Patent Docket P1256R1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Susan D. Hellman (as amended) Serial No.: 09/208,649 Filed: December 10, 1998 For: TREATMENT WITH ANTI-ErbB2 ANTIBODIES	Group Art Unit: 1642 Examiner: J. Hunt

#20
51201

DECLARATION UNDER 37 CFR §1.131

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Susan D. Desmond-Hellmann, M.D., M.P.H., do hereby declare and say as follows:

1. I am an inventor of the subject matter of the above-identified patent application. I am the sole inventor of method claims 1-13 and 24-27 of the above application. All work described hereinafter was performed by me or on my behalf in the United States of America.

2. Prior to December 12, 1996, I conceived of and reduced to practice a method of treating a human patient with a disorder characterized by overexpression of ErbB2 receptor, or with metastatic breast cancer, comprising administering a combination of an anti-ErbB2 antibody and a taxoid, in the absence of an anthracycline derivative, to the patient in an amount effective to extend the time to disease progression (TTP) in the patient.

EXHIBIT
4
Desmond-Hellmann
3/23/2018 C.A.R.

3. Evidence of the reduction to practice of the claimed invention is set forth in the exhibits attached to this declaration with dates obscured. The patient's initials in Exhibit B are also redacted to ensure confidentiality of the identity of the patient.

4. Attached as Exhibit A is the H0648g Protocol which was amended prior to December 12, 1996 to include a treatment regimen which involved combining an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative.

5. As noted in Sections 3 and 4 of the H0648g Protocol, this was a Phase III study of chemotherapy alone or in combination with recombinant humanized anti-HER2 monoclonal antibody (rhuMAb HER2) in women with HER2 overexpression who had not received prior cytotoxic chemotherapy for metastatic breast cancer.

6. Section 5.3.1 of the H0648g Protocol details the administration and dosage of rhuMAb HER2. On Day 0, a 4 mg/kg loading dose of rhuMAb HER2 was administered IV over a 90-minute period. Beginning on Day 7, patients received weekly administration of 2 mg/kg rhuMAb HER2 IV over a 90-minute period. If the first dose was well tolerated, subsequent infusions of rhuMAb HER2 were given in 30 minutes. Section 5.3.2 of the protocol explains that patients further received one of two chemotherapy regimens for a minimum of six cycles: a) cyclophosphamide and doxorubicin or epirubicin, if patients had not received anthracycline therapy in the adjuvant setting, or b) paclitaxel, if patients had received any anthracycline therapy in the adjuvant setting. The initial dose of rhuMAb HER2 preceded the first cycle of either chemotherapy regimen by 24 hours. As noted in subsection b. of Section 5.3.2, paclitaxel was given at a dose of 175 mg/m^2 over 3 hours by IV infusion. Section 5.5 explains that concomitant chemotherapy other than protocol-specified chemotherapy was not allowed during the study period. Section 8.1.1 of the H0648g Protocol states that the primary endpoints of the study were TTP and safety profile of rhuMAb HER2. The dosages of rhuMAb HER2 and paclitaxel administered extended TTP in patients treated with the combination. It is clear from these sections of the protocol, that

patients were being treated with a combination of an anti-ErbB2 antibody (rhuMAb HER2) and a taxoid (paclitaxel), in the absence of an anthracycline derivative, in an amount effective to extend TTP in the patients.

7. Case report forms (CRFs) detailing administration of rhuMAb HER2 to a patient followed by administration of paclitaxel to that patient the following day, according to Sections 5.3.1 and 5.3.2(b) of the H0648 Protocol, are attached as Exhibit B. The infusions described in Exhibit B and subsequent infusions of the combination of rhuMAb HER2 and paclitaxel for the total course of therapy were administered to the patient prior to December 12, 1996.

8. Thus, it is clear that the method I conceived of for treating a human patient with a disorder characterized by overexpression of ErbB2 receptor, or with metastatic breast cancer, comprising administering a combination of an anti-ErbB2 antibody and a taxoid, in the absence of an anthracycline derivative, to the patient in an amount effective to extend the TTP in the patient was reduced to practice before December 12, 1996.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 4/19/01

Susan D. Desmond-Hellmann, M.D., M.P.H.

PROTOCOL

TITLE: **CHEMOTHERAPY AND ANTIBODY RESPONSE EVALUATION (CARE): A PHASE III, MULTINATIONAL, RANDOMIZED STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) COMBINED WITH CHEMOTHERAPY IN PATIENTS WITH HER2 OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER**

PROTOCOL NUMBER: H0648g

STUDY DRUG: Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2)

IND: BB-IND 4517

MEDICAL MONITOR: Steven Shak, M.D.

SPONSOR: Genentech, Inc.
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DATE FINAL:

AMENDED:

EXHIBIT A

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SYNOPSIS

This protocol describes a Phase III, randomized, controlled, multinational study in patients with HER2 overexpression who have not received cytotoxic chemotherapy for metastatic breast cancer. The objective of the study is to determine the safety and efficacy of recombinant humanized anti-HER2 monoclonal antibody (rhuMAb HER2) used in addition to chemotherapy. Patients will be treated with either paclitaxel or an anthracycline-containing regimen (e.g., doxorubicin or epirubicin) as prescribed by their physician.

Approximately 450 patients will be enrolled in the study and randomized to one of two treatment arms: 1) the active arm, which consists of rhuMAb HER2 in combination with cytotoxic chemotherapy (the chemotherapy regimen must be determined prior to randomization), or 2) the control arm, which consists of cytotoxic chemotherapy alone (no study drug). All patients randomized to the active arm of the study will receive rhuMAb HER2 as a 4 mg/kg intravenous (IV) loading dose on Day 0 and then weekly at a dose of 2 mg/kg IV throughout the course of the study. Patients who are randomized to the control arm (cytotoxic chemotherapy alone, without rhuMAb HER2) will be evaluated and treated similarly to patients randomized to active treatment. Tumor evaluations will occur at prescribed intervals during the study to assess disease progression. Patients will remain on study until disease progression is documented by an independent Response Evaluation Committee.

After the completion of cytotoxic chemotherapy, those patients assigned to rhuMAb HER2 will continue to receive weekly rhuMAb HER2 infusions. Patients from the control group will be eligible to receive rhuMAb HER2 in an open-label study (H0659g) following documented progression of their disease. All patients who develop disease progression and do not enroll in the subsequent study will be followed for survival information every 2 months until termination of statistical analysis of the study.

The primary endpoint of the study will be time to disease progression. Complete and partial response rates and response duration will be determined and compared between the rhuMAb HER2 and control groups. Quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life instrument with the module for breast cancer. A supplemental instrument will be used to explore pharmacoeconomic issues in the treatment groups. Time to treatment failure, including patients who either have progressive disease or have discontinued chemotherapy due to toxicity, will be a secondary, supportive analysis.

1. INTRODUCTION

1.1 HER2 AND CANCER

Cancer of the breast is the most common malignancy occurring in women. On average, women experience a 1 in 9 chance of developing breast cancer during their lives. In the United States alone, there are approximately 185,000 new cases of breast cancer each year. Despite advances in early detection and surgical and adjuvant therapy, nearly 50,000 women will develop metastatic disease each year. Conventional, cytotoxic chemotherapy plays an important role in the management of patients with breast cancer. Reduction in tumor size can be achieved with chemotherapy. However, such treatment with chemotherapy causes patients to experience numerous side effects such as nausea, vomiting, and hair loss because of the non-specific way that such agents act on living cells. Despite such potent therapy, little impact on disease progression, overall survival, and patient quality of life has been achieved. Breast cancer remains the most common cause of non-preventable cancer death in women. New treatments specifically directed at the cancer in such a way as to delay disease progression while avoiding systemic toxicity would represent a significant advance in the care of patients.

Numerous efforts over the past few years have attempted to define the biologic factors governing tumor development, growth, and metastasis. Growth factors and their receptors are known to play critical roles in development, cell growth, and differentiation (1). Such receptors span the membrane of the cell. The extracellular domain binds to specific growth factors, while the intracellular domain transmits the growth signal. Expression of abnormal quantities of human epidermal growth factor receptor 2 (HER2) is observed in approximately 25% of tumors taken from women with breast cancer, suggesting that the overexpression of this growth factor receptor may contribute to malignant transformation and tumorigenesis (2,3,4). In most cases, overexpression of the HER2 protein, also called $p185^{HER2}$, results from gene amplification.

Overexpression of HER2 has been correlated with poor clinical outcome in patients with breast cancer. In an initial evaluation of 103 patients with breast cancer, those having more than three axillary lymph nodes were more likely to overexpress HER2 than patients with

less than three (2). In a subsequent evaluation of 86 node-positive patients with breast cancer, there was a significant correlation between the extent of gene amplification, early relapse, and short survival. The median period of disease-free survival is approximately 5-fold shorter in patients with more than five copies of the HER2 gene than in patients without gene amplification. This correlation was present even after correcting for nodal status and other prognostic factors in multivariate analyses. These findings were extended in 187 node-positive patients and indicated that gene amplification, increased amounts of mRNA (determined by Northern blotting), and protein expression (determined immunohistochemically) were also correlated with shortened survival time (3).

Several lines of evidence support a direct role for $p185^{HER2}$ overexpression in the pathogenesis and poor clinical course of human tumors (5). When the mutated gene is transfected into mouse fibroblast cells (NIH-3T3) it causes transformation, and the resulting cells are tumorigenic in the nude mouse (6,7). Additionally, transgenic mice that overexpress the *neu* gene (the rodent homolog of the human HER2 gene) develop breast cancer (8). Finally, specific antibodies to the extracellular domain of the human HER2 gene product inhibit the growth of experimental tumors that overexpress the gene (9–12). These data suggest a direct role for HER2 in both malignant transformation and enhanced tumorigenicity. Therefore, a strategy to antagonize the abnormal function of overexpressed HER2 was developed to improve the course of patients with breast cancer.

Murine monoclonal antibodies (muMAbs) were produced against the extracellular domain of the HER2 receptor. One such antibody, called 4D5, was found to inhibit the proliferation of human tumor cells overexpressing HER2. Unfortunately, chronic administration of muMAbs in humans is limited by immune responses to the non-human protein. Therefore, regions of the murine antibody that determine anti-HER2 binding specificity were inserted into the framework of a generic human antibody (13). The resulting antibody, rhuMAb HER2, binds specifically to the HER2 protein. The antibody is highly homologous to native human immunoglobulin and is therefore referred to as humanized. An additional property of rhuMAb HER2 is that it induces antibody-dependent cellular cytotoxicity (ADCC) against tumor

cell lines in the presence of human peripheral blood mononuclear cells (PBMCs).

To increase the therapeutic potential of rhuMAb HER2 therapy, clinical strategies that combine the antibody with the agents used in conventional chemotherapy have been employed. Combining rhuMAb HER2 and cisplatin in the treatment of tumors that overexpress HER2 is supported by the results from several independent experimental investigations (14–17). There is evidence that HER2 antibodies interfere with DNA repair mechanisms of cells overexpressing $p185^{HER2}$ (15). rhuMAb HER2 has also been evaluated in combination with several other chemotherapeutic drugs, including doxorubicin, thiotepa, etoposide, 5-fluorouracil (18), and paclitaxel (19). In most cases, the effect of the antibody and the cytotoxic agent is at least additive.

Thus, there are at least three mechanisms by which rhuMAb HER2 could alter the progression of breast cancer. First, the antibody can antagonize the function of the growth-signaling properties of the HER2 system. Second, the antibody may signal immune cells to attack and kill the tumor target. Third, the antibody may augment chemotherapy-induced cytotoxicity.

1.2 CLINICAL STUDIES OF rhuMAb HER2

Three Phase I and two Phase II studies of rhuMAb HER2 are complete. In the first Phase I trial (H0407g), 16 patients with HER2-overexpressing tumors received a single dose (ranging from 10 to 500 mg) of rhuMAb HER2 administered intravenously (IV). Two patients developed chills during the infusion; fever developed in 4 patients (1 in each of the dose groups).

In the second Phase I trial (H0452g), 17 patients were treated with eight weekly doses of IV rhuMAb HER2 (ranging from 10 to 500 mg). Adverse events reported were not unexpected given the study population, and no clinically significant severe adverse events were attributed to rhuMAb HER2.

