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ORIGINAL REPORT

Prognosis of Women With Metastatic Breast Cancer by *HER2* Status and Trastuzumab Treatment: An Institutional-Based Review

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ABSTRACT

Purpose
The purpose of this study was to determine whether trastuzumab improves prognosis of women with metastatic human epidermal growth factor receptor 2 (*HER2*)/*neu* –positive breast cancer beyond that of women with *HER2/neu*-negative disease.

Patients and Methods
Two thousand ninety-one women with metastatic breast cancer diagnosed from 1991 to 2007, with known *HER2/neu* status and who had not received trastuzumab in the adjuvant setting, were identified. Disease was classified into the following three groups: *HER2/neu* negative, *HER2/neu* positive without first-line trastuzumab treatment, and *HER2/neu* positive with first-line trastuzumab treatment. Overall survival (OS) was estimated using the Kaplan-Meier product-limit method and compared between groups with the log-rank test. Cox proportional hazards models were used to determine associations between OS and *HER2/neu* status after controlling for patient characteristics.

Results
One hundred eighteen patients (5.6%) had *HER2/neu*-positive disease without trastuzumab treatment, 191 (9.1%) had *HER2/neu*-positive disease and received trastuzumab treatment, and 1,782 (85.3%) had *HER2/neu*-negative disease. Median-follow-up was 16.9 months. One-year survival rates among patients with *HER2/neu*-negative disease, *HER2/neu*-positive disease and trastuzumab treatment, and *HER2/neu*-positive disease and no trastuzumab treatment were 75.1% (95% CI, 72.9% to 77.2%), 86.6% (95% CI, 80.8% to 90.8%), and 70.2% (95% CI, 60.3% to 78.1%), respectively. In a multivariable model, women with *HER2/neu*-positive disease who received trastuzumab had a 44% reduction in the risk of death compared with women with *HER2/neu*-negative disease (hazard ratio [HR] = 0.56; 95% CI, 0.45 to 0.69; $P < .0001$). This HR varied with time and was significant for the first 24 months and not significant after 24 months.

Conclusion
Our results show that women with *HER2/neu*-positive disease who received trastuzumab had improved prognosis compared with women with *HER2/neu*-negative disease.

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INTRODUCTION

Human epidermal growth factor receptor 2 (*HER2*)/*neu* is a growth factor receptor gene[1] that is amplified in approximately 20% to 25% of breast cancers with its corresponding encoded protein also being detected at abnormally high levels in these malignant cells.[2,3] Its main function is to mediate growth, differentiation, and survival of cells, thereby promoting more aggressive behavior of tumors. Thus, studies have shown that women whose tumors exhibit either amplification of the *HER2/neu* gene or overexpression of its encoded protein have a more aggressive form of breast cancer that is associated with significantly shortened disease-free and overall survival (OS) compared with women whose tumors do not over express *HER2/neu*.[2-4]

Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of the protein encoded by the *HER2/neu* gene. In 1998, after the demonstration of significant survival benefit, trastuzumab was approved by the US Food and Drug Administration as first-line treatment in combination with paclitaxel for women with metastatic *HER2/neu*-positive breast cancer.[5] After these findings, large randomized clinical trials were conducted to demonstrate the efficacy of trastuzumab in the adjuvant setting.[6-8]

The results of these trials indicated that trastuzumab significantly improved disease-free survival and OS of women with early-stage *HER2/neu*-positive breast tumors by as much as 50%. Furthermore, despite the high costs associated with incorporating trastuzumab into breast cancer treatment regimens, analyses conducted both in the United States and internationally have demonstrated the cost effectiveness of trastuzumab-based regimens both in the adjuvant[9,10] and metastatic settings.[11]

There is no doubt that the incorporation of trastuzumab has significantly altered the natural history of *HER2/neu*-positive breast tumors, converting them from a historically aggressive tumor subtype to one with improved prognostic outcomes. However, the question still remained as to whether the use of trastuzumab has been able to equalize prognostic outcomes of women with *HER2/neu*-positive breast cancer to those of women with *HER2/neu*-negative disease, a cohort historically considered to be associated with better prognosis. Thus, the goal of this retrospective study was to compare the prognosis of women with metastatic *HER2/neu*-positive breast cancer with and without the addition of trastuzumab with the prognosis of women with *HER2/neu*-negative disease.

