Received: 16 September 2021 | Revised: 20 February 2022 | Accepted: 4 March 2022

DOI: 10.1002/ijc.34024

CANCER THERAPY AND PREVENTION

Short Report

IJC INTERNATIONAL JOURNAL of CANCER

The effect of trastuzumab on cardiac function in patients with HER2-positive metastatic breast cancer and reduced baseline left ventricular ejection fraction

Nathalie I. Bouwer[1,2] | Tessa G. Steenbruggen[3] | Hánah N. Rier[4] | Jos J. E. M. Kitzen[1] | Carolien H. Smorenburg[3] | Marlies L. van Bekkum[5] | Paul C. de Jong[6] | Jan C. Drooger[7] | Cynthia Holterhues[8] | Marcel J. M. Kofflard[2] | Eric Boersma[9] | Gabe S. Sonke[3] | Mark-David Levin[1] | Agnes Jager[4]

[1]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands

[2]Department of Cardiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

[3]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[4]Department of Medical Oncology, Erasmus MC, Cancer Institute, Rotterdam, The Netherlands

[5]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, The Netherlands

[6]Department of Medical Oncology, Sint Antonius Hospital, Utrecht, The Netherlands

[7]Department of Medical Oncology, Breast Cancer Center South Holland South, Ikazia Hospital, Rotterdam, The Netherlands

[8]Department of Medical Oncology, Haga Hospital, The Hague, The Netherlands

[9]Department of Cardiology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

Correspondence
Nathalie I. Bouwer, Department of Internal Medicine, Albert Schweitzer Hospital, 3300 AK, Dordrecht, South-Holland, The Netherlands.
Email: n.i.bouwer@asz.nl

Funding information
Our study was funded by the Promotiefonds of the Albert Schweitzer Hospital, Dordrecht, The Netherlands and by Stichting A Sister's Hope and Stichting [Z]aan de Wandel. These foundations had no involvement in the conduct of the study.

Abstract

We investigated the effect of trastuzumab on cardiac function in a real-world historic cohort of patients with HER2-positive metastatic breast cancer (MBC) with reduced baseline left ventricular ejection fraction (LVEF). Thirty-seven patients with HER2-positive MBC and baseline LVEF of 40% to 49% were included. Median LVEF was 46% (interquartile range [IQR] 44%-48%) and median follow-up was 18 months (IQR 9-34 months). During this period, the LVEF did not worsen in 24/37 (65%) patients, while 13/37 (35%) patients developed severe cardiotoxicity defined as LVEF <40% with median time to severe cardiotoxicity of 7 months (IQR 4-10 months) after beginning trastuzumab. Severe cardiotoxicity was reversible (defined as LVEF increase to a value <5%-points below baseline value) in 7/13 (54%) patients, partly reversible (defined as absolute LVEF increase ≥10%-points from nadir to a value

Abbreviations: ACE, angiotensin converting enzyme; ANOVA, analysis of variance; CPM, cardio-protective medications; EBC, early breast cancer; EMA, European Medicines Agency; ESMO, European Society of Medical Oncology; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer.

Some of the data have been presented at San Antonio Breast Cancer Symposium 2020, abstract 754 and published in Cancer Research as: https://cancerres.aacrjournals.org/content/81/4_Supplement/PS13-21

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *International Journal of Cancer* published by John Wiley & Sons Ltd on behalf of UICC.

>5%-points below baseline) in 3/13 (23%) patients and irreversible (defined as absolute LVEF increase <10%-points from nadir and to a value >5%-points below baseline) in 3/13 (23%) patients. Likelihood of reversibility was numerically higher in patients who received cardio-protective medications (CPM), including ACE-inhibitors, beta-blockers and angiotensine-2 inhibitors, compared to those who did not receive any CPM (71% vs 13%, $P = .091$). Sixty-five percent of patients who received trastuzumab for HER2-positive MBC did not develop severe cardiotoxicity during a median follow-up of 18 months, despite having a compromised baseline LVEF. If severe cardiotoxicity occurred, it was at least partly reversible in more than two-thirds of the cases. Risks and benefits of trastuzumab use should be balanced carefully in this vulnerable population.

KEYWORDS

cardiotoxicity, HER2-positive metastatic breast cancer, impaired baseline LVEF, trastuzumab

What's new?

