Trastuzumab-Related Cardiotoxic Effects in Taiwanese Women
A Nationwide Cohort Study

Hsu-Chih Chien, MS; Yea-Huei Kao Yang, BSPharm; Jane P. F. Bai, AM, PhD

**IMPORTANCE** Trastuzumab is an essential medicine per the World Health Organization Model List, but its cardiac safety information in Asian women is limited.

**OBJECTIVE** To estimate the rate and the risk of heart failure (HF) and/or cardiomyopathy (CM) in Asian women undergoing trastuzumab treatment.

**DESIGN** This cohort study used the Taiwanese National Health Insurance Research Database (NHIRD), a nationwide claim database covering more than 99% of the entire Taiwanese population, to identify 23,006 women with incident breast cancer (BC) who received chemotherapy from 2006 to 2009. We grouped women per their initial treatment regimens and found 1066 new trastuzumab users. We matched trastuzumab users with nonusers by year of BC diagnosis and propensity score (PS) with the caliper widths at 0.25 standard deviation of PS (up to 4 nonusers per trastuzumab user). The study lasted from January 2006 to December 2013 with a median follow-up of 5.29 years and a landmark design to avoid immortal time bias.

**EXPOSURE** Trastuzumab.

**MAIN OUTCOMES AND MEASURES** To estimate HF and/or CM rates and time to HF and/or CM, we employed a cause-specific hazard model. Trastuzumab exposure was a time-dependent variable, while cumulative courses of chemotherapy agents with known cardiotoxic effects (including anthracyclines, taxanes, and cyclophosphamide) were defined as time-dependent covariates in the analysis model. We also performed 6 sensitivity analyses.

**RESULTS** In this cohort of 23,006 women (mean age, 50.99 years), the crude incidence of HF and/or CM was 4.03% in trastuzumab users and 2.88% in nonusers. The median time to HF and/or CM was 456 days in trastuzumab users and 966 days in nonusers. The 1-year cumulative hazard ratio was 1.86 (95% CI, 1.08-3.19). The sensitivity analyses yielded similar results.

**CONCLUSIONS AND RELEVANCE** Compared with the published results, the trastuzumab-related HF and/or CM rate was 5-fold lower in Taiwanese women with breast cancer. Nonetheless, our cohort had a similar trastuzumab-related HF and/or CM risk. Our study provides critical cardiac safety information of trastuzumab for Asian women with BC under current treatment guidelines and label information.
Trastuzumab, a humanized monoclonal antibody, is important for treating ERBB2 (formerly HER2 or HER2/neu)-overexpressed or amplified tumors, where ERBB2 is human epidermal growth factor receptor type 2. Despite cardiotoxic effects, trastuzumab significantly increases disease-free survival and overall survival in patients with ERBB2-positive breast cancer (BC) and is on the World Health Organization (WHO) Model List of essential medicines. Asian women accounted for 40% of newly diagnosed BC cases worldwide in 2012, and there are 2.29 million patients with BC in Asia. Approximately 25% of BCs in Asian women were found to overexpress ERBB2, which is similar to that observed in Western women. Our knowledge of trastuzumab-related cardiotoxic effects comes from findings in Western countries where clinical trials were conducted mainly in white women. Even though trastuzumab is expected to be effective in Asian patients with BC, based on the fact that trastuzumab is used to treat ERBB2-positive BC, its critical long-term cardiovascular safety profile in Asian patients has not yet been evaluated in a large Asian population for informed decisions at the bedside.

