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ORIGINAL REPORT

Longer-Term Assessment of Trastuzumab-Related Cardiac Adverse Events in the Herceptin Adjuvant (HERA) Trial

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See accompanying editorial on page 3407 and articles on pages 3416 and 3429

A B S T R A C T

Purpose
We investigated the incidence of cardiac adverse events in patients with early breast cancer in the Herceptin Adjuvant (HERA) trial who were treated with 1 year of trastuzumab after completion of (neo)adjuvant chemotherapy.

Patients and Methods
The HERA trial is a three-group, randomized trial that compared 1 year or 2 years of trastuzumab with observation in women with human epidermal growth factor receptor-2 (HER2) –positive early breast cancer. Eligible patients had normal left ventricular ejection fraction (LVEF; ≥ 55%) after completion of (neo)adjuvant chemotherapy with or without radiotherapy. Cardiac function was monitored throughout the trial. This analysis considers patients randomly assigned to 1 year of trastuzumab treatment or observation.

Results
There were 1,698 patients randomly assigned to observation and 1,703 randomly assigned to 1 year of trastuzumab treatment; 94.1% of patients had been treated with anthracyclines. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% *v* 0.0%; confirmed significant LVEF decreases, 3.6% *v* 0.6%) In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery; of these 59 patients, 52 were considered by the cardiac advisory board (CAB) to have a favorable outcome from the cardiac end point.

Conclusion
The incidence of cardiac end points remains low even after longer-term follow-up. The cumulative incidence of any type of cardiac end point increases during the scheduled treatment period of 1 year, but it remains relatively constant thereafter.

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INTRODUCTION

Trastuzumab benefits patients with metastatic breast cancer and improves disease-free and overall survival in the adjuvant setting.[1-4] However, trastuzumab treatment is also associated with cardiac dysfunction and congestive heart failure (CHF),[5-6] likely because the human epidermal growth factor receptor-2 (HER2/ERB2) is expressed in the adult myocardium and is believed to modulate cardiac function and anthracycline cardiotoxicity.[7-9] In the Herceptin Adjuvant (HERA) trial, we therefore prospectively monitored cardiac function and found a low incidence of severe and symptomatic CHF in the trastuzumab group at a median follow-up time of 1 year.[10] The results suggested that trastuzumab-associated cardiac dysfunction has a high rate of reversibility, a characteristic that is fundamentally different from anthracycline-associated cardiac dysfunction. After a cardiac end point, questions of clinical importance are whether cardiac function recovers and, if so, whether the patient is at risk of a subsequent left ventricular ejection fraction (LVEF) decrease. Therefore, this article describes acute recovery and the cardiac advisory board (CAB) assessment of whether the patient had a favorable outcome from the cardiac end

point or not. This manuscript reports cardiac safety during a median follow-up of 3.6 years.

PATIENTS AND METHODS

Study Design

The HERA trial was a three-group, multicenter, open-label, phase III, randomized trial involving women with HER2-positive early breast cancer. The patients were randomly assigned to observation only, 1 year of trastuzumab treatment, or 2 years of trastuzumab treatment. The primary end point was disease-free survival. The visit schedule was the same for all patients.

The results of the 1 year-trastuzumab group compared with the observation group were released and published after an interim analysis that showed a highly significant improvement in disease-free survival.[11] An article detailing cardiac safety at a median of 1 year of follow-up was published.[10] No data for the 2-year trastuzumab group has been released by the independent data monitoring committee.

A protocol amendment was made after enrollment had been completed (except for the last five patients) to allow patients in the observation group the option of switching to trastuzumab, irrespective of the time since random assignment. For patients originally randomly assigned to observation who switched to trastuzumab after the release of the trial results, only information during the observation period before the patient started trastuzumab was considered.

Eligibility Criteria

The eligibility criteria, including cardiac eligibility criteria, have been described elsewhere.[11]

Cardiac Monitoring

A cardiac questionnaire, physical examination, ECG, and assessment of LVEF by echocardiography or multiple-gated acquisition scan were performed in all three groups at baseline; at 3, 6, 12, 18, 24, 30, 36, and 48 months; and annually between year 5 and year 10 after random assignment.