While trastuzumab improves long-term survival in patients with HER2-positive metastatic breast cancer (MBC), it is contraindicated in those with reduced baseline left ventricular ejection fraction (LVEF). Here, to better understand risks to cardiac function, cardiac status was examined in a real-world cohort of trastuzumab-treated HER2-positive MBC patients with low baseline LVEF. Data show that severe cardiotoxicity was absent in 65% of patients with reduced baseline LVEF. In more than two-thirds of patients who experienced cardiotoxicity, effects on LVEF were reversed at least partly possibly by cardio-protective medications. These observations warrant further investigation of trastuzumab for patients with HER2-positive MBC with reduced baseline LVEF.

1 | INTRODUCTION

Trastuzumab has revolutionized the treatment of HER2-positive metastatic breast cancer (MBC). In conjunction with chemotherapy, objective response rates are high and long-term survival is observed in a subset of patients.[1-4] Cardiotoxicity, however, is a well-known side effect, and the reason why trastuzumab is contraindicated in patients with reduced left ventricular ejection fraction (LVEF <50%) at

TABLE 1 Difference in baseline characteristics between excluded and included patients

Clinical and treatment characteristics	Included patients n = 37 No. (%), median [IQR]	Excluded patients n = 708 No. (%), median [IQR]	*P*-value
Age (years)[a]	52 [44-62]	54 [46-61]	.457
Stage at disease presentation			.254
Metachronous MBC	30 (81)	525 (74)	
De novo MBC	7 (18)	183 (26)	
ER status[b]			.981
Positive	21 (57)	393 (56)	
Negative	16 (43)	315 (44)	
Neoadjuvant/adjuvant therapy			.327
No	16 (43)	369 (52)	
Anthracycline with trastuzumab	5 (31)	203 (29)	
Anthracycline without trastuzumab	15 (41)	99 (14)	
Other	1 (3)	37 (5)	
Duration of neoadjuvant/adjuvant trastuzumab (months)	8 [5-12]	12 [12-12]	.021
Cumulative anthracycline exposure (courses)[b]	6 [0-6]	3 [0-6]	.104

(Continues)

TABLE 1 (Continued)

Clinical and treatment characteristics	Included patients n = 37 No. (%), median [IQR]	Excluded patients n = 708 No. (%), median [IQR]	*P*-value
Radiotherapy of the breast			.339
No	16 (43)	302 (43)	
Left side	13 (35)	190 (37)	
Right side	8 (22)	159 (22)	
Previous cardiotoxicity during neoadjuvant/adjuvant treatment with trastuzumab and/or anthracycline			<.001
No	12 (32)	316 (45)	
Yes	8 (22)	23 (3)	
No neoadjuvant/adjuvant treatment	17 (46)	369 (52)	
Duration of trastuzumab administration for MBC (months)	14 [8-28]	15 [6-36]	.152
First-line treatment			.729
Trastuzumab + taxanes	16 (43)	238 (34)	
Trastuzumab + capecitabine	0 (0)	20 (3)	
Trastuzumab + vinorelbine	3 (8)	89 (13)	
Trastuzumab + pertuzumab + CT	1 (3)	20 (3)	
Trastuzumab + endocrine	7 (19)	30 (4)	
Trastuzumab monotherapy	0 (0)	15 (2)	
Other	10 (27)	296 (42)	
Median overall survival (months)	47 [30-65]	38 [20-71]	.404
LVEF (%)[a]			<.001
≥50%	0 (0)	505 (71)	
45%-49%	26 (63)	0 (0)	
40%-44%	11 (27)	0 (0)	
Cardio-protective medications use			NA
None	15 (41)	NA	
Before start of trastuzumab treatment	11 (30)	NA	
During trastuzumab treatment	11 (30)	NA	
Imaging modalities used for LVEF measurement			.299
MUGA scan	28 (76)	537 (76)	
Echocardiography	2 (5)	23 (3)	
MUGA scan + echocardiography	7 (19)	52 (7)	
BMI (kg/m^2)[a]			.780
<25	14 (38)	225 (31)	
25-30	9 (24)	193 (27)	
>30	6 (16)	68 (10)	
History of cardiac disease[a]	10 (27)	49 (7)	<.001
Diabetes mellitus[a]	3 (8)	42 (6)	.721
Hypertension[a]	18 (43)	131 (19)	.002
Hypercholesterolemia[a]	3 (8)	50 (7)	.690
Smoking[a]			.522
Current	5 (14)	70 (10)	
Former	6 (16)	60 (8)	
No	17 (46)	283 (40)	

Abbreviations: BMI, body mass index; ER, estrogen receptor; LVEF, left ventricle ejection fraction; MBC, metastatic breast cancer; MUGA, multigated acquisition scan; NA, not applicable.

