CAUSATION AND PREVENTION

Infused Therapy and Survival in Older Patients Diagnosed with Metastatic Breast Cancer who Received Trastuzumab

Robert I. Griffiths,1,2 Deepa Lalla,3 Robert J. Herbert,4 Justin F. Doan,3 Melissa G. Brammer,3 and Mark D. Danese1

Outcomes Insights, Inc., Westlake Village, CA, USA, 1 Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2 Genentech, Inc., South San Francisco, CA, USA, 3 Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

We used Surveillance, Epidemiology, and End Results–Medicare data (2000–2006) to describe treatment and survival in women diagnosed with metastatic breast cancer (MBC) who received trastuzumab. There were 610 patients with a mean age of 74 years. Overall, 32% received trastuzumab alone and 47% received trastuzumab plus a taxane. In multivariate analysis, trastuzumab plus chemotherapy was associated with a lower adjusted cancer mortality rate (Hazard Ratio [HR] 0.54; 95% Confidence Interval [CI] 0.39–0.74; \( p < .001 \)) than trastuzumab alone among patients who received trastuzumab as part of first-line therapy. Adding chemotherapy to first-line trastuzumab for metastatic breast cancer is associated with improved cancer survival.

Keywords: Breast cancers; Chemotherapy; Outcomes research

INTRODUCTION

In metastatic breast cancer (MBC) among patients with human epidermal growth factor receptor 2 (HER2) overexpressing disease, trastuzumab is indicated for use in combination with paclitaxel for first-line treatment, and as a single agent for those who have previously received one or more chemotherapy regimens (1). The safety and efficacy of trastuzumab in MBC have been evaluated in numerous clinical trials (2–10). Two were particularly relevant for establishing the current indication in MBC (1, 8). In this trial, patients were randomly assigned to receive standard chemotherapy alone (\( n = 234 \)) or standard chemotherapy plus trastuzumab (\( n = 235 \)). Standard chemotherapy consisted of doxorubicin (or epirubicin) and cyclophosphamide for women who had not previously received adjuvant therapy with an anthracycline, or paclitaxel for women previously treated with an anthracycline (average age 52 years, ranging from 25 to 77). Adding trastuzumab to standard chemother-

Correspondence to: Robert Griffiths, MS, ScD., Outcomes Insights, Inc., 340 N. Westlake Blvd., Suite 200 Westlake Village, CA 91362, USA.
email: bob@outins.com

MATERIAL AND METHODS

Data source

The source of data for this study was the National Cancer Institute's (NCI) SEER cancer registry linked to Medicare enrollment and claims data (SEER-Medicare data). This database has been described in detail elsewhere (12). Briefly, as of 2010, SEER collects and publishes cancer incidence and survival data from 17 population-based cancer registries throughout the United States covering approximately 26% of the US population (13). The registries routinely collect data on patient demographics, primary tumor site, tumor...
morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. In the SEER-Medicare data, for persons age 65 years or older, 97% are eligible for Medicare, and 93% of patients in the SEER files are matched to the Medicare enrollment file (14). At the time this study was performed, the SEER-Medicare linkage included all Medicare-eligible persons from 16 of the 17 registries through 2005 and their Medicare claims for Part A (inpatient) and Part B (outpatient and physician services) through 2006.

Patient eligibility
Patients were included in this study if they were diagnosed with MBC, defined as either (A) de novo Stage IV breast cancer between 2000 and 2005, or (B) de novo Stage 0–III breast cancer between 2000 and 2005, with a distant recurrence before the end of their Medicare claims. Distant recurrence was identified by an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code in the medical claims for secondary cancer (197.XX–198.XX), excluding in the breast (198.81, 198.82) or in the lymph nodes (196.XX) based on algorithms for identifying cancer relapse previously reported in the literature (15, 16). These algorithms were originally developed for detecting relapse of acute myelogenous leukemia (AML), and the best among them showed a sensitivity of 86% and a specificity of 99% in this disease (15). More recently, they have been applied to, but not validated in, a study on the costs of breast cancer recurrence (16). Other inclusion criteria consisted of the following: breast cancer was the first primary cancer diagnosed; patients first received trastuzumab therapy after diagnosis of MBC; and patients were enrolled in Medicare Parts A and B, with no health maintenance organization (HMO) coverage for 12 months prior to de novo diagnosis of breast cancer.

