Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease

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Purpose: **Overexpression of the HER2 protein occurs in 25% to 30% of human breast cancers and leads to a particularly aggressive form of the disease. Efficacy and safety of recombinant humanized anti-HER2 monoclonal antibody as a single agent was evaluated in women with HER2-overexpressing metastatic breast cancer that had progressed after chemotherapy for metastatic disease.**

Patients and Methods: **Two hundred twenty-two women, with HER2-overexpressing metastatic breast cancer that had progressed after one or two chemotherapy regimens, were enrolled. Patients received a loading dose of 4 mg/kg intravenously, followed by a 2-mg/kg maintenance dose at weekly intervals.**

Results: **Study patients had advanced metastatic disease and had received extensive prior therapy. A blinded, independent response evaluation committee identified eight complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% confidence interval, 11% to 21%). The median duration of response was 9.1 months; the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of patients, were infusion-associated fever and/or chills that usually occurred only during the first infusion, and were of mild to moderate severity. These symptoms were treated successfully with acetaminophen and/or diphenhydramine. The most clinically significant adverse event was cardiac dysfunction, which occurred in 4.7% of patients. Only 1% of patients discontinued the study because of treatment-related adverse events.**

Conclusion: **Recombinant humanized anti-HER2 monoclonal antibody, administered as a single agent, produces durable objective responses and is well tolerated by women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. Side effects that are commonly observed with chemotherapy, such as alopecia, mucositis, and neutropenia, are rarely seen.**

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PROTO-ONCOGENES THAT encode growth factors and their receptors contribute to the pathogenesis of human malignancies, including breast cancer.[1] The human epidermal growth factor receptor 2 (HER2) gene, also known as *neu* and c-*erb*B-2, encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$). $p185^{HER2}$ has partial homology with the epidermal growth factor receptor and shares intrinsic tyrosine kinase activity with that receptor.[2-4] HER2 is overexpressed by at least one fourth of human breast cancers,[5,6] and correlates with poor clinical outcome in women with node-positive and node-negative disease.[6-8] Additional findings from HER2-transfected cells, as well as transgenic animals, support the hypothesis that this proto-oncogene is not just a marker but directly contributes to the pathogenesis and clinical aggressiveness of tumors that overexpress HER2.[9-11] To target this specific growth factor receptor, monoclonal antibodies directed against $p185^{HER2}$ were developed.[12] In preclinical studies, these antibodies inhibited the growth of HER2-overexpressing tumor cells.[12-15]

Recombinant humanized anti-HER2 monoclonal antibody (rhuMAb HER2 [trastuzumab]) was engineered from a cloned human IgG, framework and the antigen-binding residues of the murine monoclonal antibody 4D5.[16] The antibody was humanized to minimize the immunogenicity associated with murine monoclonal antibodies and to enhance the potential for enlisting endogenous immune antitumor effects. Results of small phase II trials provided preliminary evidence that rhuMAb HER2 is safe and clinically active in women with HER2-overexpressing metastatic breast cancer.[17,18]

Based on these observations, two large clinical trials of rhuMAb HER2 were conducted in patients with HER2-overexpressing metastatic breast cancer. One trial compared

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the safety and efficacy of rhuMAb HER2 plus chemotherapy versus chemotherapy alone in first-line treatment.[19] A second trial, reported here, investigated the safety and efficacy of rhuMAb HER2 in patients with metastatic breast cancer that had progressed after one or two chemotherapy regimens for metastatic disease. The primary objectives of this trial were to determine the overall objective response rate to rhuMAb HER2 treatment as a single agent and to further characterize the safety profile of rhuMAb HER2.

PATIENTS AND METHODS

Patients

Eligible patients were women with HER2-overexpressing metastatic breast cancer. All patients had progressive disease after one or two cytotoxic chemotherapy regimens for metastatic disease and bidimensionally measurable disease. Patients were excluded if they had untreated brain metastases, bone metastases as the only disease site, concomitant malignancy not curatively treated, or a Karnofsky performance status of less than 60%. Patients were also excluded if they were pregnant, nursing, or if they had used investigational or unlicensed agents within 30 days. Informed consent was obtained and documented in writing before study entry. This study was performed after approval by local human investigations committees.