PATIENTS AND METHODS

Patient Population

Using a prospectively maintained database at the Breast Medical Oncology Department of The University of Texas M. D. Anderson Cancer Center, we retrospectively identified patients with metastatic breast cancer with known *HER2/neu* status. Patients who were male, had more than one primary cancer, received trastuzumab in the adjuvant setting, and had only locoregional metastases with no evidence of distant metastases were excluded. Patients who had *HER2/neu*-positive tumors were excluded if administration of trastuzumab was started subsequent to first-line treatment for metastatic disease. To be classified as having received trastuzumab as part of first-line treatment, patients with *HER2/neu*-positive disease had to have received trastuzumab within 6 weeks of diagnosis of first distant metastases. Variables recorded for analyses included patient demographics, tumor characteristics, site of metastases, and presence or absence of first-line trastuzumab administration. After obtaining institutional review board approval, all medical charts were used to cross-check the accuracy of the information obtained from the database.

Staging and Pathology Review

Staging of primary tumors was based on the most recent edition of the American Joint Committee on Cancer criteria (sixth edition, 2003).[12] Grading of tumors and histologic classification were based on the modified Black's nuclear grading system[13] and WHO criteria,[14] respectively. *HER2/neu* status of tumors was determined using either an immunohistochemistry (IHC) method and/or a gene amplification method using a fluorescent in situ hybridization (FISH) technique. Tumors were classified as *HER2/neu* positive if they had 3+ staining on IHC and/or gene amplification by FISH. Tumors were classified as *HER2/neu* negative if they did not exhibit either staining by IHC and/or gene amplification by FISH. Tumors exhibiting 2+ staining by IHC that was not accompanied by confirmatory FISH results were excluded from the analyses.

Statistical Analyses

The cohort was divided into the following three groups according to *HER2/neu* status and trastuzumab treatment: patients with *HER2/neu*-negative disease, patients with *HER2/neu*-positive disease who did not receive trastuzumab treatment, and patients with *HER2/neu*-positive disease who received first-line trastuzumab treatment. Patient characteristics were tabulated by *HER2/neu* status and by trastuzumab treatment. Median follow-up time was calculated as the median observation time for the whole cohort. OS was defined as the time from the date of first distant metastases to the date of death or last follow-up.

Survival estimates were obtained using the Kaplan-Meier product-limit method and compared across groups using the log-rank test. Cox proportional hazards models were then used to determine associations between OS and *HER2/neu* status after adjusting for age and year of metastasis diagnosis, site of first metastasis, grade, stage of primary disease, and hormone receptor status. Variables chosen to be included in the Cox proportional hazards model were based on their clinical significance regardless of statistical significance on univariate analysis. For the purposes of this analysis, hormone receptor status was considered as one variable, with positive status indicating estrogen receptor– and/or progesterone receptor–positive tumors and negative status indicating tumors that did not stain for either estrogen or progesterone receptors. Similarly, for grade of tumors, grades 1 and 2 were collapsed into one category. We found that the term comparing women with *HER2/neu*-positive disease who received trastuzumab compared with those with *HER2/neu*-negative disease violated the proportional hazards assumption of the Cox model according to the Grambsch-Therneau test[15] ($P = .002$). After inspection of the hazard, we addressed the issue of nonproportion by rerunning the multivariable model with the time axis partitioned at 24 months. Two models were fit; the first censored all patients still at risk at 24 months, and the second considered only patients still at risk after 24 months. The proportional hazards assumption was satisfied over these two separate time periods.