Patients were excluded for any of the following reasons: male gender; trastuzumab use prior to diagnosis of MBC; de novo diagnosis of breast cancer before age of 65 years; diagnosis made by death certificate or autopsy; death within the first month following diagnosis; or Medicare enrollment less than 12 months before diagnosis.

Treatments
For purposes of describing treatment patterns, the observation period was defined as beginning on the day MBC was diagnosed (the index date) and ending on the last day of Medicare claims (December 31, 2006) or death, whichever came first. Since, for confidentiality reasons, SEER provides only the calendar month in which cancer is diagnosed, for de novo Stage IV patients, the date of MBC diagnosis was defined as the first day of the calendar month in which they were diagnosed with breast cancer. For de novo Stage 0–III patients, the date of diagnosis was defined as the date of the first Medicare claim indicating distant recurrence. ICD-9-CM procedure codes (17) and Healthcare Common Procedure Coding System (HCPCS) codes (18) within Medicare claims were used to identify intravenous chemotherapy agents and trastuzumab administered during the observation period (19, 20).

In addition to de novo Stage, patients were further classified according to whether trastuzumab was part of their first infused therapy regimen during the observation period (first-line trastuzumab), or whether it was started after an initial course of chemotherapy during the observation period (delayed trastuzumab) (Figure 1). If trastuzumab began

Figure 1. Study population. aTotal number of patients meeting the inclusion and exclusion criteria for the study. bDe novo staging according to SEER. cIdentification of distant recurrence according to Medicare claims. dTrastuzumab part of the first treatment regimen after diagnosis of metastatic breast cancer. eTrastuzumab part of second or subsequent treatment after diagnosis of metastatic breast cancer.
within two months of the first claim for chemotherapy, or if there was no chemotherapy claim present, the patient was classified as having received first-line trastuzumab. This regimen was then classified hierarchically using ICD-9-CM and HCPCS codes as follows: trastuzumab alone; trastuzumab plus a taxane (paclitaxel or docetaxel), with or without any other agent; and trastuzumab with any other agent except a taxane. Assignment was based on having had at least one claim for each agent during two of the first 6 months following the first chemotherapy claim.

If trastuzumab began at least 2 months after the first claim for chemotherapy, the patient was classified as having received delayed trastuzumab (Figure 1). In this group, the initial chemotherapy regimen (absent trastuzumab) was classified, using the same approach above, as: anthracycline and/or cyclophosphamide with or without any other agent; taxane and/or vinorelbine with any other agent except anthracycline or cyclophosphamide; and other. The subsequent regimen that included trastuzumab was classified the same way as the first-line trastuzumab group described above. Visual inspection of the data prior to the development of this classification scheme showed that in the group receiving delayed trastuzumab, there was very little overlap between the agents used in the initial chemotherapy regimen and those used in the subsequent trastuzumab regimen.

Medicare Part D (prescription drug coverage) data were not available at the time this study was performed. Consequently, it was not possible to identify anti-estrogen or other oral therapy use in this population.

Mortality and censoring

The date of death was assigned by using the Medicare date, if available, even in cases where the SEER date also was available. The Medicare date was preferred because it is more current than the SEER date (21). In cases where the Medicare date was missing but the SEER date of death was available, the SEER date was used. All other patients were assumed to be alive at the end of the observation period (December 31, 2006), although they may have been censored earlier for other reasons, such as switching from fee-for-service to HMO coverage.

The cause of death was classified as cancer or noncancer, using the CODKM variable in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF) through 2006. Cancer mortality included all deaths due to cancer (CODKM = 001–130), and not just due to breast cancer (CODKM = 046). Noncancer mortality included all other identified causes of death, e.g., CODKM = 154 “Diseases of Heart” and CODKM = 148 “Diabetes Mellitus”. However, it excluded missing or unspecified cause of death. These patients were censored at the time of death in both the cancer and noncancer survival analysis since exploratory analysis showed that almost 90% of those with a known cause of death died of cancer. Consequently, including them as noncancer deaths could have resulted in significant misclassification. Cancer and noncancer mortality were examined separately since the benefit of cancer therapy should be manifested primarily through differences in cancer mortality, and differences in noncancer mortality could indicate selection bias, particularly confounding by indication (22).

Patient characteristics

Patients were described according to their demographic and clinical characteristics at the time MBC was diagnosed, with the exception of calculating the NCI Comorbidity Index (23) (described below), which was done at the time of de novo breast cancer diagnosis. Patient age at MBC diagnosis was stratified into five groups: 66–69; 70–74; 75–79; 80–84; and ≥85. Requiring eligible patients to have at least one year of Medicare enrollment prior to diagnosis ensured that the minimum age in the cohort was 66 years. Race/ethnicity was defined using the SEER recorded race variable as white, black, Hispanic, and other (which consists predominantly of American Indian/Native Alaskan, Native Hawaiian or Other Pacific Islander, and Asian) (24).