[a]At start of trastuzumab treatment for MBC.

[b]Estrogen receptor positivity was defined as ≥10% positive nuclear staining based on the Dutch guideline.

baseline.[5,6] In the absence of symptomatic cardiac dysfunction, however, it is possible that the benefits of trastuzumab may outweigh the risk of severe cardiotoxicity. Two studies have investigated trastuzumab initiation in patients with baseline LVEF <50%.[7,8] An observational cohort study in 20 patients with early breast cancer (EBC) and LVEF <50% at baseline found that these patients more often developed symptomatic heart failure compared to those with baseline LVEF ≥50% (25% vs 4%).[8] In a clinical trial, 3 out of 30 patients (10%) with HER2-positive breast cancer (of which 58% were diagnosed with EBC and 42% with MBC) with an initial asymptomatic LVEF of 40% to 49% who received trastuzumab, developed LVEF decline of >10%-points from baseline or LVEF ≤35% despite being treated with cardio-protective medications (CPM) carvedilol and renin-angiotensin inhibitors.[7] Long-term continuation of trastuzumab in patients with HER2-positive MBC and compromised baseline LVEF has not been investigated extensively in these studies, as maximum follow-up was only 12 months[7] and only 10% of the included patients had MBC.[8] Additionally, the effect of trastuzumab initiation without appropriate CPM remains unknown. The aim of our historic real-world cohort study was to investigate the cardiac function of patients with HER2-positive MBC who received trastuzumab despite having baseline LVEF of 40% to 49%. In addition, the effect of CPM on the cardiac function was explored.

2 | METHODS

2.1 | Patients and data collection

Patients diagnosed with HER2-positive MBC between January 2000 and December 2014 receiving trastuzumab-based treatment for advanced disease in one of eight participating Dutch hospitals were potentially eligible for our study. As previously described,[6] patients were included if they received >1 cycle of trastuzumab, had baseline LVEF ≥40% or < 50% within 30 days before the first trastuzumab administration, follow-up LVEF measurements during trastuzumab treatment, and complete clinical and medication data in the electronic medical records. Trained investigators systematically extracted clinical characteristics and LVEF measurements from medical records.

2.2 | Primary endpoints and definitions

Median follow-up was calculated from start of trastuzumab for MBC until last LVEF measurement or last trastuzumab dose, whichever came first. Interruption of trastuzumab was defined as trastuzumab discontinuation <6 months. Definitive discontinuation of trastuzumab was defined as trastuzumab discontinuation ≥6 months.

Severe cardiotoxicity was defined as LVEF <40% as per European Society of Medical Oncology (ESMO) guidelines which also do not specify a standardized interval for LVEF monitoring in the metastatic setting.[9] Reversibility of cardiotoxicity was defined as any LVEF increase to a value <5%-points below baseline value, partial reversibility as any absolute LVEF increase ≥10%-points from nadir and to a value >5%-points below baseline value, and irreversibility as any absolute LVEF increase <10%-points from nadir and to a value >5%-points below baseline value.[10] Use of CPM, including ACE-inhibitors, beta-blockers or angiotensine-2 inhibitors, was categorized into no CPM, primary CPM defined as prescription <30 days before trastuzumab initiation or secondary CPM defined as CPM prescription >1 week after start of trastuzumab.