Expression of HER2 was determined by immunohistochemical analysis of tumor tissue, collected either at the time of primary diagnosis or at recurrence, and used the 4D5 and CB11 murine monoclonal anti-HER2 antibodies. Expression was scored by a core research pathology laboratory as 0, 1+, 2+, or 3+ using standardized criteria. All enrolled patients had 2+ or 3+ overexpression using either antibody (weak to strong complete membrane staining observed in $>$ 10% of the tumor cells).

Antibody Administration

rhuMAb HER2 (trastuzumab [Herceptin]) was produced by Genentech, Inc (South San Francisco, CA) and was administered intravenously in the outpatient setting at a dose selected to maintain a minimal serum trough concentration of 10 μg/mL to 20 μg/mL. Patients received a loading dose of 4 mg/kg, followed by weekly administration of 2 mg/kg. The infusion was initially administered over 90 minutes. If the infusion was well tolerated, subsequent infusion periods were shortened to 30 minutes.

The 2-mg/kg weekly maintenance dose was continued without dosage modification. If a patient developed disease progression, the investigator could continue the 2-mg/kg dosage, increase the dose to 4 mg/kg weekly, or discontinue treatment. Additional antitumor therapy was also permitted upon disease progression.

Tumor Response

The primary end point of objective tumor response was assessed at specified time points; before treatment, at weeks 8, 16, and 24, and every 12 weeks thereafter. Responses were determined by an independent response evaluation committee (REC). Reading teams were composed of an oncologist and a radiologist, who were blinded to treatment. Responses (complete or partial responses) were confirmed 4 weeks after the initial response determination. Complete response was defined as the disappearance of radiographically, palpable, and/or visually apparent tumor. Partial response was defined as a $\geq$ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Disease progression was defined as a $\geq$ 25% increase in any measurable lesion or the appearance of a new lesion.

The prespecified secondary end points were duration of response, time to disease progression, time to treatment failure, and survival. Duration of response was defined as the time from first response to disease progression. Time to disease progression was defined as the time from enrollment to disease progression or death (whichever occurred first) and was censored at the last date of contact for patients whose disease did not progress. Time to treatment failure was defined as the time from enrollment to disease progression, death, treatment discontinuation, or initiation of a new antitumor therapy. Survival was defined as the time from enrollment to death and was censored at the date of last contact for patients who were alive.

Other Assessments

A complete physical examination, a clinical assessment, a vital sign analysis, chest x-rays, and laboratory tests were performed at predetermined intervals and at study termination. Adverse events were 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 National Cancer Institute Common Toxicity Criteria were not used to classify clinical adverse events. Laboratory abnormalities were classified by the World Health Organization grading system.

A blinded independent cardiac review and evaluation committee was established retrospectively to assess cardiac dysfunction in all rhuMAb HER2 clinical trials.[20] Clinical data from all patients enrolled in this study were thoroughly reviewed by the committee to identify all potential cases of cardiac dysfunction. The severity of cardiac dysfunction was classified using the New York Heart Association criteria.

The Quality of Life Questionnaire–C30, a questionnaire developed by the European Organization for Research and Treatment of Cancer,[21] was used to assess quality of life initially at weeks 1, 12, 24, 36, and 48, then every 12 weeks, and finally at study termination.

Blood samples were collected at predetermined intervals for the pharmacokinetic analysis of serum rhuMAb HER2 concentrations, determination of serum concentrations of the extracellular domain of the HER2 protein (shed antigen), and measurements of antibody to rhuMAb HER2. Serum rhuMAb HER2 concentrations were determined by an enzyme-linked immunosorbent assay (ELISA) with a lower limit of sensitivity of 156 ng/mL at a minimum dilution of 1/100.[17,18] Serum baseline shed antigen concentrations were determined by an ELISA with a lower limit of detection of 3.4 ng/mL. Antibodies to the Fab and Fc regions of rhuMAb HER2 were measured by ELISAs.

Statistical Methods

The final analysis of efficacy and safety was performed 15 months after enrollment of the last patient. The median follow-up for all patients was 12.8 months. Demographic and baseline characteristics were summarized by descriptive statistics.