Medicare inpatient (Part A), outpatient, and physician (Part B) claims were used to calculate an NCI Comorbidity Index for each patient (23). This approach (25, 26) entailed first removing claims that were considered to have unreliable diagnosis coding, such as those for testing procedures used to rule out conditions. Then, remaining diagnosis and procedure codes were used to identify the 15 noncancer comorbidities in the Charlson Comorbidity Index (CCI) (27). The algorithms used to identify these conditions reflect the Deyo (28) adaptation of the CCI, and include several procedure codes from the Romano (29) adaptation. A weight was assigned to each condition, and the weights were summed to obtain the index for each patient.

In the absence of performance status, we used Medicare claims to construct several medical resource utilization variables that have been shown and validated to predict performance status, (30) consisting of any inpatient admission (yes/no), any admission to the emergency room (yes/no), any use of durable medical equipment (yes/no), and any outpatient visit (yes/no) from 12 months before to 1 month after the diagnosis of MBC. In addition, we used SEER data and Medicare claims to identify prior surgery for breast cancer and radiation treatment (20, 31).

Statistical analysis

Cox proportional hazards regression analysis was used to identify treatment, demographic, and clinical factors associated with overall survival. Multivariate analyses were performed on all-cause, cancer and noncancer mortality, including the entire cohort and stratified according to whether the patient received first-line or delayed trastuzumab (total of 9 analyses). We elected to conduct stratified analyses out of concern that these two groups might have significantly different prognostic features that could confound associations between treatment and survival in a single model.

In addition to the standard approach to multivariate analyses, which included individual predictors, multivariate analyses were performed using propensity techniques, (32) in which quintile of propensity score was substituted for all independent variables except initial trastuzumab regimen (total of 9 analyses), and in which the inverse of the propensity
score was used as a weight in the regression analysis (total of 9 analyses).

Since treatment with trastuzumab following MBC diagnosis was a criterion for inclusion in this study, one concern in specifying this analysis was to avoid immortal time bias, (33) which, according to Suissa, is “a span of cohort follow-up during which, because of exposure definition, the outcome under study could not occur.” In this case, death could not occur between the time the patient was diagnosed with MBC and the time the patient first received trastuzumab. Therefore, the index date for this analysis was advanced from the date of diagnosis to 30 days after the date of the first claim for trastuzumab, to account also for the fact that additional time was required to determine whether or not patients received chemotherapy as part of their initial trastuzumab regimen.

RESULTS

Characteristics of Patients

There were 610 patients who met the study inclusion criteria (Table 1). Of these, 58% were diagnosed with Stage 0–III disease with a distant recurrence, while the remaining patients were diagnosed with de novo Stage IV disease. The median age at the time of MBC diagnosis was 73 years (mean 74 years), and 22% were age 80 years or older. Those who had a distant recurrence after being diagnosed with de novo Stage 0–III disease were significantly older ($p < .00001$). The mean time from de novo diagnosis of breast cancer to recurrence in this group was 17 months (median 13 months). The majority of patients were white race. However, those diagnosed with de novo Stage IV disease were more likely to be nonwhite ($p = .03$). Less than half of the patients were estrogen receptor (ER)—and/or progesterone receptor (PR)—positive, and differences in hormone status between the two groups were not statistically significant. Most patients had none of the comorbidities in the NCI Comorbidity Index. Finally, almost all patients in the de novo Stage 0–III group had surgery for breast cancer within 4 months of diagnosis, compared with less than 50% with de novo Stage IV disease.

Patterns of Trastuzumab Use

The mean time to initial trastuzumab following diagnosis of MBC was almost 6 months, with a median time of 2 months (Table 2). The median time in the de novo Stage 0–III with distant recurrence group was half that of the Stage IV group. However, the mean times were similar. The average duration of trastuzumab was 13 months, and it was significantly longer for those diagnosed with de novo Stage IV disease (16 months) compared with de novo Stage 0–III with distant recurrence (11 months). During trastuzumab therapy, patients received an average of 2.1 administrations per month, and there were very few calendar months during the course of therapy (6%) in which patients did not receive at least one administration of trastuzumab.