Definitions of Cardiac End Points and Acute Recovery

Cardiac safety and tolerability of trastuzumab were assessed on the basis of prespecified cardiac end points, which must take place between random assignment and the start date of new therapy for recurrent disease. Cardiac death was defined as death definitely as a result of heart failure, myocardial infarction, or documented arrhythmia or as probable cardiac death within 24 hours of a cardiac event. A significant LVEF decrease was defined as an absolute decline of at least 10 percentage points from baseline LVEF and to less than 50%. Severe CHF was defined as New York Heart Association (NYHA) class III or IV, confirmed by a cardiologist, and a significant LVEF decrease. Symptomatic CHF was defined as symptomatic CHF confirmed by a cardiologist and a significant LVEF decrease. Confirmed significant LVEF decrease was defined as an asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) significant LVEF decrease, unless the next subsequent assessment of LVEF indicated a return to levels that did not meet the definition of significant LVEF decrease; or as identified by the treatment-unblinded CAB. The primary cardiac end point of the trial was cardiac death or severe CHF. The secondary cardiac end point of the trial was confirmed significant LVEF decrease.

A patient was considered to have reached acute recovery from a cardiac end point if she had two or more sequential LVEF assessments of 50% or greater after the date of the cardiac end point. The date of acute recovery was the date of the first LVEF assessment showing an LVEF $\geq$ 50%, which was part of a sequence of two or more LVEF assessments $\geq$ 50% after the date of the cardiac end point.

Assessment of Outcome of Cardiac End Point by CAB

The CAB reviewed LVEF assessments for the patients with cardiac end points and assessed if the patients had favorable outcomes from the cardiac end points or not on the basis of trends from the patients' LVEF measurements. If the trend was that the LVEF remained constant at greater than 50% or if it improved, the CAB assessment was a favorable outcome. If the trend was that the LVEF decreased, the CAB assessment was that the outcome was not favorable. The CAB did not consider trastuzumab treatment when assessing the outcome of patients.

Safety Analysis Population and Analysis Database

The database used for this analysis contains data as of January 3, 2008. Between December 2001 and June 2005, there were 1,698 patients randomly assigned to observation and 1,703 randomly assigned to 1 year of trastuzumab treatment. The median time between finishing any type of chemotherapy and start of trastuzumab treatment was 90 days.

Twenty-one patients originally randomly assigned to 1 year of trastuzumab treatment did not receive any trastuzumab before disease recurrence and were counted in the observation safety analysis population group. Therefore, there were 1,682 patients in the trastuzumab safety analysis population arm and 1,719 patients in the observation safety analysis population arm. Four patients originally randomly assigned to observation received commercial trastuzumab. For these four patients, only information before the patient started trastuzumab was considered.

There were two patients who suffered cardiac death after the start of new therapy for recurrent disease. These two patients were not considered to have any type of cardiac end point.

Discontinuation of Trastuzumab and Dose Modification

As previously described,[11] trastuzumab had to be permanently discontinued in patients who experienced severe CHF (a primary cardiac end point), and treatment for congestive heart failure was recommended. If the patient had a confirmed significant LVEF decrease (a secondary cardiac end point) trastuzumab had to be permanently discontinued. Reasons for premature discontinuation of trastuzumab are listed in Table 1.

By June 2006, all patients in the trastuzumab group had reached the end of the scheduled 1 year of trastuzumab. A total of 172 patients (10.2%) discontinued trastuzumab for reasons other than recurrence of disease.

Statistical Analysis

The difference in incidence of cardiac adverse events between the safety analysis population groups was estimated by using an approximate 95% CI with the Hauck-Anderson correction. Time to acute recovery was defined for patients with any type of cardiac end point. For patients who reached acute recovery, time to acute recovery was the number of days between the date of cardiac end point and the date of acute recovery. For patients who had not reached acute recovery, time to acute recovery was censored at the date of the last LVEF assessment. Time to LVEF decrease after acute recovery was defined for patients who reached acute recovery after a cardiac end point.