In the third Phase I trial (H0453g), 15 patients were treated with nine weekly doses of rhuMAb HER2 (ranging from 10 to 500 mg) and three

doses of cisplatin (100 mg/m^2) administered IV every 4 weeks. Two patients discontinued because of adverse events, 1 because of Grade 3 renal toxicity and Grade 4 thrombocytopenia, and 1 because of Grade 3 renal toxicity. As would be expected in a population receiving cisplatin, episodes of nausea and vomiting occurred frequently. Hearing loss was reported by 10 patients and required discontinuation of cisplatin in 1 patient. There was no clear relationship between rhuMAb HER2 and the incidence of any of these adverse events. Administration of cisplatin did not affect the pharmacokinetics of rhuMAb HER2.

Although the small number of patients and the lack of randomization preclude any statement being made about a possible dose effect in tumor responses, 4 of 6 patients in the 250-mg and 500-mg dose groups had a partial response (defined as a 50% reduction in tumor burden). One patient in the 250-mg dose group had supraclavicular nodes and multiple pulmonary metastases pretreatment, a partial response at Day 70, and was disease-free following a second 10-week course of 250 mg of rhuMAb HER2 plus cisplatin. She remains disease-free and well as of March 1996, and has had no additional therapy in the past 3 years. No responses were seen in the lower dose groups.

In the first Phase II trial of rhuMAb HER2 (H0551g), 46 patients with metastatic breast cancer overexpressing HER2 were treated with a 250-mg IV loading dose followed by 100 mg IV weekly for 10 weeks. Twenty-one patients with responses or stable disease at Day 77 entered the maintenance program; 1 patient remains to date. rhuMAb HER2 was well tolerated in this study. No deaths were attributed to study drug. The median time to disease progression was 2.8 months. Of the 43 evaluable patients, 5 (12%) had a complete or partial response, 16 (37%) had a minor response or stable disease, and the remaining 22 (51%) had progressive disease. The duration of the five responses (one complete, four partial) ranged from 1 month to 28 months (for the complete responder). The complete responder is a 51-year-old patient whose tumor is estrogen- and progesterone receptor–negative and who had four cycles of neoadjuvant doxorubicin prior to a left modified mastectomy for a poorly differentiated carcinoma. Biopsy-proven chest wall disease recurred within 2 months

of cessation of doxorubicin. rhuMAb HER2 was initiated and a partial response was seen by Day 77. A complete response was confirmed by negative biopsies 2 months later. The patient is continuing on weekly rhuMAb HER2 and has remained free of disease for nearly 34 months.

In the second Phase II trial (H0552g), 39 patients were treated with a 250-mg IV loading dose of rhuMAb HER2, followed by 100 mg IV weekly for 8 weeks. Cisplatin was given at a dose of 75 mg/m^2 every 4 weeks, 24 hours after rhuMAb HER2 administration. Nineteen patients with responses or stable disease entered the maintenance program; as of February 1996, all patients have discontinued treatment. No deaths were attributed to rhuMAb HER2 treatment. For the 36 evaluable patients, 9 (25%) had a partial response, 9 (25%) had a minor response or stable disease, and the remaining 18 patients (50%) had progressive disease. The median time to disease progression was 3.6 months. The duration of response ranged from 1.6 to 18 months (median = 5.7 months). With one quarter of the patients having a partial response, this study showed an encouraging overall tumor response to rhuMAb HER2 plus cisplatin in refractory patients with HER2-overexpressing metastatic breast cancer.

rhuMAb HER2 was administered safely, and there were few or no changes in vital signs. Adverse events and laboratory abnormalities were not unusual for this patient population. Three patients had an elevated serum creatinine >2.2 mg/dL. Two patients had fever (>38°C) during or after infusion. The observed toxicity did not appear to be greater than that expected with cisplatin therapy (20), and the observed response rate was higher than that expected with cisplatin treatment alone in this population. However, the lack of a control group precludes any definitive conclusion about the response rates seen in this study.

No antibodies to rhuMAb HER2 were detected in any of the five clinical studies.

1.3 STUDY RATIONALE

Given the important role that HER2 plays in the pathogenesis and progression of breast cancer, it is vital to test the hypothesis that rhuMAb HER2 treatment is a valuable addition to standard

chemotherapy. While it is desirable in clinical trials to avoid introduction of bias through the use of placebo, such a strategy has proved difficult to implement during some cancer clinical trials due to the limited life expectancy and requirements for venous infusions in patients with metastatic disease. In the present study, patients randomized to a control group will undergo concomitant therapy, tumor evaluation, and general health surveillance similar to patients assigned to the active therapy group. Importantly, the occurrence of the primary endpoint, disease progression, will be assessed by a Response Evaluation Committee composed of radiologists and oncologists, who will be blinded to study treatment and uninvolved with the daily and routine care of patients in the study. In this manner, the trial will effectively compare the effect of rhuMAb HER2 administration on disease progression.

2. OBJECTIVE

The goal of this study is to determine the efficacy and safety of rhuMAb HER2 used in addition to chemotherapy in patients whose metastatic breast cancer overexpresses HER2 and who have not received cytotoxic chemotherapy.

2.1 PRIMARY OBJECTIVES

The primary objectives of the study are:

- To compare the time to disease progression (as determined by the Response Evaluation Committee) in patients receiving rhuMAb HER2 plus cytotoxic chemotherapy with those receiving chemotherapy alone
- To further characterize the safety profile of rhuMAb HER2

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To compare overall response rates (complete and partial responses) between both treatment arms (rhuMAb HER2 vs. control)
- To compare the duration of response between both treatment arms in patients who have achieved a complete or partial response

- To compare the quality of life of both treatment arms using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life instrument with the breast cancer module
- To assess the pharmacokinetics of rhuMAb HER2 when co-administered with chemotherapy
- To determine 1-year survival estimates
- To compare time to treatment failure (e.g., discontinuing due to toxicity without progression)

3. STUDY DESIGN

This is a Phase III, randomized, controlled, multinational study of chemotherapy alone or in combination with rhuMAb HER2. Approximately 450 patients with HER2 overexpression who have not received cytotoxic chemotherapy for metastatic breast cancer will be enrolled in the study. Upon signing the consent form and meeting all eligibility criteria, patients will be equally randomized to one of two treatment arms: 1) the active arm, which consists of rhuMAb HER2 in combination with cytotoxic chemotherapy (the chemotherapy regimen must be determined prior to randomization), or 2) the control arm, which consists of cytotoxic chemotherapy alone (no study drug). All patients in the study will be required to follow similar study procedures.

All patients randomized to the rhuMAb HER2 arm will receive treatment as a 4 mg/kg IV loading dose on Day 0 (the first day of rhuMAb HER2 infusion, or the day of randomization for patients in the control group), then weekly at a dose of 2 mg/kg IV throughout the course of the study. The initial dose of rhuMAb HER2 will precede either chemotherapy regimen by 24 hours. Subsequent doses of rhuMAb HER2 may be given immediately before chemotherapy (on the same day) if the initial dose of rhuMAb HER2 was well tolerated. All patients, regardless of the original randomization, will be monitored during each study visit by a clinical assessment, a symptom-directed physical examination (if appropriate), and laboratory tests (see Appendix A, Study Flowchart). Routine tumor evaluations will be conducted for all patients at prescribed intervals during the study. All adverse events will be recorded.

After the completion of cytotoxic chemotherapy, those patients assigned to receive rhuMAb HER2 will continue weekly rhuMAb HER2

infusions until disease progression is confirmed by radiographic or other objective criteria or until study termination. Patients from the control group will be eligible to receive rhuMAb HER2 in an open-label study (H0659g) following documented progression of their disease, confirmed by an independent Response Evaluation Committee (see Section 7.1).

All patients who develop disease progression and do not enroll in the subsequent study will be followed for survival information every 2 months until termination of statistical analysis of the study.

The primary endpoint of the study will be time to disease progression as determined by the Response Evaluation Committee. The complete and partial response rates and response duration will be determined and compared between the groups. Quality of life will be assessed using the EORTC quality-of-life instrument with the breast cancer module. A supplemental instrument will be used to explore pharmacoeconomic issues in the treatment groups.

4. STUDY POPULATION

The study population will consist of women with HER2 overexpression who have not received prior cytotoxic chemotherapy for metastatic breast cancer. Approximately 450 patients (225 patients in each arm) are expected to participate in this study.

4.1 ELIGIBILITY CRITERIA

Patients must fulfill all of the following criteria to be eligible for study admission:

- Metastatic breast cancer
- Overexpression of the HER2 oncogene (2+ to 3+ as determined by immunohistochemistry or fluorescence in situ hybridization [FISH]) (see Appendix B)
- Bidimensionally measurable disease (including lytic bone lesions) by radiographic means, physical examination, or photographs

  Measurable disease is defined as any mass reproducibly measurable in two perpendicular diameters by physical examination, X-ray (plain films), computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, or photographs.

Osteoblastic metastases, pleural effusions, or ascites are not considered to be measurable. Measurable lesions must be at least 1 cm in greatest dimension. Enumeration of evaluable sites of metastatic disease and number of lesions in an evaluable site (e.g., lung) must be recorded on the appropriate Case Report Form (CRF). If a large number of pulmonary or hepatic lesions are present, the six largest lesions per site will be followed.

- The ability to understand and willingness to sign a written informed consent form
- Women ≥ 18 years
- Suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening laboratory assessments of hematologic, renal, hepatic, and metabolic functions

4.2 EXCLUSION CRITERIA

Patients with any of the following will be excluded from study entry:

- Prior cytotoxic chemotherapy for metastatic breast cancer

  Patients may have received prior hormonal therapy (e.g., tamoxifen) for metastatic disease or cytotoxic therapy in the adjuvant setting.
- Concomitant malignancy that has not been curatively treated
- A performance status of < 60% on the Karnofsky scale (see Appendix C)
- Pregnant or nursing women; women of childbearing potential, unless using effective contraception as determined by the investigator
- Bilateral breast cancer (either both primary tumors must have 2+ to 3+ HER2 overexpression, or the metastatic site must have 2+ to 3+ HER2 overexpression)
- Use of investigational or unlicensed agents within 30 days prior to study entry
- Clinically unstable or untreated metastases to the brain (e.g., requiring radiation therapy)

5. STUDY MEDICATION

See the rhuMAb HER2 Investigator Brochure for more information.

5.1 FORMULATION

5.1.1 Liquid Formulation

rhuMAb HER2 will be supplied by Genentech (the Sponsor) as a sterile liquid intended for parenteral administration. Each vial contains 10 mL of liquid rhuMAb HER2 designed to deliver 5 mg/mL. The study drug is formulated in sodium acetate, sodium chloride, polysorbate 20, and Water for Injection (WFI), USP. rhuMAb HER2 will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation does not contain a preservative and is suitable for single use only.

5.1.2 Lyophilized Formulation

North America: rhuMAb HER2 will be supplied for use as a freeze-dried preparation at a nominal content of 400 mg per vial for parenteral administration. The study drug is formulated in histidine, trehalose, and polysorbate 20. Each vial is reconstituted with 20 mL of Bacteriostatic Water for Injection (BWFI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. The reconstituted solution contains 22 mg/mL rhuMAb HER2 and will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation is designed for multiple use and must be used within 28 days after reconstitution.

Australia, Europe, and New Zealand: rhuMAb HER2 will be supplied for use outside of North America as a freeze-dried preparation at a nominal content of 150 mg per vial for parenteral administration. The study drug is formulated in histidine, trehalose, and polysorbate 20. Each vial is reconstituted with 7.0 mL of Sterile Water for Injection (SWI), USP, yielding a solution of 22 mg/mL rhuMAb HER2. Reconstituted rhuMAb HER2 will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation does not contain a preservative and is suitable for single use only.

5.2 STORAGE REQUIREMENTS

Vials of rhuMAb HER2 are shipped on wet ice and must be placed in a 2°C–8°C (36°F–46°F) refrigerator immediately upon receipt to ensure optimal retention of physical and biochemical integrity. DO NOT

FREEZE. rhuMAb HER2 may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of rhuMAb HER2 results in aggregation of the protein and may create cloudy solutions. rhuMAb HER2 should be clear to slightly opalescent and colorless to pale yellow.

5.2.1 Liquid Formulation

The liquid formulation does not contain a preservative and is suitable for single use only.

5.2.2 Lyophilized Formulation

North America: The reconstituted formulation (400-mg vial) is designed for multiple use. Unused drug may be stored for 28 days at 2°C–8°C (36°F–46°F).