Response rate was evaluated in all enrolled patients (intent-to-treat analysis) and in treated patients (ie, all patients who received at least one rhuMAb HER2 dose). Response duration was evaluated in patients with partial or complete responses. Time to disease progression, time to treatment failure, and survival were evaluated by intent-to-treat analysis of all patients. Time to event end points were estimated by Kaplan-Meier survival methodology. The effect of baseline characteristics on response rates was evaluated by the χ^2 test and logistic regression

model. The risk factors for time to progression were determined by the Cox proportional hazards regression model.

The analysis of safety was performed on all patients who received at least one dose of rhuMAb HER2. Adverse events and laboratory abnormalities were summarized by descriptive statistics. Infusion-associated adverse events were evaluated by comparing the rates of events after the loading dose with the rates of the same events after subsequent infusions.

Quality-of-life data were evaluated in patients with baseline and at least one follow-up assessment. The primary analysis was a repeated-measures analysis of variance on the global quality-of-life score and four functioning scales (ie, fatigue, physical, emotional, and social functions).

The pharmacokinetic profile of rhuMAb HER2 was determined in 50 randomly selected patients. Pharmacokinetic parameters were estimated by nonlinear regression using Professional WinNonlin (v.1.5; Scientific Consulting, Inc, Cary, NC), a software program for pharmacokinetic analysis. Baseline shed antigen data were summarized; an analysis of variance on logarithmic transformation at base 10 of the absolute value of the baseline shed antigen was performed to evaluate the interaction with patient baseline characteristics.

RESULTS

A total of 222 patients were enrolled by investigators from 54 centers in the United States, Canada, Belgium, France, Germany, the United Kingdom, and Australia between April 1995 and September 1996. A total of 213 patients received at least one dose of rhuMAb HER2. Nine patients were not treated for the following reasons: brain metastases (n = 3), laboratory abnormality (n = 2), adverse event (n = 1), refusal to participate (n = 1), clinical instability (n = 1), and death (n = 1). As of the cutoff date of December 31, 1997, 179 patients (81%) had discontinued the study, 14 patients (6%) remained on the study without disease progression, and 29 patients (13%) were continuing treatment after disease progression.

Patient baseline characteristics are listed in Table 1. Less than half had estrogen receptor–positive tumors. Twenty-seven percent had ≥ 10 positive lymph nodes at the time of primary diagnosis. Thirty-seven percent had a disease-free interval of less than 12 months. Most patients (78%) had metastatic disease at multiple sites, and 72% had liver or lung involvement. All patients had received extensive previous treatment. Sixty-eight percent had prior adjuvant chemotherapy, and all had received prior chemotherapy for metastatic disease; 32% had one prior and 68% had two prior chemotherapy regimens for metastatic disease. Most had received both prior anthracycline and taxane therapy; 26% had undergone high-dose chemotherapy with bone marrow or stem-cell rescue before enrollment.

Table 1. Patient Characteristics

Characteristic		No. of Patients/No. Analyzed	%
Age, years			
Mean ± SD	50 ± 11.6		
Range	28-81		
Karnofsky score			
90% to 100%		152/211	72
80%		36/211	17
≤ 70%		23/211	11
Receptor status			
Estrogen receptor positive		85/190	45
Progesterone receptor positive		77/188	41
HER2 overexpression			
2+		50/222	22
3+		172/222	78
No. of lymph nodes at primary diagnosis			
None		42/176	24
1-9		87/176	49
≥ 10		47/176	27
Disease-free interval, months			
< 12		80/214	37
12-24		48/214	22
> 24		86/214	40
No. of metastatic sites			
1		47/214	22
2		91/214	42
≥ 3		76/214	36
Metastatic site			
Skin or soft tissue		14/214	6
Liver or lung		155/214	72
Prior therapy			
Adjuvant chemotherapy		146/214	68
Chemotherapy metastatic disease, no. of regimens		214/214	100
1		69/214	32
≥ 2		145/214	68
Prior anthracyclines		201/214	94
Prior taxanes		143/214	67
Radiotherapy		151/214	71
Hormonal therapy		122/214	57
Bone marrow or stem-cell transplantation		53/205	26

Tumor Response

The independent REC determined eight complete (4%) and 26 partial (11%) responses, for an objective response rate of 15% in the intent-to-treat population of 222 patients (Table 2). The investigators identified nine complete responses (4%) and 37 partial responses (17%), for an objective response rate of 22% in the treated population of 213 patients. In addition, there were 12 minor responses (6%), 62 patients (29%) with stable disease, and 93 patients (44%) with progressive disease. Twenty-two percent of patients were free of disease progression at 6 months.