2.3 | Statistical analyses

Categorical variables are presented as numbers and percentages. Continuous variables with a nonnormal distribution are presented

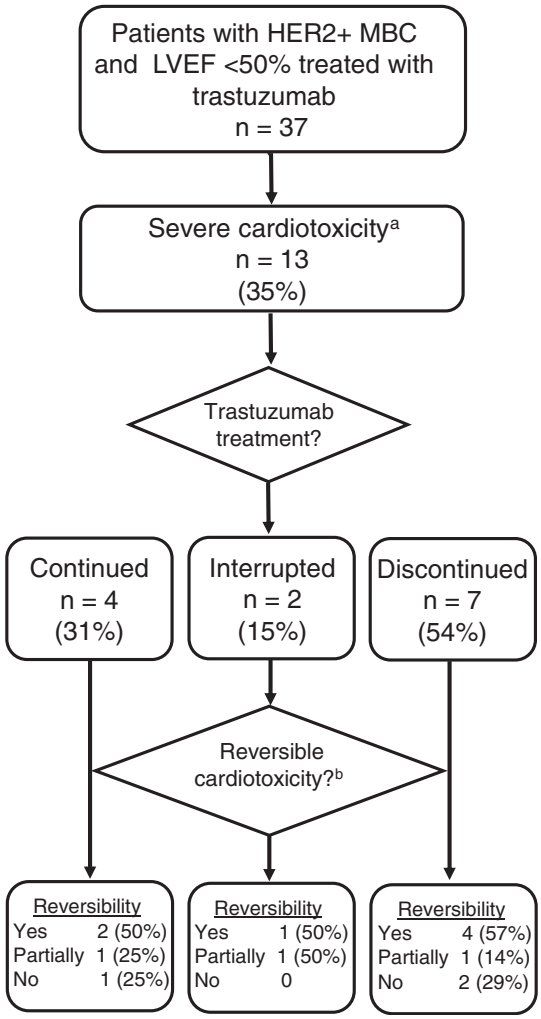

FIGURE 1 Reversibility of cardiotoxicity subdivided for the physicians' decision of trastuzumab (dis)continuation. [a]Severe cardiotoxicity was defined as absolute LVEF <40%. [b]Reversibility of severe cardiotoxicity was defined as any LVEF increase to a value <5%-points below baseline value, partially reversibility as any LVEF increase ≥10-points from nadir and to a value >5%-points below baseline value and irreversibility as an absolute LVEF increase <10%-points from nadir and to a value >5%-points below baseline value. HER2+, human epidermal growth factor receptor 2 positive; LVEF, left ventricle ejection fraction; MBC, metastatic breast cancer

as medians with interquartile range (IQR), and continuous variables with a normal distribution as means with standard deviations. Normality of continuous variables was evaluated by Shapiro-Wilk tests.

The characteristics of patients without CPM, with primary CPM and secondary CPM were compared using chi-square test for categorical variables and analysis of variance (ANOVA) test for continuous variables. Additionally, a log-rank test was used to compare the rate of reversibility between these groups. Overall survival, defined as time from diagnosis of MBC until death from any cause or last follow-up, was calculated using Kaplan-Meier survival estimates. Data analyses were performed using SPSS (version 26.0).

3 | RESULTS

3.1 | Patient characteristics

From a real-world cohort of 745 patients who received trastuzumab for HER2-positive MBC, 37 patients with a median LVEF of 46% (IQR 44%-48%) met the eligibility criteria (Figure S1). Patient and treatment characteristics are shown in Table 1. Median frequency of LVEF monitoring was 4 times annually (IQR 2-6). Included patients differed from excluded patients in shorter duration of neoadjuvant/adjuvant trastuzumab, previous cardiotoxicity during neoadjuvant/adjuvant treatment, history of cardiac disease and hypertension (Table 1).

3.2 | Severe cardiotoxicity and reversibility

Over a median follow-up of 18 months (IQR 9-34 months) and median duration of trastuzumab exposure of 14 months (IQR 8-28 months), 13 patients (35%) developed severe cardiotoxicity at a median time on trastuzumab of 7 months (IQR 4-10 months, Figure S2). Reversibility of cardiotoxicity and trastuzumab disposition is depicted in Figure 1. In 1 out of 2 patients (50%) who interrupted trastuzumab due to cardiotoxicity, trastuzumab was reintroduced for another 8 months. The development of cardiotoxicity was the cause of discontinuation in all seven patients who discontinued trastuzumab treatment. Median overall survival in all patients was 47 months (IQR 30-65 months).

