Efficacy and Safety of Trastuzumab as a Single Agent in First-Line Treatment of *HER2*-Overexpressing Metastatic Breast Cancer

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Purpose: **To evaluate the efficacy and safety of first-line, single-agent trastuzumab in women with *HER2*-overexpressing metastatic breast cancer.**

Patients and Methods: **One hundred fourteen women with *HER2*-overexpressing metastatic breast cancer were randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly.**

Results: **The objective response rate was 26% (95% confidence interval [CI], 18.2% to 34.4%), with seven complete and 23 partial responses. Response rates in 111 assessable patients with 3+ and 2+ *HER2* overexpression by immunohistochemistry (IHC) were 35% (95% CI, 24.4% to 44.7%) and none (95% CI, 0% to 15.5%), respectively. The clinical benefit rates in assessable patients with 3+ and 2+ *HER2* overexpression were 48% and 7%, respectively. The response rates in 108 assessable patients with and without *HER2* gene amplification by fluorescence in situ hybridization (FISH) analysis were 34% (95% CI, 23.9% to 45.7%) and 7% (95% CI, 0.8% to 22.8%), respectively. Seventeen (57%) of 30 patients with an objective response and 22 (51%) of 43 patients with clinical benefit had not experienced disease progression at follow-up at 12 months or later. The most common treatment-related adverse events were chills (25% of patients), asthenia (23%), fever (22%), pain (18%), and nausea (14%). Cardiac dysfunction occurred in two patients (2%); both had histories of cardiac disease and did not require additional intervention after discontinuation of trastuzumab. There was no clear evidence of a dose-response relationship for response, survival, or adverse events.**

Conclusion: **Single-agent trastuzumab is active and well tolerated as first-line treatment of women with metastatic breast cancer with *HER2* 3+ overexpression by IHC or gene amplification by FISH.**

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THE HUMAN EPIDERMAL growth factor receptor 2 (*HER2*) gene encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) and is amplified in approximately 25% to 30% of human breast cancers.[1,2] When amplified, the gene produces high levels of *HER2* cell-surface receptor expression.[3] Patients whose tumors demonstrate *HER2* gene amplification and protein overexpression have an inferior prognosis manifested by shorter disease-free and overall survival.[2-4]

Trastuzumab is a recombinant monoclonal antibody that was developed to recognize $p185^{HER2}$. The antibody was humanized to minimize the immunogenicity associated with murine monoclonal antibodies and maximize the potential for recruiting endogenous immune effector cells.[5] The results of a large phase II trial[6] indicate that trastuzumab monotherapy is active against *HER2*-overexpressing breast cancer in women who have been previously treated with chemotherapy for metastatic disease. Additionally, the results of a phase III trial[7] indicate that trastuzumab significantly enhances the activity of first-line chemotherapy and provides a survival advantage to women with *HER2*-overexpressing breast cancer. We conducted a randomized, single-blind, multicenter study to evaluate the activity and safety of two dose levels of trastuzumab as a first-line treatment in women who did not wish to receive cytotoxic chemotherapy for metastatic breast cancer. The study was designed as a preliminary exploration of the utility of a higher dose of trastuzumab compared with the dose judged to be optimal on the basis of preclinical activity estimates and phase I pharmacokinetic data.

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PATIENTS AND METHODS

Patients

Women with progressive, bidimensionally measurable, *HER2*-overexpressing metastatic breast cancer who had not received cytotoxic chemotherapy for metastatic disease were eligible for this study. *HER2* expression was determined by a central core research laboratory (Laboratory Corporation of America, Research Triangle Park, NC) using sequential immunohistochemistry (IHC) analysis with two murine monoclonal antibodies, 4D5 and CB11. Eligibility required scores of 2+ (weak to moderate) or 3+ (strong) complete membrane staining in more than 10% of tumor cells with either antibody.

Patients were excluded if they had received radiotherapy within 2 weeks. Patients were also excluded if they had bilateral breast cancer; brain or leptomeningeal metastatic disease; bone metastases as the only disease site; metastases to more than 30% of the hepatic parenchyma; other malignancy not curatively treated; clinically significant cardiac disease, infection, bleeding disorder, abnormal pulmonary function, or other significant medical condition; Karnofsky performance status of less than 70%; life expectancy of less than 6 months; leukopenia ($\leq$ 3,500/μL), granulocytopenia ($\leq$ 1,500/μL), thrombocytopenia ($\leq$ 100,000/μL), or anemia ($\leq$ 10 g/dL); or hypercalcemia ($\geq$ 11 mg/dL). Pregnant or nursing patients were excluded. Informed consent was obtained and documented in writing before study entry. This study was performed after approval by local human investigations committees.