On the basis of a Cox proportional hazards model unadjusted for other patient characteristics and a two-sided test at the $P = .05$ significance level and considering the event rates and observed unadjusted hazard ratios (HRs) comparing the treatment groups, we had a 60% power to detect a difference between the patients with *HER2/neu*-positive disease who did not receive trastuzumab and the patients with *HER2/neu*-positive disease who did receive first-line trastuzumab and a 19% power to detect a difference between the patients with *HER2/neu*-positive disease who received first-line trastuzumab and patients with *HER2/neu*-negative disease. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC) and R 2.4.1 (R Core Development Team; http://www.r-project.org/). All P values were two-sided, and $P < .05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Table 1 lists patient characteristics by *HER2/neu* status and trastuzumab treatment. The final analyses included 2,091 eligible patients diagnosed with breast cancer between 1991 and 2007. Fourteen percent of patients were diagnosed before 2000, 25% were diagnosed between 2000 and 2001, and 61% were diagnosed between 2002 and 2007. One thousand seven hundred eighty-two patients (85.2%) had *HER2/neu*-negative disease, 191 (9.1%) had *HER2/neu*-positive disease and received first-line trastuzumab for metastatic breast cancer, and 118 (5.6%) had *HER2/neu*-positive disease and did not receive trastuzumab. Median age was similar among the three subgroups, ranging from 48 to 52 years. Among patients who had *HER2/neu*-positive disease who received first-line trastuzumab, median cumulative time on trastuzumab was 11.6 months (range, 0.23 to 68.2 months).

Survival Estimates and Multivariable Model

At the time of this analysis, 1,137 patients (54.4%) have died, of whom 112 had *HER2/neu*-positive disease and received first-line trastuzumab, 72 had *HER2/neu*-positive disease and did not receive trastuzumab, and 953 had *HER2/neu*-negative disease. Median follow-up

Table 1. Patient Demographics and Clinical Characteristics According to *HER2/neu* Status and Trastuzumab Treatment

Characteristic	*HER2/neu*-Positive Patients Who Received Trastuzumab (n = 191)		*HER2/neu*-Positive Patients Who Did Not Receive Trastuzumab (n = 118)		*HER2/neu*-Negative Patients (n = 1,782)	
	No.	%	No.	%	No.	%
Diagnosis year						
Median	2002		2002		2002	
Range	1998-2006		1992-2006		1991-2007	
Age at distant metastases, years						
Median	48		52		51	
Range	25-84		21-86		22-91	
Menopausal status						
Premenopausal	94	49.2	45	39.5	813	46.4
Postmenopausal	97	50.8	69	60.5	941	53.6
Race						
Black	17	8.9	17	14.4	237	13.3
Hispanic	18	9.4	10	8.5	162	9.1
Other	17	8.9	8	6.8	90	5.1
White	139	72.8	83	70.3	1,293	72.6
Histology						
Other	13	6.9	6	5.2	273	15.5
Ductal	175	93.1	110	94.8	1,488	84.5
Stage						
I	22	11.6	14	11.9	257	14.4
II	54	28.4	39	33.1	626	35.2
III	69	36.3	39	33.1	500	28.1
IV	45	23.7	26	22.0	397	22.3
Nuclear grade						
1 or 2	30	16.6	29	26.9	574	34.5
3	151	83.4	79	73.1	1,089	65.5
Surgery type						
BCS	44	28.0	33	31.7	478	31.6
Mastectomy	113	72.0	71	68.3	1,037	68.4
HR status						
Negative	95	51.6	32	29.9	609	36.0
Positive	89	48.4	75	70.1	1,084	64.0
LVI						
Negative	78	49.7	59	54.1	847	55.4
Positive	79	50.3	50	45.9	683	44.6
First site of metastases						
Multiple	23	12.0	16	13.6	255	14.3
Visceral only	67	35.1	36	30.5	442	24.8
Visceral and bone	49	25.7	18	15.3	270	15.2
Bone only	30	15.7	27	22.9	524	29.4
Brain only	3	1.6	5	4.2	42	2.4
Other	19	9.9	16	13.6	248	13.9

Abbreviations: BCS, breast-conserving surgery; HR, hormone receptor; LVI, lymphovascular invasion.

time for the whole cohort was 16.9 months (range, 0 to 176 months). Only 295 patients (14%) were diagnosed before 2000, of whom 73 (25%) had follow-up of less than 1 year. Among patients diagnosed between 2002 and 2007, 57% and 71% of patients who were alive and dead at the time of analysis, respectively, had less than 1 year of follow-up.