3.3 | Cardiac medication

In total, 11 (30%) patients received primary CPM consisting of a beta-blocker (n = 4), ACE-inhibitor (n = 3) or both (n = 4) with 10 (27%) patients receiving secondary CPM with a beta-blocker (n = 2), ACE-inhibitors (n = 4) or both (n = 4). Reversible cardiotoxicity was observed more often in patients with CPM vs without CPM (71% vs 13% respectively, log-rank *P*-value = .091). Median nadir LVEF with primary CPM did not differ from those without CPM (LVEF 42% vs 46%, *P* = .437, Table 2). Cardiotoxicity was reversible in 3 of 4 patients (75%) receiving secondary CPM with trastuzumab interruption and for 2 of 3 patients (67%) with secondary CPM who continued trastuzumab (Figure S2). One patient receiving secondary CPM and continuing trastuzumab had partly reversible cardiotoxicity. No

TABLE 2 Clinical characteristics of patients without CPM, primary CPM or secondary CPM

Clinical and treatment characteristics	All patients (n = 37)	Patients without CPM (n = 16)	Patients with primary CPM (n = 11)	Patients with secondary CPM (n = 10)
Severe cardiotoxicity[a], n (%)	13 (35)	2 (13)	3 (27)	8 (80)
Time to cardiotoxicity, months [IQR]	7 [4-10]	8 [7-NA]	5 [3-NA]	12 [4-26]
Reversibility[b], n (%)				
No	3 (8)	1 (6)	0 (0)	2 (20)
Partial	7 (19)	0 (0)	4 (36)	1 (10)
Yes	27 (73)	2 (13)	7 (64)	8 (80)
Trastuzumab treatment, n (%)				
Continued	23 (62)	8 (03)	7 (64)	8 (80)
Interrupted	6 (16)	4 (25)	2 (18)	1 (10)
Definitive discontinued	7 (19)	3 (19)	2 (18)	2 (20)
LVEF, median % (IQR)				
Baseline	46 [44-48]	48 [46-49]	46 [43-48]	44 [41-46]
Nadir	42 [38-46]	46 [43-47]	42 [32-44]	38 [29-41]
Highest	54 [50-58]	59 [53-65]	51 [50-57]	52 [50-56]

Abbreviations: CPM, cardio-protective medications; IQR, interquartile range; LVEF, left ventricular ejection fraction.

[a]Severe cardiotoxicity was defined as LVEF <40%.

[b]Reversibility was defined as any LVEF increase to a value <5% below baseline value, partial reversibility as any absolute LVEF increase ≥10% from nadir and to a value >5% below baseline value, and irreversibility as any absolute LVEF increase <10% from nadir and to a value >5% below baseline value.

difference was observed between median nadir LVEF of patients with at least partly reversible or irreversible cardiotoxicity (LVEF 35% vs 39%, $P = .398$).

4 | DISCUSSION

The current study reports on the cardiac status of a real-world cohort of patients with HER2-positive MBC and baseline LVEF of 40% to 49% who received trastuzumab-containing systemic therapy. According to current Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommendations, trastuzumab treatment was not recommended for the 37 patients (5% of all patients with HER2-positive MBC) included in our study due to impaired LVEF.[5,11] These patients received trastuzumab over a median duration of 14 months with an overall survival of 47 months which is comparable to patients with HER2-positive MBC who received trastuzumab with LVEF ≥50% at baseline and to the excluded patients (Table 1).[6]

We showed that 65% of patients with HER2-positive MBC and an impaired baseline LVEF did not develop severe cardiotoxicity during trastuzumab treatment. Moreover, if severe cardiotoxicity occurred, it was at least partly reversible in more than two-thirds of the cases. Similar to previous reports,[7] we observed an effect of CPM on LVEF reversibility, although it was not statistically significant likely due to the underpowered small sample size. Larger, randomized studies with a longer follow-up time are warranted to further investigate whether optimal CPM can lead to trastuzumab being safely administered in this vulnerable population. For now, the risks and benefits of trastuzumab in patients with HER2-positive MBC and an impaired baseline LVEF must be balanced carefully in close collaboration with a cardiologist and in a shared-decision making context to obtain optimal patient-centered outcomes.