Table 1. Patient Characteristics

|                          | De Novo Stage of Breast Cancer$^a$ | All Patients $^b$ | p Value$^b$ |
|--------------------------|------------------------------------|------------------|-------------|
| Age at diagnosis of metastatic breast cancer |                        |                  |             |
| 66–69                    | 61 (14.3%)                         | 23 (9.7%)        | .03         |
| 70–74                    | 121 (34.0%)                        | 195 (32.0%)      |             |
| 75–79                    | 88 (24.7%)                         | 155 (25.4%)      | .03         |
| 80–84                    | 69 (19.4%)                         | 96 (15.7%)       |             |
| ≥85                      | 27 (7.6%)                          | 40 (6.6%)        |             |
| Race/ethnicity           |                                    |                  |             |
| White                    | 298 (83.7%)                        | 489 (80.2%)      | <.00001     |
| Black                    | 30 (8.4%)                          | 69 (11.3%)       |             |
| Hispanic                 | 16 (4.5%)                          | 27 (4.4%)        |             |
| Other                    | 12 (3.4%)                          | 25 (4.1%)        |             |
| Year of metastatic breast cancer diagnosis |                        |                  | <.00001     |
| 2000                     | 16 (4.5%)                          | 44 (7.2%)        |             |
| 2001                     | 41 (11.5%)                         | 78 (12.8%)       | .03         |
| 2002                     | 46 (12.9%)                         | 80 (13.1%)       |             |
| 2003                     | 50 (14.0%)                         | 92 (15.1%)       |             |
| 2004                     | 69 (19.4%)                         | 135 (22.1%)      |             |
| 2005–2006                | 134 (37.6%)                        | 181 (29.7%)      |             |
| Estrogen(ER) and progesterone (PR) receptor status |                        |                  | .54         |
| ER$^+$ and PR$^+$        | 83 (23.3%)                         | 151 (24.8%)      |             |
| ER$^+$ or PR$^+$         | 55 (15.4%)                         | 97 (15.9%)       |             |
| ER$^+$ and PR$^+$ or unknown | 218 (61.2%)                      | 362 (59.3%)      |             |
| National Cancer Institute Comorbidity Index |                  |                  | .90         |
| 0                       | 313 (87.9%)                        | 539 (88.4%)      |             |
| ≥1                      | 43 (12.1%)                         | 71 (11.6%)       |             |
| Prior surgery for breast cancer |                    |                  | <.00001     |
| Radiation                | 342 (96.1%)                        | 466 (76.4%)      |             |
| Prior inpatient admission | 192 (53.9%)                       | 351 (57.5%)      | .03         |
| Prior emergency department Visit | 217 (61.0%)           | 331 (54.3%)      | <.00001     |
| Claim for durable medical equipment |                            | 187 (30.7%)      | <.00001     |

$^a$De Novo Stage could be either Stage IV or Stage 0–III. However, all patients initially diagnosed with Stage 0–III had a distant recurrence documented in their Medicare claims to be included in the study.

$^b$All tests of significance performed using Chi Square analysis. Comparisons are de novo Stage IV to de novo Stage 0–III.
Overall, 70% of the cohort received first-line trastuzumab (Table 3). The proportion of patients diagnosed with de novo Stage IV disease was similar between patients who received first-line and those who received delayed trastuzumab. Most first-line trastuzumab patients received either monotherapy (31%) or trastuzumab plus a taxane (48%) as initial therapy following MBC diagnosis. In the delayed trastuzumab group, a slightly higher proportion of patients received trastuzumab alone (35%), and a slightly lower proportion received trastuzumab plus a taxane (45%) relative to first-line trastuzumab patients. During the observation period (2000–2006), the percent of patients receiving trastuzumab alone varied from 23 (2000) to 38% (in both 2003 and 2006).

Longitudinal “lasagna” plots (34) were constructed to illustrate the number of administrations of trastuzumab per month, the duration of trastuzumab, and gaps in administration (Figure 2) for up to 24 months following the start of treatment. These were stratified by de novo stage and first-line versus delayed use. In general, there was a broad spectrum of use in all four groups, ranging from uninterrupted treatment in excess of one year with four or more administrations in each month, to treatment lasting only one month with only one administration.

### Survival Analysis

Overall, 345 (57%) patients died during the observation period: 281 (81%) of these had cancer listed as the cause of death; 24 (7%) had a noncancer cause of death; and the remaining 40 (12%) had no cause of death listed and were censored in the cause-specific, but not the overall survival analysis. The estimated median survival was 566 days (95% Confidence Interval [CI] 495–644) in the entire cohort, 564 days (95% CI 473–644) in those who received first-line trastuzumab, and 579 days (95% CI 454–788) in those who received delayed trastuzumab.

