Genentech, Inc.

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11928

November 16, 1995

Ms. Sharon Risso
Director
DARP (HFM-585)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Subject: BB-IND 4517 recombinant humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2)
Response to FDA Request for Information
Protocol Amendment: Change in Protocol
Serial No. 055

Dear Ms. Risso:

Reference is made to Genentech's Investigational New Drug Application, BB-IND No. 4517, recombinant humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) for treating cancer patients with tumors that overexpress the HER2 proto-oncogene (submitted on April 20, 1992, Serial No. 000).

Reference is also to made to a letter Genentech received from the Agency dated June 16, 1995, in which the Agency provided comments concerning information Genentech submitted on January 5, February 16, March 7, and March 14, 1995, as it pertains to the clinical program for rhuMAb HER2.

Reference is also made a teleconference held with the Agency on October 30, 1995, to discuss proposed changes to pivotal trial H0648g. The proposed changes will allow entry of patients who have previously received doxorubicin as an adjuvant treatment for metastatic breast cancer. In the teleconference, Genentech agreed to provide the Agency with the Data Safety

Monitoring Board charter, curricula vitae of the DSMB members, and the statistical analysis plan. Those documents are under preparation and will be submitted as soon as they are available.

The purpose of this submission is to submit the amended protocol for H0648g and to respond to the Agency's questions and comments about the trial. The protocol amendment with the list of changes is attached.

Attachment: H0648g Amendment 1

A Phase III, Multinational, Double-Blind Study Comparing Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) Plus Chemotherapy Compared with Placebo Plus Chemotherapy in Patients with HER2/*neu* Overexpression Who Have Not Received Cytotoxic Chemotherapy for Metastatic Breast Cancer (Submitted March 7, 1995/Serial No. 033.)

For clarity, we have provided the Agency's questions and comments in **bold** followed by Genentech's responses in normal type.

1. **With regard to the revised clinical protocol H0648g, entitled "A Phase 3, Multinational Double-Blind Study Comparing Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) Plus Cyclophosphamide and Doxorubicin with Placebo Plus Cyclophosphamide and Doxorubicin in Patients with HER2/*neu* Overexpression Who Have Not Received Prior Cytotoxic Chemotherapy for Metastatic Breast Cancer", we have the following comments:**

   a. **The primary efficacy endpoint of this trial is time to progression, analyzed at 12 months after the last patient has been entered and will include all eligible patients. This endpoint must be supported by neutral or positive trends in favor of the rhuMAb HER2 plus chemotherapy arm for the secondary endpoints of overall response rate, complete response rate, and quality of life assessment. If the effect of addition of the monoclonal antibody to the combination of cyclophosphamide and doxorubicin results in a lowered response rate due to growth arrest rather than tumor reduction, the benefit of such therapy will be of uncertain patient benefit. In the setting of metastatic disease, a durable complete or major partial response is expected to correlate with improvement in disease-related**

symptomatology while disease stabilization, even if prolonged, may not provide much symptomatic relief to the patient.

We acknowledge that a positive result on time to progression as the primary efficacy endpoint for patients receiving rhuMAb HER2 compared to those receiving placebo must be supported by neutral or positive trends in favor of response rates and quality of life in order to show a correlation of increased time to progression with clinical benefit to the patient.

b. **We note that there will be an interim analysis to estimate the treatment effect and determine whether the sample size or duration of follow-up should be adjusted. This is necessary because you have no data that suggest that addition of the monoclonal antibody will prolong the time to progression or, if it did, by what magnitude. The clinical impact of a delay in the median time to progression will need to be weighed against any adverse effects of the therapy.**

The purpose of the interim analysis is to verify the estimate of time to progression in the control group. In designing the trial, the number of patients and the duration of follow-up was based on the assumption that metastatic breast cancer patients treated with doxorubicin and cyclophosphamide had a median time to progression of 8 months. However, we do not know the median time to progression for patients with HER2 overexpressing tumors.

At the time of the interim efficacy analysis, the Data Safety Monitoring Board (DSMB) will review the safety data as well. The follow-up period will not be extended if, in the opinion of the DSMB, there is an increased risk to patients of developing serious adverse events.

c. **The protocol states that the dose modification for non-hematologic toxicities will be carried out at the investigator's discretion. The protocol would be improved if uniform guidelines for dose adjustments were provided; however, since the protocol is blinded there should not be bias in the manner in which dose adjustments are made by individual investigators.**

We agree there should be no bias in dose reduction for non-hematologic toxicities in this comparative study. To ensure compliance with the dose and administration section of the package insert for branded doxorubicin, we are amending the protocol to introduce mandated dose reduction for increased bilirubin. (See Attachment 1, Section 5.4.). Additonal recommendations are made for dose reduction or delay for hematologic and other non-hematologic toxicities. (See Appendix F.)

d. **Please confirm that all concomitant medications (including days of therapy and daily dose), blood transfusions, and hospitalizations will be recorded. The reason for initiation of new medications and the reasons for hospitalization and duration of hospitalization must also be recorded. In particular, the daily dose of narcotics or any other agents which may be used for palliation must be available in order to attempt to interpret the quality of life data.**

We confirm that the concomitant medication case report form (CRF) designed for this study will collect the name of <u>all</u> medications taken, the indication (i.e., the reasons for the initiation of new medications), total daily dose, and start and stop date of medication. If medications are taken on an as needed basis (PRN), sites have been instructed to enter the dose typically taken at each dosing. Sites have been instructed to list <u>all</u> medications used, as well as all blood transfusion information. Our Medical Information and Drug Experience (MIDE) safety database captures whether a serious adverse event involves a hospitalization, is life-threatening, is a new cancer, etc. Our original CRFs collected the serious adverse event, but did not request duration of hospitalization information. At your request, we are amending the serious adverse event CRFs to capture the hospitalization information so as to adequately link the serious event with duration of hospitalization in our clinical database.

e. **Please clarify how you will analyze quality of life assessments in patients who receive palliative, local radiotherapy or in whom other palliative measures are undertaken.**

The effect of the local radiotherapy on the quality of life can be positive or negative, depending on when the quality of life questionnaire is administered and when the patient receives radiotherapy. Two sets of analysis will be performed: one ignoring the information on local radiotherapy and the other including the information on the local radiotherapy as a covariate.