An important limitation of the current study is that most LVEFs (78%) were measured with the MUGA scans which have large inter-observer and intraobserver variations[12] possibly explaining why physicians are more likely to continue trastuzumab in asymptomatic patients with LVEFs below 50%. Second, our definition of cardiotoxicity reversibility remains relative as it is defined as LVEF increase to baseline value, which remains compromised in this population. Third, due to the small sample size (n = 37), our study is underpowered to assess the impact of CPM on cardiac function during trastuzumab therapy and its effect on reversibility of LVEF declines. Fourth, we were also unable to capture clinical symptomatology to further delineate the impact of trastuzumab on cardiac function in our study population. Finally, only 3 (8%) patients received dual HER2-targeted therapy including pertuzumab which is the current standard treatment for patients with HER2-positive MBC. However, as pertuzumab does not increase the risk of cardiotoxicity,[13] the results of our study are likely to be applicable to current routine clinical practice. Despite these limitations, we were able to investigate the cardiac function after initiating trastuzumab in patients with HER2-positive MBC and LVEF of 40% to 49% during a median follow-up of 18 months, which provides insight for further prospective research.

5 | CONCLUSION

Despite having an impaired baseline LVEF, 65% of patients who received trastuzumab for HER2-positive MBC did not develop severe cardiotoxicity during a median follow-up of 18 months. If severe cardiotoxicity occurs, it was at least partly reversible in about two-thirds of the cases. Risks and benefits of trastuzumab in this vulnerable population should be balanced carefully.

ACKNOWLEDGEMENTS

We thank Caroline Pauwels-Heemskerk for her assistance with identifying patients in the Netherlands Cancer Institute's tumor registry and Jorine Rigterink for her assistance with collecting data in the Netherlands Cancer Institute.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

AUTHOR CONTRIBUTIONS

Nathalie I. Bouwer, Mark-David Levin and Agnes Jager designed the study. All authors participated in the data acquisition. Nathalie I. Bouwer, Tessa G. Steenbruggen, Agnes Jager, Mark-David Levin and Gabe S. Sonke performed the data analysis and interpretation. Nathalie I. Bouwer conducted the statistical analyses. Nathalie I. Bouwer, Tessa G. Steenbruggen, Agnes Jager, Mark-David Levin and Gabe S. Sonke performed the manuscript editing. All authors have read and approved the final version of the article. The work reported in the study has been performed by the authors, unless clearly specified in the text.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed in our study involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for this comprehensive data collection was obtained from the Medical Ethics Commission of each participating hospital. Informed consent was waived by institutional review boards for our study.

ORCID

Nathalie I. Bouwer https://orcid.org/0000-0002-2048-2233

REFERENCES

1. Baselga J, Manikhas A, Cortes J, et al. Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel

in HER2-positive metastatic breast cancer. *Ann Oncol*. 2014;25:592-598.
2. Gullo G, Zuradelli M, Sclafani F, Santoro A, Crown J. Durable complete response following chemotherapy and trastuzumab for metastatic HER2-positive breast cancer. *Ann Oncol*. 2012;23:2204-2205.
3. Wong Y, Raghavendra AS, Hatzis C, et al. Long-term survival of de novo stage IV human epidermal growth receptor 2 (HER2) positive breast cancers treated with HER2-targeted therapy. *Oncologist*. 2019;24:313-318.
4. Steenbruggen TG, Bouwer NI, Smorenburg CH, et al. Radiological complete remission in HER2-positive metastatic breast cancer patients: what to do with trastuzumab? *Breast Cancer Res Treat*. 2019;178:597-605.
5. *Herceptin* [package insert]. San Francisco, CA: Genentech, Inc.
6. Bouwer NI, Steenbruggen TG, van Rosmalen J, et al. Cardiotoxicity during long-term trastuzumab use in patients with HER2-positive metastatic breast cancer: who needs cardiac monitoring? *Breast Cancer Res Treat*. 2021;186:851-862.
7. Lynce F, Barac A, Geng X, et al. Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. *Breast Cancer Res Treat*. 2019;175:595-603.
8. Nowsheen S, Aziz K, Park JY, et al. Trastuzumab in female breast cancer patients with reduced left ventricular ejection fraction. *J Am Heart Assoc*. 2018;7:e008637.
9. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31:171-190.
10. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2014;15:1063-1093.
11. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783-792.
12. Skrypniuk JV, Bailey D, Cosgriff PS, et al. UK audit of left ventricular ejection fraction estimation from equilibrium ECG gated blood pool images. *Nucl Med Commun*. 2005;26:205-215.
13. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Bouwer NI, Steenbruggen TG, Rier HN, et al. The effect of trastuzumab on cardiac function in patients with HER2-positive metastatic breast cancer and reduced baseline left ventricular ejection fraction. *Int J Cancer*. 2022;151(4):616-622. doi:10.1002/ijc.34024