Table 2 lists 1-, 2-, and 5-year survival estimates by patient characteristics. Median survival for the whole cohort was 28.6 months (95% CI, 26.5 to 30.5 months). One-year survival rates among patients with *HER2/neu*-negative disease, *HER2/neu*-positive disease and first-line trastuzumab treatment, and *HER2/neu*-positive disease and no trastuzumab were 75.1% (95% CI, 72.9% to 77.2%), 86.6% (95% CI, 80.8% to 90.8%), and 70.2% (95% CI, 60.3% to 78.1%), respectively, with differences among the three groups being statistically significant ($P = .028$; Fig 1). This represented an absolute increase in 1-year survival of 11.5% when comparing patients with *HER2/neu*-positive disease who had received trastuzumab with patients with *HER2/neu*-negative disease. Similarly, at 2 years, an absolute difference of 8.3% was observed. Five-year survival estimates were similar among the patients with *HER2/neu*-negative disease and those with *HER2/neu*-positive disease who had received trastuzumab.

Figure 2 shows the survival curves stratified by hormone receptor status. Among women with hormone receptor–negative

Table 2. Overall Survival Estimates at 1, 2, and 5 Years

Characteristic	1-Year Overall Survival		2-Year Overall Survival		5-Year Overall Survival		
	%	95% CI	%	95% CI	%	95% CI	*P*
Total	76.00	74 to 77.9	55.00	52.5 to 57.4	23.70	21 to 26.4	
HER2							.753
Negative	75.10	72.9 to 77.2	54.90	52.2 to 57.5	24.50	21.6 to 27.5	
Positive	80.70	75.7 to 84.8	55.60	49.3 to 61.4	19.70	13.6 to 26.5	
Treatment group							.028
Trastuzumab	86.60	80.8 to 90.8	63.20	55.4 to 69.9	23.40	15.4 to 32.5	
HER2 negative	75.10	72.9 to 77.2	54.90	52.2 to 57.5	24.50	21.6 to 27.5	
No trastuzumab	70.20	60.3 to 78.1	41.30	30.9 to 51.4	13.20	5.9 to 23.4	
Subset							< .0001
HER2 positive/HR positive and received trastuzumab	89.50	80.8 to 94.4	68.90	57.4 to 77.8	29.70	17.5 to 42.9	
HER2 positive/HR positive and no trastuzumab	70.20	57.6 to 79.7	44.70	31.9 to 56.6	14.50	5.7 to 27.0	
HER2 positive/HR negative and received trastuzumab	83.90	74.8 to 90.0	58.20	47.1 to 67.7	17.70	7.9 to 30.7	
HER2 positive/HR negative and no trastuzumab	62.10	40.6 to 77.7	23.80	8.0 to 44.3	8.90	0.8 to 30.3	
HER2 negative/HR positive	84.90	82.5 to 87.0	68.50	65.3 to 71.5	31.30	27.2 to 35.4	
HER2 negative/HR negative	56.00	51.5 to 60.0	27.50	23.4 to 31.8	7.90	5.0 to 11.7	
Age at metastases, years							.531
< 50	76.50	73.5 to 79.3	55.30	51.6 to 58.8	25.10	21.2 to 29.2	
≥ 50	75.50	72.8 to 78.1	54.70	51.4 to 57.9	22.40	18.9 to 26.2	
Menopausal status							.354
Premenopausal	76.80	73.8 to 79.5	55.50	51.8 to 59.1	24.10	20.2 to 28.2	
Postmenopausal	75.30	72.5 to 77.8	54.60	51.2 to 57.8	24.10	20.2 to 28.2	
Race							< .0001
Black	63.30	56.8 to 69	39.40	32.6 to 46.1	13.40	7.9 to 20.4	
Hispanic	75.00	67.6 to 81	48.80	40.2 to 56.9	23.30	13.8 to 34.3	
Other	85.40	76.9 to 90.9	71.10	60.2 to 79.5	34.30	21.4 to 47.6	
White	77.70	75.4 to 79.8	57.30	54.4 to 60	24.70	21.7 to 27.9	
Histology							.105
Other	80.50	75.1 to 84.8	60.30	53.5 to 66.5	26.20	18.6 to 34.4	
Ductal	75.30	73.1 to 77.3	54.00	51.4 to 56.6	23.40	20.6 to 26.3	
Stage							< .0001
I	79.80	74.4 to 84.2	58.30	51.5 to 64.4	29.00	21.6 to 36.8	
II	73.20	69.6 to 76.5	50.80	46.5 to 55	21.90	17.7 to 26.5	
III	69.70	65.5 to 73.4	47.40	42.7 to 51.9	15.80	11 to 21.4	
IV	84.80	81.1 to 87.8	67.70	62.9 to 72	31.50	25.8 to 37.3	
Nuclear grade							< .0001
1 or 2	90.40	87.7 to 92.5	73.40	69.2 to 77.1	39.50	33.7 to 45.2	
3	68.50	65.8 to 71.1	45.90	42.8 to 48.9	16.50	13.7 to 19.6	
Surgery type							.183
BCS	74.50	70.4 to 78.1	50.40	45.5 to 55.1	21.80	16.8 to 27.2	
Mastectomy	76.70	74.1 to 79.1	55.40	52.2 to 58.6	24.20	20.7 to 27.9	
No. of nodes removed							.036
≤ 10	70.90	66.1 to 75.1	48.50	43.1 to 53.7	23.20	17.7 to 29.1	
> 10	77.60	74.9 to 79.9	55.70	52.4 to 58.8	23.70	20.2 to 27.4	
HR status							< .0001
Negative	60.30	56.3 to 64	32.30	28.4 to 36.2	9.70	6.7 to 13.4	
Positive	84.40	82.1 to 86.4	67.10	64.1 to 69.9	30.00	26.2 to 33.8	
LVI							.018
Negative	77.30	74.4 to 80	57.00	53.4 to 60.5	24.40	20.5 to 28.4	
Positive	73.90	70.5 to 76.9	50.60	46.7 to 54.5	22.60	18.5 to 27	
First site of metastases							< .0001
Multiple	55.00	48.6 to 61	31.00	24.7 to 37.6	12.70	7.5 to 19.3	
Visceral only	76.40	72.4 to 79.9	53.90	49.1 to 58.4	22.50	17.8 to 27.6	
Visceral and bone	72.20	66.8 to 76.9	48.90	42.7 to 54.7	12.60	7.6 to 18.9	
Bone only	89.10	86.2 to 91.5	74.40	70.2 to 78.1	36.70	30.9 to 42.4	
Brain only	45.90	29.9 to 60.5	33.40	18.7 to 48.8	15.00	4.4 to 31.6	
Other	77.00	71.2 to 81.9	48.70	41.6 to 55.4	23.50	16.2 to 31.6	