The median duration of response to rhuMAb HER2, in the patients identified as complete or partial responses by the REC, was 9.1 months (range, 1.6 to > 26 months) (Fig 1). Eight (24%) of 34 patients with a response were free of disease progression at the cutoff date. Among all treated patients, the median time to disease progression was 3.1

Table 2. Tumor Response

Population	No. of Patients	Complete Responders		Partial Responders		Objective Response Rate (%)	95% CI
		No. of Patients	%	No. of Patients	%		
REC assessment							
All enrolled, intent-to-treat	222	8	4	26	12	15	11-21
All treated	213	8	4	26	12	16	11-22
Investigators' assessment							
All enrolled, intent-to-treat	222	9	4	37	17	21	16-27
All treated	213	9	4	37	17	22	16-28

months (range, 0 to > 28 months); the median time to treatment failure was 2.4 months (range, 0 to > 28 months).

The median time to treatment failure among the 34 patients with a response was 11 months (range, 2 to > 28 months). In contrast, for the prior regimen of cytotoxic chemotherapy in these patients, the median time to treatment failure was 5.4 months (range, 0 to 27.4 months). The median duration of survival in all patients was 13 months (range, 0.5 to > 30 months) (Fig 1).

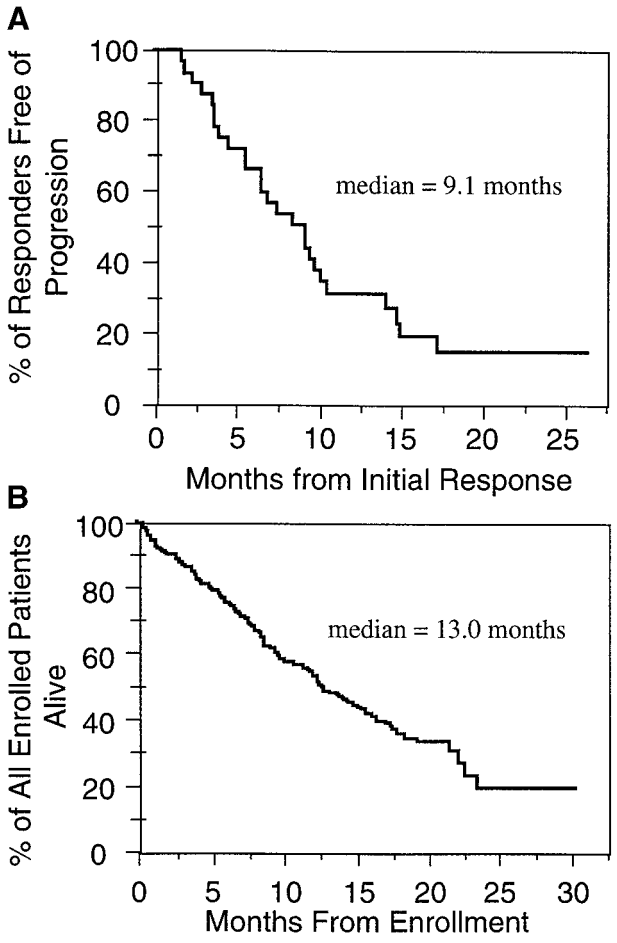

Fig 1. (A) Kaplan-Meier plots of the duration of response in patients with tumor response (complete or partial response) and (B) survival in all enrolled patients.

In general, the efficacy of rhuMAb HER2 was observed consistently across patient subgroups, with a few exceptions. Patients whose tumors overexpressed HER2 at the 3+ level tended to have higher response rates than those with a 2+ level of overexpression (18% *v* 6%; $P = .06$). Patients whose time to first relapse was more than 6 months tended to have higher response rates than those who relapsed earlier (20% *v* 9%; $P = .03$). Of note, tumor responses were observed in 12 (11%) of 109 patients with liver metastases, and in 14 (26%) of 53 patients with prior transplants. In a multivariate logistic regression analysis, none of the patient baseline characteristics were independently predictive of tumor response.

