Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients With HER2/*neu*-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment

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Purpose: To determine the toxicity, pharmacokinetics, response rate, and response duration of intravenous (IV) administration of recombinant, humanized anti-p185^{HER2} monoclonal antibody (rhuMAb HER2) plus cisplatin (CDDP) in a phase II, open-label, multicenter clinical trial for patients with HER2/*neu*-overexpressing metastatic breast cancer.

Patients and Methods: The study population consisted of extensively pretreated advanced breast cancer patients with HER2/*neu* overexpression and disease progression during standard chemotherapy. Patients received a loading dose of rhuMAb HER2 (250 mg IV) on day 0, followed by weekly doses of 100 mg IV for 9 weeks. Patients received CDDP (75 mg/m^2) on days 1, 29, and 57.

Results: Of 37 patients assessable for response, nine (24.3%) achieved a PR, nine (24.3%) had a minor response or stable disease, and disease progression occurred in 19 (51.3%). The median response duration was 5.3 months (range, 1.6-18). Grade III or IV toxicity was observed in 22 of 39 patients (56%). The toxicity profile reflected that expected from CDDP alone with the most common toxicities being cytopenias (n = 10), nausea/vomiting (n = 9), and asthenia (n = 5). Mean pharmacokinetic parameters of rhuMAb HER2 were unaltered by coadministration of CDDP.

Conclusion: The use of rhuMAb HER2 in combination with CDDP in patients with HER2/*neu*-overexpressing metastatic breast cancer results in objective clinical response rates higher than those reported previously for CDDP alone, or rhuMAb HER2 alone. In addition, the combination results in no apparent increase in toxicity. Finally, the pharmacology of rhuMAb HER2 was unaffected by coadministration with CDDP.

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THE HER2/*neu* GENE encodes a 185-kd transmembrane protein that is a member of the type I family of growth factor receptors. Amplification of this gene is found in approximately 25% of human breast cancers and results in overexpression of the 185-kd encoded receptor tyrosine kinase, which is homologous to the epidermal growth factor receptor (EGFR). Overexpression of p185$^{HER2/neu}$ is an independent predictor of both relapse-free and overall survival in patients with breast cancer.[1-4] In addition, overexpression of this gene has prognostic significance in patients with ovarian,[2] gastric,[5] endometrial,[6] and salivary gland malignancies.[7] In breast cancer, overexpression of HER2/*neu* is also associated with a number of other adverse prognostic factors that include advanced pathologic stage,[4] number of metastatic axillary lymph nodes,[2] absence of estrogen and progesterone receptors,[8] increased S-phase fraction,[9] DNA ploidy,[10] and high nuclear grade.[11] A role for the HER2/*neu* alteration in metastasis has also been suggested given the increased occurrence of visceral metastasis[12] and micrometastatic bone marrow disease in patients with HER2/*neu* overexpression.[13] Like many other cell-surface receptors, a soluble form of the extracellular domain (ECD) of p185$^{HER2/neu}$ can be shed from the surface of tumor cells and is detectable in the sera of experimental animals that bear HER2/*neu*-overexpressing xenografts, as well as in the sera of approximately 20% to 25% of patients with locally advanced or metastatic breast cancer.[14-16] Patients with elevated serum levels of shed HER2/*neu* ECD have a decreased response to hormonal therapy and shortened overall survival compared with patients without shed HER2/*neu* ECD.[14,16]

A murine monoclonal anti-HER2 antibody, 4D5, known to have antiproliferative activity against HER2/*neu*-overex-

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pressing human breast carcinoma cells in vitro and against breast cancer xenografts with HER2/*neu* overexpression in vivo, was humanized, which resulted in a human immunoglobulin (IgG1) molecule with retained murine sequences only in the complementarity determining regions. The resultant molecule has improved binding affinity to the extracellular domain of HER2/*neu* (kd = 0.1 nM *v* 0.3 nM for murine 4D5) and similar growth inhibitory activity against HER2/*neu*-overexpressing cell lines and xenografts.[17]