For patients who had at least one LVEF value of less than 50% after the date of acute recovery, the time to LVEF decrease after acute recovery was the number of days between the date of acute recovery and the date of the first LVEF value less than 50% after reaching acute recovery. For patients who had no LVEF value less than 50% and, therefore, no LVEF decrease after acute recovery, time to LVEF decrease after acute recovery was censored at the date of last LVEF assessment.

Table 1. Summary of Reasons for Discontinuation of Trastuzumab

Reason for Discontinuation	Trastuzumab for 1 Year (N = 1,682)	
	No.	%
Cardiac disorder	86	5.1
Other adverse event	32	1.9
Death	3	0.2
Recurrence of disease	90	5.4
Refused treatment	42	2.5
Other reason	9	0.5
Total	262	15.6

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Table 2. Summary of Cardiac End Points for Safety Analysis Populations

	Analysis by Population					
	Observation Only (n = 1,719)		Trastuzumab for 1 Year (n = 1,682)		Incidence in Trastuzumab *v* Observation	
End Point	No.	%	No.	%	Difference	95% CI
Cardiac death	1	0.1	0	0.0	−0.1	−0.2 to 0.1
Severe CHF	0	0	13	0.8	0.8	0.3 to 1.2
Symptomatic CHF	2	0.1	32	1.9	1.8	1.1 to 2.5
Confirmed significant LVEF decrease	11	0.6	60	3.6	2.9	1.9 to 3.9
Any type of cardiac end point	12	0.7	73	4.3	3.6	2.6 to 4.7
At least one significant LVEF decrease	49	2.9	164	9.8	6.9	5.2 to 8.6

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

RESULTS

Cardiac End Points

The incidence of cardiac end points is listed in Table 2. One patient in the observation group suffered cardiac death. As expected, the incidence of severe CHF (0.8% *v* 0.0%; 95% CI for the difference, 0.3% to 1.2%), symptomatic CHF (1.9% *v* 0.1%; 95% CI for the difference, 1.1% to 2.5%), and confirmed significant LVEF decrease (3.6% *v* 0.6%; 95% CI for the difference, 1.9% to 3.9%) was significantly higher in the trastuzumab group compared with observation. The 73 patients with cardiac end points have been observed for a median of 25.1 months (range, 0.0 to 33.1 months) after the cardiac end point.

Cumulative Incidence of Cardiac End Points

The cumulative incidence of cardiac death or severe CHF (Fig 1A), cardiac death, severe CHF or symptomatic CHF (Fig 1B), and any type of cardiac end point (Fig 1C) were calculated by original randomly assigned group with a competing risk of a disease-free survival event. The patients originally randomly assigned to observation had an additional competing risk of switching to trastuzumab, which noticeably reduced the number of patients at risk of a cardiac end point. The cumulative incidence of any type of cardiac end point among patients randomly assigned to 1 year of trastuzumab treatment increased during the scheduled trastuzumab treatment period of 1 year, but it remained approximately constant thereafter (Fig 1C).

Acute Recovery After a Cardiac End Point

Acute recovery after a cardiac end point for the trastuzumab group is summarized in Table 3. The cumulative proportion of patients with a cardiac end point who reached acute recovery by time from cardiac end point is shown in Figure 2A. It should be noted that Figure 2A is based on the small number of patients with a cardiac end point.

Among the 73 patients with a cardiac end point, 59 (80.8%) reached acute recovery. The median time to acute recovery was 6.4 months (range, 0 to 33.1 months). The 59 patients who reached acute recovery have been observed for a median of 20.9 months (range, 2.5 to 51.6 months) after reaching acute recovery.

There were three patients in the trastuzumab group who did not have two or more LVEF assessments after the date of the cardiac end point. These patients lacked sufficient LVEF information to determine if the patient reached acute recovery and were considered among the 14 patients who did not reach acute recovery.