Significant correlations were detected between time to disease progression and patient baseline characteristics. In a univariate analysis, the median time to disease progression was longer among patients whose tumors overexpressed HER2 at the 3+ level (3.3 *v* 1.9 months; $P = .0034$), who had relapsed more than 6 months after treatment (3.4 *v* 2.1 months; $P = .0045$), who had a Karnofsky score of 100% or 90% versus less than 90% (3.2 or 3.5 *v* 2.0 months; $P = .0068$), or who had one or two versus ≥ three metastatic sites (3.5 or 3.2 *v* 2.3 months; $P = .001$). In a multivariate proportional hazards model, three factors (number of metastatic sites at study entry, level of HER2 overexpression, and months to first relapse) significantly ($P < .05$) affected time to disease progression.

A number of patients were treated after disease progression with 4 mg/kg rhuMAb HER2 as a single agent. Of the 34 patients treated with 4 mg/kg as a single agent, three patients, each of whom had an initial partial response or minor response to the 2-mg/kg dose, had a subsequent partial response to 4 mg/kg.

Quality-of-Life Assessment

One hundred fifty-four patients completed the EORTC Quality of Life Questionnaire–C30 at baseline and at week 12. Before disease progression, treatment with rhuMAb

HER2 was associated with maintenance of health-related quality of life, as measured by the physical function, role function, social function, global quality-of-life, and fatigue scales. However, after disease progression, overall health-related quality of life declined. The subset of 34 patients with a response had clinically meaningful improvements in the evaluated parameters. A detailed analysis of quality of life will be published separately.

Pharmacokinetics and Shed Antigen

The mean volume of distribution (38.0 mL/kg) approximated the serum volume. The mean steady-state concentration was 59.7 μg/mL. The mean elimination half-life was 6.2 days. Among the 195 patients with pharmacokinetic data, the mean peak and trough serum concentrations of rhuMAb HER2 after the first dose were 100.3 μg/mL and 25.0 μg/mL, respectively. The trough serum concentrations tended to increase through week 20 and, thereafter, tended to plateau (Fig 2). To minimize the potential confounding effect of the declining number of assessable patients over time, trough concentrations were evaluated in a subset of 37 patients who had data through week 36. Similar findings were observed in this subset, except that the trough concentrations tended to plateau after week 12 (data not shown). Mean trough concentrations at weeks 7 and 8 were higher in complete (70.3 μg/mL) and partial (58.4 μg/mL) responders than in nonresponders (44.3 μg/mL; $P < .001$).

Serum concentrations of baseline shed antigen were below the detectable level in 73 (38%) of 191 patients, between 3.4 ng/mL and 100 ng/mL in 78 patients (41%), between 100 ng/mL and 500 ng/mL in 28 patients (15%), and above 500 ng/mL in 12 patients (6%). Patients whose tumors overexpressed HER2 at the 3+ level had higher median shed antigen concentrations (16.2 ng/mL) than patients whose tumors overexpressed HER2 at the 2+ level (3.4 ng/mL; $P < .0001$). No significant correlations were demonstrable between shed antigen concentrations and response status.

Safety

Patients who received at least one dose of rhuMAb HER2 were evaluated for safety. Chemotherapy was added to rhuMAb HER2 in 36 patients after disease progression. This safety analysis included adverse events occurring before disease progression unless otherwise noted. The median number of infusions was 12 (range, 1 to 96). A total of 210 patients (99%) experienced at least one adverse event; 88 patients (41%) had severe adverse events. When events were limited to those that the investigator considered to be possibly or probably related to treatment (hereafter, treatment-related events), 179 patients (84%) experienced at least one adverse event; only 29 patients (14%) had severe events. Severe treatment-related adverse events that occurred in