In multivariate analysis that included the entire cohort, (Table 4) trastuzumab plus chemotherapy was associated with statistically significantly lower cancer mortality (Hazard Ratio [HR] 0.67; 95% CI 0.51–0.88; \( p < .01 \)), but not non-cancer mortality.

In stratified analysis, (Table 5) first-line trastuzumab plus chemotherapy was associated with statistically significantly lower cancer mortality (HR 0.54; 95% CI 0.39–0.74; \( p < .001 \)). However, adding chemotherapy to delayed trastuzumab had no impact on cancer mortality. Findings from the propensity score analysis were consistent with those from the standard regression analysis (Figure 3).
Figure 2. Patterns of trastuzumab use. Each row of data represents a single patient. Each colored rectangle within each row represents one month, ordered chronologically following the beginning of trastuzumab therapy, up to a maximum of 24 months. Dark blue rectangles indicate more administrations of trastuzumab in that month; light blue rectangles indicate fewer administrations; orange rectangles indicate no administrations of trastuzumab while the patient was still observed in the data set; and clear rectangles indicate that the patient was no longer observed in the data because of death or the end of the observation period. Within each of the four figures, patients are ordered from high (top of figure) to low number of trastuzumab administrations during 48 months following the beginning of therapy, a measure of both the intensity and duration of trastuzumab therapy. MBC—Metastatic breast cancer.
| Patient Characteristic                              | All Cause Mortality 95% Confidence Interval | Cancer Mortality 95% Confidence Interval | NonCancer Mortality 95% Confidence Interval |
|---------------------------------------------------|---------------------------------------------|----------------------------------------|--------------------------------------------|
|                                                   | Hazard Ratio | Lower | Upper | p Value | Hazard Ratio | Lower | Upper | p Value | Hazard Ratio | Lower | Upper | p Value |
| Trastuzumab regimen included chemotherapy          |               |       |       |         |               |       |       |         |               |       |       |         |
| Without chemotherapy                               |               |       |       |         |               |       |       |         |               |       |       |         |
| With chemotherapy                                  |               |       |       |         |               |       |       |         |               |       |       |         |
| Trastuzumab timing                                 |               |       |       |         |               |       |       |         |               |       |       |         |
| First-line                                        |               |       |       |         |               |       |       |         |               |       |       |         |
| Delayed                                           |               |       |       |         |               |       |       |         |               |       |       |         |
| Age at diagnosis of metastatic breast cancer       |               |       |       |         |               |       |       |         |               |       |       |         |
| 66–69                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 70–74                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 75–79                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 80–84                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| ≥85                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Race                                              |               |       |       |         |               |       |       |         |               |       |       |         |
| White                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| Hispanic                                          |               |       |       |         |               |       |       |         |               |       |       |         |
| Other                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| Stage at breast cancer de novo diagnosis           |               |       |       |         |               |       |       |         |               |       |       |         |
| 0–III                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 0 IV                                              |               |       |       |         |               |       |       |         |               |       |       |         |
| National Cancer Institute Comorbidity Index       |               |       |       |         |               |       |       |         |               |       |       |         |
| 0                                                 |               |       |       |         |               |       |       |         |               |       |       |         |
| 1                                                 |               |       |       |         |               |       |       |         |               |       |       |         |
| 2                                                 |               |       |       |         |               |       |       |         |               |       |       |         |
| ≥3                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Year trastuzumab therapy began                     |               |       |       |         |               |       |       |         |               |       |       |         |
| 2000                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2001                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2002                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2003                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2004                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2005                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| 2006                                             |               |       |       |         |               |       |       |         |               |       |       |         |
| Estrogen (ER) and progesterone (PR) receptor status|               |       |       |         |               |       |       |         |               |       |       |         |
| ER+/PR−                                           |               |       |       |         |               |       |       |         |               |       |       |         |
| ER+/PR+                                           |               |       |       |         |               |       |       |         |               |       |       |         |
| ER−/PR−                                           |               |       |       |         |               |       |       |         |               |       |       |         |
| ER−/PR+                                           |               |       |       |         |               |       |       |         |               |       |       |         |
| Prior surgery for breast cancer                   |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Radiation                                         |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Inpatient admission                                |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Durable medical equipment                         |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Emergency department visit                        |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |
| Outpatient visit                                  |               |       |       |         |               |       |       |         |               |       |       |         |
| No                                                |               |       |       |         |               |       |       |         |               |       |       |         |
| Yes                                               |               |       |       |         |               |       |       |         |               |       |       |         |