Australia, Europe, and New Zealand: The reconstituted formulation (150-mg vial) does not contain a preservative and is suitable for single use only.

5.3 ADMINISTRATION AND DOSAGE

5.3.1 rhuMAb HER2

On Day 0, a 4 mg/kg loading dose of rhuMAb HER2 will be administered IV over a 90-minute period. Beginning on Day 7, patients will receive weekly administration of 2 mg/kg rhuMAb HER2 IV over a 90-minute period. If this first dose is well tolerated, subsequent infusions of rhuMAb HER2 may be given in 30 minutes. For patients in whom the initial or subsequent doses are not well tolerated, for example due to fever or chills, subsequent infusions may be shortened only after a dose is well tolerated.

rhuMAb HER2 will be administered in an outpatient setting. When study medication is administered to a patient, a physician and emergency resuscitation equipment must be available in the clinic for the duration of each visit. Patients must remain under medical supervision for 1 hour following completion of the initial loading dose of rhuMAb HER2. If no adverse events occur with the first shortened infusion, the postinfusion observation period for the second infusion

may be shortened to 30 minutes and eliminated entirely with the third and subsequent infusions.

5.3.2 Chemotherapy

Patients will receive one of two chemotherapy regimens for a minimum of six cycles, provided their disease is not progressing:
a) cyclophosphamide and doxorubicin or epirubicin, if patients have not received anthracycline therapy in the adjuvant setting, or b) paclitaxel, if patients have received any anthracycline therapy in the adjuvant setting. The initial dose of rhuMAb HER2 will precede the first cycle of either chemotherapy regimen by 24 hours. Subsequent doses of rhuMAb HER2 may be given immediately before chemotherapy administration if the initial dose of rhuMAb HER2 was well tolerated. If the first dose of rhuMAb HER2 was not well tolerated, subsequent infusions should continue to precede chemotherapy administration by 24 hours. Patients may continue to receive chemotherapy beyond six cycles if, in the opinion of the treating physician, they are continuing to receive treatment benefit.

a. Cyclophosphamide and Doxorubicin or Epirubicin

Cyclophosphamide 600 mg/m^2 will be given either by IV push over a minimum period of 3 minutes or by infusion over a maximum period of 2 hours, according to institutional protocol. Patients should be adequately hydrated according to institutional protocol.

Investigators are reminded of the potential cardiotoxic complications of accumulating doses of anthracyclines.

Doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 will be given either by slow IV push over a minimum period of 3–5 minutes or by infusion over a maximum period of 2 hours, according to institutional protocol. Care must be taken to avoid extravasation.

b. Paclitaxel

Paclitaxel will be given at a dose of 175 mg/m^2 over 3 hours by IV infusion.

All patients receiving paclitaxel will be premedicated with:

Agent	Dose	Route	Duration
Dexamethasone (or its equivalent)	20 mg ×2	PO	12 and 6 hours prior to paclitaxel
Diphenhydramine (or its equivalent)	50 mg	IV	30 minutes prior to paclitaxel
Cimetidine (or another H_2 blocker)	300 mg	IV	30 minutes prior to paclitaxel

PO = by mouth.

Refer to the Taxol® for Injection Concentrate package insert for solution preparation and administration.

5.4 GUIDELINES FOR DOSE MODIFICATION

No dose escalation of cyclophosphamide, doxorubicin, or paclitaxel will be allowed.

See Appendix D for suggested guidelines for dose modifications due to hematologic and nonhematologic toxicities. If carried out, any such modifications must be consistent with the investigator's best judgment for the patient's welfare. The study drug (rhuMAb HER2) should be continued throughout dose modification or delay of the cytotoxic agents.

5.5 CONCOMITANT/EXCLUDED THERAPY

If medically necessary, patients may receive radiotherapy to localized sites of disease (e.g., bone) that will not be utilized to evaluate antitumor response.

Investigational or unlicensed agents, immunotherapy, chemotherapy (other than protocol-specified), hormonal therapy (e.g., tamoxifen, megestrol acetate, fluoxymesterone, or aminoglutethimide), or radiotherapy directed at the treatment of indicator lesions are not allowed during the study period. If any of the above therapies are administered, the patient will be considered to have progressive disease.

Patients on chronic low-dose steroids (< 10 mg of prednisone equivalent per day) for preexisting medical conditions (e.g., stable brain

lesions) may continue steroid use as necessary at the investigator's discretion. Dexamethasone or its equivalent will be utilized as part of the premedication for paclitaxel therapy (see Section 5.3.2b) and may be used as part of an antiemetic regimen prior to chemotherapy.

6. PATIENT MONITORING

6.1 PREADMISSION EVALUATIONS (see Appendix A)

Preadmission screening tests and evaluations will be used to determine the eligibility of each candidate for study inclusion. All preadmission evaluations must be assessed within 3 weeks prior to randomization. The results of all tests listed below will be entered on the CRF provided.

- Complete medical history, including prior cancer history
- Complete physical examination
- Weight, height, body surface area (BSA)
- Karnofsky performance status (see Appendix C)
- Chest X-ray (anteroposterior [AP] and lateral)
- Baseline assessment of tumor: a radiographic assessment of all sites of disease

  A bone scan should be performed if the patient has not had a normal bone scan within 3 months of study entry. A bone scan will not be used to follow bone lesions. An abdominal CT scan should be performed if the patient has abnormal liver chemistries, abdominal pain, or a past abnormal abdominal CT scan, ultrasound, or magnetic resonance imaging (MRI). A chest CT scan should be performed if the chest X-ray shows evidence of mediastinal disease.

  A photographic assessment will be made of all cutaneous lesions.
- Serum pregnancy test (women of childbearing potential)
- Hematology (complete blood count [CBC] with differential and platelet count)
- Chemistry panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, cholesterol, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, triglycerides, uric acid)

6.2 STUDY EVALUATIONS (see Appendix A)

Day 0 (baseline) is the first day of rhuMAb HER2 infusion or the day of randomization for patients in the control group. All tests should be performed prior to administration of study medication. It is vital that patients undergo the following evaluations regardless of their assignment to the active or control arms of the study.

6.2.1 Tests

a. Complete Physical Exam

Weeks 8, 20, 32, 44, and every 12 weeks thereafter; study termination

b. Clinical Assessment (includes weight, Karnofsky performance status, adverse event review, concomitant medications, and symptom-directed physical examination, if appropriate)

Weeks 1 and 2, then every other week through study termination

c. Vital Signs (including respiratory rate, BP, temperature, and pulse)

Evaluate predose and at the end of the infusion

Weekly beginning on Day 0 through study termination for patients randomized to the active arm; Weeks 1 and 2, then every other week through study termination for patients randomized to the control arm

d. Chest X-Ray (AP and lateral)

Weeks 8, 20, 32, 44, and every 12 weeks thereafter; study termination

e. Tumor Assessment (a radiographic or visual assessment of all disease sites)

The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study, e.g., the same contrast protocol for CT scans.

Patients having a complete or partial response should have the radiographic study documenting that response repeated 4 weeks following the initial response determination.

Patients with symptoms suggestive of progressive disease (see Section 7.2) may have tumor assessment studies done at times

other than those described in the protocol at the investigator's discretion.

Weeks 8, 20, 32, 44, and every 12 weeks thereafter; study termination

f. *Noninvasive cardiac evaluation (ECHO, MUGA)*

Immediately (next patient visit); Weeks 20 and 32; study termination

g. Laboratory Tests (see Appendices E and F)

- Serum pregnancy test (women of childbearing potential)

  Weeks 20 and 44; study termination

- Hematology (CBC with differential and platelet count)

  Local laboratory hematology may be performed as needed for patient management.

  Weeks 8, 20, 32, 44, and every 12 weeks thereafter; study termination

- Chemistry panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, cholesterol, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, triglycerides, uric acid)

  Weeks 8, 20, 32, 44, and every 12 weeks thereafter; study termination

h. EORTC Quality-of-Life Instrument and Supplemental Questionnaire

These evaluations must be given to patients in both the active and control arm before the first cycle of chemotherapy is administered.

Weeks 1, 8, 20, 32, 44, and every 12 weeks thereafter; study termination

i. Blood Concentration Measurements (to be performed on selected patients) (see Appendix G):

- Serum Pharmacokinetics of rhuMAb HER2

  Just prior to each dose and at the end of infusion of each dose of rhuMAb HER2, 2 mL of blood (yielding approximately 1.0 mL of serum) will be drawn at the times indicated to measure the serum pharmacokinetics of rhuMAb HER2 on the first 50 patients randomized to receive rhuMAb HER2 and, following the introduction of the lyophilized formulation of

rhuMAb HER2, from the first 50 patients assigned to the lyophilized formulation.

Weeks 1 (Day 0), 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter; study termination

The preinfusion pharmacokinetic sample will be used to obtain preinfusion antibody measurements (see below).

- Serum Antibodies to rhuMAb HER2

  Preinfusion antibody measurements will be obtained from the preinfusion pharmacokinetic sample. Samples will be obtained from the first 50 patients randomized to receive rhuMAb HER2 and, following the introduction of the lyophilized formulation of rhuMAb HER2, from the first 50 patients randomized to the lyophilized formulation.

  Weeks 1 (Day 0), 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter; study termination

- Serum Shed Antigen Concentrations

  Three milliliters of blood (yielding approximately 1.5 mL of serum) will be obtained from all patients (active and control arms) at Week 1 prior to rhuMAb HER2 administration, or prior to the first cycle of chemotherapy for control arm patients for measurement of circulating concentrations of shed antigen (extracellular domain of the receptor).

  Additionally, 3 mL of blood (yielding approximately 1.5 mL of serum) will be collected prior to infusion of rhuMAb HER2 at the times indicated below from the first 50 patients randomized to receive rhuMAb HER2 and, following the introduction of the lyophilized formulation of rhuMAb HER2, from the first 50 patients randomized to the lyophilized formulation.

  Weeks 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter; study termination

j. Blood Concentration Measurements (to be performed at selected study sites only) (see Appendix G):

- Special Studies

  Eight milliliters of blood (yielding approximately 2.5 mL of serum and 1.5 mL of plasma) will be obtained from all patients (active and control arms) at Week 1 prior to rhuMAb HER2 administration, or prior to the first cycle of chemotherapy for control arm patients to better define the mechanism of action of

rhuMAb HER2. (These studies will not represent efficacy parameters.)

Additionally, 8 mL of blood (yielding approximately 2.5 mL of serum and 1.5 mL of plasma) will be collected only from patients randomized to rhuMAb HER2 at Weeks 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter, and at study termination.

k. Research Studies

Additional metastatic site biopsies may be performed on selected patients and at selected study centers for research studies.

6.3 POST-TREATMENT FOLLOW-UP

All serious cardiac adverse events will be followed until event resolution, study closure, or death. All serious *noncardiac* adverse events that are ongoing at study drug discontinuation will be followed until resolution or for 2 weeks, whichever occurs first. In addition, patients who discontinue prior to Week 8 will be contacted at Week 8 (Day 56) to assess for serious adverse events that have occurred since study drug discontinuation.

7. PROGRESSION AND RESPONSE CRITERIA

7.1 RESPONSE EVALUATION COMMITTEE

The radiographs and/or photographs of all patients will be reviewed by an independent group of clinicians performing response evaluation. This group of clinicians will remain blinded as to treatment group assignment to avoid the potential for introduction of bias. The consensus evaluation of this committee will serve as the official response evaluation for the study. The committee will be composed of impartial oncologists and radiologists.

For the purposes of analysis and enrollment into the subsequent protocol (H0659g), progression will be as determined by the Response Evaluation Committee. However, treating physicians may base their evaluation and treatment decisions on their interpretation of the clinical data. In cases of doubt, investigators are encouraged to consider the determination of the Response Evaluation Committee.

All study sites must send all pertinent radiographic and/or photographic assessments on all patients to the location designated in the Study

Procedure Manual. The radiographs and/or photographs will then be forwarded to the Response Evaluation Committee.

When disease progression has occurred, patients will not be eligible to begin rhuMAb HER2 therapy until that progression has been verified by the Response Evaluation Committee.

7.2 RESPONSE CRITERIA

Progressive Disease: Objective evidence of an increase of 25% or more in any measurable lesion. Progressive disease will also include those instances where new lesions have appeared. For bone lesions, progression will be defined as a 25% increase in objective measurement by plain film, CT, or MRI; symptomatic new lesions not due to fracture; or requirement for palliative radiotherapy.