According to the Herceptin Adjuvant (HERA) trial, one of largest clinical trials that followed 5099 participants to study the long-term cardiac safety of trastuzumab, the highest incidence of severe congestive heart failure occurred within 24 months, and the cumulative incidence of severe congestive heart failure was 0.8% at a median 8-year follow-up, which is slightly higher than the 0.54% reported by others at the end of the second year following first dose. Nonetheless, the results were uninformative for Asian patients because they only accounted for 12.4% of patients in the HERA trial. Reports from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and North Central Cancer Treatment Group N9831 Adjuvant Breast Cancer Trial (NCCTG N9831) showed that almost all cardiovascular events (CE), including definite or probable cardiac death or symptomatic congestive heart failure with reduced left ventricular ejection fraction (LVEF), occurred within 2 years after trastuzumab initiation. The cumulative CE incidence ranged from 2.8% to 3.0% at the 3-year and 7-year follow-up, respectively. However, race information was not available in the primary protocols of NSABP B-31 or NCCTG N9831.

The long-term cardiovascular safety in Asian trastuzumab users in other settings is also scarce. The Japan Breast Cancer Research Group (JBCRG) reported that most of grade 3 or 4 cardiotoxic effects, defined by National Cancer Institute Common Terminology Criteria for Adverse Events, occurred within a year of trastuzumab initiation; the 3-year cumulative incidence was 0.54% (11 cases) in 2024 patients with early breast cancer across 56 institutions. Single-center reports from Saudi Arabia, Singapore, and China showed that the overall percentages of LVEF reduction ranged from 11.2% to 39.1%. Disappointingly, these studies lacked comparison groups or had small sample sizes.

According to the trastuzumab label, clinical trials conducted during its development were only comprised of a small percentage of Asians. As Asian patients with BC differed from those of Western countries in their underlying cardiovascular diseases and age of diagnosis, a large, population-level cohort study is needed to enable health care providers and patients to make informed decision during the course of treating BC. In this study, we aim to estimate the risk of trastuzumab-related heart failure (HF) and/or cardiomyopathy (CM) in the Asian population by using the claims data of Taiwan National Health Insurance (NHI), which has covered more than 99% of the entire Taiwanese population over the last 2 decades, with patient-level medication records systematically compiled and stored.

**Key Points**

**Question** What is the incidence and risk of heart failure (HF) and/or cardiomyopathy (CM) among Asian trastuzumab users with breast cancer?

**Findings** In this nationwide cohort study of Taiwanese women with incident breast cancer the crude incidence of HF and/or CM was significantly higher in trastuzumab users compared with nonusers.

**Meaning** The findings provide critical trastuzumab cardiac safety information for Asian patients with breast cancer.

**Method**

**Data Sources**

We extracted data on women with a diagnosis of BC from the Taiwan National Health Insurance Research Database and confirmed the cohort with data from the Catastrophic Illness Patient Database, for which histologic confirmation of BC is required for recruitment (eAppendix in the Supplement).

**Study Participants**

The institutional review board of National Cheng Kung University Hospital approved and granted this study a waiver of informed consents from participants. We identified patients with incident BC of all stages using the *International Classification of Diseases, Ninth Revision (ICD-9)* code 174 from January 1, 2006, to December 31, 2009. We included women that received at least 1 dose of chemotherapy, and patients with incomplete data or a cancer history were excluded. To remove immortal time bias, we set the index date for each patient to 180 days following chemotherapy initiation. We excluded those who were dead or diagnosed with HF and/or CM prior to being indexed. Overall, 23 006 women were included in total. Details of the study scheme and patient numbers can be found in the eAppendix in the Supplement.

**Analytic Variables and Definitions**

The observation period was from the index date to the end of 2013, to death, or to the development of HF and/or CM, whichever occurred first. As published previously, we estimated the incident HF and/or CM by employing *ICD-9* diag-
nosis codes in inpatient, outpatient, and emergency department records, including hypertensive heart disease with HF (ICD-9 code 402.x1), hypertensive heart and chronic kidney disease with HF (ICD-9 codes 404.x1 and 404.x3), cardiomyopathies (ICD-9 code 425), HF (ICD-9 code 428), and cardiogenic shock (ICD-9 code 785.5). Patients were considered to have HF and/or CM if there was at least 1 claim in inpatient records or 2 claims that were more than 30 days apart in outpatient and/or emergency department record.