*Not applicable - insufficient patients in this group to calculate estimate.
| Table 5. Multivariate Survival Analysis, Cancer Mortality Stratified by First-line Versus Delayed Trastuzumab |
|--------------------------------------------------------|
| **Patient Characteristic** | **First-Line Trastuzumab** | **Delayed Trastuzumab** | **p Value** |
| **Trastuzumab regimen included chemotherapy** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 0.54 | 0.39 | 0.74 | .<.001 | 1.44 | 0.77 | 2.69 | .25 |
| **Age at diagnosis of metastatic breast cancer** | | | | |
| 66–69 | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| 70–74 | 1.28 | 0.71 | 2.34 | .41 | 1.04 | 0.42 | 2.57 | .93 |
| 75–79 | 1.10 | 0.59 | 2.02 | .77 | 1.58 | 0.40 | 6.28 | .52 |
| 80–84 | 2.58 | 0.96 | 6.94 | .06 | 16.61 | 1.04 | 265.20 | .05 |
| ≥85 | 4.54 | 1.18 | 17.33 | .03 | NA* | NA | NA | NA |
| **Race/ethnicity** | | | | |
| White | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Black | 1.18 | 0.72 | 1.93 | .51 | 0.95 | 0.41 | 2.22 | .90 |
| Hispanic | 1.12 | 0.59 | 2.12 | .72 | 0.54 | 0.12 | 2.49 | .43 |
| Other | 1.05 | 0.40 | 2.72 | .92 | 1.18 | 0.42 | 3.37 | .75 |
| **Stage at breast cancer de novo diagnosis** | | | | |
| 0–III | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| IV | 0.91 | 0.61 | 1.37 | .66 | 1.26 | 0.65 | 2.45 | .49 |
| **National Cancer Institute Comorbidity Index** | | | | |
| 0 | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| 1 | 1.38 | 0.76 | 2.51 | .29 | 0.44 | 0.13 | 1.51 | .19 |
| 2 | 1.03 | 0.45 | 2.35 | .94 | 1.52 | 0.17 | 13.83 | .71 |
| ≥3 | 0.59 | 0.08 | 4.45 | .61 | NA | NA | NA | NA |
| **Year trastuzumab therapy began** | | | | |
| 2000 | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| 2001 | 1.24 | 0.58 | 2.67 | .58 | 0.53 | 0.11 | 2.52 | .42 |
| 2002 | 1.20 | 0.58 | 2.47 | .62 | 1.10 | 0.25 | 4.79 | .90 |
| 2003 | 1.49 | 0.72 | 3.09 | .28 | 1.31 | 0.31 | 5.59 | .71 |
| 2004 | 1.19 | 0.58 | 2.44 | .64 | 1.18 | 0.27 | 5.11 | .83 |
| 2005 | 0.85 | 0.40 | 1.78 | .66 | 0.54 | 0.12 | 2.40 | .42 |
| 2006 | 1.14 | 0.45 | 2.87 | .78 | 0.17 | 0.01 | 1.93 | .15 |
| **Estrogen (ER) and Progesterone (PR) receptor status** | | | | |
| ER−/PR− | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| ER+/PR− | 0.59 | 0.41 | 0.86 | .01 | 1.68 | 0.88 | 3.21 | .12 |
| ER−/PR+ | 0.64 | 0.41 | 0.99 | .04 | 0.61 | 0.28 | 1.32 | .21 |
| ER+/PR+ | 0.58 | 0.20 | 1.66 | .31 | 1.13 | 0.08 | 16.29 | .93 |
| **Prior surgery for breast cancer** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 0.74 | 0.50 | 1.22 | .15 | 0.34 | 0.17 | 0.70 | <.01 |
| **Radiation** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 0.97 | 0.72 | 1.31 | .84 | 1.54 | 0.78 | 3.02 | .21 |
| **Inpatient admission** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 1.37 | 0.97 | 1.93 | .07 | 1.59 | 0.94 | 2.69 | .09 |
| **Emergency department visit** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 1.24 | 0.77 | 2.00 | .38 | 1.24 | 0.47 | 3.32 | .66 |
| **Outpatient visit** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 2.43 | 0.69 | 8.60 | .17 | 5.57 | 0.63 | 49.02 | .12 |
| **Durable medical equipment** | | | | |
| No | Hazard Ratio | 95% Confidence Interval | Reference Category | Hazard Ratio | 95% Confidence Interval | p Value |
| Yes | 0.91 | 0.66 | 1.27 | .59 | 1.11 | 0.54 | 2.27 | .78 |

