

## Original Investigation

# Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer

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**IMPORTANCE** Trastuzumab is a life-saving therapy but is associated with symptomatic and asymptomatic left ventricular ejection fraction (LVEF) decline. We report the cardiac toxic effects of a nonanthracycline and trastuzumab-based treatment for patients with early-stage human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu)-positive breast cancer.

**OBJECTIVE** To determine the cardiac safety of paclitaxel with trastuzumab and the utility of LVEF monitoring in patients with node-negative, ERBB2-positive breast cancer.

**DESIGN, SETTING, AND PARTICIPANTS** In this secondary analysis of an uncontrolled, single group study across 14 medical centers, enrollment of 406 patients with node-negative, ERBB2-positive breast cancer 3 cm, or smaller, and baseline LVEF of greater than or equal to 50% occurred from October 9, 2007, to September 3, 2010. Patients with a micrometastasis in a lymph node were later allowed with a study amendment. Median patient age was 55 years, 118 (29%) had hypertension, and 30 (7%) had diabetes. Patients received adjuvant paclitaxel for 12 weeks with trastuzumab, and trastuzumab was continued for 1 year. Median follow-up was 4 years.

**INTERVENTIONS** Treatment consisted of weekly 80-mg/m<sup>2</sup> doses of paclitaxel administered concurrently with trastuzumab intravenously for 12 weeks, followed by trastuzumab monotherapy for 39 weeks. During the monotherapy phase, trastuzumab could be administered weekly 2-mg/kg or every 3 weeks as 6-mg/kg. Radiation and hormone therapy were administered per standard guidelines after completion of the 12 weeks of chemotherapy. Patient LVEF was assessed at baseline, 12 weeks, 6 months, and 1 year.

**MAIN OUTCOMES AND MEASURES** Cardiac safety data, including grade 3 to 4 left ventricular systolic dysfunction (LVSD) and significant asymptomatic LVEF decline, as defined by our study, were reported.

**RESULTS** Overall, 2 patients (0.5%) (95% CI, 0.1%-1.8%) developed grade 3 LVSD and came off study, and 13 (3.2%) (95% CI, 1.9%-5.4%) had significant asymptomatic LVEF decline, 11 of whom completed study treatment. Median LVEF at baseline was 65%; 12 weeks, 64%; 6 months, 64%; and 1 year, 64%.

**CONCLUSIONS AND RELEVANCE** Cardiac toxic effects from paclitaxel with trastuzumab, manifesting as grade 3 or 4 LVSD or asymptomatic LVEF decline, were low. Patient LVEF was assessed at baseline, 12 weeks, 6 months, and 1 year, and our findings suggest that LVEF monitoring during trastuzumab therapy without anthracyclines could be simplified for many individuals.

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In the United States, breast cancer is the most common female cancer and the second most common cause of cancer death in women.<sup>1</sup> Amplification or overexpression of the human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu) oncogene is present in approximately 20% to 25% of primary invasive breast cancers.<sup>2</sup> Trastuzumab has demonstrated a significant improvement in outcomes of women with early-stage breast cancer in key adjuvant trials, but most of these trials contained an anthracycline-based therapy followed by trastuzumab with or without a taxane in women with either node-positive or node-negative, high-risk breast cancer (usually defined as tumor size >1 cm or >2 cm).<sup>3-8</sup> However, several studies from the pretrastuzumab era suggest a higher risk of recurrence for patients with ERBB2-positive, node-negative tumors compared with those with ERBB2-negative tumors of the same size.<sup>9-11</sup> Recent retrospective studies have demonstrated a benefit from the combination of chemotherapy and trastuzumab in those with node-negative breast cancer and a time trend increase in the use of these agents.<sup>12-14</sup>