If you have any questions or comments concerning this submission, please contact Roxanne Bales, Senior Manager, Regulatory Affairs of my staff at (415) 225-1024.

Sincerely,

M. David MacFarlane, Ph.D.
Vice President
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1992.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1 NAME OF SPONSOR
Genentech, Inc.

2 DATE OF SUBMISSION
November 16, 1995

3 ADDRESS *(Number, Street, City, State and Zip Code)*
460 Point San Bruno Boulevard
South San Francisco, California 94080-4990

4 TELEPHONE NUMBER *(Include Area Code)*
(415) 225-1557

5 NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical Code)*
Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAbHER2)

6 IND NUMBER *(if previously assigned)*
BB-IND 4517

7 INDICATION(S) *(Covered by this submission)*
Treatment of Cancer Patients with Tumors that Overexpress the HER2 Proto-oncogene

8 PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ☐ PHASE 2 ■ PHASE 3 ☐ OTHER _____ *(Specify)*

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10 IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 0 5 5

11 THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
■ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

■ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED
		DIVISION ASSIGNMENT

PROTECTIVE ORDER MATERIAL

GENENTECH 0000040

FORM FDA 1571 (6 92) **PREVIOUS EDITION OBSOLETE**

CONTENTS OF APPLICATION

This application contains the following items: *(check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☒ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Tom Twaddell, M.D.
Associate Director

15 NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Barry Sherman, m.D., Vice President, Medical Affairs
Timothy G. Terrell, DVM, Ph.D., Director, Pathobiology and Toxicology

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17 SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
M. David MacFarlane, Ph.D. Vice President, Regulatory Affairs		
18 ADDRESS *(Number, Street, City, State and Zip Code)* 460 Point San Bruno Boulevard South San Francisco, California 94080-4990	19 TELEPHONE NUMBER *(Include Area Code)* (415) 225-1557	20 DATE 11/17/97

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

PROTOCOL AMENDMENT SUMMARY

TITLE:	**A PHASE III, MULTINATIONAL, DOUBLE-BLIND STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) PLUS CHEMOTHERAPY COMPARED WITH PLACEBO PLUS CHEMOTHERAPY IN PATIENTS WITH HER2/*neu* OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	H0648g
IND:	BB-IND 4517
MEDICAL MONITOR:	Thomas Twaddell, M.D.
SPONSOR:	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	20 January 1995
AMENDMENT 1:	13 November 1995

13 NOVEMBER 1995 AMENDMENT

RATIONALE

Protocol H0648g has been amended to:

- Address comments and questions raised in recent correspondence from the FDA

  The exclusion criterion for hepatic function has been modified, and a dose reduction schedule for doxorubicin has been added that is consistent with FDA-approved product information.

- Expand the patient population available for entry into this study by permitting prior anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubucin) in the adjuvant setting

  If, in the opinion of the investigator, paclitaxel represents the best therapy for this cohort of patients, they may receive paclitaxel. A dose reduction schedule for paclitaxel has also been added.

- Clarify the study rationale because of the addition of paclitaxel
- Clarify blood sampling requirements for serum pharmacokinetics, serum antibodies to rhuMAb HER2, and serum shed antigen
- Add a supplemental questionnaire to examine pharmacoeconomic issues in both treatment groups
- Address issues raised by the Data Safety Monitoring Board related to the interim analysis
- Add a section pertaining to breaking the study blind, in compliance with regulatory reporting requirements and European Good Clinical Practice guidelines
- Add a 60-day post-treatment follow-up to assess adverse events
- Incorporate name and phone number changes of the contract research organization (CRO)

  Names and phone numbers of CRO contacts in Australia and New Zealand have been added.

The title of the protocol has been simplified. The Introduction has been condensed because the identical information appears in the Investigator Brochure. Minor changes have been made to improve clarity and consistency. New information appears in italics. This amendment represents cumulative changes to the original final protocol.

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SYNOPSIS

Previously Read:

This protocol describes a Phase III randomized, placebo-controlled, double-blind, multinational study to determine the safety and efficacy of rhuMAb HER2 plus cyclophosphamide and doxorubicin compared with placebo plus cyclophosphamide and doxorubicin. Approximately 450 patients with HER2/*neu* overexpression who have not received prior cytotoxic chemotherapy for metastatic breast cancer will be enrolled in the study and randomized to one of two treatment groups.

rhuMAb HER2 will be administered as a 4 mg/kg...An equivalent amount of placebo will be administered on the same schedule....After the completion of cytotoxic chemotherapy, rhuMAb HER2 or placebo will be continued weekly according to the original randomization until disease progression or study termination.

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 two groups....

Now Reads:

This protocol describes a Phase III, randomized, placebo-controlled, double-blind, multinational study in patients with HER2/*neu* 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-p185^{HER2} monoclonal antibody* (rhuMAb HER2) *used in addition to chemotherapy.*

All patients will receive either rhuMAb HER2 as a 4 mg/kg...*or* an equivalent amount of placebo on the same schedule....*Patients who have not received anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubucin) in the adjuvant setting will receive* cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) IV beginning on Day 1, then every 3 weeks on the day following rhuMAb HER2 administration, for a total of six cycles. *If the patient received anthracycline therapy in the adjuvant setting and if, in the opinion of the investigator, the patient would benefit from*

paclitaxel therapy, she may receive paclitaxel (175 mg/m^2) over 3 hours IV beginning on Day 1, then every 3 weeks on the day following administration of either rhuMAb HER2 or placebo, for a total of six cycles. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy and there is no dose-limiting toxicity (defined as WHO Grade 3 or 4 neuropathy), paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.