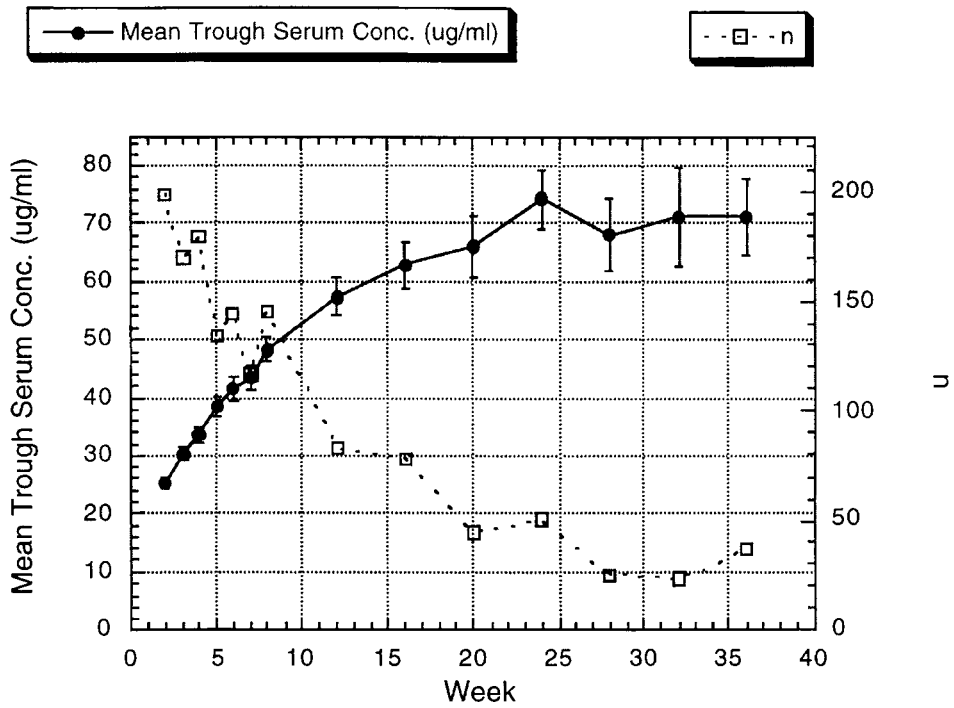

Fig 2. Mean trough (±SD) serum concentrations of rhuMAb HER2 for all patients for whom data were available (n = number of patients).

more than one patient were pain (n = 9), chills (n = 5), dyspnea (n = 2), and abdominal pain (n = 2).

Six patients (3%) discontinued the study because of adverse events, four before disease progression and two after disease progression. One patient developed an anaphylactoid reaction during the first dose. One patient withdrew from treatment after developing tuberculosis, and one patient withdrew from treatment because of atherosclerotic heart disease. The other three patients discontinued the study because of adverse events experienced before initiation of rhuMAb HER2 treatment.

The most common adverse events seemed to be related to the initial infusion, particularly fever, chills, pain, asthenia, nausea, vomiting, and headache (Table 3). These adverse events were mild to moderate in intensity and were rarely severe. Often, the infusion was temporarily interrupted. The symptoms were usually successfully treated with acetaminophen, diphenhydramine, and/or meperidine and usually did not recur with subsequent infusions. For example, 40% of patients experienced fever and/or chills during or shortly after the first infusion, but less than 3% of these patients experienced recurrent fever or chills. Temperature exceeded 38°C in 20 (10%) of 209 patients after the loading dose only, in eight patients (4%) after a subsequent infusion, and in five (2%) after multiple infusions. Only two patients (1%) had temperatures that exceeded 39°C. Therefore, 176 patients (84%) did not have postinfusion temperatures that exceeded 38°C.

Table 3. Adverse Events in >10% of 213 Patients Treated With at Least One Dose of rhuMAb HER2, Including Those Not Related to Treatment

	Any Adverse Event		Severe Adverse Event	
Adverse Event	No. of Patients	%	No. of Patients	%
Pain	103	48	17	8
Asthenia	97	46	6	3
Fever	81	38	2	1
Nausea	77	36	2	1
Chills	76	36	5	2
Vomiting	60	28	1	0.5
Cough increased	58	27	1	0.5
Headache	56	26	4	2
Diarrhea	55	26	3	1
Dyspnea	49	23	10	5
Abdominal pain	47	22	4	2
Chest pain	44	21	3	1
Back pain	42	20	1	0.5
Infection	41	19	1	0.5
Insomnia	34	16	0	
Rhinitis	33	15	0	
Anorexia	27	13	0	
Anxiety	27	13	0	
Constipation	27	13	1	0.5
Pharyngitis	27	13	0	
Dizziness	26	12	0	
Rash	26	12	0	
Flu syndrome	23	11	1	0.5
Pruritus	23	11	1	0.5