The most significant toxic effect of trastuzumab, especially following an anthracycline-based therapy, is symptomatic congestive heart failure (CHF) that has been reported from 0.9% to 4% and significant asymptomatic cardiac decline ranging from 4% to 19% in clinical trials.<sup>3-8,15-19</sup> After the anthracycline phase, most symptomatic CHF and asymptomatic left ventricular ejection fraction (LVEF) decline occurred during the period of trastuzumab administration.<sup>3-8,15-19</sup> Unlike cardiac toxic effects associated with anthracyclines, LVEF decline following trastuzumab therapy is not dose related and is considered to be mostly reversible.<sup>20</sup> Most previous clinical trials involving trastuzumab included patients who were exposed to anthracyclines, but it is not clear how much the anthracyclines contributed to trastuzumab-mediated cardiac dysfunction. To reduce cardiac and noncardiac toxic effects with the hope of maintaining a high degree of effectiveness, we conducted a trial of weekly paclitaxel with trastuzumab in patients with early-stage ERBB2-positive breast cancer. The overall study results have been previously reported, and this article highlights the detailed cardiac data that have been collected.<sup>21</sup>

## Methods

This was a secondary analysis of an uncontrolled, single group study across 14 medical centers of weekly administration of paclitaxel with trastuzumab in patients with node-negative, ERBB2-positive breast cancer.<sup>21</sup> The study was approved by the institutional review board at each site, and written informed consent was obtained from each patient. Race, ethnicity, and sex were defined by each patient to demonstrate the enrolled patient population (Table 1).

The primary endpoint was disease-free survival. Grade 3 and 4 left ventricular systolic dysfunction (LVSD), as defined by the National Cancer Institute Common Toxicity Criteria Adverse Events (NCI CTCAE) version 3.0, was a secondary end-

### At a Glance

- We evaluated cardiac toxic effects of 406 patients receiving paclitaxel and trastuzumab for early-stage ERBB2-positive breast cancer.
- Overall, 2 patients (0.5%) (95% CI, 0.1%-1.8%) developed grade 3 left ventricular systolic dysfunction (LVSD).
- Thirteen patients (3.2%) (95% CI, 1.9%-5.4%) had significant asymptomatic left ventricular ejection fraction (LVEF) decline, 11 of whom completed study treatment.
- Median LVEF was 65% at baseline; 64%, 12 weeks; 64%, 6 months; and 64%, 1 year.
- Cardiac toxic effects from paclitaxel with trastuzumab, manifesting as grade 3 to 4 LVSD or asymptomatic LVEF decline, were low.

point. Grade 3 LVSD is symptomatic CHF responsive to intervention, and grade 4 LVSD is refractory CHF. Other adverse cardiac events were also classified per the NCI CTCAE grading system version 3.0. This study protocol required longitudinal assessment of left ventricular systolic function using LVEF quantified by transthoracic echocardiogram (ECHO) or radio-nuclide multigated acquisition scan (MUGA) at baseline, 12 weeks, 6 months, and 1 year after starting protocol-specified therapy. Patients who went off treatment early due to CHF were required to have follow-up LVEF assessments 3, 6, and 12 months after the CHF event.

The study population was defined as all patients who received any amount of protocol therapy. Diagnosis of grade 3 to 4 LVSD (ie, symptomatic CHF) during protocol therapy required cessation of trastuzumab therapy. For these patients, we reported the registration date, protocol therapy starting date, off-treatment date, number of cycles administered, and LVEF percentages. Trastuzumab was interrupted for asymptomatic declines in LVEF within the following 2 categories: a 10% to 15% decrease from a baseline LVEF that was less than the local lower limit of normal for LVEF, or a decrease greater than or equal to 16% (eTable 1 in the Supplement). All patients with interval development of asymptomatic LVEF decline requiring interruption of trastuzumab underwent repeated LVEF assessment using the same modality after an interval of 4 weeks. If the LVEF did not recover to a "continue" category as defined by study guidelines (eTable 1 in the Supplement), and if 2 consecutive holds were required, then the patient would be withdrawn from study treatment. Investigators were strongly urged to schedule MUGA scans or ECHOs at the same radiology facility where the patient's baseline scan was done, and we used the baseline LVEF to compare with LVEF assessed at 12 weeks, 6 months, and 1 year. The incidence of grade 3 to 4 LVSD was determined with the 95% CI.