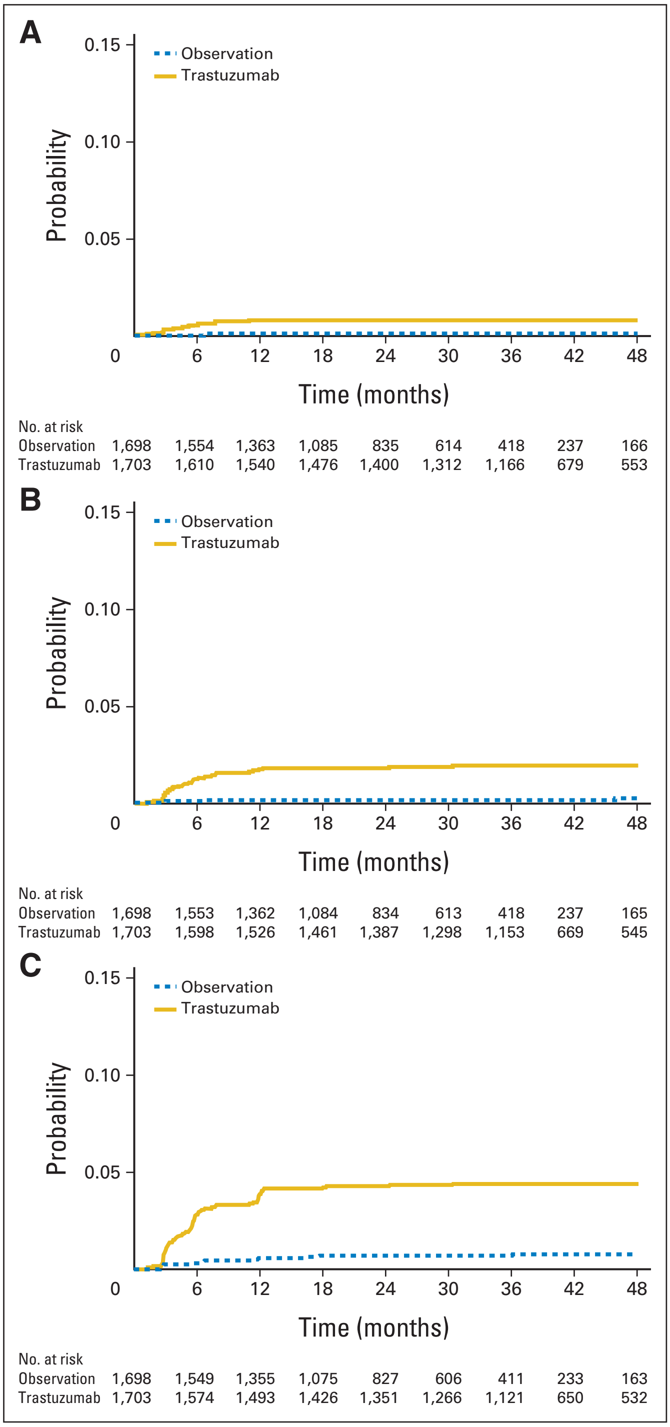

Fig 1. The cumulative incidence of competing risks by randomized group showing the risk of (A) cardiac death or severe congestive heart failure (CHF), (B) cardiac death or severe CHF or symptomatic CHF, or (C) any cardiac end point.

Table 3. Summary of Acute Recovery After Cardiac End Point Trastuzumab Safety Analysis Population Group

Cardiac End Point	No.	%	Median (months)*	Range (months)†
Severe CHF (n = 13)				
Reached acute recovery	9	69.2		
Time to acute recovery			11.6	1.3-28.7
Occurrence of LVEF drop to < 50% after acute recovery	3	33.3		
Time to LVEF drop to < 50% after acute recovery			25.8	3.0-25.8
Symptomatic CHF (n = 32)				
Reached acute recovery	25	78.1		
Time to acute recovery			5.5	0.0-28.7
Occurrence of LVEF drop to < 50% after acute recovery	8	32.0		
Time to LVEF drop to < 50% after acute recovery			27.7	3.0-34.7
Confirmed significant LVEF drop (n = 60)				
Reached acute recovery	50	83.3		
Time to acute recovery			6.3	0.0-33.1
Occurrence of LVEF drop to < 50% after acute recovery	14	28.0		
Time to LVEF drop to < 50% after acute recovery			—	2.5-51.6
Any type of cardiac end point (n = 73)				
Reached acute recovery	59	80.8		
Time to acute recovery			6.4	0.0-33.1
Occurrence of LVEF drop to < 50% after acute recovery	17	28.8		
Time to LVEF drop to < 50% after acute recovery			—	2.5-51.6