Reports of serious cardiac events in this trial and in the large comparative trial of rhuMAb HER2 in combination with chemotherapy,[19] prompted a retrospective analysis of all cardiac events. Cardiac dysfunction was manifested as congestive heart failure, cardiomyopathy, and/or a decrease in ejection fraction (> 10%). Ten patients (4.7%) were identified, including three whose cardiac events occurred after the cutoff date. Nine of these patients had received anthracycline therapy and had at least one risk factor for anthracycline-induced cardiomyopathy, such as a cumulative doxorubicin dose of more than 400 mg/m^2 (n = 6), radiotherapy to the left chest (n = 3), age over 70 years (n = 3), or history of hypertension (n = 1). One patient had never received anthracycline therapy, and had significant cardiac disease at study entry. The majority of these cardiac events were clinically significant. The most severe outcome occurred in a 39-year-old woman who had received a cumulative doxorubicin dose of approximately 450 mg/m^2 and had a cardiac ejection fraction of 60% at study entry. After 18 infusions of rhuMAb HER2, she had two episodes of severe cardiac dysfunction, each of which improved after aggressive therapy. She died 2 days after her last infusion of rhuMAb HER2 because of presumed ventricular arrhythmia. This was the only death that was considered to be possibly related to rhuMAb HER2 treatment. Cardiac status was stable in six of eight patients with cardiac dysfunction who continued to receive rhuMAb HER2. Two patients with decreased ejection fraction remained asymptomatic.

Laboratory results were rarely abnormal during treatment before disease progression. No cases of World Health Organization grade 4 hematologic abnormalities were present. Nine (4%) of 211 patients experienced grade 3 hematologic abnormalities, which were manifested by leukopenia (n = 3), neutropenia (n = 2), thrombocytopenia (n = 3), or decreased hemoglobin (n = 1). Twenty (9%) of 212 patients experienced at least one grade 3 hepatic laboratory abnormality, which was manifested by elevated alkaline phosphatase (n = 11), AST (n = 9), ALT (n = 5), or total bilirubin (n = 1). Seven patients (3%), all with disease involving the hepatobiliary system, experienced at least one grade 4 hepatic laboratory abnormality, which was manifested by elevated alkaline phosphatase (n = 6), AST (n = 4), or total bilirubin (n = 1). Grade 3 or 4 elevations in liver function tests were associated with disease progression in 16 patients.

Only one (0.5%) of 211 patients had detectable levels of antibodies against rhuMAb HER2. Treatment was stopped after nine infusions because of disease progression, when antibody measurements revealed antibody formation against the Fab region of rhuMAb HER2. Peak serum concentrations of rhuMAb HER2 fell from more than 40 μg/mL between days 0 and 36 to 11.4 μg/mL on day 50. No clinical signs or symptoms of allergy were observed. Adverse events were reviewed in the 36 patients who were treated after disease progression with rhuMAb HER2 combined with cytotoxic chemotherapy. Diverse chemotherapy regimens were used, and no unexpected toxicity findings were observed.

DISCUSSION

The results of this trial indicate that rhuMAb HER2 is active as a single agent and produces durable objective responses in women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. The 15% objective response rate is noteworthy in view of the study design and patient population. Objective response was defined by strict criteria and by independent REC review. The investigators' response rate of 21% was higher than the REC assessment.

The study population had a very poor prognosis. All patients had tumors that overexpressed HER2. Most patients had visceral disease because of the requirement for bidimensionally measurable disease; patients whose only assessable disease site was bone, a population with generally indolent disease, were ineligible. Patients were heavily pretreated. The great majority had received multiple chemotherapy regimens, and approximately one fourth had undergone bone marrow or stem-cell transplantation.