### Statistical Analysis

The planned sample size of 400 was based on the primary endpoint of disease-free survival. The statistical design and sample size considerations have been described in a previous study.<sup>21</sup> The incidence of grade 3 to 4 LVSD and asymptomatic LVEF decline were secondary endpoints. For this analysis, the incidence of grade 3 to 4 LVSD and asymptomatic LVEF decline

were analyzed as binary outcomes. Rates of grade 3 to 4 LVSD and asymptomatic LVEF decline and 95% CIs were calculated using the Wilson method.<sup>22</sup> With a planned sample size of 400 patients, the estimated half-width of the Wilson 95% CI was 0.5% with 0 cases of grade 3 to 4 LVSD observed; 1.1%, 4; 1.4%, 8; 1.7%, 12; 2.0%, 16; and 2.2%, 20.

To explore the association between baseline characteristics and occurrence of cardiac toxic effects, relative risks (RR), and 95% CIs were calculated using robust variance estimates.<sup>23,24</sup> Statistical analyses were performed using SAS 9.3 (SAS Institute Inc) and R version 2.6.1 (Revolution Analytics) statistical software.

### Patients

Eligible patients had node-negative ERBB2-positive (immunohistochemistry 3-positive or fluorescence in situ hybridization-amplified with ratio 2.0 or greater) breast cancer with a tumor 3 cm or smaller. Patients with a micrometastasis in a lymph node were later allowed with study amendment on May 19, 2009. Patients with a baseline LVEF less than 50%, history of myocardial infarction, CHF, uncontrolled hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg), or hemodynamically significant pericardial effusion were excluded from this study.

### Treatment

Treatment consisted of weekly 80-mg/m<sup>2</sup> doses of paclitaxel administered concurrently with trastuzumab intravenously for 12 weeks, followed by trastuzumab monotherapy for 39 weeks (eFigure 2 in the Supplement). During the monotherapy phase, trastuzumab could be administered weekly 2-mg/kg or every 3 weeks 6-mg/kg. Radiation and hormone therapy were administered per standard guidelines after completion of the 12 weeks of chemotherapy.

## Results

From October 9, 2007, to September 3, 2010, 410 patients were enrolled and 406 started protocol therapy. All 406 patients completed treatment as of September 8, 2011. The median follow-up was 4 years. The median patient age was 55 years, 118 (29%) patients had a history of hypertension, and 30 (7%) patients had a history of diabetes (Table 1). The majority of patients with hypertension (84%) and diabetes (83%) were at least 50 years of age (Table 2). There were 356 (88%) patients who completed about a year of protocol therapy and 50 (12%) who did not. The 50 patients who did not complete about a year of protocol therapy were taken off the study for the following reasons: 2 for grade 3 LVSD; 2, persistent grade 2 LVSD; 1, grade 3 arrhythmia; 1, grade 3 sinus tachycardia; 1, grade 2 palpitations; 42, noncardiac reasons; and 1, reason unknown. Overall, 7 (1.7%) patients discontinued protocol treatment for cardiovascular reasons but only 4 (1.0%) patients discontinued due to LVSD (95% CI, 0.3%-2.5%).