Antibody Administration

Trastuzumab (Herceptin) was supplied by Genentech, Inc (South San Francisco, CA) and was administered intravenously in the outpatient setting. Patients were randomized to receive one of two dosing regimens by a method that balanced distribution within study centers; patients, but not investigators, were blinded to dose. Patients received a standard loading dose of 4 mg/kg followed by 2 mg/kg weekly or a higher loading dose of 8 mg/kg followed by 4 mg/kg weekly. Randomization was used to ensure that estimates of the efficacy outcomes within each dose level would not be biased by assigning patients with worse prognosis to the higher dose group.

The infusion was initially administered over 90 minutes. If it was well tolerated, subsequent infusion periods were shortened to 30 minutes. The weekly maintenance dose was continued until disease progression.

Assessments

The investigators assessed the primary end point of objective tumor response at 8, 16, and 24 weeks and then every 12 weeks. No independent assessments of response or progression by an external committee were made in this study. Complete response was defined as the disappearance of all radiographically or visually apparent tumor; complete response in the skin or chest wall was confirmed by biopsy. Partial response was defined by a $\geq$ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Complete and partial responses were confirmed 4 weeks after the initial response determination. Minor response was defined as a 25% to 49% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. For partial and minor response, no new lesions appeared and no existing lesions progressed. Stable disease was defined as no change greater than 25% in the size of measurable lesions and no appearance of new lesions. Disease progression was defined as a 25% or greater increase in any measurable lesion or the appearance of a new lesion. Clinical benefit was defined post hoc as complete, partial, or minor response or stable disease longer than 6 months.

The secondary end points were duration of response, time to disease progression, survival, and quality of life (QOL). The duration of response was defined as the time from first response to disease progression. Time to onset of response was defined as time from randomization to the initial partial or complete response. Time to disease progression was defined as the time from randomization to documented disease progression, death, or addition of excluded therapy (eg, immunotherapy, chemotherapy, hormonal therapy, or radiotherapy) and was censored at the last date of contact for patients whose disease did not progress. Survival was defined as the time from randomization to death and was censored at the date of last contact for patients who were alive.

A complete physical examination, clinical assessment, analysis of vital signs, chest x-rays, and laboratory tests were performed at predetermined intervals and at study termination. Blood samples were collected at predetermined intervals for measurement of antibody to the Fab and Fc regions of recombinant human monoclonal antibody *HER2* by enzyme-linked immunosorbent assay (ELISA).

Adverse events were noted throughout the study and classified as mild, moderate, or severe. A mild adverse event was defined as annoying but not affecting baseline status or hindering the patient's normal functioning level. A moderate adverse event was uncomfortable and impaired normal function but was not hazardous to health. A severe adverse event caused severe discomfort, severely limited or prevented normal function, and was a definite hazard to health. The European Organization for Research and Treatment of Cancer's Quality of Life C30 questionnaire with the module for breast cancer (BR-23)[8] was used to assess QOL at baseline, every 12 weeks, and at study termination.

A retrospective analysis was performed in the subset of patients who had available tissue samples to determine gene amplification by fluorescence in situ hybridization (PathVysion fluorescence in situ hybridization [FISH] assay; Vysis, Inc, Downers Grove, IL). This laboratory analysis was conducted without access to any demographic or outcome data.

Statistical Analysis

This study was designed to explore the activity and tolerability of trastuzumab at two dose levels in patients who had not previously received treatment. No formal statistical comparisons were made between the two dose groups. The total sample size was set at 100 patients. This sample size allowed estimation of the response rate to within a standard error of 5%. The final analysis of efficacy and safety was performed 18 months after enrollment of the last patient. The median duration of follow-up for all patients was 19 months (range, 1.2 to 45.9 months). Demographic and baseline characteristics were summarized by descriptive statistics. χ^2 test for 2×2 or 2×3 tables was used to compare the distribution of baseline characteristics between patients receiving the 2 and 4 mg/kg doses.