Approximately 450 patients will be enrolled in the study and randomized to *either the rhuMAb HER2 or placebo arm, and will be stratified according to the type of metastatic disease: visceral (e.g., liver or lung) versus superficial (e.g., skin, chest wall, and peripheral lymph node), and according to prior anthracycline therapy (yes/no).*

After the completion of cytotoxic chemotherapy, rhuMAb HER2 or placebo will be continued weekly according to the original randomization until disease progression or study termination. *Patients will be evaluated for adverse events 60 days after discontinuing study drug and will be followed for survival information every 2 months.*

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 placebo treatment* groups....

SECTION 1: INTRODUCTION

In addition to condensing the text, the following revisions were made:

SECTION 1.2: PRECLINICAL STUDIES OF rhuMAb HER2

Added:

Characterization of the serum pharmacokinetics of rhuMAb HER2 in the presence of doxorubicin combined with cyclophosphamide or in the presence of doxorubicin or paclitaxel alone was conducted in female rhesus monkeys at doses that approximate human clinical doses on a body weight basis. Single-dose IV administration of rhuMAb HER2

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was well tolerated and did not alter the disposition of any agent administered.

SECTION 1.4: STUDY RATIONALE

Previously Read:

Worldwide, doxorubicin-based regimens, especially those combined with cyclophosphamide, play an important role in therapy for the initial presentation of metastatic breast cancer (25). In vivo nude mouse xenograft models utilizing HER2 transfected cell lines have demonstrated an additive effect in reducing tumor volume when rhuMAb HER2 is given in combination with doxorubicin, compared with rhuMAb HER2 or doxorubicin given alone (22). It is anticipated that, in a population of previously untreated patients with HER2 overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to a doxorubicin-based regimen will enhance efficacy compared with a doxorubicin-based regimen alone.

Now Reads:

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. Cyclophosphamide and doxorubicin or paclitaxel are currently important chemotherapy agents in the treatment of breast cancer. In vivo nude mouse xenograft models utilizing HER2 transfected cell lines have demonstrated an additive effect in reducing tumor volume when rhuMAb HER2 is given in combination with doxorubicin, compared with rhuMAb HER2 or doxorubicin given alone (20,*23*). *Similar findings using a different in vivo model were reported with rhuMAb HER2 and paclitaxel (21,23).* It is anticipated that, in a population of patients with HER2 overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cytotoxic chemotherapy* will enhance efficacy.

SECTION 2: OBJECTIVE

Previously Read:

The objective of this study is to determine the safety and efficacy of rhuMAb HER2 plus cyclophosphamide and doxorubicin compared with

placebo plus cyclophosphamide and doxorubicin in patients with HER2/*neu* overexpression who have not received prior cytotoxic chemotherapy for metastatic breast cancer.

Study endpoints are:

Primary:

- To compare the time to disease progression in patients receiving rhuMAb HER2 plus cyclophosphamide and doxorubicin with those receiving placebo plus cyclophosphamide and doxorubicin....

Secondary:

- To compare overall response rates (complete and partial responses) between both treatment groups
- To compare the duration of response between both treatment groups in patients who have achieved a complete or partial response
- To compare the quality of life of both treatment groups using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life instrument with the breast cancer module
- To define the pharmacokinetic profile of rhuMAb HER2 when co-administered with cyclophosphamide and doxorubicin....

Now Reads:

The objective of this study is to determine the safety and efficacy of rhuMAb HER2 *used in addition to chemotherapy* in patients with HER2/*neu* overexpressing metastatic breast cancer who have not received prior cytotoxic chemotherapy.

Study endpoints are:

Primary:

- To compare the time to disease progression in patients receiving rhuMAb HER2 plus *either* cyclophosphamide and doxorubicin *or paclitaxel* with those receiving placebo plus *either* cyclophosphamide and doxorubicin *or paclitaxel*....

Secondary:

- To compare overall response rates (complete and partial responses) between both treatment *arms (rhuMAb HER2 versus placebo)*
- 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 define the pharmacokinetic profile of rhuMAb HER2 when co-administered with *either* cyclophosphamide and doxorubicin *or paclitaxel*....

SECTION 3: STUDY DESIGN

Previously Read:

This is a Phase III, randomized, placebo-controlled, double-blind, multinational study comparing rhuMAb HER2 plus cyclophosphamide and doxorubicin with placebo plus cyclophosphamide and doxorubicin. Approximately 450 patients with HER2/*neu* overexpression who have not received prior 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 groups.

rhuMAb HER2 will be administered as a 4 mg/kg...An equivalent amount of placebo will be administered on the same schedule....

Now Reads:

This is a Phase III, randomized, placebo-controlled, double-blind, multinational study comparing rhuMAb HER2 plus *either* cyclophosphamide and doxorubicin *or paclitaxel* with placebo plus *either* cyclophosphamide and doxorubicin *or paclitaxel*. Approximately 450 patients with HER2/*neu* 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*.

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All patients will receive either rhuMAb HER2 as a 4 mg/kg...*or* an equivalent amount of placebo on the same schedule....*Patients who have not received anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubucin) in the adjuvant setting will receive* cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) IV beginning on Day 1, then every 3 weeks on the day following rhuMAb HER2 administration, for a total of six cycles.

Added:

If the patient received anthracycline therapy in the adjuvant setting and if, in the opinion of the investigator, the patient would benefit from paclitaxel therapy, she may receive paclitaxel (175 mg/m^2) over 3 hours IV beginning on Day 1, then every 3 weeks on the day following administration of either rhuMAb HER2 or placebo, for a total of six cycles. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy as defined below, and if there is no dose-limiting toxicity defined as WHO Grade 3 or 4 neuropathy, paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.