### Changes in LVEF

Baseline LVEF values were between 50% and 55% in 40 (10%) patients, and greater than 55% in 366 (90%) patients

**Table 1. Patient Characteristics**

Characteristic	No.
<b>Total patients</b>	<b>406</b>
Age, median (range), y	55 (24-85)
Sex, No. (%)	
Male	1 (<1)
Female	405 (100)
Race, No. (%)	
White	351 (86)
African American	28 (7)
Asian	11 (3)
Other	16 (4)
Ethnicity, No. (%)	
Hispanic or Latino	9 (2)
Non-Hispanic	374 (92)
Ethnicity not known	23 (6)
History of hypertension, No. (%)	
Yes	118 (29)
No	288 (71)
History of diabetes, No. (%)	
Yes	30 (7)
No	376 (93)

(eTable 2 in the Supplement). Of the 40 patients with baseline LVEF of less than or equal to 55%, 26 (65%) were at least 50 years of age. Overall, the majority of patients had a decline in LVEF from baseline of less than 10% (84% at 12 weeks; 80%, 6 months; and 74%, 1 year), and only a minority of patients had a decline in LVEF from baseline of 10% to 15% (7% at 12 weeks; 9%, 6 months; and 9%, 1 year) and greater than or equal to 16% (<1% at 12 weeks; 1%, 6 months; and 2%, 1 year). The LVEF values were well preserved throughout treatment as median (range) 65% (50%-81%) at baseline; 64% (45%-81%), 12 weeks; 64% (45%-83%), 6 months; and 64% (41%-90%), 1 year (Table 3).

### Grade 3 to 4 LVSD

Out of 406 patients who started protocol therapy, 2 (0.5%) patients developed grade 3 LVSD (95% CI, 0.1%-1.8%), one of whom was a woman in her 60s taking medications for hyperlipidemia on study entry and who had developed symptomatic CHF 11 months after starting treatment. Her LVEF assessments were 55% at baseline; 54%, 12 weeks; 60%, 6 months; and 37%, 11 months. She did not resume trastuzumab per study stipulation. Subsequent treatment with lisinopril achieved full resolution of CHF symptoms and a restoration of LVEF to 60% at 16 months and 66% at 27 months (eTable 3 and eFigure 1 in the Supplement). The other patient was a woman in her 50s taking a  $\beta$ -blocker for a diagnosis of arrhythmogenic right ventricular dysplasia. Her LVEF was 66% at baseline and 61% at 12 weeks, and it declined to 50% at 6 months, which coincided with the onset of symptoms of CHF. Trastuzumab therapy was terminated. Medical management with a regimen of furosemide, ramipril, and carvedilol was initiated, and she became asymptomatic with subsequent LVEF assessments of 51% at

Table 2. Distribution of Age in Patients With Hypertension and Diabetes Mellitus

Characteristic	Patients		
	All	Hypertension	Diabetes Mellitus
Patients, No.	406	118	30
Age, median (range), y	55 (24-85)	61 (40-85)	59 (40-76)
Age group, No. (%), y			
<50	132 (33)	19 (16)	5 (17)
50-59	137 (34)	32 (27)	10 (33)
60-69	96 (24)	45 (38)	11 (37)
>70	41 (10)	22 (19)	4 (13)

Table 3. Summary of LVEF at Protocol-Specified Time Points and Changes From Baseline Values

Characteristic	No. (%)			
	Baseline	12 weeks	6 mo	1 y
LVEF reduction from baseline				
<10%		343 (84)	325 (80)	302 (74)
10%-15%		29 (7)	36 (9)	35 (9)
≥16%		2 (<1)	5 (1)	7 (2)
Required, not evaluated <sup>a</sup>		7 (1)	9 (2)	22 (5)
Not required <sup>b</sup>		25 (6)	31 (8)	40 (10)
LVEF level, %				
Median (range)	65 (50-81)	64 (45-81)	64 (45-83)	64 (41-90)

Abbreviation: LVEF, left ventricular ejection fraction.

<sup>a</sup> Patients for whom cardiac evaluation was required but reported as not completed were counted as *required but not evaluated*.

<sup>b</sup> Cardiac evaluations were not required for patients who went off protocol

therapy due to noncardiac toxic effects. Assessments after the off-treatment visit for patients who went off treatment before completing 1-year protocol-specified therapy due to noncardiac toxic effects were counted as *not required*.