Response rates were calculated in all enrolled patients (intent-to-treat analysis), in assessable patients (ie, all patients who received at least one dose of therapy and underwent tumor evaluation after baseline), and in subsets of assessable patients defined by baseline risk factors. Confidence intervals were computed using the normal approximation to the binomial distribution. Time to onset of objective response and duration of response were evaluated in patients with complete or partial responses. The median time to onset of objective response was calculated. Duration of response, time to disease progression, and survival were evaluated by Kaplan-Meier survival methodology. Adverse events were summarized by descriptive statistics in all patients who received at least one dose of trastuzumab.

QOL data were evaluated in patients with baseline and at least one follow-up assessment. The primary analysis was a repeated-measures analysis of variance (ANOVA) on the global QOL score and four functioning scales (ie, fatigue and physical, emotional, and social functions). Scale scores were calculated, and missing data after the last available assessment were imputed by carrying forward the last observation to the end of the 48-week study period.[9] For the analysis of total exposure up to week 48, the worst possible score was assigned to patients who died before week 48.

RESULTS

Patients

Investigators enrolled 114 patients who had *HER2* overexpression at the 2+ or 3+ level and had not previously received cytotoxic chemotherapy for their metastatic breast cancer in this multi-institutional study, which was conducted at 18 centers in the United States (n = 17) and Canada (n = 1). The actual enrollment exceeded the planned enrollment, because several patients were undergoing review of their pathologic material at the predetermined closure date. All patients who tested positive for *HER2* overexpression were allowed to enter the study. Reasons for study discontinuation were disease progression (n = 89 [78%]), patient request (n = 11 [10%]), adverse event (n = 2 [2%]), noncompliance (n = 1 [1%]), and study closure (n = 11 [10%]). Protocol violations consisted of continuation of trastuzumab after disease progression and initiation of chemotherapy (n = 8 [7%]), bone-only metastases (n = 2 [2%]), Karnofsky performance status of 60 (n = 2 [2%]), lack of distant metastases (n = 1 [1%]), and noncompliance (n = 1 [1%]). There were also minor eligibility exceptions, such as prestudy assessment outside protocol-specified windows, lack of pulmonary function testing or abnormal results, and metastatic disease not histologically confirmed. Patients were fairly evenly distributed between the two dose groups on the basis of protocol violations and baseline demographic features (Table 1). Overall, 65 patients (57%) received previous hormonal treatment, 42 patients (37%) as adjuvant therapy and 48 patients (42%) for metastatic disease. The mean loading dose for patients randomized to receive the standard dose was 4 mg/kg (range, 3.0 to 4.2 mg/kg) followed by 2 mg/kg weekly (range, 1.8 to 2.1 mg/kg). The mean loading dose for patients randomized to receive the higher dose was 8 mg/kg (range, 7.4 to 8.4 mg/kg) followed by 4 mg/kg weekly (range, 3.5 to 4.4 mg/kg). The median number of doses received was 16 (range, one to 162 doses). The median number of missed doses was one.

Efficacy

In the intent-to-treat analysis of all enrolled patients, there were seven complete and 23 partial responses, for an objective response rate of 26% (95% confidence interval [CI], 18.2% to 34.4%). An additional 13 patients had a minor response or stable disease for longer than 6 months for a clinical benefit (complete response + partial response + minor response + stable disease > 6 months) rate of 38% (95% CI, 28.8% to 46.9%). Three patients were not assessable because of lack of metastatic breast cancer (n = 1), patient-requested study removal after one dose of trastuzumab (n = 1), and patient-requested study removal after four doses and no postbaseline tumor evaluation (n = 1). In assessable patients, there were seven complete and 22 partial responses for an objective response rate of 26% (95% CI, 18.0% to 34.3%).

Responses were observed in many subsets of assessable patients (Table 2). Response rates were similar regardless of the dose of trastuzumab. Responses also occurred in patients with hormone receptor–positive and hormone receptor–negative tumors, lung or liver metastases, disease-free interval of 12 months or less and more than 12 months, and previous adjuvant doxorubicin or transplant. However, responses were seen only in patients whose tumors overexpressed *HER2* at the 3+ level and not at the 2+ level.

A significant number of censored observations, attributable to nonprogression at longer than 12 months of follow-up, preclude an accurate assessment of the median duration of response and the time to disease progression in the responding group. Seventeen (57%) of 30 patients with an objective response and 22 (51%) of 43 patients with clinical benefit had not experienced disease progression at longer than 12 months of follow-up.