Previous work has shown that treatment with monoclonal antibodies directed against EGFR in combination with the cytotoxic drug cisplatin (CDDP) resulted in a marked reduction in both size and number of human epidermoid carcinoma xenografts that overexpressed EGFR.[18] Using a similar experimental approach, we have shown a synergistic, cytocidal effect against cell lines and xenografts with HER2/*neu* overexpression by using monoclonal anti-HER2/*neu* antibodies plus CDDP.[19] The mechanism of this effect appears to involve a decreased capacity of HER2/*neu*-overexpressing cells to repair CDDP-induced DNA adducts after pretreatment with anti-HER2/*neu* antibodies.[19-21] This activity, which we have termed receptor-enhanced chemosensitivity (REC), has potential clinical application based on the fact that (1) the dose-effect relationship of the anti-HER2/*neu* antibody plus CDDP is synergistic, (2) this synergistic effect is specific for cells that overexpress the HER2/*neu* receptor, (3) the combination of CDDP plus anti-HER2/*neu* antibody results in a two-log increase in cell killing, and (4) the combination yields pathologic complete remissions against HER2/*neu*-overexpressing human breast carcinoma xenografts in athymic mice.[19]

Pursuant to these preclinical observations, a series of phase I clinical trials were initiated and conducted at the University of California at Los Angeles to determine the safety and pharmacology of the murine monoclonal antibody 4D5, as well as the recombinant, humanized anti-$p185^{HER2}$ antibody monoclonal (rhuMAb HER2), both alone and in combination with CDDP. These studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models. In addition, administration of this anti-HER2/*neu* antibody was safe; the only toxicity was low-grade fever that occurred with the first infusion and/or pain at the site of known tumor deposits in a minority of patients. Moreover, these studies showed that rhuMAb HER2 was not immunogenic in contrast to murine monoclonal antibody 4D5. Finally, the phase I studies showed that the combination of rhuMAb HER2 and CDDP showed significant antitumor efficacy, with four of 15 patients who achieved objective responses, which included three partial responses and one sustained complete remission that lasted in excess of 5.5 years without subsequent treatment. Based on these findings, we designed the current phase II trial with the following objectives: (1) to determine the overall response rate and response duration of intravenous (IV) rhuMAb HER2 plus CDDP in an open-label, multicenter clinical trial for patients with HER2/*neu*-overexpressing metastatic breast cancer who have shown disease progression while undergoing standard chemotherapy treatment; (2) to document the tolerance and toxicity of rhuMAb HER2 plus CDDP; and (3) to determine the pharmacokinetics of rhuMAb HER2 when administered in combination with CDDP.

PATIENTS AND METHODS

Eligibility Criteria

Women aged from 18 to 75 years with a primary histologic diagnosis of invasive breast cancer, with radiographically or visually measurable and assessable metastatic disease documented by physical examination or radiographic findings, were considered for enrollment. Patients were required to have evidence of overexpression (2 + to 3 +) of the HER2/*neu* proto-oncogene in their malignant cells as determined by immunohistochemical analysis (Roche Biomedical Laboratories, Research Triangle Park, NC), and were required to have documentation of objective tumor progression while receiving active chemotherapy for breast cancer. No therapy of any kind (cytotoxic, cytokine, or hormonal) was allowed within the 3 weeks before study entry. In addition, no therapy with mitomycin or nitrosoureas was allowed within 6 weeks of study entry. A Karnofsky performance status (KPS) greater than 60%; life expectancy of 3 months or greater; normal serum calcium level ($\leq$ 10.5 mg/dL); and preserved cardiac, renal (serum creatinine level $\leq$ 1.5 mg/dL, creatinine clearance $\geq$ 60 mL/min, $\leq$ 2 + proteinuria), hepatic (bilirubin level $\leq$ 1.5 mg/dL), pulmonary (forced expiratory volume in 1 second $\geq$ 70% of predicted value), hematologic (WBC count $\geq$ 3,000/μL, granulocyte count $\geq$ 1,500/μL, platelet count $\geq$ 125,000/μL), and coagulation (prothrombin time $<$ 14 seconds, partial thromoplastin time $<$ 35 seconds) function were all required. All patients signed a written, internal review board–approved, informed consent document. Patients were excluded for active infection, pregnancy or lactation, significant cardiac disease (New York Heart Association class III or IV), known hemorrhagic diathesis, hepatic metastases that involved greater than 50% of the liver parenchyma, lymphangitic pulmonary metastasis, CNS metastasis, bone-only metastasis, prior treatment with CDDP or other cisplatin analogues, previous therapy with a monoclonal or polyclonal antibody, or concomitant use of any investigational agent.