7 months; 54%, 8 months; and 56%, 18 months (eTable 3 and eFigure 1 in the Supplement). Both patients were medically managed by their cardiologists for CHF. Overall, these 2 patients had at least 2 potential risk factors for cardiac dysfunction. Both patients were older than 50 years of age, and one had baseline LVEF of only 55% while the other had arrhythmogenic right ventricular dysplasia due to fatty infiltration of the right ventricle. Most patients with arrhythmogenic right ventricular dysplasia will have left ventricular involvement over time resulting in biventricular failure.

### Incidence of Asymptomatic Decrease in LVEF

Overall, 13 (3.2%) patients (95% CI, 1.9%-5.4%) experienced an asymptomatic LVEF decline significant enough to require trastuzumab interruption per study criteria (eTable 3 in the Supplement). Two patients discontinued protocol therapy. Another patient had significant asymptomatic LVEF decline that did not recover during the 4-week study timeframe. However, she was not taken off study and trastuzumab was continued, which was a study violation. Of the 3 patients with persistent asymptomatic (ie, lasting ≥4 weeks) LVEF decline (grade 2 LVSD), 2 were at least 50 years of age and had a baseline LVEF of only 55%. One of these patients also had hypertension and diabetes, was on cardiac medications (amlodipine and atenolol) at baseline for hypertension, and did not have additional medications at the time of trastuzumab cessation. The

other patient had cardiac medications (lisinopril, losartan, and carvedilol) added (eTable 3 in the Supplement).

Of the 10 remaining patients with significant asymptomatic LVEF decline during treatment, 6 had already completed 1 year of therapy when a significant asymptomatic LVEF decline occurred at the end of treatment, and 2 patients had cardiac medications added. Because these patients had completed therapy already, any follow-up LVEF monitoring was at the physician's discretion. The other 4 patients experienced significant asymptomatic LVEF decrement and recovered appropriately before completing 1 year of therapy. Only 1 patient had cardiac medication added, but the other 3 patients did not. Of these 10 patients, only 3 patients had 2 cardiovascular risk factors (≥50 years of age and hypertension), and 2 patients were taking antihypertensive medication at baseline and 1 was not. Of note, in the 10 patients, all but 1 patient had baseline LVEF greater than 55%. Overall, in these 13 (3.2%) patients with significant asymptomatic LVEF decline, only 5 had at least 2 cardiovascular risk factors, and notably, only 3 had baseline LVEF of 55%. We performed an exploratory analysis to assess the relationship between baseline characteristics and cardiac outcomes, and there appeared to be a correlation between a low baseline LVEF of 55% or less and higher incidence of significant asymptomatic LVEF decline or grade 3 to 4 LVSD (risk ratio [RR], 0.30; 95% CI, 0.10-0.90;  $P = .05$ ) (Table 4).

Table 4. Cross-tabulation of Baseline Characteristics and Grade 3 to 4 LVSD or Asymptomatic LVEF Decline

Characteristic	Total Patients, No.	No. (%)		Relative Risk (95% CI)	P Value
		No Cardiac Toxic Effects	Grade 3 to 4 LVSD or Asymptomatic LVEF Decline		
Age at study entry, y					
<50	132	126 (95)	6 (5)	NA	.58
≥50	274	265 (97)	9 (3)	0.72 (0.26-1.99)	
Baseline LVEF, %					
≤55 y	40	36 (90)	4 (10)	NA	.05
>55 y	366	355 (97)	11 (3)	0.30 (0.10-0.90)	
History of hypertension					
Yes	118	113 (96)	5 (4)	NA	.77
No	288	278 (97)	10 (3)	0.82 (0.29-2.35)	
History of diabetes					
Yes	30	27 (90)	3 (10)	NA	.09
No	376	364 (97)	12 (3)	0.32 (0.10-1.07)	

Abbreviations: LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NA, not applicable.