We extracted from National Health Insurance Research Database all the comorbid conditions and corresponding treatments starting a year prior to diagnosis (eMethods in the Supplement), as well as medication records of BC diagnosis and treatments within 180 days of first chemotherapy (eMethods in the Supplement).

Target Therapy, Chemotherapy, and Radiation Therapy Exposure
We defined women who received trastuzumab within 180 days of first chemotherapy as the exposed group. We analyzed trastuzumab and radiation therapy as unidirectional time-dependent variables in the primary analysis; that is, patients were considered as nontrastuzumab users until starting trastuzumab therapy, and thereafter, they were always considered trastuzumab users until the end of the observation period (eMethod in the Supplement). We also calculated individual cumulative courses of cardiotoxic chemotherapy agents, including anthracyclines, taxanes, and cyclophosphamide (eMethod in the Supplement).

Propensity Score Model
We identified the comparison group of nonusers by propensity score (PS) matching.26 We applied a multivariate logistic regression model to estimate the PS for patients receiving trastuzumab within 180 days after chemotherapy initiation. We then estimated the risk of HF and/or CM after PS matching to control confounding factors and to ensure the comparativeness between both trastuzumab user and nonuser groups. Potential confounders and covariates related to the outcome, such as medication records and comorbidities at baseline, were included in the PS model (eMethod in the Supplement).

Statistical Analysis
Descriptive statistics and a cause-specific hazard model were employed for data analysis. The 1-year adjusted cumulative hazard ratio (aHR) was estimated using the PS matched cohort, where each woman in the exposed group was matched with 4 nonusers by the year of BC diagnosis and caliper widths of 0.25 standard deviation of PS.27 We included radiotherapy, exposure of trastuzumab, and cumulative cycles of anthracyclines, taxanes, and cyclophosphamide as time-dependent variables in the model.

In addition, we also estimated the cumulative risk of HF and/or CM at different time points following trastuzumab initiation. We also performed 2 subgroup and 6 sensitivity analyses (eMethod in the Supplement). All statistical analyses were performed using SAS statistical version 9.4 (SAS Institute Inc). Statistical tests were 2-sided, and a P value less than .05 was considered significant.

Results

Cohort Characteristics
Patient characteristics of the full cohort are presented in eTable 1 in the Supplement, and descriptions of the full cohort are detailed in the eAppendix in the Supplement. Overall, there were 1051 trastuzumab users and 3794 nonusers in the matched cohort. Cohort demographic information of the matched cohort is presented in the Table. The baseline characteristics are generally balanced after matching.

Trastuzumab Use
There were 2850 trastuzumab users in the full cohort, and there were 1051 trastuzumab users in the matched cohort. The median (range) time from first chemotherapy treatment to trastuzumab initiation was 277 (0-1798) days; the median (range) number of trastuzumab was 13 (1-184) doses. The median duration of trastuzumab exposure was 329 days (eTable 2 in the Supplement). Among the 1066 patients receiving trastuzumab within 180 days following first chemotherapy, 661 patients were treated with anthracycline-based chemotherapy regimens while the rest received anthracycline-free regimens.

Incidence of HF and/or CM
The crude HF and/or CM incidence of trastuzumab users was significantly higher than that of nonusers (4.03% vs 2.88%; P < .001), and the population attributable risk was 1.15% (Figure 1). After adjustment for age, National Cancer Institute Comorbidity Index, radiation therapy, hospital grade, and year of diagnosis, the 4-year cumulative incidence in trastuzumab users was 2.85% (95% CI, 2.24%-3.62%) and 1.68% (95% CI, 1.54%-1.83%) in nonusers. The crude incidence of HF and/or CM was higher in trastuzumab users compared with nonusers among those younger than 65 years (trastuzumab users, 3.55%; nonusers, 2.28%; P = .01) but was not significantly different between the 2 groups in older women (trastuzumab users, 6.67%; nonusers, 7.83%; P = .59). The population attributable risk among younger users was 1.27%. The median time to HF and/or CM was 456 days in trastuzumab users and 966 days in nonusers (P < .001).