Study Design

Eligible patients received a 250-mg loading dose of rhuMAb HER2 IV day 0, followed by 100 mg IV weekly for a total of eight doses. Patients also received CDDP 75 mg/m^2 day 1 of treatment, with repeat doses on days 29 and 57. Clinical response was assessed on day 70. Responsive patients or patients with stable disease were eligible for entry onto a maintenance phase program after day 70. The maintenance

phase protocol consisted of rhuMAb HER2 100 mg IV weekly plus CDDP 75 mg/m^2 IV every 4 weeks until disease progression or prohibitive toxicity ensued.

Treatment Plan

A baseline pretreatment evaluation that included a complete history and physical examination, 12-lead ECG, chest radiograph, serum pregnancy test, complete blood count, urinalysis, creatinine clearance, serum chemistries (which included hepatic function tests), coagulation studies, hepatitis serologies, audiologic testing, pulmonary function tests, and baseline tumor measurements was performed within 2 weeks before study entry. Study patients were monitored weekly by physical examination, complete blood counts, serum chemistries, and coagulation studies. All rhuMAb HER2 doses were administered in 250 mL of 0.9% sodium chloride solution infused IV over 90 minutes. Vital signs were recorded before each dose, at the end of the infusion, and 1 hour postinfusion. Serum samples were collected just before and 1 hour after each rhuMAb HER2 dose for pharmacokinetic analysis of rhuMAb HER2, presence of shed p185^{HER2} ECD, and detection of anti–rhuMAb HER2 antibodies. All CDDP doses were administered 1 day after scheduled rhuMAb HER2 doses, consisted of CDDP 75 mg/m^2 diluted in 500 mL of 0.9% sodium chloride solution, and were administered IV over 60 minutes after hydration with a minimum of 500 mL of 5% dextrose/0.9% sodium chloride solution. After CDDP administration, patients received an additional 500 mL of 5% dextrose/0.9% sodium chloride solution. Additional hydration, mannitol, furosemide, and electrolyte solutions were administered as medically indicated. Antiemetic therapy consisted of dexamethasone 20 mg IV before CDDP administration and ondansetron 0.15 mg/kg IV before CDDP administration and 1.5 and 3.5 hours after the CDDP infusion. A graded toxicity scale based on the modified National Cancer Institute criteria was used to assess toxicity. Dose modification of CDDP to 50% of the original dose was performed for grades I to II nephrotoxicity or grades III to IV gastrointestinal toxicity. For any other grades III to IV toxicity, treatment was reinstituted at doses of CDDP of 50 mg/m^2 and rhuMAb HER2 of 50 mg IV after resolution of toxicity. Response criteria were defined as follows: complete response, disappearance of all radiographically and/or visually apparent tumor; partial response, reduction of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions with no new lesions detected; minor response, a reduction of 25% to 49% in the sum of the products of the perpendicular diameters of all measurable lesions with no new lesions detected; stable disease, not meeting the criteria for response or progression; and progressive disease, objective evidence of an increase of 25% in any measurable lesion or the appearance of any new lesion. All objective responses were assessed by an independent response evaluation committee comprised of a medical oncologist and radiologist who were otherwise not involved in the conduct of this study.

*Detection of HER2/*neu *Oncogene Overexpression in Clinical Tissue Specimens*

Patterns of HER2/*neu* expression were evaluated by a modification of published immunohistochemical techniques that used a murine monoclonal antibody (4D5) directed against HER2/*neu*.[2,22] Four-micron sections from formalin-fixed, paraffin-embedded tissues were cut and mounted on positively charged slides. Tissue sections were deparaffinized and endogenous peroxidase activity was quenched with 1% hydrogen peroxide in methanol. Sections were digested with 1 mg/mL of protease in phosphate buffered saline (PBS) and allowed to incubate with horse serum to block nonspecific antibody binding. Primary antibody (4D5; Genentech, Inc, South San Francisco, CA) was applied (10 μg/mL) and sections were allowed to incubate at 4°C for 18 hours. Sections were washed with PBS and treated with a biotinylated antimouse secondary antibody (Vector Laboratories, Inc, Burlingame, CA). After rinsing with PBS, sections were incubated with avidin-biotinylated enzyme complex (Vector Laboratories, Inc). Sections were then rinsed in PBS, and antibody binding was detected by staining with a diaminobenzidine/hydrogen peroxide chromogen solution. Sections were rinsed in deionized water, counterstained in Harris hematoxylin, dehydrated through graded alcohols, cleared in xylene, and coverslipped. The scoring system for interpretation of HER2/*neu* immunostaining is as follows: 0, 10% or less of tumor cells show any level of positive staining; 1 +, barely perceptible light membranous rimming that may not totally encircle the cell membrane; 2 +, light to moderate membranous rimming that totally encircles the membrane; and 3 +, moderate to strong membrane rimming that totally encircles the membrane.