Abbreviations: HR, hormone receptor; BCS, breast-conserving surgery; LVI, lymphovascular invasion.

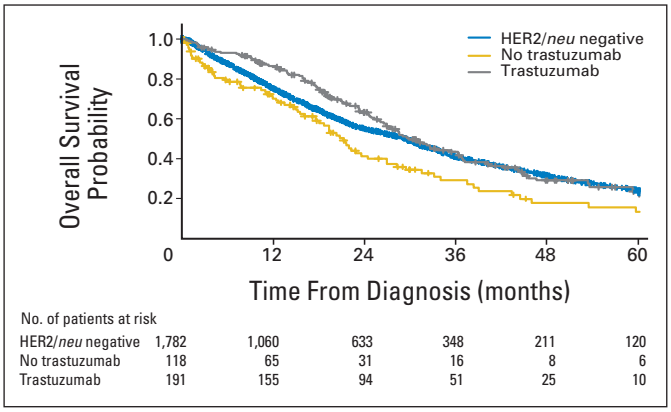

Fig 1. Overall survival by trastuzumab treatment group.

Table 3. Multivariable Model

Variable	Hazard Ratio	95% CI	*P*
No trastuzumab *v HER2* negative	1.23	0.95 to 1.60	.123
Trastuzumab *v HER2* negative	0.56	0.45 to 0.69	< .0001
HR positive *v* HR negative	0.53	0.46 to 0.61	< .0001
Age at metastasis (continuous)	1.01	1.00 to 1.01	.052
Diagnosis year (continuous)	1.05	1.01 to 1.08	.004
Grade 3 *v* 1/2	1.72	1.47 to 2.01	< .0001
Stage			
II *v* I	1.23	1.01 to 1.51	.042
III *v* I	1.53	1.24 to 1.88	< .0001
IV *v* I	0.83	0.66 to 1.03	.095
Visceral and other metastases *v* bone only	1.46	1.24 to 1.72	< .0001
Multiple metastases and brain *v* bone only	2.62	2.14 to 3.20	< .0001

Abbreviation: HR, hormone receptor.

breast cancer, patients with *HER2/neu*-positive breast cancer treated with trastuzumab had superior survival when compared with women with triple-negative breast cancer or with women with *HER2/neu*-positive breast cancer who did not receive trastuzumab ($P < .001$). Among women with hormone receptor–positive breast cancer, a different pattern was seen; women with *HER2/neu*-negative breast cancer and women with *HER2/neu*-positive disease treated with trastuzumab had superior survival compared with women with *HER2/neu*-positive disease who did not receive trastuzumab ($P < .001$). One-, 2-, and 5-year survival estimates for each group are listed in Table 2.