Risk of HF and/or CM
At 1 year after the index date in our matched cohort, trastuzumab significantly increased the risk of HF and/or CM (aHR, 1.86; 95% CI, 1.08-3.19). The risk seemed to decrease gradually after the first year, resulting in the cumulative aHR of 1.26...
Table. Patient Characteristics According to First Adjuvant Treatment After PS Matching

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Users in Matched-Population, Patients (%)</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trastuzumab User (n = 1051)</td>
<td>Trastuzumab Nonusers (n = 3794)</td>
</tr>
<tr>
<td>Year of diagnosis</td>
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<tr>
<td>2006</td>
<td>163 (15.51)</td>
<td>507 (14.94)</td>
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<td>2007</td>
<td>191 (18.17)</td>
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<td>2008</td>
<td>201 (19.12)</td>
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<td>2009</td>
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<td>939 (24.75)</td>
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<td>45-54</td>
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<td>55-64</td>
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<td>65-74</td>
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<td>≥75</td>
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<td>Outpatient visits 1 y prior to</td>
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<td>845 (80.40)</td>
<td>3104 (81.81)</td>
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<td>Surgery</td>
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<tr>
<td>Neoadjuvant</td>
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<td>693 (18.27)</td>
</tr>
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<td>Anthracycline use</td>
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<td>2783 (73.35)</td>
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<td>Taxane use</td>
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<td>1791(47.21)</td>
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<td>Cyclophosphamide use</td>
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<td>2972 (78.33)</td>
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<td>185 (17.60)</td>
<td>672 (17.71)</td>
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<tr>
<td>Medication</td>
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<td>811 (21.38)</td>
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<td>816 (21.51)</td>
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<td>Non DPD-CCB</td>
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<td>84 (2.21)</td>
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<td>722 (19.03)</td>
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<tr>
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<td>58 (5.52)</td>
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<tr>
<td>ARB</td>
<td>88 (8.37)</td>
<td>313 (8.25)</td>
</tr>
<tr>
<td>CAD</td>
<td>32 (3.23)</td>
<td>116 (3.56)</td>
</tr>
<tr>
<td>DM</td>
<td>95 (9.04)</td>
<td>340 (9.86)</td>
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(continued)
(95% CI, 0.85-1.87) at year 4 (eTable 3 in the Supplement). The cumulative aHRs at different time points are shown in Figure 2. We acquired similar results from sensitivity analyses. A competing risk regression analysis did not change the risk outcome (aHR, 1.95; 95% CI, 1.22 -3.16) compared with the primary analysis.
Discussion

To our knowledge, our study is the first observational study leveraging a nationwide claims database to address the knowledge gap of the cardiac safety of trastuzumab in Asian women with BC.

Compared with the published results, the trastuzumab-related HF and/or CM rate in our cohort was 5-fold lower while the risk was similar. The absolute HF and/or CM rate differed between trastuzumab users and trastuzumab nonusers (4.48% vs 3.30%). The 1-year cumulative HR was 1.86 (95% CI, 1.08-3.19). The incidence in our cohort was a quarter or less of that reported. In an observational study of breast cancer women across all ages, the adjusted HF and/or CM rates of trastuzumab users and trastuzumab nonusers were 18.5% and 4.5%, respectively, based on our estimation using the reported incidences.

Low HF and/or CM Incidence in Asian Trastuzumab Users

The mean age of our cohort was 51.44 years with more than 90% of participants under 65 years of age, consistent with the finding that Asian patients at diagnosis were 10 years younger than their Western counterparts.