Pharmacokinetics of rhuMAb HER2

The concentration of rhuMAb HER2 in serum was measured by means of an enzyme-linked immunosorbent assay (ELISA) with the ECD of p185^{HER2} as the coat antigen. In this ELISA format, 100 μL of p185^{HER2} (Genentech, Inc) was added to MaxiSorp 96-well microtiter plates (Nunc, Roskilde, Denmark) at 1 mg/mL in 0.05 mol/L of sodium carbonate, pH 9.6. After overnight incubation at 2° to 8°C, the plates were washed three times with ELISA wash buffer (PBS that contained 0.05% Tween-20) using a Biotek EL304 platewasher (Bio-tek Instruments, Inc, Winooski, VT). The plates were then blocked with 200 μL per well of ELISA diluent (PBS that contained 0.5% bovine serum albumin [BSA]; 0.05% Tween-20; and 0.05% Proclin300, pH 7.2) for 1 to 2 hours at ambient temperature with agitation. After blocking, plates were washed again three times with ELISA wash buffer. Subsequently, 100 μL of standards, samples, or controls were added to duplicate wells and allowed to incubate for 1 hour at ambient temperature. The standard curve range for the assay is 1.56 to 100 μg/mL. After the sample/standard incubation, the plates were washed six times with ELISA wash buffer and 100 μl of goat antihuman IgG Fc-horseradish peroxidase (HRP), freshly diluted to its optimal concentration in ELISA diluent, was added to the plates. After a 1-hour incubation, the plates were washed six times in ELISA wash buffer and 100 μL of PBS, pH 7.2, that contained 2.2 mmol/L of orthophenylene diamine (Sigma Chemical Co, St Louis, MO) and 0.012% (vol/vol) hydrogen peroxide (Sigma Chemical Co) were added to each well. When color had fully developed, the reaction was stopped with 100 μL per well of 4.5 mol/L of sulfuric acid. The absorbencies of the well contents were read at 492 nm minus 405 nm reference absorbance using an automatic plate reader (Molecular Devices, Palo Alto, CA). A four-parameter curve fit program was used to generate the standard curve, from which sample and control concentrations were interpolated.

Detection of Anti-rhuMAb HER2 Antibodies in Serum

An antibody titer ELISA was developed to measure the presence and titer of antibodies against rhuMAb HER2 in human sera. The positive control in the ELISA was an antiserum prepared against rhuMAb HER2 in cynomologous monkeys. The negative control was a human serum pool prepared from a panel of healthy donors. Briefly, 100 μL of rhuMAb HER2 was added to 96-well microtiter plates at 1 μg/mL in 0.05 mol/L of sodium carbonate buffer, pH 9.6. After overnight

incubation at 4°C, plates were washed with ELISA wash buffer (PBS that contained 0.05% Tween-20 and 0.01% thimerosal) and blocked for 1 hour with ELISA diluent (PBS that contained 0.05% Tween-20, 0.5% BSA, and 0.01% thimerosal). Subsequently, 50 µL of sample, positive control, or negative control and 50 µL of biotin-rhuMAb HER2 were added to appropriate wells and allowed to incubate for 1 hour at room temperature (RT). The titer of the positive control was determined by an initial 1:100 dilution of the sample followed by serial 1:2 dilutions. The plates were washed in ELISA wash buffer, then 100 µL of PBS that contained 2.2 mmol/L of orthophenylene diamine (OPD) and 0.012% hydrogen peroxide was added to each well. The colorimetric reaction was quenched with 100 µL of 4.5 mol/L of sulfuric acid and absorbance was measured at 492-nm wavelength in an automated plate reader. Intra-assay and interassay variability averaged 2.6% and 12.1%, respectively.

