such as comorbidities, adverse events, metastases, performance status, date of death, and adjuvant/neoadjuvant treatments.\textsuperscript{2} Our analysis is also limited by the relatively short median follow-up of the cohort. Despite these limitations, the results suggest that the benefit of pertuzumab, trastuzumab, and docetaxel combination therapy demonstrated in clinical trials is being realized in real-world populations.