Complete Response: Disappearance of all radiographically and/or visually apparent tumor for a minimum period of 4 weeks. Skin and chest wall complete responses must be confirmed by biopsy.

Partial Response: A reduction of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum period of 4 weeks. No new lesions may have appeared, nor may any lesion have progressed in size.

Note: Patients having a complete or partial response should have the radiographic study documenting that response repeated 4 weeks following the initial response determination.

Minor Response: A reduction of 25% to 49% in the sum of the products of the perpendicular diameters of all measurable lesions. No new lesions may have appeared, nor may any lesion have progressed in size.

Stable Disease: No change of greater than 25% in the size of measurable lesions. No new lesions may have appeared.

8. STATISTICAL CONSIDERATIONS

8.1 RESPONSE VARIABLES (ENDPOINTS)

8.1.1 Primary Endpoints

The primary endpoints of the study are:

- Time to disease progression
- Safety profile of rhuMAb HER2

8.1.2 Secondary Endpoints

The secondary endpoints of the study are:

- Response rates
- Duration of response
- Quality-of-life assessment
- Pharmacokinetics of rhuMAb HER2
- One-year survival
- Time to treatment failure

8.2 STATISTICAL ANALYSIS

8.2.1 Efficacy Analysis

The final analysis will commence 12 months following enrollment of the last patient.

The primary efficacy variable is time to disease progression documented by radiographic or other objective evaluation, such as photography or physical examination and confirmed by the Response Evaluation Committee. Time to progression is defined as time from randomization to documented disease progression or death due to disease. If patients receive immunotherapy, chemotherapy (other than protocol-specified), hormonal therapy, or radiotherapy during the study period, data collected concurrently with, or following, the additional therapy will not be included in the analysis. Such patients will be treated as treatment failures (progressive disease) at the time of the additional therapy. For all patients who do not progress at the time of the analysis, time to progression will be censored at the last date of follow-up. Time to disease progression will be compared between the two treatment arms (rhuMAb HER2 vs. control). The primary analysis

will include all eligible patients (intent-to-treat) and will be based on the pooled chemotherapy groups.

Kaplan-Meier estimates will be used to describe the time to disease progression in the two treatment arms. Median time to progression with 95% confidence limits will be calculated. A log rank test will be used to compare the two treatment arms with respect to time to progression.

The Cox proportional hazards model will be used to determine the risk factors for time to progression and to evaluate any possible interactions with treatment. The following baseline characteristics will be considered in the analysis: age, estrogen receptor status, level of HER2 overexpression (2+ vs. 3+), number of metastatic sites, prior exposure to anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubicin), performance status at study entry, location of metastases, prior hormonal therapy (yes/no), prior adjuvant chemotherapy (yes/no), geographic region (North America, Europe, or Australia/New Zealand),and time from primary diagnosis to metastatic disease. Only variables that show imbalance at baseline or significantly affect the efficacy variable will be included in the model.

To compare overall response rates (complete and partial), two sets of analyses will be performed, one based on the intent-to-treat approach (all enrolled patients) and one based on data from evaluable patients only. Evaluable patients are all eligible patients who complete at least one cycle of therapy and undergo a tumor evaluation subsequent to baseline. Additionally, patients who die before their tumor evaluation as a result of metastatic breast cancer will be considered evaluable (progressive disease). In the intent-to-treat analysis all nonevaluable patients will be considered nonresponders.

To compare the response rates between the two treatment arms, evaluate the effect of any covariates, and assess interactions, a standard statistical methodology for categorical data (the chi-squared test and logistic regression model) will be applied. The same baseline characteristics mentioned above will be considered. Only those variables that show imbalance at baseline or significantly affect the efficacy variable will be included in the model.

Response duration will be measured from time of best response to the development of progressive disease. Patients still responding to the treatment at the time of the analysis will be censored for duration of response at the last contact date. Standard survival methodology will be applied to estimate the response duration and compare the two treatment arms.

Time to treatment failure is defined as time from randomization to documented disease progression, or treatment discontinuation due to toxicity. For patients still on therapy or attending study visits at the time of the analysis, time to treatment failure will be censored at the last treatment date or last study visit date. Standard survival methodology will be applied to estimate time to treatment failure and to compare the two arms.

Survival will be measured from randomization until death. For all patients still alive at the time of the analysis or lost to follow-up, survival time will be censored at the last contact date. Kaplan-Meier estimates will be applied to obtain the 1-year survival curves. Survival will be compared between early and late (e.g., at disease progression) treatment with rhuMAb HER2.

8.2.2 Analysis of Treatment Group Comparability

In addition to all the baseline characteristics, the following variables will be compared between the control and active arm:

- Length and intensity of co-administered chemotherapy
- Dropout rates
- Timing and intensity of other concomitant therapy
- Frequency of discrepancies of the tumor evaluation between the physician's assessment and the Response Evaluation Committee's assessment.
- Frequency of unscheduled tumor evaluations

The impact of those variables on the efficacy endpoints will be also evaluated.

8.2.3 Quality-of-Life Assessment

The quality-of-life questionnaire QLQ-C30, developed by the EORTC with the module for breast cancer (BR23), will be used to evaluate the quality of life (21) (see Appendix H). Five functioning scales (physical, role, cognitive, emotional, and social) and a global quality-of-life score will be compared between the treatment groups. Repeated measures analysis of variance will be used to analyze the data. To test the hypothesis of no difference in quality of life between the treatment groups, a significance level of 1% will be applied to each test of the five functioning scales and to the global score.

The 13 questions in the supplemental questionnaire (see Appendix I) pertain to pharmacoeconomics and are exploratory in nature, and will be evaluated outside the scope of the protocol. They will be described and analyzed in a separate report.

8.2.4 Assessment of Pharmacokinetics

Trough (immediately predose) and peak (at the end of the infusion) serum concentrations of rhuMAb HER2 will be determined in selected patients ($n = 100$) in the study. These patients will include the first 50 receiving the current formulation of rhuMAb HER2 and the first 50 receiving the new, lyophilized formulation of rhuMAb HER2.

No formal pharmacokinetic analysis will be conducted on the peak and trough levels. Graphical and tabular summaries will be prepared (average levels across the time course of the study) for each formulation of rhuMAb HER2. In addition, separate summaries will be prepared for those patients receiving cyclophosphamide and doxorubicin (or epirubicin) and those receiving paclitaxel, to investigate possible effects of these agents on the pharmacokinetics of rhuMAb HER2.

8.2.5 Safety Analysis

All patients who receive any amount of either rhuMAb HER2 or chemotherapy will be included in the safety analysis. Any incidence of adverse events will be recorded and classified according to body region and severity.

Laboratory data will be listed for each patient and values outside of the reference range will be flagged. Clinically significant changes from baseline in laboratory parameters will be tabulated.

8.3 RANDOMIZATION

Patients will be randomized by telephone to either rhuMAb HER2 or to the control arm. The randomization will be done in such a way that the two treatment arms will be balanced within each chemotherapy regimen (doxorubicin [or epirubicin]/cyclophosphamide or paclitaxel) within the three types of metastatic disease: visceral (e.g., liver or lung) versus superficial (e.g., skin, chest wall, and peripheral lymph node) versus bone only and within the three geographic regions (North America, Europe, and Australia/New Zealand).

8.4 DATA SAFETY MONITORING BOARD AND INTERIM ANALYSIS

The Phase II program evaluated the safety of rhuMAb HER2 alone and co-administered with cisplatin. Currently there are no safety data available on rhuMAb HER2 co-administered with either cyclophosphamide and doxorubicin or paclitaxel. The Data Safety Monitoring Board (DSMB) will be evaluating the safety of the co-administered therapy in an ongoing fashion in this Phase III trial. It is expected that no more than four safety analyses will occur. The first safety analysis will be performed after 60 patients complete two cycles (8 weeks) of therapy. The timings of the additional analyses will be decided by the DSMB and will be based on the accrual rate.

There are no known data from patients with HER2 overexpressing tumors estimating time to disease progression. The sample size calculation is based on the assumption that the median time to progression on the standard therapy is 8 months (based on data from all patients, not just HER2 overexpressors). Hence, there is a need for an interim analysis to assess this assumption and to evaluate extending the follow-up period, if needed, to assure a 90% power to detect the difference in time to progression.

In evaluating time to disease progression for safety and in making the decision to extend the follow-up period, the DSMB will be guided by a formal group sequential analysis. The log rank statistics will be used to compare treatment and control groups with respect to the primary

endpoint of time to disease progression. The formal stopping boundaries will be determined by an asymmetric generalization of a one-sided symmetric design (22). In the notation of Emerson and Fleming (22), the upper (b_k) and lower (a_k) boundaries at the k-th analysis are determined by the formulas

$$b_k = k^{p_b} G_b$$

$$a_k = k\delta_1 - k^{p_a} G_a$$

$$\delta_1 = \frac{m^{p_b} G_b + m^{p_a} G_a}{m}$$

where m is the maximum number of analyses planned and p_b and p_a are the parameters specifying the upper and lower boundary relationships. For example, a value of $p_b = 0.0$ ($p_a = 0.0$) defines the O'Brien-Fleming type of boundary and $p_b = 0.5$ ($p_a = 0.5$) defines the Pocock type of boundary. The upper and lower critical values G_b and G_a are obtained through a numerical integration and provide a group sequential test with the appropriate statistical size. The asymmetric design allows for the introduction of a more stringent upper boundary than lower boundary, making stopping for efficacy more difficult than stopping for safety.

In this study design the upper stopping boundary relationship is specified by $p_b = -0.3$ (a boundary relationship more conservative than an O'Brien-Fleming type of boundary), and a lower stopping boundary relationship is specified by $p_a = 0.2$ (a boundary intermediate between O'Brien-Fleming and Pocock boundaries).

Two analyses of time to disease progression, interim and final, are planned during the study. The interim analysis is planned for 6 months after the accrual of the last patient. The purpose of this analysis is to evaluate the need for extending the follow-up period beyond 1 year. If additional safety analyses are recommended by the DSMB, the study design allows two additional analyses of the primary endpoint. The type I error will be controlled according to methods described by Lan and DeMets (23), and the power will be controlled according to other described methods. (Pampallona S, Tsiatis AA, Kim K. Spending functions for the type I and type II error probabilities of group sequential tests [unpublished observations, 1994].) The maximal number of

events will be adjusted to maintain the type I error at 0.05 and the statistical power at approximately 0.90. The above strategy is an extension of the strategy applied by the EaSt software package.

8.5 SAMPLE SIZE AND POWER

Estimates of the sample size required to demonstrate efficacy with regard to time to disease progression are based on the following assumptions:

- Median time to progression for the control arm is 8 months
- Median time to progression for the rhuMAb HER2 plus chemotherapy arm is 12 months (50% increase in time to progression)
- At least a 1-year accrual period
- One-year follow-up time
- Twenty percent loss to follow-up
- Two-tailed log rank test
- Ninety percent power at the 5% significance level

Based on these assumptions, the conservative total sample size is 450.

9. ADVERSE EVENT REPORTING

Adverse event information will be collected for the duration of the study. Genentech (or their authorized representative) is responsible for meeting adverse event reporting requirements as required by the U.S. FDA and appropriate national and local health authorities.

An adverse event is any untoward medical occurrence in a research subject treated with an investigational product during a clinical trial or post-treatment follow-up period, regardless of causality assessment. This includes adverse clinical or laboratory findings, intercurrent illness, or an exacerbation or progression of a disease/condition present at baseline.

An adverse event is considered serious if it: 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongation of an existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a congenital anomaly/birth defect in the

offspring of an exposed research subject, 6) is a newly diagnosed cancer other than metastatic breast cancer or progression of existing breast cancer, or 7) requires intervention to prevent permanent impairment/damage to a body function or structure. (Note: Changes in dosage, discontinuation of therapy, and routine treatment with a prescription medication are not in themselves considered serious by this last criterion.)

An adverse event is considered nonserious if it does not meet any of the serious criteria.

An unexpected adverse event is any adverse event not identified in nature or severity in the current Investigator Brochure.

Patients should be instructed to report any adverse event to the investigator (Principal Investigator or any subinvestigator). Investigators should assess adverse events in all patients (active and control arms) at each visit. Each adverse event, regardless of causality assessment, must be recorded on the appropriate Adverse Event Case Report Form (CRF).