Detection of p185$^{HER2/neu}$ ECD in Serum

The method for detection of shed HER2 ECD levels in serum is an ELISA-based assay and has been described in detail elsewhere.[23] Briefly, the ELISA uses pairs of anti-HER2 monoclonal antibodies (Genentech, Inc) that recognize mutually exclusive determinants of the ECD of p185$^{HER2/neu}$. Wells were coated overnight at 4°C with MAb 7F3, which does not compete with rhuMAb HER2 for shed HER2 ECD binding. Assay standards (recombinant, p185$^{HER2/neu}$ ECD) and patient samples were added to appropriate wells and allowed to incubate for 2 hours. After a wash step, secondary antibody was added (MAb 4D5 to detect free shed HER2 ECD and MAb 2C4 to detect total shed HER2 ECD) for 2 hours. The bound conjugate was detected with OPD substrate and the resulting absorbance was measured at a 490-nm wavelength. The range of the assay is 2.75 to 1,800 ng/mL in serum or plasma.

RESULTS

Patient Characteristics

Thirty-nine patients were enrolled onto the study, and their characteristics are listed in Table 1. Patients ranged in age from 29 to 75 years. Eighty-six percent of the patients had a KPS of 90% or greater. High levels of HER2/*neu* overexpression (3+) were observed in 82% of the patients. Twenty-four of 37 patients (65%) who had measurements of serum shed HER2/*neu* ECD performed before treatment had levels greater than 2.75 ng/mL (the lower limit of detection in the ELISA assay). Only one third of the patients for whom hormone receptor data were available were either estrogen receptor– or progesterone receptor–positive, consistent with previous studies that showed an inverse correlation between HER2/*neu* overexpression and hormone receptor expression.[24] Twenty-seven of the 39 patients (69%) were postmenopausal at diagnosis, and a majority of the patients had a high disease burden, with 18 of 39 patients (46%) who had three or more sites of metastatic disease. This patient population had been heavily pretreated before study entry, with 35 of 39 patients (90%) in whom two or more prior chemotherapeutic regimens had failed for metastatic disease. In addition, all patients had to show resistance to standard chemotherapy as evidenced by tumor progression while receiving chemotherapy treatment to be eligible for this trial.

Table 1. Patient Characteristics

Characteristic	No.	%
Age, years		
Mean	50	
Range	29-75	
Karnofsky performance status, % (n = 37)		
100	22	59
90	10	27
80	4	11
70	1	3
Level of HER2/*neu* overexpression		
2 +	7	18
3 +	32	82
Detection of shed HER2 ECD (n = 37)		
Receptor status		
Estrogen receptor–positive (n = 37)	13	35
Progesterone receptor–positive (n = 36)		
Menopausal status		
Premenopausal	10	26
Postmenopausal	27	69
Perimenopausal	2	5
No. of metastatic sites		
1	7	18
2	14	36
≥ 3	18	46
Sites of metastasis		
Lung	19	49
Lymph node	19	49
Bone	18	46
Chest wall/skin	17	44
Liver	14	36
Breast	4	10
Ovary	1	2.5
Eye	1	2.5
No. of prior chemotherapy regimens for metastatic disease		
1	4	10
2	18	46
≥ 3	17	44
Prior hormonal therapy	21	54
Prior radiotherapy	27	69

NOTE. N = 39.

Toxicity

Toxicity data are listed in Table 2. During the main study, 105 cycles of CDDP were administered in combination with 314 weekly IV doses of rhuMAb HER2. During the maintenance phase, an additional 81 cycles of CDDP and 434 doses of rhuMAb HER2 were administered. Thirty-seven patients had KPS assessed at baseline and at least once during the course of the study. The KPS remained unchanged in 19 patients (the majority of whom had