After adjusting for patient characteristics, patients with *HER2/neu*-positive disease who did not receive trastuzumab had a nonsignificant increased hazard of death compared with patients with *HER2/neu*-negative disease (HR = 1.23; 95% CI, 0.95 to 1.60; $P = .123$; Table 3). Compared with patients with *HER2/neu*-negative disease, patients with *HER2/neu*-positive disease who received first-line trastuzumab treatment had a significantly decreased hazard of death (HR = 0.56; 95% CI, 0.45 to 0.69; $P < .0001$). As a result of nonproportionality of the Cox models, the models were rerun partitioning the time axis at 24 months. These models showed that the decreased hazard of death among women with *HER2/neu*-positive disease who received trastuzumab compared with those with *HER2/neu*-negative disease was significant during the first 24 months (HR = 0.45; 95% CI, 0.34 to 0.59; $P < .0001$) and not significant thereafter (HR = 0.91; 95% CI, 0.64 to 1.28; $P = .58$).

DISCUSSION

To our knowledge, this is the largest single-institution study to compare survival differences among women with stage IV breast cancer based on *HER2/neu* status and trastuzumab treatment. Significant differences in unadjusted OS estimates of 11.5% and 8.3% were observed in the first and second year after diagnosis, respectively, of stage IV disease favoring patients with *HER2/neu*-positive disease who did receive trastuzumab compared with patients with *HER2/neu*-negative disease. In the multivariable model, after adjusting for clinically relevant patient and tumor characteristics, women with *HER2/neu*-positive disease who received trastuzumab had a 44% decreased risk of death compared with women with *HER2/neu*-negative disease. As expected, the group with the poorest prognosis was women who had *HER2/neu*-positive disease who did not receive trastuzumab.

Our study indicated that by 5 years of follow-up, survival outcomes were similar between women with *HER2/neu*-positive disease who received trastuzumab and those with *HER2/neu*-negative disease. However, these results must be interpreted with caution because the number of patients at risk decreased substantially after 3 years, making it difficult to detect meaningful differences. Moreover, not all patients who received trastuzumab as first-line treatment for metastatic disease received it in subsequent lines of treatment.

Over the last decade, research has focused on characterizing various subtypes of breast cancer in an effort to better define prognostic outcomes and individualize therapeutic strategies to achieve the

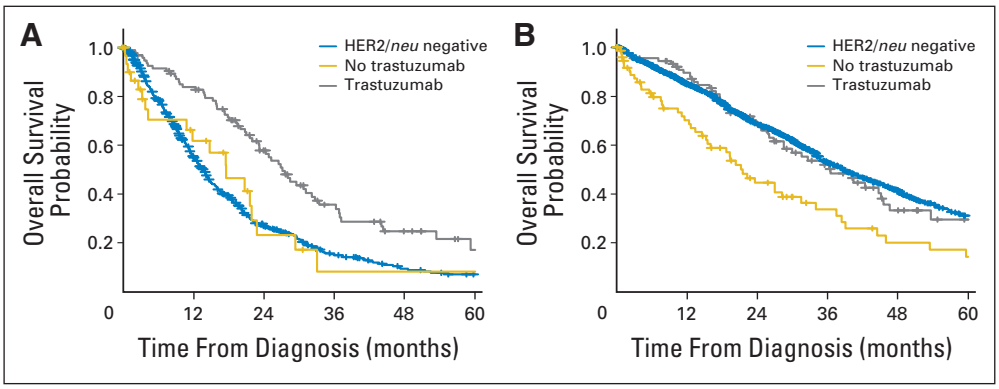

Fig 2. Overall survival stratified by trastuzumab treatment group and according to hormone receptor (HR) status: (A) HR-negative disease and (B) HR-positive disease.