Whenever possible, a diagnosis or syndrome should be recorded as the primary adverse event, rather than individual associated signs and symptoms. If the diagnosis or syndrome is unknown, then the sign, symptom, clinically significant laboratory abnormality, etc., should be recorded. (Note: Clinically significant laboratory abnormalities are those that are identified as such by the investigator and/or those that require intervention.)

Serious Adverse Events occurring in patients in the active arm of the study should be reported to the contract research organization for this study (*Covance Clinical and Periapproval Services, Inc.*) within 24 hours of their occurrence. This can be done by faxing a completed Serious Adverse Event Fax cover sheet and Serious Adverse Event CRF and concomitant medications page, or by direct telephone communication. A completed Serious Adverse Event Fax cover sheet, CRF, and concomitant medications page should follow all telephone reports.

Study sites in the United States and Canada must contact:

Pat Devitt
Covance Clinical and Periapproval Services, Inc.
210 Carnegie
Princeton, NJ 08540-6233

Office Telephone: (800) 621-8901, extension 4293
Home Telephone: (908) 764-9059
Fax: (609) 243-0358

Study sites in Europe must contact:

Adrian Foulkes
Covance Clinical and Periapproval Services, Inc.
Foundation Park
7 Roxborough Way
Maidenhead
Berkshire SL63UD
United Kingdom

Office Telephone: *01628-548-000*
Cellular Telephone: *0385-342-304*
Fax: *01628-411-423*

Study sites in Australia and New Zealand must contact:

Robyn Philip
Covance Clinical and Periapproval Services, Inc.
51 Rawson Street, Suite 303
Epping NSW 2121
Australia

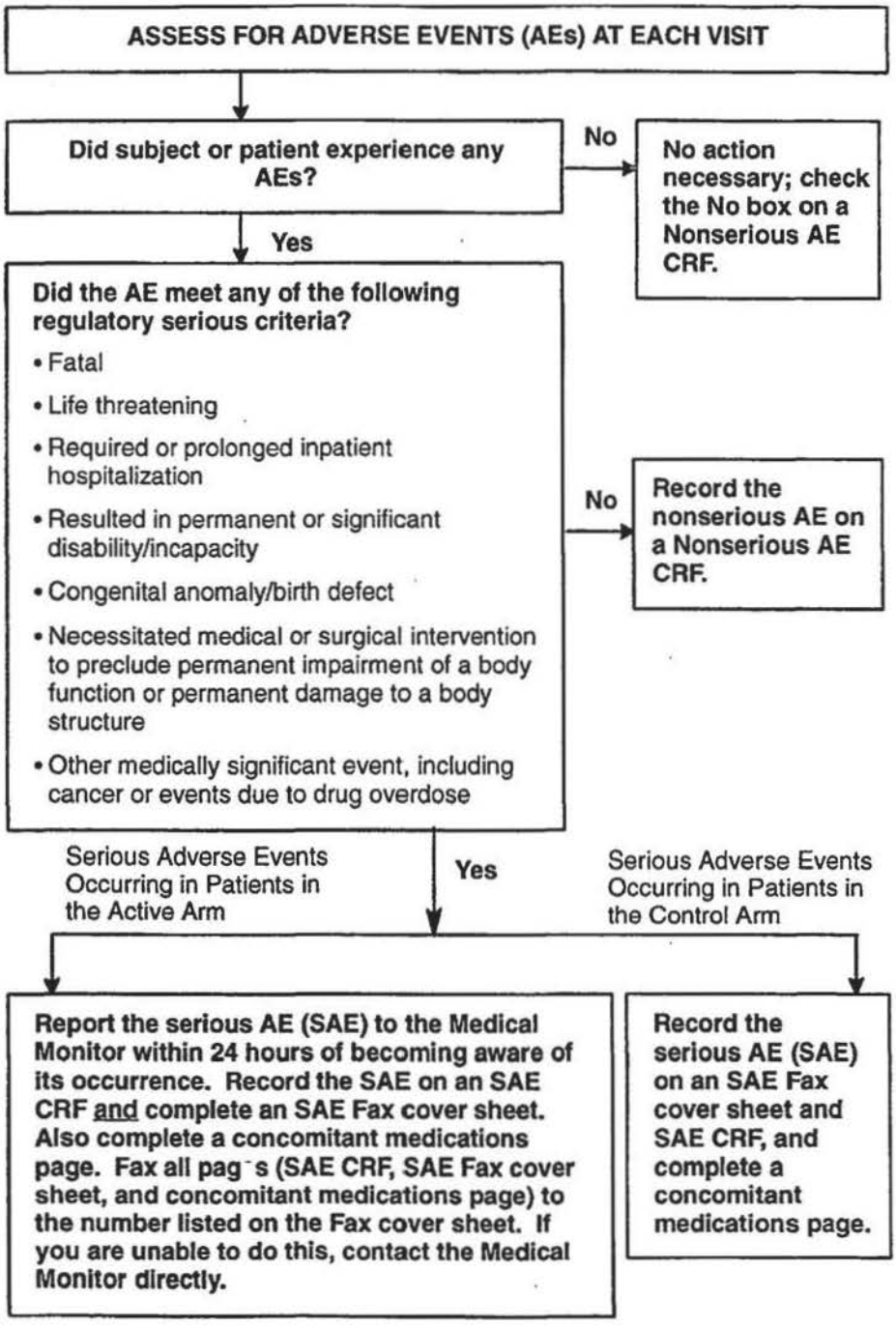
Office Telephone: *2-9869-1811*
Cellular Telephone (Australia): *0411-10-4509*
(New Zealand): *61-411-10-4509*
Fax: *2-9868-5936*

Events that led to study withdrawal or study drug discontinuation, *regardless of treatment assignment,* must be reported, including those that are serious by regulatory definition. Serious adverse events that begin after discontinuation of study therapy may be reported to Genentech at the discretion of the investigator (e.g., if the investigator believes that the adverse event is unusual in character or severity or likely to have been caused by study drug). However, active collection of adverse events post-study will not occur.

Serious *noncardiac* adverse events that are not resolved at the time of study withdrawal or study drug discontinuation will be followed until resolution or for 2 weeks, whichever occurs first. *Patients who have experienced a serious adverse cardiac event will be followed until event resolution, study closure, or death.* In addition, patients who discontinue prior to Week 8 will be contacted at Week 8 (Day 56) to assess serious adverse events that have occurred since study drug discontinuation.

Nonserious adverse events should be recorded on the appropriate Nonserious Adverse Event CRF. These CRFs will be collected by a Genentech representative at every site visit or as otherwise instructed.

Algorithm for Reporting Adv rse Events during Clinical Trials



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10. DISCONTINUATION

10.1 PATIENT DISCONTINUATION

Patients are encouraged to comply with all aspects of evaluation and treatment throughout the study. While patients may discontinue study drug therapy at any time during the study, they should be encouraged to continue to be evaluated and treated as described in the protocol.

Patients who discontinue the study will not be replaced.

10.2 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of an adverse drug reaction in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Quality or quantity of data recording is inaccurate or incomplete

11. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This protocol, the Informed Consent document, and relevant supporting information must be submitted to the Institutional Review Board/Ethics Committee (IRB/EC) for review and must be approved before the study is initiated. (See the Reporting Requirements Section.) The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and applicable national and local health authorities' IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC advised of the progress of the study and of any changes made in the protocol as deemed appropriate but, in any case, at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse reactions.

12. INFORMED CONSENT REQUIREMENTS

Sample Informed Consents (or Patient Information/Informed Consents, if applicable) will be provided to each site. In addition to the Sample Informed Consent, it is expected that the investigator will obtain a specific informed consent for each biopsy from any patient prior to or

during the patient's participation in this study. The study will be conducted in accordance with U.S. FDA and applicable national and local health authorities' informed consent requirements.

An Informed Consent document must be provided to Genentech for review and approval prior to submission to the IRB/EC. No major deviations should be made from the Sample Informed Consent. The final IRB/EC-approved document must also be provided to Genentech for regulatory purposes.

The Informed Consent document will be provided in the local language and must be signed by the patient prior to her participation in the study.

Signed consent forms must remain in the patient's study file(s) and be available for verification by study monitors at any time.

13. STUDY MONITORING REQUIREMENTS

Site visits will be conducted by a Genentech representative to inspect study data, patients' medical records, and CRFs in accordance with U.S. and European Good Clinical Practices and the respective local and national government regulations and guidelines (if applicable).

The Principal Investigator will permit authorized representatives of Genentech, the U.S. FDA, and the respective national or local health authorities to inspect facilities and records relevant to this study.

14. CASE REPORT FORMS

CRFs will be supplied by Genentech representatives. The original completed CRF should be handled in accordance with instructions from Genentech or Genentech representatives.

All CRFs should be filled out completely by examining personnel or the study coordinator. The CRF is reviewed and signed by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. Changes or corrections must be dated and initialed by the person making the change.

When making changes, cross out the original entry with a single line. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

15. STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the "Investigational New Drug Retrieval Record" (INDRR-1) or "Acknowledgment of Receipt" form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed to patients should be maintained at the study site by using the "Drug Inventory Log."

After being accounted for by the Genentech study monitor or representative, all partially used or empty containers should be crushed or incinerated at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the "Inventory of Returned Clinical Material" form as directed by Genentech.

All forms will be supplied by Genentech or a Genentech representative.

16. REPORTING REQUIREMENTS

16.1 STUDY INITIATION

Prior to the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 (for all studies conducted under U.S. IND regulations) to be signed by all Principal Investigators
- The names of any subinvestigator(s) must appear on this form. Investigators must complete all regulatory documentation as required by national law.
- Original HPB Form 3005 (Canada only), signed by each Canadian investigator involved in the study
- Current curricula vitae of the Principal Investigator and all subinvestigators
- IRB/EC name and address; Department of Health and Human Services (DHHS) number, if applicable, or membership list

- Written documentation of IRB/EC approval of protocol (identified by Genentech protocol number, date, title, and date of approval) and Informed Consent document (identified by Genentech protocol number, date, title, and date of approval)
- A copy of the IRB/EC-approved consent form (that was previously approved by Genentech)
- Written documentation of IRB/EC review and approval of any advertising materials to be used for study recruitment, if applicable; these materials must also be reviewed and approved by the Genentech Legal Department
- A signed Clinical Research Agreement
- Certified translations of IRB/EC approval letters, pertinent correspondence, and informed consent form (when applicable)
- A signed and dated protocol signature page (Europe only)

16.2 STUDY COMPLETION

Data and materials that are required by Genentech before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- CRFs (including correction forms) properly completed by appropriate study personnel and signed by the investigator
- Completed Drug Accountability Records (INDRR-1 or Acknowledgment of Receipt, Drug Inventory Log, and Return of Clinical Material forms)
- Statement of outcome for each serious adverse event reported
- Copies of protocol, amendments, and IRB/EC approval/notification, if appropriate
- A signed and dated protocol amendment signature page (Europe only)
- A summary of the study prepared by the Principal Investigator
- All regulatory documents (e.g., curricula vitae, U.S. FDA Form 1572)

17. DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to her personal physician or other appropriate medical personnel responsible for her welfare.

Data generated by this study must be available for inspection on request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB(s)/EC(s), if appropriate.

18. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable (international) local health authorities are notified. Genentech will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the principal investigator must comply with U.S. FDA IND regulations and with those of the relevant national and local health authorities.