Criteria for continuation of paclitaxel beyond six cycles are as follows (see Section 7 for definitions of response criteria):

- *Complete Response: Patient may receive up to two more cycles of paclitaxel*
- *Minor Response or Partial Response: Patient may receive additional cycles of paclitaxel until stabilization of best response, disease progression, or dose-limiting toxicity*

  A maximum number of 10 cycles of paclitaxel will be given.
- *Stable Disease or Progressive Disease: Patient will not receive any further paclitaxel therapy*

Previously Read:

One year after enrollment enrollment of the last patient, those patients randomized to rhuMAb HER2 who have not developed disease progression will be eligible to continue on that therapy in an open-label extension program. Those patients randomized to placebo will be

followed for disease status until progression or study termination. All patients who develop disease progression will be followed for survival information every 2 months until termination of statistical analysis of the study.

The primary endpoint of the study...The complete and partial response rates and response duration will be determined and compared between the two groups....

Now Reads:

One year after enrollment of the last patient, those patients randomized to rhuMAb HER2 who have not developed disease progression will be eligible to continue on that therapy. Those patients randomized to placebo will be followed for disease status until progression or study termination. All patients who develop disease progression will be followed for survival information every 2 months until termination of statistical analysis of the study. *At some study sites, patients will be eligible to receive open-label rhuMAb HER2 treatment in a separate study protocol.*

The primary endpoint of the study...The complete and partial response rates and response duration will be determined and compared between the groups... *A supplemental instrument will be used to explore pharmacoeconomic issues in the treatment groups.*

SECTION 4: STUDY POPULATION

SECTION 4.2: EXCLUSION CRITERIA

Deleted:

- Prior treatment with doxorubicin, epirubicin, mitoxantrone, or daunorubicin in an adjuvant setting

Added:

- *Prior hypersensitivity to products containing Cremophor® EL (e.g., cyclosporine or teniposide for injection)*

  Note: *This criterion applies only to patients who have received prior adjuvant anthracycline therapy.*

Previously Read:

- Hepatic function: bilirubin ≥2 mg/dL (34.2 µmol/L)
- Coagulation function: prothrombin time ≥14 sec

Now Reads:

- Hepatic function: bilirubin ≥*1.2* mg/dL (*20.5* µmol/L)

  A patient will not be excluded with a bilirubin of up to 2.0 mg/dL (34.2 µmol/L) if the elevation is due to a benign cause such as proven Gilbert's syndrome.
- Coagulation function: prothrombin time >*15* sec

SECTION 5: STUDY MEDICATION

Added:

5.2 *STORAGE REQUIREMENTS*

rhuMAb HER2 storage instructions have been added.

SECTION 5.3: ADMINISTRATION AND DOSAGE

Previously Read:

5.3.2 Cyclophosphamide and Doxorubicin

Cyclophosphamide and doxorubicin will be supplied by the pharmacy at the investigative site as Cytoxan® for Injection and Adriamycin PFS®, respectively.

Now Reads:

5.3.2 *Chemotherapy*

Patients will receive one of two chemotherapy regimens in addition to rhuMAb HER2 or placebo: a) cyclophosphamide and doxorubicin, 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.

a. Cyclophosphamide and Doxorubicin

Cyclophosphamide and doxorubicin will be supplied by the pharmacy at the investigative site as Cytoxan® for Injection and Adriamycin PFS®, respectively, *if available. Generic equivalents*

approved by the regulatory authorities in the country of administration will be allowed.

Added:

b. *Paclitaxel (also see Section 3)*

Patients who have received any anthracycline in the adjuvant setting may receive paclitaxel, supplied by the pharmacy as Taxol® for Injection Concentrate, beginning on Day 1, then every 3 weeks on the day following administration of rhuMAb HER2 or placebo, for a total of six cycles.

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

Paclitaxel will be given at a dose of 175 mg/m^2 over 3 hours by IV infusion. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy (see Section 3), and if there is no dose-limiting toxicity defined as WHO Grade 3 or 4 neuropathy, paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.

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

Previously Read:

5.3 DOSE MODIFICATION FOR CYCLOPHOSPHAMIDE AND DOXORUBICIN

If a Grade 4 hematologic toxicity occurs (see Appendix B and Section 6.3), administration of cyclophosphamide and doxorubicin must

be delayed until granulocytes are $\geq 1000/mm^3$ ($1.0 \times 10^9/L$) and platelet counts $\geq 100,000/mm^3$ ($100 \times 10^9/L$).

Filgrastim may be administered in subsequent courses following an episode of neutropenia. In such cases, filgrastim may be given at the investigator's discretion according to institutional protocol. The use of filgrastim in cycles of cytotoxic chemotherapy following an episode of febrile neutropenia is especially encouraged to maintain an appropriate dose intensity.

Dose modifications for nonhematologic toxicities will be carried out at the investigator's discretion.

Now Reads:

5.4 *GUIDELINES FOR* DOSE MODIFICATION

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

See Appendix F 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 or placebo) should be continued throughout dose modification or delay of the cytotoxic agents.

SECTION 5.5: CONCOMITANT/EXCLUDED THERAPY

Deleted:

Dexamethasone or other corticosteroids must not be part of the antiemetic regimen. Otherwise, the antiemetic regimen of the investigator's choice may be used.

Added:

Patients on chronic low-dose steroids (< 10 mg of prednisone equivalent per day) for pre-existing medical conditions 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).