*Not applicable-insufficient patients in this group to calculate estimate.*
Figure 3. Sensitivity of trastuzumab hazard ratio to changes in the multivariate survival analysis. This figure presents the results of three sets (all patients, patients receiving first-line trastuzumab, patients receiving delayed trastuzumab) of nine multivariate survival analyses (three each for all-cause, cancer, and noncancer mortality) designed to test the sensitivity of the findings reported in Tables 4 and 5 to changes in the approach to multivariate analysis. Standard multivariate survival analyses (S) were performed with all individual patient variables included in the model. Propensity multivariate survival analyses were performed with either propensity score quintile (PQ) included in the model as a substitute for all patient variables except trastuzumab plus chemotherapy, or using propensity score as a weight (PSW). The y-axis indicates the hazard ratio for trastuzumab plus chemotherapy compared with trastuzumab alone. Triangles represent the estimated hazard ratio for trastuzumab plus chemotherapy compared with trastuzumab alone from the corresponding model on the x-axis. Bars around each triangle represent the upper and lower bounds of the 95% confidence interval for the hazard ratio. Confidence intervals that overlap the horizontal line at the hazard ratio of 1.0 indicate that the estimated hazard ratio for trastuzumab plus chemotherapy is not significant at $p = .05$. 

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DISCUSSION

We conducted a study using SEER-Medicare to identify patterns of infused therapy and survival in a cohort of older women who received trastuzumab therapy for MBC. Our findings show that following diagnosis of MBC, 70% of the cohort received first-line trastuzumab therapy, while the remainder received delayed trastuzumab. As first-line treatment in MBC, trastuzumab is indicated for use in combination with paclitaxel (1). However, we found that almost one-third of these older patients who received first-line trastuzumab received it without infused chemotherapy. The use of trastuzumab monotherapy first-line was more common in patients diagnosed with de novo Stage 0–III disease and a distant recurrence, compared with de novo Stage IV disease (37% versus 24%). This suggests that the decision to select trastuzumab monotherapy versus trastuzumab in combination with one or more chemotherapy agents may have been influenced by prior use of chemotherapy in the adjuvant setting. Also, since this study was conducted in patients diagnosed with breast cancer from 2000–2005, the discrepancy between the labeled indication and what we observed may well reflect the impact of two important clinical trials of first-line trastuzumab monotherapy for MBC, (5, 7) both of which were published several years after trastuzumab was approved by the Food and Drug Administration (FDA).

Overall, the results of the multivariate analysis show that adding chemotherapy to trastuzumab improves survival in patients with MBC. More detailed examination indicates that this is true only for those who received trastuzumab as first-line therapy and for cancer mortality alone. The findings were robust to several different analytic approaches, including propensity techniques.

The finding that adding chemotherapy to first-line trastuzumab was associated with improved survival relative to trastuzumab alone raises important questions with regard to the optimal treatment regimen in these patients. According to one recent review, (2) at the time the patients in our study were treated there had not been a randomized study of trastuzumab with or without chemotherapy. However, a recently published randomized trial of trastuzumab monotherapy versus trastuzumab plus docetaxel as first-line therapy in MBC, (10) was stopped early after an interim analysis showed a significantly lower mortality rate in the patients receiving chemotherapy with trastuzumab (HR for survival 2.72 p = .04). Upon inverting the HR for survival, we find that the HR for overall mortality (0.37) in this trial was similar to the HR ratio for cancer mortality among patients receiving first-line trastuzumab plus chemotherapy (0.54) in our study. Therefore, our findings based on data from routine clinical practice appear to support the findings from this recent trial, and suggest they apply to elderly patients.

The main limitation of this study, as with any observational study that compares the effects of alternative interventions, is the possibility that patients were selected into the treatment groups for reasons related to survival, (22, 35, 36) and that we failed to account for these reasons in our analyses. Although no approach completely eliminates confounding by indication in observational studies, (36) we took several steps to minimize its impact here. One possibility is that patients with poorer performance status or more comorbidity were selected to receive trastuzumab monotherapy due to concerns about the toxicity of chemotherapy. (22) SEER-Medicare does not include performance status. Consequently, using Medicare claims we constructed several medical resource use variables that have been validated to predict ECOG and Karnofsky performance status (30). Also, we examined cancer and noncancer mortality based on the rationale that any real benefit of cancer treatment should be observed only through cancer-specific mortality, and that differences in noncancer mortality suggest confounding by indication (22). In this study, we found adding chemotherapy to trastuzumab was associated with a significantly lower rate of cancer but not noncancer mortality.