## Discussion

This regimen of paclitaxel and trastuzumab without an anthracycline has already demonstrated exceptional outcomes with 3-year disease-free survival exceeding 98.7%.<sup>21</sup> In this analysis, we also demonstrate that it is well-tolerated, with incidence of grade 3 to 4 LVSD (CHF) of only 0.5% (95% CI, 0.1%-1.8%). This is consistent with the data from the study by Slamon et al (BCIRG 006)<sup>7,25</sup> and the phase II trial by Jones et al<sup>26</sup> on docetaxel and cyclophosphamide with trastuzumab.<sup>7,26</sup> The incidence of grade 3 to 4 LVSD for both studies was 0.4% with a nonanthracycline taxane-trastuzumab combination.<sup>5,26</sup> In this study, the 2 patients who developed grade 3 LVSD had at least 2 cardiovascular risk factors and experienced CHF during active therapy at 6 and 11 months, respectively, with subsequent recovery. Only 13 (3.2%) (95% CI, 1.9%-5.4%) of 406 patients demonstrated a significant asymptomatic decline in LVEF requiring trastuzumab interruption per protocol. Of these 13 patients, 3 had persistent LVEF decline, and 2 patients were removed from study while 1 continued therapy, which was a study violation. The remaining 10 patients completed trastuzumab therapy as planned. In these 13 patients, 5 had at least 2 cardiovascular risk factors.

These results compared favorably with the combined analysis of NSABP B-31 and N9831 in the study by Romond et al,<sup>3</sup> in which 14.2% of patients did not complete 1 year of trastuzumab due to significant asymptomatic LVEF deterioration.<sup>3</sup> The low incidence of LVEF decline in our study was most likely attributable to the absence of the anthracycline. In addition, over the last decade, there has been a higher threshold to stop trastuzumab as a result of asymptomatic left ventricular dysfunction given the growing appreciation of the benefits of trastuzumab therapy and collaboration between cardiologists and oncologists.<sup>27</sup> In our study, 88% of patients completed 1 year of therapy, includ-

ing the patients who resumed therapy after a temporary interruption for asymptomatic LVEF decline. This was favorable when compared with the phase II study by Jones et al<sup>26</sup> in which only 82% of patients completed the full year of therapy.

Previous data suggest that late cardiac toxic effects from trastuzumab therapy is rare in oncology clinical trials. Seven-, 8-, and 9-year follow-up data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31,<sup>28</sup> Herceptin Adjuvant (HERA)<sup>6</sup> trial, and North Central Cancer Treatment Group (NCCTG) N 9831 trial,<sup>15</sup> respectively, described no increase in the New York Heart Association class III to IV heart failure and/or cardiac death rate, with events occurring mainly during active therapy.<sup>6,28</sup> In addition, cardiac events reported for 2 trials of dose-dense chemotherapy with anti-ERBB2 agents occurred mainly during active therapy, with 5- and 7-year follow-up data, respectively.<sup>19</sup> When extrapolating the information from these data to our study with a median follow-up of 4 years, it is likely that the 0.5% incidence of grade 3 LVSD with paclitaxel and trastuzumab will not change over time with a longer follow-up.

In contrast, recent claims-based reports have shown that heart failure and/or cardiomyopathy rates exceeded those reported by other prospective studies with long-term follow-up durations.<sup>6,15,19,28</sup> For example, Bowles et al<sup>29</sup> conducted a population-based retrospective cohort study of 12 500 women with invasive breast cancer who were treated with no chemotherapy, anthracycline, trastuzumab, anthracycline and trastuzumab, or other chemotherapies. In this study, only 0.9% of patients received trastuzumab without an anthracycline. At 1, 3, and 5 years, the respective rates of heart failure and/or cardiomyopathy were 3.6%, 7.8%, and 12.1% with trastuzumab without an anthracycline. These findings were similar to those reported in articles by Chen et al,<sup>30</sup> Chavez-MacGregor et al,<sup>31</sup> and Ezaz et al.<sup>32</sup> The patient populations in these retrospective studies were much older, with mean ages ranging from 60 to 76 years old.<sup>29-32</sup> The

higher rates in these retrospective studies, when compared with well-designed prospective trials, could be due to an overestimation of the true risk of cardiac toxic effects in claims-based studies and/or that the patients in prospective clinical trials were healthier and younger by selection. Finally, retrospective claims-based data were also limited due to a lack of rigorous adjudication of events.