SECTION 6: PATIENT MONITORING (see Appendix A)

SECTION 6.1: PREADMISSION EVALUATIONS (see Appendix A)

The sedimentation rate was deleted from the hematology evaluation. Also deleted were:

- EORTC quality-of-life instrument
- Shed antigen (extracellular domain of the receptor)
- Antibodies to rhuMAb HER2

SECTION 6.2: STUDY EVALUATIONS (see Appendix A)

SECTION 6.2.1: Tests

Revisions to this section include:

- Changing Week 38 to Week 36
- Adding the New York Heart Association Classification of Functional Cardiac Capacity to the study termination visit
- Adding a note to the Week 16 measurement of cardiac ejection fraction that patients receiving paclitaxel will not be measured
- Rescheduling the EORTC Quality-of-Life Instrument and Supplemental Questionnaire to Weeks 1 (Day 0), 8, 16, 24, and every 12 weeks thereafter, and at study termination

SECTION 8: STATISTICAL CONSIDERATIONS

SECTION 8.2: STATISTICAL ANALYSIS

SECTION 8.2.1: Efficacy Analysis

Previously Read:

The primary efficacy variable is...Time to disease progression will be compared between the two treatment arms. The primary analysis will include all eligible patients (intent-to-treat).

The Cox proportional hazards model...The following baseline characteristics will be considered in the analysis: age, estrogen receptor status, level of HER2 overexpression (+2 versus +3), number of positive lymph nodes, number of metastatic sites,...

Now Reads:

The primary efficacy variable is...Time to disease progression will be compared between the two treatment arms *(rhuMAb HER2 versus placebo)*. The primary analysis will include all eligible patients (intent-to-treat) *and will be based on the pooled chemotherapy groups.*

The Cox proportional hazards model...The following baseline characteristics will be considered in the analysis: age, estrogen receptor status, level of HER2 overexpression (+2 versus +3), number of metastatic sites, *prior exposure to anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubicin),...*

Previously Read:

Survival will be measured from...Two survival curves will be estimated: one for all eligible patients and one for patients who did not receive immunotherapy, chemotherapy (other than protocol-specified), hormonal therapy, or radiotherapy.

Now Reads:

Survival will be measured from...*The analysis will be stratified according to the therapeutic options chosen after discontinuation from this protocol.*

SECTION 8.2.3: Quality-of-Life Assessment

Added:

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

SECTION 8.3: RANDOMIZATION AND BLINDING

Previously Read:

Patients will be randomized by telephone to either rhuMAb HER2 plus cyclophosphamide and doxorubicin, or to placebo plus cyclophosphamide and doxorubicin. The randomization will be done in

such a way that the two treatment arms will be balanced within each participating center, and also balanced by visceral (e.g., liver or lung) disease versus superficial (e.g., skin, chest wall, and peripheral lymph node) disease.

Now Reads:

Patients will be randomized by telephone to either rhuMAb HER2 plus *chemotherapy* or placebo plus *chemotherapy. The chemotherapy regimen will be either* cyclophosphamide and doxorubicin *or paclitaxel, depending on whether or not the patient received anthracycline therapy in the adjuvant setting.* The randomization will be done in such a way that the two treatment arms will be balanced within each participating center, *within each chemotherapy regimen, and within the two types of metastatic* disease: visceral (e.g., liver or lung) versus superficial (e.g., skin, chest wall, and peripheral lymph node).

Previously Read:

8.4 DATA SAFETY MONITORING BOARD AND INTERIM ANALYSIS

The Phase II program did not include studies with rhuMAb HER2 plus cyclophosphamide and doxorubicin, hence there are no safety data for the co-administered therapy. The safety of the co-administered therapy will be assessed in an ongoing fashion in this Phase III trial. The Data Safety Monitoring Board (DSMB) will evaluate safety in a blinded group analysis. This safety analysis will be performed after 40 patients complete two cycles of therapy.

The sample size calculation is based on the assumption that the median time to progression on the standard therapy is 8 months (which, assuming a roughly exponential distribution, translates to a progression-free rate of 35.9% at 1 year). There are no known data from patients with HER2/*neu* overexpressing tumors that support this assumption. Hence, there is a need for an administrative analysis to re-evaluate the progression-free rate at 1 year for patients on standard therapy only.

Prior to the final analysis and based on the collected data, the DSMB will be presented with an estimate of the progression-free rate for

patients on the standard arm therapy only. If the estimate is 36% or less (which translates to a median time to progression of 8 months or less), the final analysis will be initiated. If the estimate is 39.6% or more (which translates to a median time to progression of 9 months or more), the follow-up period will be extended accordingly beyond 1 year to assure that there is 90% power to detect the difference in time to progression.

The purpose of the above analysis is not to test a hypothesis, but to evaluate the need for an extension of the follow-up period. It has been shown previously that these types of analyses have a negligible effect on the probability of rejection of the null hypothesis when it is true (27).

Now Reads:

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 unblinded safety analyses will occur. The first* safety analysis will be performed after *60* patients complete two cycles *(6 weeks)* of therapy. *The timings of the additional analyses will be decided by the DSMB and will be based on the accrual rate.*

The sample size calculation is based on the assumption that the median time to progression on the standard therapy is 8 months. There are no known data from patients with HER2/*neu* overexpressing tumors that support this assumption. 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 logrank 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 (25). In the notation of Emerson and Fleming (25), 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 progression, interim and final, are planned during the study. The interim analysis is planned for 18 months after the accrual of the first 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 (26), 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.

SECTION 8.5: SAMPLE SIZE AND POWER

Previously Read:

Estimates of the sample size...are based on the following assumptions:

- median time to progression for the cyclophosphamide and doxorubicin arm is 8 months
- median time to progression for the rhuMAb HER2 plus cyclophosphamide and doxorubicin arm is 12 months (50% increase in time to progression)...

Now Reads:

Estimates of the sample size...are based on the following assumptions:

- Median time to progression for the *placebo plus chemotherapy* arm is 8 months
- Median time to progression for the rhuMAb HER2 plus *chemotherapy* arm is 12 months (50% increase in time to progression)...

SECTION 9: ADVERSE EVENT REPORTING (see also Section 6.3 and Appendix B)

Added:

9.1 BREAKING THE STUDY BLIND

Only in the event of a serious adverse event that the investigator feels cannot be adequately treated without knowing the identity of the study medication may the medication code be broken by the investigator for a particular patient. The investigator should consult with Corning Besselaar, Inc., prior to breaking the medication code.