best survival outcomes. Gene expression profiling has identified up to six molecular subtypes that are based on both hormone receptor and *HER2/neu* status of tumors.[16] In a cohort of 49 women with locally advanced breast cancer, Sørlie et al[17] reported that OS and relapse-free survival were the poorest for patients with the basal-like and *HER2/neu*-positive breast tumor subtypes compared with women with luminal breast tumor subtypes. Among women with luminal breast tumor subtypes, those with luminal A breast tumors (estrogen receptor positive– and/or progesterone receptor positive– and *HER2/neu*-negative tumors) had better survival outcomes compared with those with luminal B breast tumors (estrogen receptor positive– and/or progesterone receptor positive– and *HER2/neu*-positive tumors). These results have since been replicated using other data sets,[18] suggesting that different breast tumor subtypes may be distinct biologic entities. However, in these cohorts, patients did not receive trastuzumab as part of their treatment regimens. On the basis of the results of our study, we hypothesize that prognostic outcomes typically attached to these subtypes may have changed. It is possible that women with luminal A, B, and *HER2/neu* breast tumor subtypes in the trastuzumab era have similar prognostic outcomes that are far superior to women who have basal-like tumors, as shown in Figure 2 and Table 2. However, speculation is based on results derived from retrospective data set analyses involving women with metastatic breast cancer and will need to be confirmed in a prospective fashion.

Although the prognosis of the different breast tumor subtypes may be shifted by the use of trastuzumab, hormone receptor status remains an important prognostic factor. After controlling for *HER2/neu* status, trastuzumab treatment, and other patient and disease characteristics, women with hormone receptor–positive disease had a decreased risk of death compared with women with hormone receptor–negative disease (HR = 0.53; 95% CI, 0.46 to 0.61; $P < .001$). This finding highlights the fact that even in the presence of trastuzumab, hormone receptor status is still an important prognostic factor among women with stage IV disease.

The association between the incidence of CNS metastases and *HER2/neu* status of breast tumors has been the focus of several studies. In a large retrospective study of more than 9,000 patients with nonmetastatic breast cancer who were enrolled onto a number of prospective clinical trials conducted by the International Breast Cancer Study Group, none of whom had received trastuzumab, Pestalozzi et al[19] reported a cumulative incidence for the development of CNS metastases of 6.8% among women with *HER2/neu*-positive disease compared with 3.5% among women with *HER2/neu*-negative disease ($P < .001$). Several retrospective studies have also reported high rates of CNS metastases among women with *HER2/neu*-positive disease receiving trastuzumab, ranging from 25% to 43%, rates that are much higher than historical controls.[20-23] Because we selected women based on known *HER2/neu* status and excluded patients with unknown *HER2/neu* status, we were unable to define the true incidence of brain metastases among the different groups in our cohort. However, our group has previously looked at the prognostic outcomes of women with breast cancer and CNS metastases based on both *HER2/neu* status and trastuzumab treatment.[24] We reported that women with *HER2/neu*-negative disease had both shorter times to development of CNS metastases (HR = 1.50; 95% CI, 1.15 to 1.95; $P = .003$) and an increased risk of death after the development of CNS metastases (HR = 1.66; 95% CI, 1.31 to 2.12; $P < .0001$) compared with women with *HER2/neu*-positive disease who had received trastuzumab as part of their treatment regimen. Thus, regardless of the effect of trastuzumab on incidence of CNS metastases, a question that will be answered with longer follow-up of prospective trials, evidence indicates that trastuzumab has also improved outcomes of women with *HER2/neu*-positive breast cancer and CNS metastases beyond that of a comparative group of women with *HER2/neu*-negative disease.

We acknowledge that the study is limited by a number of biases inherent with the retrospective nature of the study design. First, among patients with *HER2/neu*-positive disease who received trastuzumab as part of first-line treatment for metastatic disease, the receipt of treatment and duration of treatment with trastuzumab varied according to physician preference. Second, the range of year of diagnosis for women with *HER2/neu*-positive disease who did not receive trastuzumab included much earlier years compared with the other two comparative groups, a fact that reflects change in practice patterns after US Food and Drug Administration approval of trastuzumab. One could argue that earlier year of diagnosis may unfairly bias the results of this group toward a more unfavorable outcome. However, our multivariable models were adjusted for year of diagnosis. Regardless of these limitations, the study design stands on the strength of its comparative groups—a design unlikely to be replicated in future prospective clinical trials. Moreover, the results obtained are consistent with the known efficacy of trastuzumab among women with *HER2/neu*-positive disease.