Risk factors associated with trastuzumab-related cardiac toxic effects include anthracycline exposure and age 50 years and older.<sup>28,33-36</sup> Our exploratory analysis suggests an association between a low baseline LVEF 55% or less and incidence of asymptomatic LVEF decline and grade 3 to 4 LVSD. In addition, multivariate analyses identified borderline low LVEF of less than 55%, hypertension, and high body mass index as predisposing risk factors for trastuzumab-induced cardiac toxic effects, whereas influences of diabetes, valvular heart disease, and coronary artery disease were not statistically significant.<sup>28,34,36,37</sup> Concurrent trastuzumab with radiation does not increase cardiac toxic effects.<sup>28,36,38</sup> In our study of 406 patients, 40 (10%) had baseline LVEF of 55% or less and 26 (6%) had baseline LVEF of 55% or less and were 50 years of age or older. Additionally, 118 (29%) patients had a history of hypertension, 30 (7%) had diabetes, and the majority of patients with hypertension (84%) and diabetes (83%) were at least 50 years of age. Given the low incidence in our study of cardiac dysfunction where patients did not receive an anthracycline, serial monitoring may be reserved for patients considered at a higher risk of developing cardiac toxic effects, as well as those with signs and symptoms of CHF or other cardiac symptoms. If this approach to screening was implemented in this study, many LVEF assessments would have been avoided for the majority of asymptomatic patients with baseline LVEF greater than 55% without coexisting cardiovascular risk factors. The extent to which such rationalized LVEF surveillance might reduce interruption of trastuzumab, reduce cost, and have an effect on cardiovascular and cancer prognoses requires investigation. Moreover, we advocate for closer collaboration between cardiologists and oncologists in determining the best strategies in identifying patients who are at risk of devel-

oping heart failure such that the patient can complete the course of trastuzumab therapy without interruption.

This study had some limitations. First, LVEF quantifications by ECHOs or MUGAs did not follow a standard protocol, and a core laboratory was not used for analyses. Thus, data on interobserved and intraobserved variability and reproducibility of LVEF reports in this study were lacking. However, this limitation was common to many chemotherapy trials that included cardiovascular safety endpoints. Second, certain patient groups that were considered at higher risk for trastuzumab-associated cardiac toxic effects, such as those with a history of myocardial infarction or CHF, were excluded from this study. As such, study findings and recommendations for a reduced number of LVEF assessments cannot be generalized to such patients. Third, it is increasingly clear from emerging cardiac literature that LVEF may not be the best marker of cardiac contractility.<sup>39</sup> Fourth, data for certain cardiovascular risk factors such as hyperlipidemia, cerebrovascular disease, and prior coronary revascularizations were not consistently collected. Fifth, management of deteriorations in LVEF during treatment was directed at the physician's discretion, and variation in management likely influenced likelihood of recovery in LVEF.

## Conclusions

There was a low incidence of grade 3 to 4 LVSD (0.5%) and asymptomatic deteriorations in LVEF (3.2%) during treatment with paclitaxel (0.5%) and trastuzumab (3.2%). The favorable cardiovascular safety profile of trastuzumab in this nonanthracycline setting suggests that baseline LVEF assessment may be sufficient for the majority of patients, with serial LVEF assessments reserved for patients considered at a higher risk for cardiac toxic effects. A prospective trial to include a uniform assessment and management of cardiovascular risk factors, as well as a central review of LVEF data in patients receiving a nonanthracycline regimen with anti-ERBB2 therapy, will be needed to help further define which patients may require less intensive LVEF monitoring.

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