The investigator-reported objective response rate in these patients approached the 20% to 27% response rate reported for standard second-line chemotherapy in patients who have failed anthracycline-containing regimens.[22] The response rate to single agent vinorelbine in anthracycline-resistant patients is 16%,[23] and that to paclitaxel given by 24-hour infusion is approximately 23%.[24] Higher response rates have been reported for some second-line agents, such as docetaxel, which yielded a 41% response rate in three phase II trials.[25] However, the complete response rate (2%), median duration of response (6 months), and median duration of survival (10 months) in the docetaxel trials were not superior to the findings in this study. Furthermore, the response duration in patients receiving rhuMAb HER2 in this study (9.1 months) compared very favorably with the duration associated with previous chemotherapy in responders (5.2 months). Finally, the secondary end points in the current study may improve with additional follow-up because, at the cutoff date, approximately one quarter of responders had not experienced treatment failure and 82% of patients with a response remained alive.

An important difference between rhuMAb HER2 and most standard chemotherapy agents is tolerability. Typical chemotherapy-induced complications, such as alopecia, mucositis, and hematologic toxicity, occurred in no more than 4% of patients. The most common adverse events were fever, chills, and other acute and self-limited symptoms. These infusion-associated symptoms occurred in approximately 40% of patients during or shortly after the loading dose was administered and were usually treatable with acetaminophen and diphenhydramine or, less commonly, meperidine. Symptoms rarely recurred with subsequent infusions. Only one patient was discontinued from the study because of infusion-associated symptoms. Only two other patients were discontinued from the study because of adverse events that were considered by the investigator to be treatment-related.

The most clinically significant adverse events in this trial were signs and symptoms of cardiac dysfunction, which after careful retrospective analysis of all patients, were identified in 10 patients (4.7%). Two of these patients remained asymptomatic with a decreased ejection fraction. Signs and symptoms improved after standard medical therapy for congestive heart failure in the remaining eight patients. One patient died because of a presumed ventricular arrhythmia. The contribution of rhuMAb HER2 could be not be excluded; therefore, this death was considered possibly related to treatment.

The low incidence of cardiac dysfunction in this trial makes it difficult to identify predisposing risk factors. Cardiac adverse events were not anticipated before study initiation, and noninvasive cardiac monitoring was not mandated for this study. Anthracycline exposure is a recognized risk factor.[26] In fact, the observed incidence of cardiac dysfunction was slightly higher than the 2% incidence that would be expected in patients who had received a cumulative doxorubicin dose of approximately 325 mg/m^2.[27]

The pharmacokinetic profile of rhuMAb HER2 observed in the current study was consistent with the results of previous phase II trials.[17,18] The elimination half-life of 6 days enables the use of a weekly administration schedule. Approximately 90% of treated patients achieved the trough serum concentration of 20 μg/mL that was defined as efficacious in the animal models. A study of single-agent rhuMAb HER2 at a higher weekly dose of 4 mg/kg is underway. Importantly, the level of baseline shed antigen did not influence the likelihood of tumor response, which

indicates that this antigen does not interfere with the activity of rhuMAb HER2. The average steady-state serum trough concentration of rhuMAb HER2 (~70 μg/mL) is greatly in excess of the level of baseline shed antigen.

rhuMAb HER2 produced objective responses in a wide variety of patients. Response rates seemed to be higher among patients with higher levels of HER2 overexpression and among those with a longer time to first relapse. Although three factors were significantly associated with prolonged time to disease progression (ie, HER2 overexpression at the 3+ level, > 6 months to first relapse, and single metastatic disease site), objective responses were observed across the spectrum of patient characteristics.

A second large trial was recently completed to evaluate the safety and efficacy of rhuMAb HER2 in combination with chemotherapy.[19] Addition of rhuMAb HER2 to first-line chemotherapy with anthracycline-cyclophosphamide or paclitaxel significantly increases clinical benefit, as assessed by time to progression, response rate and duration, and survival. The results of the rhuMAb HER2 clinical trials suggest that a better understanding of genetic alterations in cancer can lead to new targeted approaches to cancer treatment.

In summary, this study supports the use of rhuMAb HER2 for women with HER2-overexpressing metastatic breast cancer. The benefits of this therapy, durable objective responses, and favorable toxicity profile indicate that rhuMAb HER2 is an important new treatment option for women who have tumors that overexpress HER2.

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