In conclusion, the results of our study provide evidence of the fact that trastuzumab has not only beneficially altered the natural history of women with *HER2/neu*-positive breast tumors, but also has improved their prognostic outcomes beyond those of women with *HER2/neu*-negative disease. When we repeated our multivariable model using patients with *HER2/neu*-positive disease who did not received trastuzumab as the reference group (data not shown), as expected, we found that patients with *HER2/neu*-positive disease who received first-line trastuzumab had a significantly decreased risk of death (HR = 0.45; 95% CI, 0.33 to 0.63; $P < .0001$), emphasizing the point that trastuzumab is now the standard of care among patients with *HER2/neu*-positive disease. Several questions still remain that need to be answered. First, the duration of trastuzumab treatment in both the adjuvant and metastatic setting is a territory that is still being explored, and we await the results of clinical trials that are attempting to answer this question. Second, it will be important for trastuzumab efficacy trials to report long-term follow-up so that the effect of trastuzumab on the incidence of CNS metastases can be determined. Regardless, the introduction of trastuzumab into the treatment paradigm of women with *HER2/neu*-positive breast cancer is probably the most important breakthrough in the management of breast cancer seen this decade, and with the advent of other forms of targeted therapy currently under study, we are bound to see even more improvement in prognostic outcomes of women with breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Coussens L, Yang-Feng TL, Liao YC, et al: Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 230:1132-1139, 1985

2. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-182, 1987

3. Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707-712, 1989

4. Seshadri R, Firgaira FA, Horsfall DJ, et al: Clinical significance of HER-2/neu oncogene amplification in primary breast cancer: The South Australian Breast Cancer Study Group. J Clin Oncol 11: 1936-1942, 1993

5. 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 344:783-792, 2001

6. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353: 1673-1684, 2005

7. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672, 2005

8. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al: Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354:809-820, 2006

9. Liberato NL, Marchetti M, Barosi G: Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 25:625-633, 2007

10. Garrison LP Jr, Lubeck D, Lalla D, et al: Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. Cancer 110:489-498, 2007

11. Lidgren M, Wilking N, Jonsson B, et al: Cost-effectiveness of HER2 testing and trastuzumab therapy for metastatic breast cancer. Acta Oncol 47:1018-1028, 2008

12. Singletary SE, Allred C, Ashley P, et al: Staging system for breast cancer: Revisions for the 6th edition of the AJCC Cancer Staging Manual. Surg Clin North Am 83:803-819, 2003

13. Black MM, Speer FD: Nuclear structure in cancer tissues. Surg Gynecol Obstet 105:97-102, 1957

14. The World Health Organization: The World Health Organization Histological Typing of Breast Tumors–Second Edition. Am J Clin Pathol 78:806-816, 1982

15. Grambsch P, Therneau T: Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515-526, 1994

16. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumors. Nature 406:747-752, 2000

17. Sørlie T, Perou CM, Tibshirani R, et al: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869-10874, 2001

18. Sorlie T, Tibshirani R, Parker J, et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 100:8418-8423, 2003

19. Pestalozzi BC, Zahrieh D, Price KN, et al: Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol 17:935-944, 2006

20. Bendell JC, Domchek SM, Burstein HJ, et al: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 97:2972-2977, 2003

21. Weitzen R, Zach L, Kaufman B, et al: High incidence of brain metastases in patients on trastuzumab for advanced cancer. Proc Am Soc Clin Oncol 21:316, 2002 (abstr 1936)

22. Wardley AM, Danson S, Clayton AJ, et al: High incidence of brain metastases in patients treated with trastuzumab for metastatic breast cancer at a large cancer center. Proc AM Soc Clin Oncol 21:61a, 2002 (abstr 241)

23. Heinrich B, Brudler O, Siekiera W, et al: Development of brain metastasis in metastatic breast cancer responding to treatment with trastuzumab. Proc Am Soc Clin Oncol 22:37, 2003 (abstr 147)

24. Dawood S, Broglio K, Esteva FJ, et al: Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol 19: 1242-1248, 2008