REFERENCES

1. Cross M, Dexter TM. Growth factors in development, transformation, and tumorigenesis. Cell 1991;64:271–80.

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APPENDIX A

Study Flowchart
H0648g

	Days –21 to –0 Preadmission	Week						Every 12 weeks after Week 44	Study Termination
		1 (Day 0)	1 (Day 1)	8	20	32	44		
rhuMAb HER2 Administration		x[a,b]							
Cyclophosph./Doxorub. or Paclitaxel Administration			x[c]						
Complete Medical History	x								
Complete Physical Exam	x			x[b]	x[b]	x[b]	x[b]	x[b]	x
Clinical Assessment		x[b,d]							x
Weight, Height, BSA	x								
Karnofsky Performance Status	x	x[b,d]							x
Vital Signs		x[b,e]							x
Chest X-ray (AP, Lateral)	x			x[b]	x[b]	x[b]	x[b]	x	x
Tumor Assessment	x			x[b]	x[b]	x[b]	x[b]	x[b]	x
Noninvasive Cardiac Monitoring (ECHO, MUGA)		*x*[f]			*x*	*x*			*x*
Serum Pregnancy Test	x[g]				x[b,g]		x[b,g]		x
Hematology (CBC with Diff., Plts.)	x			x[b]	x[b]	x[b]	x[b]	x[b]	x
Chemistry Panel	x			x[b]	x[b]	x[b]	x[b]	x[b]	x
EORTC Quality-of-Life and Supplemental Questionnaire		x[b]		x[b]	x[b]	x[b]	x[b]	x[b]	x
Serum Pharmacokinetics		x[h,i,j]		x[h,j]	x[h,j]	x[h,j]	x[h,j]	x[h,j]	x
Serum Ab to rhuMAb HER2		x[b,i,j]		x[b,j]	x[b,j]	x[b,j]	x[b,j]	x[b,j]	x

APPENDIX A (cont'd)

Study Flowchart
H0648g

	Days –21 to –0 Preadmission	Week						Every 12 weeks after Week 44	Study Termination
		1 (Day 0)	1 (Day 1)	8	20	32	44		
Serum Shed Antigen		x[b,i,j,k]		x[b,j]	x[b,j]	x[b,j]	x[b,j]	x[b,j]	x
Special Studies		x[b,k,l,m]		x[b,l,m]	x[b,l,m]	x[b,l,m]	x[b,l,m]	x[b,l,m]	x

[a] Day 0 is the first day of rhuMAb HER2 administration. On Day 0, 4 mg/kg rhuMAb HER2 will be given; thereafter, 2 mg/kg will be given. rhuMAb HER2 will be given 24 hours before chemotherapy at Week 1, and given on the same day as (and prior to) chemotherapy subsequently, if well tolerated.

[b] All tests should be performed prior to rhuMAb HER2 administration or first cycle of chemotherapy (for patients on control arm).

[c] Either cyclophosphamide and doxorubicin or paclitaxel will be administered every 3 weeks for six cycles: Weeks 1, 4, 7, 10, 13, and 16. See Section 5.3.2 of the protocol for additional information on paclitaxel administration.

[d] Weeks 1 and 2, then every other week through study termination. Includes weight and Karnofsky status.

[e] Vital signs will be checked preinfusion and at the end of the infusion. Weekly through study termination beginning on Day 0 for active arm patients; Weeks 1 and 2, then every other week through study termination for control arm patients.

[f] *Immediately (at next patient visit).*

[g] Women of childbearing potential.

[h] Predose and at the end of infusion.

[i] Weekly for the first 4 weeks.

[j] Will be collected from the first 50 patients receiving rhuMAb HER2 and from the first 50 patients receiving the lyophilized formulation of rhuMAb HER2.

[k] Collected from all patients (active and control arms) at Week 1 only.

[l] To be performed at selected study sites only.

[m] Collected only from active arm patients at Weeks 2, 3, 4, and specified intervals.

APPENDIX B

Determination of HER2 Overexpression

To be eligible for the trial, the patient must have a tumor that overexpresses the HER2 receptor. Determination of HER2 overexpression will be accomplished using either immunohistochemistry or fluorescence in situ hybridization (FISH). Roche Biomedical Laboratories (RBL) in Research Triangle Park, North Carolina, will perform assays for HER2 overexpression on a set of 10 slides submitted to them by the treating institution. Alternatively, RBL will prepare a set of slides from a block submitted to them from the treating institution. If the institution wishes to send a paraffin block rather than slides to RBL, the institution must select the block that contains the best tumor specimen and submit only that block. The results for both assays will be reported by RBL as indeterminate, 0, 1+, 2+, or 3+. For study eligibility purposes, 2+ to 3+ overexpression by either assay will be sufficient for study entry.

A Specimen Handling and Shipping Procedures Manual will be provided to each site prior to study initiation.

APPENDIX C

Evaluation of Performance Status (Karnofsky Scale)

Scale (%)	Description
100	Normal; no complaints (ECOG 0)
90	Able to carry on normal activities; minor signs or symptoms of disease (ECOG 0)
80	Normal activity with effort (ECOG 1)
70	Cares for self. Unable to carry on normal activity or to do active work (ECOG 1)
60	Requires occasional assistance but able to care for most of his/her needs (ECOG 2)
50	Requires considerable assistance and frequent medical care (ECOG 2)
40	Disabled; requires special care and assistance (ECOG 3)
30	Severely disabled; hospitalization indicated though death not imminent (ECOG 3)
20	Very sick. Hospitalization necessary. Active supportive treatment necessary (ECOG 4)
10	Moribund (ECOG 4)
0	Dead

Reference: Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. Use of the nitrogen mustards in the palliative treatment of carcinoma with particular reference to bronchogenic carcinoma. Cancer 1948;1:634–56.

APPENDIX D

Guidelines for Dose Modification

A. Cyclophosphamide and Doxorubicin

1. Cardiac Toxicity

   Strong consideration should be given to stopping doxorubicin if any clinical evidence of cardiotoxicity is seen. Detailed information on the cardiotoxicity can be found in the doxorubicin package insert.

2. Hematologic Toxicity

   Both cyclophosphamide and doxorubicin doses may be decreased in subsequent cycles by 50% if the granulocyte nadir is $<500/mm^3$ or the platelet count is $<30,000/mm^3$. Alternatively, filgrastim may be used according to institutional protocol in subsequent cycles at the investigator's discretion rather than dose reduction or delay for neutropenia. Therapy should be withheld when the granulocyte count is $<1000/mm^3$ or the platelet count is $<75,000/mm^3$.

3. Hepatic Dysfunction

   In patients with a baseline bilirubin below 1.2 mg/dL, the dose reduction of doxorubicin for hyperbilirubinemia will be as follows:

Bilirubin	
1.2–3.0 mg/dL (20.5–51.3 µmol/L)	Give 1/2 normal dose
>3.0 mg/dL (51.3 µmol/L)	Give 1/4 normal dose

   In patients with benign hyperbilirubinemia at study entry, dose reductions of doxorubicin will be carried out at the investigator's discretion.

4. Gastrointestinal Toxicity

   For severe mucositis with vesiculation and/or ulcers, withhold cyclophosphamide and doxorubicin until mucositis clears, then reinstate at 75% of full dose. If tolerated, 100% of dose should be given in subsequent cycles. Alternatively, filgrastim may be used according to institutional protocol in subsequent cycles at the investigator's discretion.

5. Renal Impairment

The following dose adjustments are suggested in the cyclophosphamide dose for elevated serum creatinine:

Serum Creatinine	or	Creatine Clearance	
>1.7 mg/dL (150 µmol/L)		40–60 mL/min	Give 3/4 of dose
>2.0 mg/dL (177 µmol/L)		<40 mL/min	Give 1/2 of dose

B. Paclitaxel

1. Hematologic Toxicity

Patients should not be retreated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

2. Gastrointestinal Toxicity

For severe mucositis with vesiculation and/or ulcers, withhold paclitaxel until mucositis clears, then reduce to 135 mg/m^2. If tolerated, 100% of dose should be given in subsequent cycles.

3. Neurological Toxicity

If WHO Grade 3 or 4 toxicity occurs (intolerable paresthesias and/or marked motor loss [see Appendix B]), paclitaxel should be stopped.

4. Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel. To avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with

corticosteroids (such as dexamethosone), diphenhydramine, and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

APPENDIX E

Directions for Shipment of Laboratory Specimens to SciCor, Inc.
(for Sites in the United States, Canada, and Europe)

A. The following tests will be performed by SciCor:

CBC with Differential and Platelet Count

Serum Chemistry Panel

Serum Pregnancy Test

B. Specimen Requirements and Collection Instructions

Please follow the instructions provided by SciCor on the requisition form in each test kit.

C. Shipping Instructions

All specimens will be shipped to SciCor via courier or Federal Express. Packing and shipping instructions can be found in the manual supplied by SciCor.

SciCor, Inc.
8211 SciCor Drive
Indianapolis, IN 46214-2985
(800) 327-7270

D. Questions or Information

United States and Canada:
Pat Devitt
Covance Clinical and Periapproval Services, Inc.
210 Carnegie
Princeton, NJ 08540-6233
Office Telephone:
(800) 621-8901, extension 4293

Europe:
Adrian Foulkes
Covance Clinical and Periapproval Services, Inc.
Foundation Park
7 Roxborough Way
Maidenhead
Berkshire SL63UD
United Kingdom
Office Telephone: 01628-548-000
Cellular Telephone: *0385-342-304*

APPENDIX F

Directions for Shipment of Laboratory Specimens to Douglass Laboratories (for Sites in Australia and New Zealand)

A. The following tests will be performed by Douglass Laboratories:

CBC with Differential and Platelet Count

Serum Chemistry Panel

Serum Pregnancy Test

B. Specimen Requirements and Collection Instructions

Please follow the instructions provided by Douglass Laboratories on the requisition form in each test kit.

C. Shipping Instructions

All specimens will be shipped to Douglass Laboratories via courier or World Courier. Packing and shipping instructions can be found in the manual supplied by Douglass Laboratories.

Douglass Laboratories
95 Epping Road
North Ryde, NSW 2113
Australia
Telephone: (02) 807-300 or (800) 222-365

D. New Zealand Specimen Handling

All laboratory tests and specimen collections in New Zealand will be performed by local laboratories. Please refer to local laboratory manuals for specimen collection, storage, and shipping instructions.

E. Questions and Information

Robyn Philip
Covance Clinical and Periapproval Services, Inc.
51 Rawson Street, Suite 303
Epping NSW 2121
Australia
Office Telephone: *2-9869-1811*
Cellular Telephone: (Australia): 0411-10-4509
(New Zealand): 61-411-10-4509

APPENDIX G

Directions for Obtaining, Storing, and Shipping Blood Samples

The following blood samples will be collected and sent by the investigator to SciCor, Inc., Douglass Laboratories, or local laboratories for storage. SciCor, Douglass, or the local laboratory will supply kits containing all necessary collection tubes and labels and will be responsible for forwarding the samples to Genentech or Roche Biomedical Laboratories (RBL). Refer to the appropriate manuals for complete instructions.

A. Serum Pharmacokinetics of rhuMAb HER2 (to be conducted by Genentech)
Note: These measurements will be performed on the first 50 patients randomized to receive rhuMAb HER2 and on the first 50 patients randomized to receive the lyophilized formulation of rhuMAb HER2.

1. Specimen Requirements

   The investigators will supply the appropriate laboratory with serum samples taken prior to and at the end of the infusion of rhuMAb HER2 in accordance with the protocol.

   Serum will be collected preinfusion for both pharmacokinetic and antibody measurements at Weeks 1 (Day 0) through 4, then at Weeks 8, 20, 32, 44, and every 12 weeks thereafter, and at study termination.

2. Collection, Labeling, and Storage Instructions for 2 mL of Blood

   a. Draw 2 mL of blood into a glass red top vacutainer tube. USE ONLY TUBES SUPPLIED BY SCICOR, DOUGLASS, OR THE LOCAL LABORATORY.

   b. Allow the sample to clot at room temperature for approximately 45 minutes. Centrifuge and separate the serum from the clot.

   c. Pipet approximately 1 mL of serum into tube.

   d. Complete labels and requisitions according to instructions in the appropriate manual.

   e. Freeze the samples at or below –20°C until ready for shipment.

B. Serum Antibodies to rhuMAb HER2 (to be conducted by Genentech)
Note: These measurements will be performed on the first 50 patients randomized to receive rhuMAb HER2 and on the first 50 patients randomized to receive the lyophilized formulation of rhuMAb HER2.

1. Specimen Requirements

The investigators will supply the appropriate laboratory with serum samples taken prior to the infusion of rhuMAb HER2 in accordance with the protocol.

Serum will be collected preinfusion for measurement of antibodies to rhuMAb HER2 beginning at Week 1 (Day 0) for the first 4 weeks, then at Weeks 8, 20, 32, 44, and every 12 weeks thereafter, and at study termination.

2. Collection, Labeling, and Storage Instructions for 2 mL of Blood

Serum for the antibody measurement may be obtained from the blood sample drawn for the pharmacokinetic measurement. Refer to instructions for collecting the serum pharmacokinetic sample.

C. Serum Shed Antigen Concentrations (to be conducted by RBL)
Note: These measurements will be performed at baseline on all patients (active and control) at Week 1 (prior to study drug or first cycle of chemotherapy for control arm patients); on the first 50 patients randomized to receive rhuMAb HER2; and on the first 50 patients randomized to receive the lyophilized formulation of rhuMAb HER2.