The median time to disease progression was similar for patients treated with trastuzumab 4 or 2 mg/kg weekly (3.8 months [95% CI, 2.4 to 5.5 months] *v* 3.5 months [95% CI, 3.3 to 5.1 months]). The median duration of survival for all enrolled patients was 24.4 months (95% CI, 16.9 to 31.7 months), which included 49 censored observations for patients who were alive (n = 46) or lost to follow-up (n = 3). The median duration of survival was similar for patients who received trastuzumab 4 or 2 mg/kg weekly (25.8 months [95% CI, 13.3 to 34.7 months] *v* 22.9 months [95% CI, 16.0 to 37.1 months]) (Fig 1).

Retrospective HER2 *Gene Amplification Analysis*

A retrospective analysis of tumor *HER2* gene amplification was performed on archived pathology slides, which were available from a total of 111 patients, including 108 who were assessable. The response rate was 34% (95% CI, 23.9% to 45.7%) in patients whose tumors amplified *HER2* compared with 7% (95% CI, 0.8% to 22.8%) in those whose tumors did not (Table 2). The median time to progression was 4.9 months (95% CI, 3.4 to 8.0 months) in patients

Table 1. Patient Characteristics

Characteristic	Trastuzumab 2 mg/kg (n = 59)		Trastuzumab 4 mg/kg (n = 55)		Total (N = 114)	
	No. Patients/ No. Analyzed	%	No. Patients/ No. Analyzed	%	No. Patients/ No. Analyzed	%
Age, years						
Mean ± SD	54 ± 13.6		54 ± 14.9		54 ± 14.2	
Range	28-86		30-83		28-86	
Karnofsky score						
90 to 100	44	75	40	73	84	74
80	8	14	9	16	17	15
≤ 70	5	8	6	11	11	10
Not reported	2	3	0		2	2
Estrogen receptor status						
Positive	22	37	30	55	52	46
Negative	33	56	24	44	57	50
Not reported	4	7	1	2	5	4
Progesterone receptor status						
Positive	21	36	25	45	46	40
Negative	33	56	27	49	60	53
Not reported	5	8	3	5	8	7
HER2 overexpression						
IHC 2+	13	22	14	25	27	24
IHC 3+	46	78	41	75	87	76
HER2 amplification						
$FISH^+$	40	68	42	76	82	72
$FISH^-$	17	29	12	22	29	25
Sample not available	2	3	1	2	3	3
No. lymph nodes at diagnosis						
None	9	15	12	22	21	18
1 to 9	28	47	23	42	51	45
≥ 10	11	19	9	16	20	18
Not reported	11	19	11	20	22	19
Disease-free interval*						
≤ 12 months	23	39	9	16	32	28
12 to 24 months	14	24	22	40	36	32
> 24 months	21	36	24	44	45	39
Not reported	1	2	0		1	1
No. metastatic sites						
1 or 2	40	68	38	69	78	68
3 or 4	17	29	17	31	34	30
≥ 5	1	2	0		1	1
Not reported	1	2	0		1	1
Metastatic site†						
Lung or liver	34	58	42	76	76	67
Other	25	42	13	24	38	33
Adjuvant therapy						
Chemotherapy	41	69	36	65	77	68
Anthracycline	31	53	26	47	57	50
Radiotherapy	29	49	23	42	52	46
Hormonal therapy	20	34	22	40	42	37
Stem-cell transplantation	8	14	6	11	14	12

*$P < .02$.
†$P < .05$.

whose tumors amplified *HER2* compared with 1.7 months (95% CI, 1.5 to 3.3 months) in those whose tumors did not (Fig 2).

QOL

Seventy-four patients completed the QOL questionnaire at baseline and at week 12. The scores for each of the five subscales were generally unchanged between baseline and weeks 12, 24, 36, and 48. Improvements were seen in global QOL and the fatigue subscale; these changes were evaluated by repeated-measures ANOVA. When patients were stratified according to response, responders tended to show improvements in each of the five subscales at week 12, which gradually declined over the next 36 weeks. In contrast, nonresponders showed slight deterioration at week 12 and additional deterioration with each follow-up assessment.