Table 2. Grade 3 or 4 Clinical Adverse Events, Irrespective of Causality

Event	Grade 3		Grade 4	
	No.	%	No.	%
Main study (n = 39)				
Accidental injury	1	3	0	0
Back pain	1	3	0	0
Infection	2	5	0	0
Dyspnea	2	5	0	0
Anorexia	1	3	0	0
Nausea and/or vomiting	7	18	0	0
Increased AST	1	3	0	0
Increased alkaline phosphatase	1	3	0	0
Hyperbilirubinemia	3	8	1	3
Nephrotoxicity	0	0	1	3
Asthenia	5	13	0	0
Hypertonia	1	3	0	0
Leukopenia	2	5	0	0
Anemia	3	8	0	0
Thrombocytopenia	4	10	0	0
Maintenance phase (n = 19)				
Hyperglycemia	1	5	0	0
Sepsis	0	0	1	5
Cardiomyopathy	1	5	0	0
Nausea and/or vomiting	2	10	1	5
Hyperbilirubinemia	1	5	0	0
Peripheral neuropathy	2	10	0	0
Leukopenia	1	5	0	0
Anemia	1	5	0	0
Thrombocytopenia	4	21	0	0

KPS > 80%), improved in two patients, and decreased in 16 patients. Four patients experienced weight loss in excess of 10% of their baseline body weight during the study. Four patients experienced fever greater than 38°C during rhuMAb HER2 infusion or at the postinfusion measurement. There was no significant difference in blood pressure between pretreatment and posttreatment measurements across all treatment days. During the main study, 22 of 39 patients (56%) experienced at least one episode of grade III or IV toxicity. The most frequent grade III toxicities observed were nausea and/or vomiting in seven patients (18%), asthenia in five patients (13%), thrombocytopenia in four patients (10%), anemia in three patients (8%), and leukopenia in two patients (5%). One episode of reversible grade IV nephrotoxicity was registered during the main study, and this patient's renal function recovered after 9 days. One patient developed grade IV hyperbilirubinemia during the main study. This event was believed to be disease-related rather than treatment-related. During the maintenance phase, 10 of 19 patients (53%) experienced grade III or IV toxicity. The most frequent grade III toxicities were thrombocytopenia, four patients (21%); nausea and/or vomiting, two patients (10%); and peripheral neuropathy, two patients (19%). Two patients experienced grade IV toxicity during the maintenance phase, one patient with sepsis and another with gastrointestinal toxicity. Grade III/IV toxicity reported as possibly related to rhuMAb HER2 was infrequent and was reported in six of 39 patients (15%). These events consisted of grade III cytopenia in three patients, grade III nausea or anorexia in two patients, grade III asthenia in one patient, and grade III hyperbilirubinemia in one patient. In most of these cases, we were not able to dissociate toxicity possibly related to rhuMAb HER2 from toxicity likely caused by CDDP or the patient's underlying disease. There was no report of grade IV toxicity attributable to rhuMAb HER2 administration. We observed no evidence of increased toxicity in those tissues that are known to express $p185^{HER2}$, ie, lung, gastrointestinal tract, CNS, or skin, nor was there any toxicity at the IV injection site. Three patients discontinued the main study treatment because of toxicity or intercurrent medical illness (two with nephrotoxicity and one with hepatic failure), and one patient discontinued the maintenance phase as a result of cardiomyopathy. The latter patient had a cumulative anthracycline dose of 420 mg/m^2 and had also received prior chest-wall irradiation. This patient also had a history of concurrent hypertension and diabetes. Four patients died before day 70; however, in each case, patients had been removed from the study because of disease progression before death. In summary, the toxicities observed were consistent with those previously reported for CDDP alone in a heavily pretreated population of breast cancer patients (Table 3).

Response and Response Duration

Tumor response was evaluated on day 70 during the main study and every 10 weeks during the maintenance phase protocol. Patients with symptoms or suspected progressive disease could have tumor assessment at any time during the course of the study. Thirty-seven of the 39 patients enrolled (95%) were assessable for tumor response (Table 4). Assessable patients were defined as those who met all eligibility criteria, received at least one dose of therapy, and underwent response evaluation other than at baseline. Patient deaths before tumor evaluation were considered assessable (progressive disease). Two patients were not assessable for tumor response because of adverse events before tumor assessment. During the main study, the median number of doses of rhuMAb HER2 per patient was nine (range, one to nine doses). The median number of doses of CDDP per patient was three, and the average administered dose was 74 mg/m^2. Three patients missed one dose of CDDP or received dose reduction as dictated by the study guidelines. Nineteen patients (49%) entered the maintenance phase protocol, in

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