All unblinding cards will have a masked area that will conceal the identity of the drug and lot number. If an emergency occurs that requires immediate unblinding and the investigator cannot contact Corning Besselaar, Inc., the study drug treatment may be unblinded by scratching off the masked area of the card.

In all cases where unblinding occurs, a written explanation must be provided by the Principal Investigator on the patient's CRF.

A table has been added delineating by country the names and phone numbers of persons to contact at Corning Besselaar, Inc.

APPENDICES

APPENDIX A: Study Flowchart

The flowchart was revised to reflect changes made to the study design, preadmission and study evaluations, and post-treatment follow-up period.

APPENDIX I: Directions for Obtaining, Storing, and Shipping Blood Samples

Appendix I (formerly Appendix G) has been revised 1) to include Douglass Laboratories in Australia and local laboratories in New Zealand, and 2) to reflect changes made in blood sample requirements.

Added:

APPENDIX F: ***Guidelines for Dose Modification***

APPENDIX H: ***Directions for Shipment of Laboratory Specimens to Douglass Laboratories (for sites in Australia and New Zealand)***

***APPENDIX K*: Supplemental Questionnaire (Protocol H0648g)**

PROTOCOL

TITLE:	**A PHASE III, MULTINATIONAL, DOUBLE-BLIND STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) PLUS CHEMOTHERAPY COMPARED WITH PLACEBO PLUS CHEMOTHERAPY IN PATIENTS WITH HER2/*neu* OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	H0648g
IND:	BB-IND 4517
MEDICAL MONITOR:	Thomas Twaddell, M.D.
SPONSOR:	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	20 January 1995
AMENDED:	13 November 1995

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SYNOPSIS

This protocol describes a Phase III, randomized, placebo-controlled, double-blind, multinational study in patients with HER2/*neu* 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-p185^{HER2} monoclonal antibody* (rhuMAb HER2) *used in addition to chemotherapy.*

All patients will receive either rhuMAb HER2 as a 4 mg/kg intravenous (IV) loading dose on Day 0, then weekly at a dose of 2 mg/kg IV throughout the course of the study, *or* an equivalent amount of placebo on the same schedule. *Patients who have not received anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubucin) in the adjuvant setting will receive* cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) IV beginning on Day 1, then every 3 weeks on the day following rhuMAb HER2 administration, for a total of six cycles. *If the patient received anthracycline therapy in the adjuvant setting and if, in the opinion of the investigator, the patient would benefit from paclitaxel therapy, she may receive paclitaxel (175 mg/m^2) over 3 hours IV beginning on Day 1, then every 3 weeks on the day following administration of either rhuMAb HER2 or placebo, for a total of six cycles. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy and there is no dose-limiting toxicity (defined as WHO Grade 3 or 4 neuropathy), paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.*

Approximately 450 patients will be enrolled in the study and randomized to *either the rhuMAb HER2 or placebo arm, and will be stratified according to the type of metastatic disease: visceral (e.g., liver or lung) versus superficial (e.g., skin, chest wall, and peripheral lymph node), and according to prior anthracycline therapy (yes/no).*

After the completion of cytotoxic chemotherapy, rhuMAb HER2 or placebo will be continued weekly according to the original randomization until disease progression or study termination. *Patients will be evaluated for adverse events 60 days after discontinuing study drug and will be followed for survival information every 2 months.*

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 placebo treatment* 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.

1. INTRODUCTION

1.1 HER2 AND CANCER

Growth factors and their receptors are known to play critical roles in development, cell growth, and differentiation (1). Many receptors possess intrinsic tyrosine kinase activity that is activated upon interaction of the receptor with its cognate ligand. Abnormal expression of human epidermal growth factor receptor 2 (HER2) is frequently observed in a number of primary tumors, suggesting that the overexpression of this growth factor receptor may contribute to transformation and tumorigenesis. In most cases, HER2 protein overexpression is thought to result from gene amplification and has been correlated with poor clinical outcome in patients with breast and ovarian cancers that overexpress HER2. Approximately 25% to 30% of patients with breast and ovarian cancers overexpress HER2 (2,3). Similar correlations may exist for lung adenocarcinoma and gastric cancers.

Several lines of evidence support a direct role for $p185^{HER2}$ (the HER2 gene product) expression in the pathogenesis and poor clinical course of human tumors. First, mutation of the rat HER2 homolog, the *neu* proto-oncogene, is associated with the induction of neuroblastomas (4,5). Second, when the gene is transfected into mouse fibroblast cells (NIH-3T3) it causes transformation, and the resulting cells are tumorigenic in the nude mouse (6,7). Studies using a nonmutated, human HER2 gene have demonstrated that NIH-3T3 cell transformation efficiency, as well as tumorigenicity in the nude mouse, are directly related to the level of HER2 gene expression (8). Additionally, studies utilizing the mutated rat *neu* gene to develop transgenic mice have revealed that animals expressing high levels of the mutated *neu* transgene (9) as well as normal *neu* (10) develop breast cancer. Finally, specific antibodies to the extracellular domain of the membrane-based protein encoded by the *neu* gene or the human HER2 gene will inhibit the growth of tumors that express the gene (11–14). These data are consistent with a direct role for the HER2 proto-oncogene in both malignant transformation and enhanced tumorigenicity, and indicate a potential target for cancer therapy.

1.2 PRECLINICAL STUDIES OF rhuMAb HER2

Murine monoclonal antibodies (muMAbs) were produced against the extracellular domain of the HER2 receptor to inhibit the proliferation of human tumor cells overexpressing $p185^{HER2}$. rhuMAb HER2, the humanized version of muMAb 4D5, was engineered by inserting the complementarity-determining regions (CDRs) of muMAb 4D5 into the framework of a consensus human IgG_1 (15). rhuMAb HER2 binds the extracellular domain of the HER2 receptor with three times greater affinity than does muMAb 4D5. rhuMAb HER2 is comparable to muMAb 4D5 in blocking SK-BR-3 proliferation; however, unlike muMAb 4D5, it induces antibody-dependent cellular cytotoxicity (ADCC) against tumor cell lines in the presence of human peripheral blood mononuclear cells (PBMCs).