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

Subsequent LVEF Decrease to Less Than 50% After Acute Recovery and Evidence of Progressive Cardiac Disease

The cumulative proportion of patients who had a subsequent LVEF decrease to less than 50% after reaching acute recovery by time from reaching acute recovery is shown in Figure 2B. It should be noted that Figure 2B is based on the small number of patients with a cardiac end point who reached acute recovery. Among the 59 patients in the trastuzumab group who reached acute recovery, 42 patients had all subsequent LVEF assessments ≥ 50%, and 17 patients had at least one subsequent LVEF decrease to less than 50%. The CAB reviewed the 17 patients with at least one subsequent LVEF decrease and found evidence of progressive cardiac disease in only six patients. The remaining 11 of 17 patients were assessed by the CAB as having a favorable outcome.

The CAB assessment of one patient who reached acute recovery and who had all subsequent LVEF assessments ≥ 50% was undetermined. Fifty-two (88.1%) of the 59 patients who reached acute recovery were assessed by the CAB as having a favorable outcome from the cardiac end point.

CAB Assessment of Outcome From the Cardiac End Point

A flow chart of the CAB assessment for the 73 patients in the trastuzumab group is shown in Figure 3. Among these 73 patients, the CAB assessment was that 57 (78.1%) had a favorable outcome, including five patients who did not reach acute recovery, and that 14 (19.2%) did not have a favorable outcome, including six patients who reached acute recovery. The CAB assessment was undetermined for two patients.

Among the 14 patients who did not reach acute recovery, the CAB assessment was that five had a favorable outcome, eight did not have a favorable outcome, and one was undetermined. For patients in the trastuzumab group, Appendix Figure A1 (online only) illustrates the proportion of patients who had any type of cardiac end point, the proportion with a cardiac end point who reached acute recovery, and the proportion who reached acute recovery assessed by the CAB as having a favorable outcome.

Description of Patient-Related Predictive Factors

We investigated if there was a pattern of chemotherapy treatment or cardiac medication in patients who were assessed by the CAB as not having a favorable outcome from the cardiac end point.

Previous Anthracyclines

Nearly all (94.1%) of the patients enrolled had been treated with anthracyclines. Of the 73 patients in the trastuzumab group with a cardiac end point, 70 had been treated with anthracyclines. Of the 12 patients in the observation group with a cardiac end point, 11 had been treated with anthracyclines.

Patients Who Did Not Have a Favorable Outcome to the Cardiac End Point

Of the 14 patients in the trastuzumab group assessed by the CAB as not having a favorable outcome from the cardiac end point, 13 had been treated with anthracyclines. Cardiac medication was reported for seven of these 14 patients; however, there was no consistent use of a particular type of cardiac medication.

DISCUSSION

The predominant cardiovascular adverse effect of trastuzumab is the induction of cardiac contractile dysfunction, a complication that previously has been associated mainly with anthracycline treatment. In the HERA trial, the incidence of cardiac dysfunction in the

trastuzumab arm at a median follow-up time of 1 year was 0.6% for severe CHF and 7.0% for left ventricular (LV) dysfunction.[10] Results from the HERA trial suggest that trastuzumab-associated cardiac dysfunction has a high rate of reversibility,[10] a characteristic that is fundamentally different from anthracycline-associated cardiac dysfunction. However, several questions remained unanswered: Does the incidence of cardiac end points increase with longer follow-up time? When do the cardiac events predominantly occur? What is the cardiac prognosis of a patient after a cardiac end point? What are the risk factors and outcomes of patients with progressive cardiac dysfunction after trastuzumab treatment? Does trastuzumab treatment worsen anthracycline-associated cardiac dysfunction?