Table 2. Tumor Response in Assessable Patients

Subset	Objective Response		Clinical Benefit*	
	No.	%	No.	%
All assessable patients, n = 111 (95% CI)	29	26 (18.0-34.3)	42	38
Trastuzumab				
2 mg/kg weekly, n = 58 (95% CI)	14	24 (13.1-35.2)	20	34
4 mg/kg weekly, n = 53 (95% CI)	15	28 (16.2-40.4)	22	42
Estrogen receptor				
Positive, n = 52	12	23	19	36
Negative, n = 54	16	30	21	39
Progesterone receptor				
Positive, n = 46	10	22	16	35
Negative, n = 57	18	32	24	42
Lung or liver metastases, n = 74	16	22	24	32
Disease-free interval				
≤ 12 months, n = 30	6	20	9	30
> 12 months, n = 81	23	28	33	41
Previous adjuvant doxorubicin, n = 57	18	32	23	41
Previous transplant, n = 14	5	36	6	43
HER2				
3+, n = 84	29	35	40	48
2+, n = 27	0	0	2	7
FISH				
Positive, n = 79	27	34	38	48
Negative, n = 29	2	7	3	10

*Clinical benefit = complete, partial, or minor response or stable disease > 6 months.

Safety

All 114 patients who received at least one dose of trastuzumab were included in the analysis of safety. Adverse events occurred in all but one patient (99%). When events were limited to those that the investigator considered to be possibly or probably related to treatment (hereafter, treatment-related events), 87 patients (76%) experienced at least one adverse event.

The most common treatment-related adverse events were chills (n = 28 [25%]), asthenia (n = 26 [23%]), fever (n = 25 [22%]), pain (n = 21 [18%]), and nausea (n = 16 [14%]). Most treatment-related adverse events were mild to moderate in intensity; only 10 patients (9%) had severe events. Infusion-related side effects were much more common with the first infusion and less likely with subsequent infusions. The only severe treatment-related adverse events that occurred in more than one patient were pain (n = 2 [2%]) and asthenia (n = 3 [3%]). There was no statistically significant association between trastuzumab dose and the occurrence of adverse events (Table 3). However, numerical increases in fever, chills, and dyspnea in the higher dose group suggest that some dose-effect relationship may exist.

Severe laboratory abnormalities were uncommon and included anemia (n = 2 [2%]), leukopenia (n = 2 [2%]), pancytopenia (n = 1 [1%]), thrombocytopenia (n = 1 [1%]), and hypercalcemia (n = 1 [1%]). No patients had detectable levels of antibodies against trastuzumab.

Reports of serious cardiac events in other trials[6,7] prompted a retrospective analysis of all cardiac events associated with any trastuzumab trial by an independent, blinded cardiac review and evaluation committee. Cardiac dysfunction was defined as congestive heart failure, cardiomyopathy, or a decrease in ejection fraction (> 10% points). Of six patients referred to the cardiac review and evaluation committee, three were considered to have cardiac dysfunction. The first patient had a history of myocardial infarction, previous anthracycline therapy, and baseline left-ventricular ejection fraction (LVEF) of 35% to 40%. After 1 year of trastuzumab therapy, her LVEF was 31% while withholding cardiac drugs. The second patient had a history of hypertension and coronary and cerebrovascular disease. After 28 weeks of trastuzumab, bilateral atrial and right ventricular enlargement and tricuspid regurgitation were noted; subsequently, intermittent pleural effusions developed. Trastuzumab was discontinued in both of these patients, and no additional intervention was required for cardiac events. The third patient had reduction in LVEF after relief of pericardial tamponade, which was attributed to breast cancer.

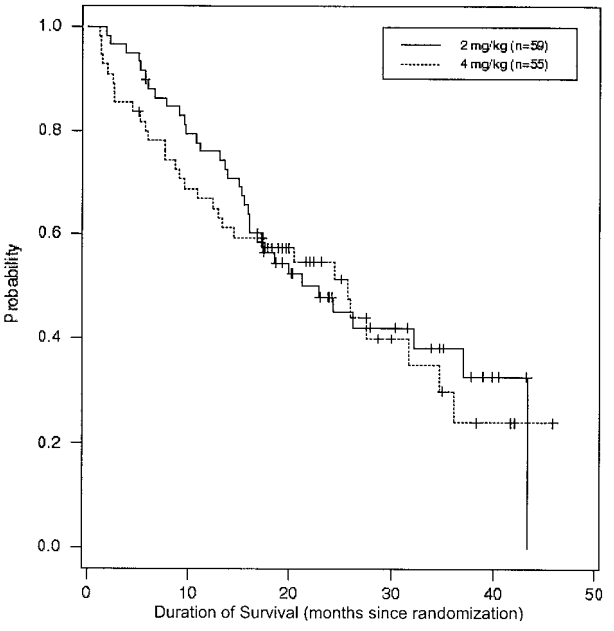

Fig 1. Kaplan-Meier plot of the duration of survival by trastuzumab dose in all enrolled patients. No statistically significant difference was noted between the two groups.