1. Specimen Requirements

The investigators will supply the appropriate laboratory with serum samples taken prior to the start of the infusion of rhuMAb HER2 in accordance with the protocol.

Serum will be collected preinfusion for serum shed antigen measurements beginning at Week 1 for all patients, then at Weeks 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter, and at study termination

for the first 50 patients receiving rhuMAb HER2 and the first 50 patients receiving the lyophilized formulation of rhuMAb HER2.

2. Collection, Labeling, and Storage Instructions for 3 mL of Blood

   a. Draw 3 mL of blood into a glass red top vacutainer tube. USE ONLY TUBES SUPPLIED BY SCICOR, DOUGLASS, OR THE LOCAL LABORATORY.

   b. Allow the sample to clot at room temperature for approximately 45 minutes. Centrifuge and separate the serum from the clot.

   c. Pipet approximately 1.5 mL of serum into the appropriately labeled tube.

   d. Complete labels and requisitions according to instructions in the appropriate manual.

   e. Freeze the samples at or below –20°C until ready for shipment.

D. Special Studies (to be conducted by Genentech)
Note: These measurements will be performed at selected study sites only.

1. Specimen Requirements

   The investigators will supply the appropriate laboratory with serum and plasma samples taken prior to the start of the infusion of rhuMAb HER2 in accordance with the protocol.

   Serum will be collected preinfusion for special studies beginning at Week 1 for all patients. Serum will be collected from patients randomized to rhuMAb HER2 only at Weeks 2, 3, 4, 8, 20, 32, 44, and every 12 weeks thereafter, and at study termination.

2. Collection, Labeling, and Storage Instructions for 5 mL of Blood (Serum)

   a. Draw 5 mL of blood into a glass red top vacutainer tube. USE ONLY TUBES SUPPLIED BY SCICOR, DOUGLASS, OR THE LOCAL LABORATORY.

   b. Allow the samples to clot at room temperature for approximately 45 minutes. Centrifuge and separate the serum from the clot.

   c. Pipet approximately 2.5 mL of serum into tube.

d. Complete labels and requisitions according to instructions in the appropriate manual.

e. Freeze the samples at or below –20°C until ready for shipment.

3. Collection, Labeling, and Storage Instructions for 3 mL of Blood (Plasma)

   a. Draw 3 mL of blood into a glass blue top vacutainer tube.

   b. Centrifuge for a minimum of 15 minutes at room temperature.

   c. Pipet approximately 1.5 mL of plasma into tube.

   d. Complete labels and requisitions according to instructions in the appropriate manual.

   e. Freeze the samples at or below –20°C until ready for shipment.

Samples should be shipped on 5–7 lb (2.25–3.15 kg) of dry ice to ensure receipt in the frozen state. Shipping instructions can be found in the supplied manuals.

If questions or problems arise, contact one of the following persons:

United States and Canada:
Pat Devitt
Covance and Periapproval Services, Inc.
Office Telephone:
(800) 621-8901, extension 4293

Europe:
Adrian Foulkes
Covance and Periapproval Services, Inc.
Office Telephone: 01628-548-000
Cellular Telephone: *0385-342-304*

Australia and New Zealand:
Robyn Philip
Covance and Periapproval Services, Inc.
Office Telephone: *2-9869-1811*
Cellular Telephone (Australia): 0411-10-4509
(New Zealand): 61-411-10-4509

APPENDIX H

European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire QLQ-C30 with Breast Cancer Module BR23

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): _____

		No	Yes
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2.	Do you have any trouble taking a long walk?	1	2
3.	Do you have any trouble taking a short walk outside of the house?	1	2
4.	Do you have to stay in a bed or a chair for most of the day?	1	2
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
6.	Are you limited in any way in doing either your work or doing household jobs?	1	2
7.	Are you completely unable to work at a job or to do household jobs?	1	2

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4

Please go on to the next page

During th past w k:	Not at All	A Little	Quit a Bit	Very Much
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall physical condition during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Pati nts s m times r port that th y hav th following symptoms or problems. Pl as indicat th ext nt to which you hav xperienc d thes symptoms or pr bl ms during th past w k.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past <u>four</u> weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

During th past week:	Not at All	A Littl	Quite a Bit	V ry Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

APPENDIX I

Supplemental Questionnaire
(Protocol H0648g

For the following questions, please circle the number between 1 and 7 that best applies to you:

Q1. How much, if any, negative impact have the treatments you receive for your breast cancer had on your daily life and physical condition during the past week?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NO NEGATIVE IMPACT						A GREAT DEAL OF NEGATIVE IMPACT

Q2. How much of the time during the past week have you felt the future looks hopeful and promising?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NONE OF THE TIME						ALL OF THE TIME

Q3. How much trouble or inconvenience have you had as a result of having to come to the clinic or hospital for your medical treatment?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NO TROUBLE OR INCONVENIENCE						A GREAT DEAL OF TROUBLE OR INCONVENIENCE

Q4. How often during the past week have you felt good about yourself?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NONE OF THE TIME						ALL OF THE TIME

Q5. How much of the time have you found the weekly visits to the clinic or hospital for your medical care to be reassuring or supportive?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NONE OF THE TIME						ALL OF THE TIME

Q6. How often during the past week did you lose hope in the fight against your breast cancer?

(PLEASE CIRCLE ONE NUMBER)

1	2	3	4	5	6	7
NONE OF THE TIME						ALL OF THE TIME

APPENDIX I (cont'd)

Supplemental Questionnaire
(Protocol H0648g

The following questions ask about your activity level during the past week.

Q7a. During the **past week,** on how many days did you stay in bed more than half of the day because of your health?

(PLEASE CIRCLE NUMBER OF DAYS)

0 1 2 3 4 5 6 7

b. During the **past week,** on how many days did you cut down on your usual activities more than half of the day because of your health?

(PLEASE CIRCLE NUMBER OF DAYS)

0 1 2 3 4 5 6 7

The next set of questions ask you about any medical care you have received other than care you receive during your regular visits for this study.

Q8a. During the past **2 months**, how many times have you been admitted to the hospital for any reason?

(CIRCLE NUMBER OF TIMES)

0 1 2 3 4 5 or more

If you have been hospitalized, please indicate:

b. The total number of days you were hospitalized during the past **2 months**.

(CIRCLE NUMBER OF DAYS)

0 1 2 3 4 5 6 7 8 9 10 11 or more

c. The number of these days spent in the intensive care unit or coronary care unit during the past **2 months**.

(CIRCLE NUMBER OF DAYS)

0 1 2 3 4 5 6 7 8 9 10 11 or more

Q9. During the past **2 months**, how many times were you seen in an emergency room for any reason?

(CIRCLE NUMBER OF DAYS)

0 1 2 3 4 5 6 7 8 9 10 11 or more

Q10a. During the past **2 months**, apart from times you were in the hospital or visiting an emergency room, how many times have you seen a doctor for any reason? (DO NOT INCLUDE REGULAR STUDY VISITS.)

(PLEASE CIRCLE NUMBER OF TIMES)

0 1 2 3 4 5 6 7 8 9 10 11 or more

b. How many of these visits occurred at the study site?

(PLEASE CIRCLE NUMBER OF TIMES)

0 1 2 3 4 5 6 7 8 9 10 11 or more

APPENDIX I (cont'd)

Supplemental Questionnaire
(Protocol H0648g

The following questions are about your background. This information is for statistical purposes only. Answers will be kept confidential. The information you give will be combined with the responses of others taking this survey, and you will not be identifiable in any way. The questionnaires will be mailed directly to Technology Assessment Group in a sealed envelope.

Q11. What is the highest level of education you have completed?

(CIRCLE ONE NUMBER)

1. SOME HIGH SCHOOL
2. HIGH SCHOOL GED OR TRADE SCHOOL
3. SOME COLLEGE
4. COLLEGE
5. GRADUATE DEGREE

Q12. What was your total household income before taxes for the last calendar year?

(CIRCLE ONE NUMBER)

1. UNDER $20,000
2. $20,000 - $39,999
3. $40,000 - $59,999
4. $60,000 - $79,999
5. $80,000 OR OVER

Q13. Are you:

(CIRCLE ONE NUMBER)

1. SINGLE, NEVER MARRIED
2. MARRIED
3. LIVING WITH A PARTNER
4. SEPARATED
5. DIVORCED
6. WIDOWED

Investigator's Signature for Protocol Amendment

CHEMOTHERAPY AND ANTIBODY RESPONSE EVALUATION (CARE): A PHASE III, MULTINATIONAL, RANDOMIZED STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) COMBINED WITH CHEMOTHERAPY IN PATIENTS WITH HER2 OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER

(Protocol H0648g-A3)

I have read Amendment 3 to the above-named protocol and agree to abide by all provisions of the amendment.

Protocol Number: H0648g-A3

Investigator's Name: _____

Date: _____

Signature: _____

Sponsor: Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990 U.S.A.

SAMPLE INFORMED CONSENT

PROTOCOL H0648g: CHEMOTHERAPY AND ANTIBODY RESPONSE EVALUATION (CARE): A PHASE III, MULTINATIONAL, RANDOMIZED STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) COMBINED WITH CHEMOTHERAPY IN PATIENTS WITH HER2 OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER

PURPOSE AND BACKGROUND

rhuMAb HER2 is an experimental humanized monoclonal antibody produced by Genentech using recombinant DNA technology. Antibodies are proteins that can protect the body from foreign invaders such as bacteria and viruses by binding to substances called antigens. rhuMAb HER2 is a monoclonal antibody to cancer cells and may be able to control tumor growth. rhuMAb HER2 has been well tolerated by patients with breast cancer for periods of over 12 months in previous clinical trials.

Your doctor has explained your metastatic breast cancer to you. You have cancer that is resistant to surgical removal. Both paclitaxel and the combination of cyclophosphamide and doxorubicin are commonly used as chemotherapy regimens for treating breast cancer. Although neither the combination of rhuMAb HER2 and cyclophosphamide and doxorubicin nor the combination of rhuMAb HER2 and paclitaxel have been used together in humans, it is anticipated that rhuMAb HER2 in combination with these chemotherapies may be more effective than either regimen used alone. Your participation in this research study will help to determine whether or not rhuMAb HER2 administered into the bloodstream can delay further growth or shrink tumors in patients with breast cancer. Approximately 450 patients will participate in this clinical trial worldwide.

PROCEDURES

Prior to entering the study, you will undergo a screening examination that will include a complete medical history and physical examination (including blood pressure, pulse, temperature, and height), a chest X-ray, laboratory blood tests, and a pregnancy test, if appropriate. If you are pregnant or nursing, you will be

_____ Initials

excluded from participation in the study. If you are a woman of childbearing potential, you must be using effective contraception.

This is a "randomized" study, which means that you will be assigned by chance to receive one of the following treatments:

1. rhuMAb HER2 plus either cyclophosphamide and doxorubicin or paclitaxel, or
2. cyclophosphamide and doxorubicin or paclitaxel alone

Note: If you have received doxorubicin or a similar agent as preventive therapy following your initial surgery, you may receive paclitaxel as the chemotherapy in this study if your doctor thinks it is the best therapy for you.

If you are randomized to receive rhuMAb HER2 plus chemotherapy, in the first week a dose of four milligrams of rhuMAb HER2 for every kilogram you weigh will be administered intravenously (a needle will be put through your skin into your vein) into your bloodstream for 90 minutes, followed by a 60-minute observation period. Once a week thereafter, you will receive an intravenous dose of two milligrams of rhuMAb HER2 for every kilogram you weigh. If you receive the initial dose of rhuMAb HER2 without incident, you may receive subsequent doses over a 30-minute period. If the shortened infusion period is well tolerated, the postinfusion observation period for the second infusion may be shortened to 30 minutes and eliminated entirely with the third and subsequent infusions. Either cyclophosphamide and doxorubicin or paclitaxel will be given intravenously every 3 weeks for a minimum of 16 weeks. You will receive medications to minimize nausea and vomiting caused by the chemotherapy. After you complete the 16-week chemotherapy regimen, you will continue to receive weekly infusions of rhuMAb HER2 according to the initial randomization for the duration of your participation in the study.

If you are randomized to receive chemotherapy alone, your health status will be evaluated every other week, similar to those receiving the weekly rhuMAb HER2 infusions.