We now show that, after a median follow-up time of 3.6 years, the incidence of severe CHF and LV dysfunction in the trastuzumab group remained low at 0.8% and 9.8%, respectively. Similarly, the rate of discontinuation of trastuzumab as a result of cardiac disorders was low (5.1%). Despite these reassuring results, and because anthracycline cardiac adverse effects typically become manifest 5 to 10 years after the initial exposure, longer follow-up of cardiac safety is still required. Preclinical data suggests that trastuzumab could worsen anthracycline-associated cardiotoxicity.[9]

All occurrences of severe symptomatic CHF failure and 51 (85%) of 60 confirmed significant LVEF decreases in the trastuzumab group occurred during the scheduled trastuzumab treatment period. After a cardiac end point, questions of clinical importance are whether cardiac function recovers and, if so, whether the patient is at risk of a subsequent LVEF decrease. Therefore, we defined acute recovery, and the CAB assessed if the patient had a favorable outcome from the cardiac end point or not on the basis of the patients' LVEF trends. Approximately 80% of patients (57 of 73 patients) in the trastuzumab group with cardiac end points were assessed by the CAB as having a favorable outcome. Among the patients in the trastuzumab group who reached acute recovery from a cardiac end point (59 of 73 patients; 80.8%), most were assessed by the CAB as having a favorable outcome (52 of 59 patients; 88.1%). Among the 59 patients who reached acute recovery, 15 patients in the absence of any additional trastuzumab treatment had a subsequent LVEF drop to 50%, though we do not know the cause of the subsequent LVEF decrease; nine of these 15 patients were assessed by the CAB as having a favorable outcome. Given that the majority of cardiac end points in the trastuzumab group occurred during the scheduled treatment period, reaching acute recovery after a cardiac end point may influence treatment decisions outside clinical trials. In the HERA trial, patients who had a confirmed significant LVEF decrease discontinued trastuzumab treatment.

The relatively good prognosis after a cardiac end point also sheds light on the pathophysiology of trastuzumab-associated cardiac dysfunction. Preclinical data indicate that inhibition of myocardial HER2/ERB2 leads to changes in the tertiary structure of the cardiac contractile apparatus (likely a reversible condition) but does not induce myocardial cell death (likely a progressive condition).[12] This may explain why cardiac contractile dysfunction is predominantly seen during trastuzumab treatment and appears to have a high rate of reversibility. In contrast, anthracyclines can induce myocardial cell death that leads to a maladaptive cardiac remodeling with progressive cardiac dysfunction and heart failure.[13] This suggests that the approximately 80% of patients (57 of 73 patients) in the trastuzumab group with a cardiac end point assessed by the CAB as having a favorable outcome may have primarily trastuzumab-associated cardiac dysfunction. Among the approximately 20% of patients (14 of 73 patients) in the trastuzumab group assessed by the CAB as not having a favorable outcome from the cardiac end point, almost all (13 of 14) had been treated with anthracyclines. In these 13 patients, it is possible that trastuzumab treatment worsened anthracycline-associated cardiac dysfunction.

In the HERA trial, nearly all of the patients enrolled had been treated with anthracyclines. We have insufficient information to assess the influence of cardiac medication on the prognosis of patients in the trastuzumab group with a cardiac end point.

In conclusion, given the benefit in disease-free and overall survivals of 1 year adjuvant trastuzumab in patients with HER2-positive early breast cancer, the low incidence of cardiac end points with longer term follow-up, and the suggestion that trastuzumab-induced cardiac dysfunction may be reversible, adjuvant trastuzumab should be considered as a standard treatment option for patients who fulfill the HERA trial eligibility criteria.