DISCUSSION

The results of this trial indicate that trastuzumab is active as a single agent and produces durable objective responses in women with *HER2*-overexpressing breast cancer who have not previously received chemotherapy for their metastatic disease. The response rate was 26%; the clinical benefit rate was 38% in all assessable patients and 48% in the subset whose tumors overexpressed *HER2* at the 3+ level by IHC. Although an accurate assessment of the median duration of response was not possible because of censoring, 57% of the responding patients were known to be free of disease progression at 12 months or more of follow-up, underscoring the durability of the responses. These findings are noteworthy in view of the poor prognosis in this population.[2-4,10] In addition, patients had lung or liver metastases (67%) because of the requirement for bidimensionally measurable disease. Furthermore, most patients had received adjuvant chemotherapy (68%), which included an anthracycline (50%) or high-dose therapy with stem-cell rescue (12%).

This trial was designed as a companion to the pivotal trials of trastuzumab in women with *HER2*-overexpressing breast cancer. In one of these pivotal trials, trastuzumab was administered as a single agent to 222 patients with previously treated metastatic breast cancer in a phase II study.[6] In that study, trastuzumab produced response rates of 15% determined by the response evaluation committee and 20% determined by investigators, median response duration of 9 months, and median survival of 13 months.[6] The collective results of these trials justify additional exploration of trastuzumab as first-line therapy to determine whether its optimal use is earlier in the course of metastatic disease.

The present trial targeted a patient population similar to that of the phase III trial in which patients were randomized to receive chemotherapy with or without trastuzumab as first-line therapy.[7] In that trial, chemotherapy consisted of an anthracycline and cyclophosphamide (AC) or, if patients had previously received adjuvant anthracycline therapy, paclitaxel. The response rate was 42% for AC alone in anthracycline-naive patients and 17% for paclitaxel in anthracycline-exposed patients; the response rate was higher when trastuzumab was added to AC (56%, $P = .02$) or paclitaxel (41%, $P = .001$). The median duration of survival was 25.1 months for trastuzumab and chemotherapy, 26.8 months for trastuzumab and AC, and 22.1 months for trastuzumab and paclitaxel. Compared with the survival findings from the present trial (24 months [95% CI, 16.9 to 31.7 months]), these results suggest that patients do not incur a major survival disadvantage if they receive trastuzumab alone as first-line therapy for metastatic disease. Of course, conclusions based on cross-study comparisons are

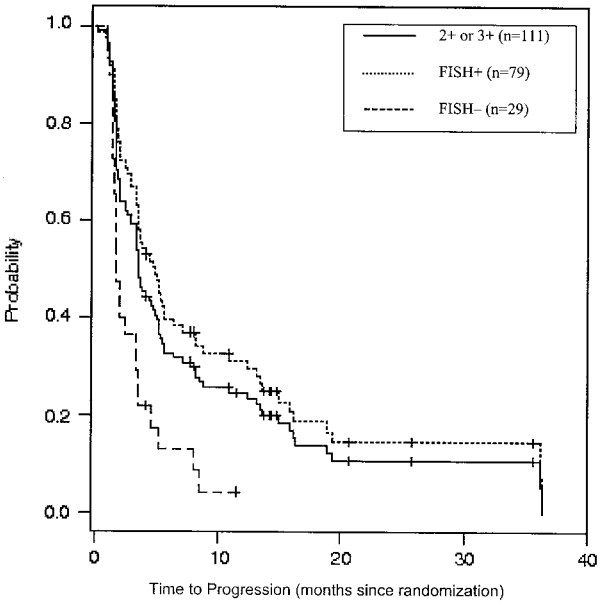

Fig 2. Kaplan-Meier estimates of time to disease progression in 111 assessable patients with *HER2* overexpression by IHC, 79 with *HER2* gene amplification by FISH, and 29 without *HER2* gene amplification. Time to disease progression for FISH+ patients was significantly longer than for FISH$^-$ patients ($P < .0001$).