Approximately 1–2 tablespoons (15–30 milliliters) of blood will be collected at designated visits for routine laboratory testing and other studies. In addition, about 2 teaspoons (8 milliliters) of blood may be requested from selected

_____ Initials

patients at selected centers for special studies. The samples of fluid and blood taken from you will enable your doctors and researchers to learn more about the effects of this form of treatment and the properties of the drug. By agreeing to participate in this study, you are also agreeing to allow the doctors and researchers to examine and use such samples for any scientific purpose. You will be monitored closely during the study period by the use of laboratory evaluations (blood and urine tests) and physical examination. X-rays, computerized tomography (CAT scan), or magnetic resonance imaging (MRI) will be used periodically to evaluate your tumor status. You will be asked to complete a questionnaire about your quality of life periodically during the study. You will also be asked to complete an optional supplemental questionnaire. You may choose not to answer any questions that make you uncomfortable. Refusing to answer will not affect your participation in the study.

The duration of your participation in the study depends on how your cancer responds to treatment. The therapy will continue until your tumor grows, prohibitive toxicity occurs, you or your physician wish to discontinue treatment, or until Genentech (the Sponsor of the study) finds it necessary to limit or terminate this study. If your tumor grows, you will be contacted approximately every 2 months to follow up on your health status. If you were randomized to chemotherapy alone, you will be eligible to receive rhuMAb HER2 in another study following documented progression of your disease.

Your physician may discuss the possibility of performing a skin biopsy. If so, he or she will explain the procedure to you.

POSSIBLE RISKS AND DISCOMFORT

rhuMAb HER2 has been safely administered to humans. Fever (usually low grade) has occurred during and after administration of rhuMAb HER2 at an incidence of approximately 10%–20% in cancer patients. Pain has occurred at the site of metastatic tumors following the administration of rhuMAb HER2 in a few patients. Gastrointestinal disorders, including abdominal pain, dyspepsia, diarrhea, nausea, vomiting, anorexia, and dehydration, have been reported. The following additional events have been reported as possible effects of rhuMAb HER2 therapy: worsening of previously existing neuropathy (a disease of the nerves in the arms or legs); anemia; low white blood cell and platelet counts; nose bleeding; headaches; anxiety; abnormal sensations; dizziness;

_____ Initials

tremors; nervousness; difficulty breathing; wheezing; asthma; fatigue; malaise; pain in the back, chest, pelvis, and at the injection site; and laboratory abnormalities such as albuminuria, bilirubinemia, hypokalemia, and hypomagnesemia.

In ongoing studies of rhuMAb HER2 *alone or* with cytotoxic chemotherapy, the following events have been reported: allergic reactions or anaphylaxis, breathlessness, rash and wheezes, and fever with low white blood cell counts. *Congestive heart failure with symptoms of shortness of breath and edema have been observed in patients who have received rhuMAb HER2 alone and with cytotoxic chemotherapy. There is a possibility that the administration of rhuMAb HER2 may increase the risk of getting this side effect when used together with doxorubicin or epirubicin. You will be monitored with noninvasive tests for cardiac function on a regular basis to detect cardiac abnormalities.*

Possible side effects of this treatment may include complications from the intravenous catheter that may result in infection or bleeding. There is some potential health risk of radiation exposure from X-rays; however, this risk is considered small.

The rhuMAb HER2 you may receive in this study may contain benzyl alcohol, a preservative that has been associated with toxicity in newborns. The formulation of rhuMAb HER2 containing benzyl alcohol should not be administered to anyone with a known sensitivity to benzyl alcohol.

The long-term effects of rhuMAb HER2 are unknown. Since the effect of rhuMAb HER2 on the reproductive system or developing fetus is unknown, patients who are of childbearing potential must use effective contraception while participating in this study. As is true for any experimental drug, unknown and potentially life-threatening side effects could occur with rhuMAb HER2. You will be given any new information that could affect your willingness to continue participating in this study.

The most common side effects of cyclophosphamide and doxorubicin therapy are nausea and vomiting, hair loss, inflammation of the lining of the mouth, and a decrease in white blood cells (which fight infection) and platelets (which help

_____ Initials

blood clot). Heart damage (occasionally fatal) may occur with doxorubicin therapy. Cyclophosphamide may cause sterility and cessation of menstrual periods. Safe use of doxorubicin and cyclophosphamide in pregnancy has not been established. While data are inconclusive at this time, fetal abnormalities have been reported. Additional information on the side effects of cyclophosphamide and doxorubicin is available from your physician.

Paclitaxel has been associated with severe hypersensitivity reactions, including death in one patient. You will receive medications to prevent these reactions from occurring. With the use of these medications, severe reactions are now rare. The principal side effects of paclitaxel include a decrease in white blood cells and platelets, neuropathy, anemia, muscle aches, hair loss, nausea, vomiting, diarrhea, inflammation of the mucous membranes, and, rarely, a disturbance in heart rhythm that might require therapy. Additional information on the side effects of paclitaxel is available from your physician.

POSSIBLE BENEFITS

rhuMAb HER2 has not been previously used in combination with cyclophosphamide and doxorubicin chemotherapy, nor with paclitaxel chemotherapy. However, rhuMAb HER2 has been used in combination with another chemotherapeutic agent, and results have shown that in some patients tumors may grow more slowly than they would without treatment with rhuMAb HER2. However, you may receive little or no benefit from rhuMAb HER2 plus either cyclophosphamide and doxorubicin or paclitaxel treatment. It is hoped that additional information gained in this study may be useful in the treatment of other patients with breast cancer.

ALTERNATIVE TREATMENT

You may choose a more standard treatment for your disease, such as other chemotherapy regimens or radiation therapy (in a few special circumstances), or decide not to be treated at all. Your doctor will discuss these options with you. If you decide not to participate in this study, other choices are available to you without prejudice.

CONFIDENTIALITY

All or part of your medical records may be reviewed and analyzed by the U.S. Food and Drug Administration (FDA), other national health authorities

_____ Initials

(where applicable), and representatives of Genentech, the manufacturer of rhuMAb HER2. If information is published in a medical journal, you will not be identified by name, picture, or any other personally identifying information. The FDA or other national authorities may inspect the research and clinical records without removal of identifying information. However, the usual medical records precautions will be taken to maintain the privacy and confidentiality of your records.

TERMINATION OF PATIENT PARTICIPATION

Your participation in this clinical trial may be ended at any time for medical reasons or because Genentech finds it necessary to limit or terminate this clinical trial.

COMPENSATION

You will not receive money or any other form of compensation for participating in this clinical trial. All costs of your treatment, except for those required specifically and solely for this study, are your responsibility. The study drug, rhuMAb HER2, will be provided free of charge for the duration of the study. If your doctor prescribes paclitaxel for you and the cost is not reimbursed by the medical payer covering your medical expenses, paclitaxel will be provided free of charge for the duration of the study.

RESEARCH-RELATED INJURIES

In the event that your participation in this study results in a medical problem, treatment will be made available. No reimbursement for such treatment or financial compensation is available.

QUESTIONS

If you have any questions about the study, safety, or procedures of the study, or in the event of injury, you may contact Dr. _____ at _____. You may also call _____ at _____ for information on experimental patients' rights.

_____ Initials

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

My participation in this study is voluntary and I may withdraw from the study at any time without prejudice or loss of benefits to which I am otherwise entitled. I have received a copy of this consent form and I am aware that the investigator at my hospital will also retain a copy in his or her files. I hereby give my consent to participate in this clinical trial.

_____
Patient Name (print)

_____ _____
Patient Signature Date

_____
Investigator Name (print)

_____ _____
Investigator Signature Date

If applicable:

_____
Witness Name (print)

_____ _____
Witness Signature Date

_____ Initials

Corning Besselaar Princeton, USA

rhuMAb HER2

PROTOCOL: H0648g

PATIENT INIT.

PATIENT NUMBER: 2292-8001

WEEK

* PLEASE TYPE OR PRINT USING A BLACK BALLPOINT PEN

WEEK 1 (DAY 0) INFUSION

PRIOR TO INFUSION:

1. OBTAIN SAMPLES FOR CENTRAL LABORATORY ASSESSMENTS AS WELL AS PK/Ab, SHED ANTIGEN (AND SPECIAL STUDIES, IF APPROPRIATE). ATTACH COPY OF SCICOR LABORATORY REPORT.
2. WEIGHT: 052.5 ☐ lb ☑ kg KARNOFSKY STATUS: 90 %
3. RECORD ALL NEW MEDICATIONS, CHANGES IN DOSE, OR DISCONTINUED MEDICATIONS SINCE BASELINE ON THE MEDICATIONS PAGE AT WEEK 8.
4. HAVE PATIENT COMPLETE THE QUALITY OF LIFE QUESTIONNAIRE. INSERT THE COMPLETED QUESTIONNAIRE BEHIND THIS PAGE.

INFUSION DATA:

DATE OF INFUSION: DD MON YY

START TIME OF INFUSION (24 HOUR CLOCK): 14:55

STOP TIME OF INFUSION: 15:45

TOTAL DOSE RECEIVED: 117.0 mg

LABEL (LOT) # USED: 01

VITAL SIGNS

		TEMPERATURE (CHECK °F OR °C)	BLOOD PRESSURE (mmHg)	HEART RATE bpm	RESP. RATE resp/min
1	PRE-INFUSION (COLLECT PK/Ab, SHED Ag SAMPLES AND, IF APPLICABLE, SPECIAL STUDIES)	097.8 ☐°C ☑°F	110/068 systolic/diastolic	084	16
2	END OF INFUSION (COLLECT PK SAMPLES)	097.4 ☐°C ☑°F	118/070 systolic/diastolic	094	24
3	1 HOUR POST-INFUSION	098.6 ☐°C ☑°F	698/060 systolic/diastolic	088	16
4	FOLLOW-UP #1 TIME OF ASSESSMENT 24 HOUR CLOCK: :	☐°C ☐°F	/ systolic/diastolic		
5	FOLLOW-UP #2 TIME OF ASSESSMENT 24 HOUR CLOCK: :	☐°C ☐°F	/ systolic/diastolic		

PAGE 11

EXHIBIT B

PROTOCOL H 0 6 4 8 g | PATIENT INIT. | PATIENT NUMBER 2292-3001 | WEEK

* PLEASE TYPE OR PRINT USING BLACK BALLPOINT PEN

ADMINISTRATION OF CHEMOTHERAPY

(TO BE ADMINISTERED ONE DAY FOLLOWING ADMINISTRATION OF HER2 OR PLACEBO AT WEEKS 1,4 AND 7)

DOXORUBICIN ☑ N/A: PATIENT RECEIVING PACLITAXEL

1 LIST BRAND NAME	DATE OF ADMINISTRATION	BSA (m2)	TOTAL DOSE RECEIVED (mg)
1.	DD MON YY		
2.	DD MON YY		
3.	DD MON YY		

CYCLOPHOSPHAMIDE ☑ N/A: PATIENT RECEIVING PACLITAXEL

2 LIST BRAND NAME	DATE OF ADMINISTRATION	BSA (m2)	TOTAL DOSE RECEIVED (mg)
1.	DD MON YY		
2.	DD MON YY		
3.	DD MON YY		

PACLITAXEL (TAXOL®)

☐ N/A: PATIENT RECEIVING DOXORUBICIN AND CYCLOPHOSPHAMIDE

3 DATE OF ADMINISTRATION	BSA (m2)	TOTAL DOSE RECEIVED (mg)
1. DD MON YY	1.57	275
2. DD MON YY	~~N/A~~ 1.57 + ca 4cc i	275
3. DD MON YY	1.57 ~~N/A~~ 4cc	275

Corning Besselaar
Princeton, USA

PROTOCOL: H 0 6 4 8 g PATIENT INIT. PATIENT NUMBER: 2 2 9 2 - 3 0 0 1

* PLEASE TYPE OR PRINT USING BLACK BALLPOINT PEN

PACLITAXEL (TAXOL®)

THIS PAGE IS TO BE COMPLETED IF PACLITAXEL (TAXOL®) INFUSIONS ARE CONTINUED TO WEEKS 19, 22, 25, 28

☐ NOT APPLICABLE

TO BE ADMINISTERED ONE DAY FOLLOWING ADMINISTRATION OF HER 2 OR PLACEBO

3 WEEK	DATE OF ADMINISTRATION	BSA (m2)	TOTAL DOSE RECEIVED (mg)
1. 20	DD MON YY	1.60	275
2. 23	DD MON YY	1.60	275
3. 26	DD MON YY	1.60	275
4.	DD MON YY		

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Princeton, USA