Preclinical studies with rhuMAb HER2 directed against $p185^{HER2}$ indicate that receptor binding of the antibody has a cytostatic effect on tumor growth. However, these xenograft models in athymic mice do not permit ADCC to occur, since human PBMCs are not present. To increase the cytotoxic 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 $p185^{HER2}$ is supported by the results from several independent experimental investigations (16–19). Although the specifics of the underlying mechanism of interaction are unknown, there is evidence that HER2 antibodies interfere with DNA repair mechanisms of cells overexpressing $p185^{HER2}$ (17). rhuMAb HER2 has also been evaluated in combination with several other chemotherapeutic drugs, including doxorubicin, thiotepa, etoposide, and 5-fluorouracil (20), and paclitaxel (21). In most cases, the effect of the antibody and the cytotoxic agent is at least additive. Toxicology studies were conducted in mice and rhesus monkeys; no drug-related effects were observed.

Characterization of the serum pharmacokinetics of rhuMAb HER2 in the presence of doxorubicin combined with cyclophosphamide or in the presence of doxorubicin or paclitaxel alone was conducted in female rhesus monkeys at doses that approximate human clinical doses on a body weight basis. Single-dose IV administration of rhuMAb HER2

was well tolerated and did not alter the disposition of any agent administered.

1.3 CLINICAL STUDIES OF rhuMAb HER2

Three Phase I studies of rhuMAb HER2 were conducted. In the first trial (H0407g), 16 patients with HER2 overexpressing tumors received a single dose (ranging from 10 to 500 mg) of rhuMAb HER2 administered IV. Two patients developed chills during the infusion; fever developed in four patients (one in each of the dose groups). In the second 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 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. Four patients experienced Grade III or IV thrombocytopenia, two developed Grade III or IV granulocytopenia, and two developed Grade III or IV nephrotoxicity. All of the patients experiencing thrombocytopenia had been heavily pretreated with cytotoxic chemotherapy. Other adverse events included ototoxicity, nausea, and vomiting. In all three studies, no antibodies to rhuMAb HER2 were detected.

Although the small number of patients and the lack of randomization preclude any statement being made about a possible dose effect in tumor responses, four of six 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 December 1994, and has had no additional therapy in the past 20 months. No responses were seen in the lower dose groups.

Pharmacokinetic analyses showed the antibody was cleared slowly from the circulation, and half-lives ranged from 1.5 days to 2 weeks as

the dose increased. Administration of cisplatin did not affect the pharmacokinetics of rhuMAb HER2.

Two Phase II, open-label, multicenter studies of rhuMAb HER2 are ongoing. In the first trial (H0551g), 46 patients with metastatic breast cancer (2+ to 3+ overexpression of HER2) were treated with a 250-mg IV loading dose followed by 100 mg IV weekly for 10 weeks. Patients with responses or stable disease at Day 77 were eligible for a maintenance program; 19 patients have entered to date. Although failing treatment for metastatic disease was not required for study entry, the median number of prior chemotherapy regimens was three. rhuMAb HER2 was well tolerated, and clinical events were rarely attributable to study drug. One patient who subsequently achieved a sustained partial response of 9 months' duration had chest pain at a site of metastatic disease that was judged to be severe at the time of antibody administration. Seven patients (15%) had fever (>38°C) during infusion of rhuMAb HER2 at least once during the study. No hematologic or laboratory toxicity was attributed to study drug; no patients discontinued treatment because of rhuMAb HER2 toxicity.

Forty patients are presently evaluable for tumor response status. One patient with a chest wall recurrence within 2 months of neoadjuvant doxorubicin had a partial response at Day 77. A complete response was confirmed by negative biopsies 2 months later and has continued for 10 months. Three patients have had partial responses; two of the responses involved metastatic disease in the liver.

In the second 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. Patients with responses or stable disease were eligible for a maintenance program; 18 patients have entered to date. The median number of prior chemotherapy regimens was two. Thirty-four patients are presently evaluable for response. One patient with multiple pulmonary nodules has had a complete response, and seven patients have had partial responses.

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 (22), 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.

1.4 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. Cyclophosphamide and doxorubicin or paclitaxel are currently important chemotherapy agents in the treatment of breast cancer. In vivo nude mouse xenograft models utilizing HER2 transfected cell lines have demonstrated an additive effect in reducing tumor volume when rhuMAb HER2 is given in combination with doxorubicin, compared with rhuMAb HER2 or doxorubicin given alone (20,23). *Similar findings using a different in vivo model were reported with rhuMAb HER2 and paclitaxel (21,23).* It is anticipated that, in a population of patients with HER2 overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cytotoxic chemotherapy* will enhance efficacy.

2. OBJECTIVE

The objective of this study is to determine the safety and efficacy of rhuMAb HER2 *used in addition to chemotherapy* in patients with HER2/*neu* overexpressing metastatic breast cancer who have not received prior cytotoxic chemotherapy.

Study endpoints are:

Primary:

- To compare the time to disease progression in patients receiving rhuMAb HER2 plus *either* cyclophosphamide and doxorubicin *or paclitaxel* with those receiving placebo plus *either* cyclophosphamide and doxorubicin *or paclitaxel*
- To further characterize the safety profile of rhuMAb HER2

Secondary:

- To compare overall response rates (complete and partial responses) between both treatment *arms (rhuMAb HER2 versus placebo)*
- 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 define the pharmacokinetic profile of rhuMAb HER2 when co-administered with *either* cyclophosphamide and doxorubicin *or paclitaxel*
- To determine 1-year survival estimates

3. STUDY DESIGN

This is a Phase III, randomized, placebo-controlled, double-blind, multinational study comparing rhuMAb HER2 plus *either* cyclophosphamide and doxorubicin *or paclitaxel* with placebo plus *either* cyclophosphamide and doxorubicin *or paclitaxel*. Approximately 450 patients with HER2/*neu* 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*.