Although the coefficients for trastuzumab plus chemotherapy were similar for cancer and noncancer mortality, it is important to note that only 24 patients (8% of those with a known cause of death) had a noncancer cause of death. Consequently, the coefficients in these models are unstable and their direction and significance can be determined by a few individuals. Finally, we used two different approaches to multivariate survival analysis: the standard approach in which all patient characteristics were included as independent variables, and propensity techniques (32) in which propensity score quintile was substituted for the vector of independent variables except treatment, and alternatively where the raw propensity score was used as a weight. It should be noted, however, that propensity techniques do not account for unobserved confounding covariates (32). Instrumental variable approaches have been applied to SEER-Medicare analysis, but to our knowledge not in small cohorts such as ours.

A second limitation of this study is that we did not include a comparator group of patients who did not receive trastuzumab. The main reason is that, presently, SEER-Medicare does not include information on HER2 status. It can be inferred that any patient who received trastuzumab had HER2 overexpressing disease, based on the fact that Medicare does not pay for trastuzumab without a positive HER2 test result. However, it is not possible to identify patients who are HER2 positive but who do not receive trastuzumab. Since HER2 overexpression is a significant predictor of both overall survival and time to relapse in patients with breast cancer, (37) the absence of HER2 test results is a significant barrier to conducting comparative effectiveness research (e.g. chemotherapy with versus without trastuzumab) on trastuzumab using this database, because one cannot identify a HER2 positive control group. Second, while trastuzumab was first approved by FDA in September 1998, (38) a Medicare reimbursement code specifically for trastuzumab did not become effective until January 1, 2000. Therefore, we were unable to document the use of trastuzumab during the first year following approval.

Third, as illustrated, patterns of trastuzumab use were diverse, ranging from long, uninterrupted periods with multiple administrations per month to short periods with only...
one administration per month. While this diversity makes it difficult to assess the outcomes effects of trastuzumab under "optimal use," our analysis does reflect its impact in routine clinical practice.

Fourth we used an algorithm based on Medicare claims (15, 16) to identify distant recurrence (metastatic disease) among those patients who were initially diagnosed with Stage 0–III disease. Although claims-based algorithms for identifying relapse/reurrence have been validated in AML, (15) they have not been validated in breast cancer. One study conducted before the development of the algorithms for AML found that Medicare claims within 3 months of the SEER date of breast cancer diagnosis correctly identified only 60% of those with distant Stage disease at diagnosis according to SEER (39). One important difference, however, is that we used claims to identify recurrence in those previously diagnosed and staged using SEER data.

Nevertheless, to gain additional insight on this issue, we applied this algorithm to a much larger cohort of women in SEER-Medicare who were diagnosed with early-Stage (stage I–III) breast cancer, and who received adjuvant chemotherapy. In this cohort, the cumulative rate of recurrence we observed, approximately 30% after 4 years, was similar to that for anthracycline- and CMF- (cyclophosphamide, methotrexate, fluorouracil) based regimens for early breast cancer in older women as reported by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (40). Also, the distribution of sites of distant recurrence was consistent with what has been previously reported.

Finally, we did not investigate the use of trastuzumab in the adjuvant setting since it was not approved for this indication until 2006.

Despite the aforementioned limitations, to our knowledge, this is the first study to describe the use of trastuzumab for MBC in a large cohort of older women diagnosed with breast cancer. It shows treatment patterns consistent with the literature published around the time treatment decisions within the cohort were being made, but less consistent with the product labeling. Also, aside from one recent trial discussed above (10), we are unaware of any other study, observational or experimental, comparing survival in patients who receive trastuzumab alone versus in combination with chemotherapy for MBC. Our findings suggest trastuzumab in combination with chemotherapy is more effective than trastuzumab alone when used as first-line therapy for MBC. Since almost one-third of the first-line trastuzumab patients in our cohort received trastuzumab alone, a potential area for further research would be investigating the reasons clinicians and patients might elect to use trastuzumab monotherapy instead of trastuzumab plus chemotherapy.

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DECLARATION OF INTEREST

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