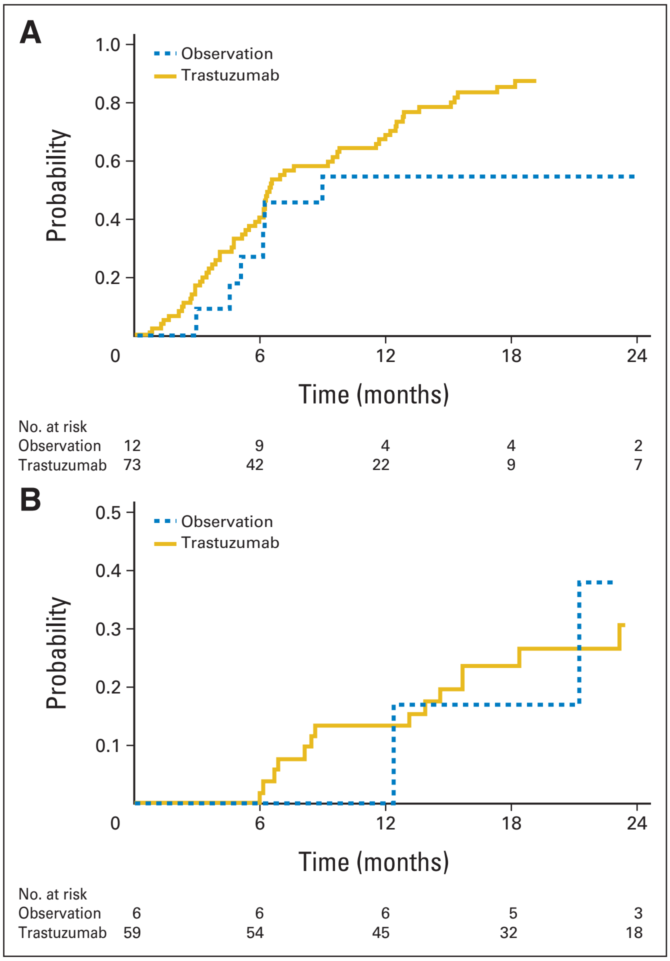

Fig 2. The cumulative incidence by safety analysis population group among patients with any type of cardiac end point of (A) reaching acute recovery and (B) subsequent left ventricular ejection fraction decrease to less than 50% after reaching acute recovery.

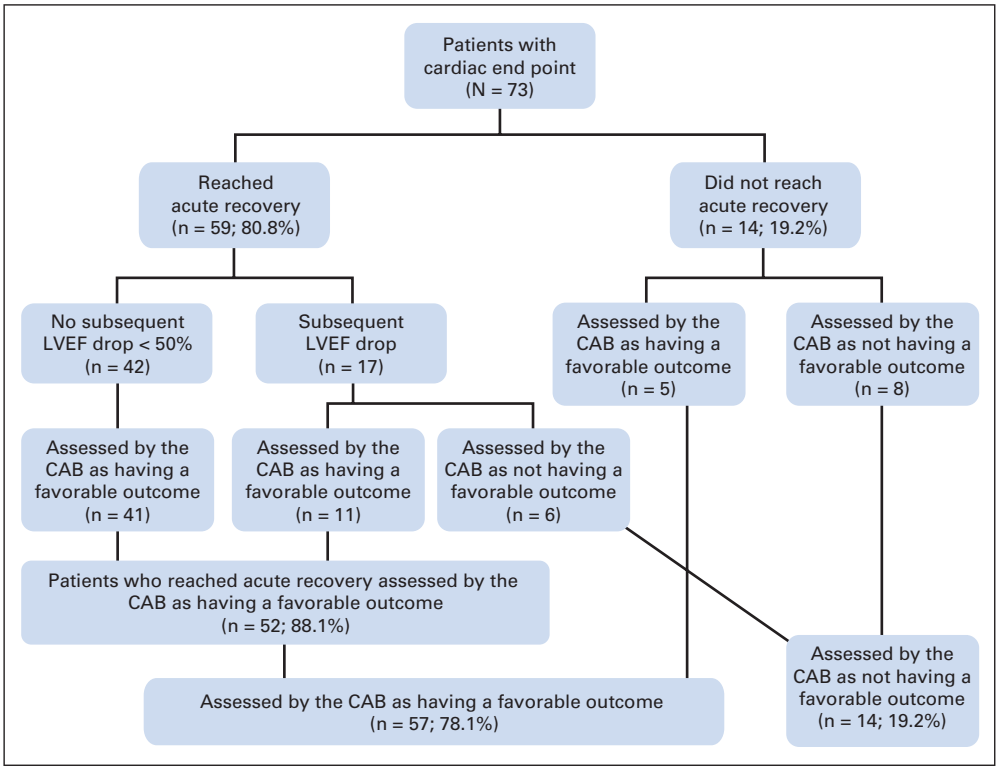

Fig 3. Flow chart of the cardiac advisory board (CAB) assessment for patients with any type of cardiac end point in the trastuzumab group. The CAB assessment was undetermined for two patients. LVEF, left ventricular ejection fraction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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