The low HF and/or CM incidences that we observed raised the question of whether differences in risk factors such as age, anthracycline exposure, and cardiovascular comorbidities are responsible or whether the HF and/or CM risk is in fact lower among Asians. Further comparison with a US study with adjustment for age, NCI score, radiation therapy, hospital grade and diagnose year revealed that the 4-year HF and/or CM cumulative incidences in our cohort were lower across treatment groups. The incidences in our cohort and in the US study population per treatment group were 2.7% vs 16.5% for trastuzumab plus anthracycline users, 2.8% vs 9.9% for trastuzumab users, 1.4% vs 3.5% for anthracycline users, and 0.7% vs 3.7% for women receiving neither trastuzumab nor anthracycline.

Figure 1. Cumulative Incidence of HF and/or CM Events Among Women Diagnosed With Breast Cancer Between 2006 and 2009 by Initial Adjuvant Chemotherapy Group

A Trastuzumab

B Trastuzumab and anthracycline

The cumulative incidence between groups were significantly different (P < .001) at all listed time points, and the differences lasted until the end of observation periods. A indicates anthracycline; CM, cardiomyopathy; HF, heart failure; T, trastuzumab.
anthracyclines. The results implicated that the low HF and/or CM incidence in the Taiwanese patient population (mainly Han Chinese) was not merely because of age and comorbid status. Of note, while we demonstrated profound lower incidences regardless of concomitant anthracycline, we still could not discount the effect of anthracycline toxic effects because the details of exact dosing schedules of trastuzumab and chemotherapy agents were not available to allow a head-to-head comparison.

Interestingly, despite the similarity in BC treatment guidelines in Japan, Taiwan, and the United States, Asian studies have reported lower HF and/or CM incidences among treatment-naive trastuzumab users than the US studies. Japanese trastuzumab users with early-stage BC had a lower grade 3 or 4 cardiotoxic effect incidence (11 of 2024 women) than the clinical trial populations (0.5%-4%, depending on concurrent chemotherapy regimens).18 Interestingly, the Multi-Ethnic Study of Atherosclerosis (MESA) indicated Chinese Americans had a lower risk of HF when compared with other ethnicities. Further research is warranted regarding whether ethnicity influences the trastuzumab-related HF and/or CM risk, as well as the underlying risk factors among Asian patients to help mitigate this serious safety risk.

Evaluation of Health Behavior Bias
Patient health awareness, if ignored, could jeopardize the validity of statistical analysis. To avoid health awareness bias, we chose active comparators after PS matching and performed a subgroup analysis. The distributions of variables relevant to health awareness (BC screening every 2 years and the number of outpatient visits in 1 year prior to BC diagnosis) were balanced after matching. The subgroup analysis confirmed that our result was not biased by health behavior.

Consideration of Exposed Periods
We performed a sensitivity analysis based on the initial trastuzumab exposure status (model 1, similar to intention to treat). The result supported that our finding was robust in either a fixed exposure status or a time-dependent variable setting.

We also considered the lag period of trastuzumab-related HF and/or CM by modifying the exposure period (model 2). Referencing the clinical trial findings on the time to HF and/or CM and the reversibility of trastuzumab-related HF and/or CM that showed that 71.4% to 92.4% of women who had trastuzumab-related HF acutely recovered at a median time of 4.3 to 9.7 months, we defined the risk period as 6 months after the last dose (model 2). The results of models 1 and 2 support the robustness of our findings.

Consideration of Follow-up Periods
As time-dependent variables were included in our Cox model, we estimated the cumulative HRs at different time points and found the point estimates of aHR shifted toward null during the follow-up duration. We referenced follow-up reports of clinical trials that most of the HF and/or CM events occurred within 1 year of the first trastuzumab dose and performed primary and sensitivity analyses of the 1-year cumulative aHR. Furthermore, as nearly 90% of the patients in our cohort survived for at least 1 year, choosing the observation period of 1 year also minimized the effect of competing risk. We also calculated the cumulative aHRs at 6-monthly intervals until the fourth year after index date. The decline...
of cumulative aHRs indicated that the effect of trastuzumab on HF and/or CM was reduced with time, which was, in part, because of a relatively short trastuzumab exposure (71.40% of the patients received <2 courses of trastuzumab). Our finding echoed the published clinical trials that showed a minimum increase of newly diagnosed HF and/or CM cases 2 years after trastuzumab initiation.8,9