Table 3. Adverse Events in > 20% of 114 Patients Treated With at Least One Dose of Trastuzumab, Including Those Not Related to Treatment

	Trastuzumab 2 mg/kg (n = 59)				Trastuzumab 4 mg/kg (n = 55)			
	Any		Severe		Any		Severe	
Type of Response	No.	%	No.	%	No.	%	No.	%
Any	58	98			55	100		
Any treatment-related	40	68			47	85		
Pain	35	59	5	8	32	58	5	9
Asthenia	31	53	4	7	32	58	4	7
Nausea	22	37	2	3	26	47	1	2
Fever	21	36	1	2	25	45	0	
Headache	17	29	2	3	21	38	1	2
Chills	13	22	0		22	40	1	2
Infection	21	36	0		14	25	1	2
Diarrhea	21	36	1	2	13	24	3	5
Rash	12	20	0		21	38	0	
Vomiting	15	25	1	2	18	33	2	4
Abdominal pain	15	25	1	2	18	33	2	4
Back pain	12	20	3	5	19	35	4	7
Cough	16	27	0		14	25	0	
Chest pain	15	25	2	3	11	20	1	2
Peripheral edema	13	22	0		12	22	0	
Dyspnea	9	15	0		14	25	1	2

limited by the potential for bias, regardless of the similarities of their study populations.

The higher dose of trastuzumab showed no apparent benefit over the standard dose based on the efficacy end points in this relatively small trial. Objective responses were seen in patients with different prognostic factors, such as hormone receptor status, site of metastases, duration of disease-free interval, and previous adjuvant therapy. In contrast, objective responses were not detected in the subset of patients whose tumors overexpressed *HER2* at the 2+ level. Objective responses have been detected in this subset of patients in other studies,[6,7] but the response rates were consistently lower than in those with *HER2* overexpression at the 3+ level.

A retrospective analysis was performed to explore the correlation between *HER2* gene amplification by FISH and clinical outcome.[11] The 34% response rate in the subset of assessable patients with gene amplification was noteworthy because it approached the response rate associated with first-line chemotherapy with or without trastuzumab.[7] The data from this and the trastuzumab pivotal trials[6,7] suggest that FISH is a superior method for selecting patients likely to benefit from trastuzumab therapy.

The safety profile of trastuzumab is different from that of most standard chemotherapy agents. Toxicities typically associated with chemotherapy, such as alopecia, stomatitis, and bone marrow suppression, occurred in less than 10% of patients in this trial (data not shown) and may or may not have been related to treatment. In this and previous trastuzumab trials,[6,7] most of the common, treatment-related adverse events occurred after the first infusion and became much less frequent after the second and subsequent infusions. These acute, infusion-related events were characterized by chills, fever, and nausea. There was no clear evidence of a relationship between dose and the severity or frequency of adverse events. QOL did not diminish during treatment with trastuzumab and, in fact, seemed to improve in patients who had objective responses. Similar findings were seen in patients who received single-agent trastuzumab for previously treated metastatic breast cancer.[6]

The most clinically significant adverse event attributed to trastuzumab has been cardiac dysfunction.[6,7] In a blinded, retrospective analysis of all cardiac events in the present trial, an independent committee determined that three patients had cardiac events. Two of the three patients had histories of significant cardiac disease, and one had received adjuvant anthracycline therapy. The cardiac event in the third patient was attributed to underlying breast cancer. After discontinuation of trastuzumab, none of these patients required additional intervention for cardiac events. In other trials, signs and symptoms usually responded to standard medical therapy for congestive heart failure.[6,7] An analysis of cardiac events in all trials involving trastuzumab is underway in an effort to identify risk factors.

The present results (the preliminary findings of which were originally published in abstract form[12-14]) have led to randomized clinical trials designed to additionally assess the optimal clinical use of trastuzumab as first-line treatment of patients with metastatic breast cancer. These trials will provide important information regarding the sequence of

therapies that provides maximal efficacy and preserves the QOL. In conclusion, single-agent trastuzumab is an active and well tolerated option for first-line treatment of women who have metastatic breast cancer with 3+ *HER2* overexpression by IHC or with gene amplification by FISH.

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APPENDIX

The appendix is available online at www.jco.org.

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