Consideration of Comparators
Cardiovascular complications can be affected by malignancy and the toxic effects of drugs used.35 Although staging cancer is part of the standard of care, information on metastatic status was not available. To adequately evaluate the risk, the variables considered in comparator selection included baseline cardiovascular comorbidities and corresponding medication, oncological therapies that are known to have cardiotoxic effects, as well as surrogates for BC staging. Initial treatment strategies including imaging check-ups, procedures, and medications were also included because they were considered surrogate markers for staging.

To avoid immortal time bias owing to oncological therapies and grouping after initiation of observation,22 we adopted a landmark conditional analysis with time-varying covariates. As radiotherapy and endocrine therapy were often given after the first course of chemotherapy, we defined the index date of 180 days following chemotherapy initiation per the longest duration of a treatment course.36 Then we allowed changing from the nonexposed group to the exposed group unidirectionally.

Consideration on the Risk of Competing Events
The results of the 2 extreme scenarios37 shifting toward the null implied that the positive result might be influenced by different causes of death in users and nonusers. We applied a competing risk regression model38 to consider both survival and competing causes of death in users and nonusers. We applied a competing risk regression model38 to consider both survival and HF and/or CM scenarios and confirmed the result of our primary analysis, thereby eliminating the effect of competing risks on our risk estimation.

Limitations
We were unable to investigate the safety of trastuzumab among women with metastatic BC because metastatic status was not available. To overcome this issue, we applied a new user design with PS matching to ensure comparativeness between users and nonusers. We balanced the distributions of variables between these 2 groups after matching by considering metastatic status, including surgery type, receipt of chemotherapy after surgery, intravenous bisphosphonates, and types of imaging checkups prior to chemotherapy. As a result, proper comparators were used even without the information of tumor staging.

Though it is unknown whether nonusers had chosen to pay out of pocket for trastuzumab, the number of patients who would have been able to afford trastuzumab was deemed very small because trastuzumab is very expensive. Even if we had had misclassification due to lack of information, this would have driven the results toward to null, rather than overestimated the risk.

Although we did not have information regarding the validity of the diagnostic codes, we found that the baseline HF and/or CM incidences were similar between trastuzumab nonusers of similar ages in our cohort and those in the published US study.24 As the point estimate of the HF and/or CM risk was unchanged in the sensitivity analysis (model 3), our finding was robust.

Lastly, we were unable to account for unmeasured confounders of HF and/or CM, including smoking, obesity, cardiotoxic substance exposure, healthy behavior, and socioeconomic status30; this limitation is unfortunately shared by nearly all claims database observational studies.

Conclusions
This population-based study is the first nationwide cohort study to evaluate the HF and/or CM risk of trastuzumab in the Asian population. The trastuzumab-related HF and/or CM rate was 5-fold lower and the time to HF and/or CM was longer. Nonetheless, our cohort had a similar trastuzumab-related HF and/or CM risk. Our results suggest that Asian and United States BC populations share trastuzumab-related cardiac risk under current clinical treatment guidelines and label information. Our finding also provides useful information for clinicians and Asian patients to make informed decisions.
Trastuzumab-Related Cardiotoxic Effects in Taiwanese Women

B, et al; Herceptin Adjuvant (HERA) Trial Study


Incidence and mortality worldwide: sources, 5
receptor 2-positive breast cancer.
trastuzumab as adjuvant therapy for patients with
comparing doxorubicin and cyclophosphamide
years of median follow-up in the Herceptin
et al. Trastuzumab-associated cardiac events at 8
8
CD006243.

REFERENCES