All patients will receive either rhuMAb HER2 as a 4 mg/kg intravenous (IV) loading dose on Day 0, then weekly at a dose of 2 mg/kg IV throughout the course of the study, *or* an equivalent amount of placebo on the same schedule. *Patients who have not received anthracycline therapy (e.g., doxorubicin, epirubicin, mitoxantrone, idarubicin, or daunorubucin) in the adjuvant setting will receive* cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) IV beginning on Day 1, then every 3 weeks on the day following rhuMAb HER2 administration, for a total of six cycles.

If the patient received anthracycline therapy in the adjuvant setting and if, in the opinion of the investigator, the patient would benefit from paclitaxel therapy, she may receive paclitaxel (175 mg/m^2) over 3 hours IV beginning on Day 1, then every 3 weeks on the day

following administration of either rhuMAb HER2 or placebo, for a total of six cycles. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy as defined below, and if there is no dose-limiting toxicity defined as WHO Grade 3 or 4 neuropathy, paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.

Criteria for continuation of paclitaxel beyond six cycles are as follows (see Section 7 for definitions of response criteria):

- *Complete Response: Patient may receive up to two more cycles of paclitaxel*
- *Minor Response or Partial Response: Patient may receive additional cycles of paclitaxel until stabilization of best response, disease progression, or dose-limiting toxicity*

  A maximum number of 10 cycles of paclitaxel will be given.
- *Stable Disease or Progressive Disease: Patient will not receive any further paclitaxel therapy*

After the completion of cytotoxic chemotherapy, rhuMAb HER2 or placebo will be continued weekly according to the original randomization until disease progression determined by radiographic or other objective criteria or until study termination. Patients will be monitored during each study visit by a clinical assessment, a symptom-directed physical examination (if appropriate), vital signs, and laboratory tests (see Appendix A, Study Flowchart). All adverse events will be recorded. WHO Recommendations for Grading of Acute and Subacute Toxicity will be used (see Appendix B).

One year after enrollment of the last patient, those patients randomized to rhuMAb HER2 who have not developed disease progression will be eligible to continue on that therapy. Those patients randomized to placebo will be followed for disease status until progression or study termination. All patients who develop disease progression will be followed for survival information every 2 months until termination of statistical analysis of the study. *At some study sites, patients will be eligible to receive open-label rhuMAb HER2 treatment in a separate study protocol.*

The primary endpoint of the study will be time to disease progression. 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/*neu* overexpression (by immunohistochemistry) who have not received prior cytotoxic chemotherapy for metastatic breast cancer. Approximately 450 patients (225 patients in each group) 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:

- Women between the ages of 18 and 75 years
- Histologically confirmed metastatic breast cancer

  Histologic confirmation may be waived by Genentech in rare circumstances, e.g., when medically contraindicated.
- Histologically documented primary breast cancer or biopsy of metastatic site showing 2+ to 3+ overexpression of the HER2 oncogene by immunohistochemistry (see Appendix C)
- Bidimensionally measurable disease 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 (CAT), magnetic resonance imaging (MRI), ultrasound, or photographs. Lesions on bone scan, 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.

- Cardiac ejection fraction >45% by echocardiography or radionuclide angiography
- The ability to understand and willingness to sign a written informed consent form

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.
- *Prior hypersensitivity to products containing Cremophor® EL (e.g., cyclosporine or teniposide for injection)*

  Note: *This criterion applies only to patients who have received prior adjuvant anthracycline therapy.*
- Previous therapy with a monoclonal or polyclonal antibody
- Prior cytokine therapy for cancer
- Bone metastases as the only site of measurable and evaluable disease

  Lesions on bone scan, osteoblastic metastases, pleural effusions, or ascites are not considered measurable disease for this study.
- Hormonal therapy, such as tamoxifen, megestrol acetate, fluoxymesterone, or aminoglutemide within 2 weeks prior to study entry
- Use of investigational or unlicensed agents within 30 days prior to study entry
- Radiotherapy within 2 weeks prior to study entry
- Previous or concomitant malignancy other than curatively treated carcinoma in situ of cervix or basal cell carcinoma of skin
- History of brain or leptomeningeal metastatic disease
- A performance status of <60% on the Karnofsky scale (see Appendix D)
- Clinically significant cardiac disease, i.e., New York Heart Association Class III or IV (see Appendix E), history of congestive heart failure, or history of myocardial infarction within 6 months of study entry
- Clinically significant active infections

- Known hemorrhagic diathesis or active bleeding disorder
- Pregnant or nursing women; women of childbearing potential, unless using effective contraception as determined by the investigator
- Bilateral breast cancer (unless both primary tumors have 2+ to 3+ HER2 overexpression)
- Renal function: creatinine ≥ 1.7 mg/dL (150 µmol/L); ≥ 2+ proteinuria
- Hepatic function: bilirubin ≥ *1.2* mg/dL (*20.5* µmol/L)

  A patient will not be excluded with a bilirubin of up to 2.0 mg/dL (34.2 µmol/L) if the elevation is due to a benign cause such as proven Gilbert's syndrome.
- Coagulation function: prothrombin time > *15* sec
- Hematologic status: white blood cells (WBC) ≤ 3500/mm^3 (3.5×10^9/L); granulocytes ≤ 1500/mm^3 (1.5×10^9/L); platelets ≤ 100,000/mm^3 (100×10^9/L); hemoglobin ≤ 10 g/dL (6.2 mmol/L)
- Pulmonary function: FEV_1 or PEFR < 60% of predicted value
- Elevated serum calcium (≥ 11 mg/dL [2.7 mmol/L])

5. STUDY MEDICATION

5.1 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. The formulation does not contain a preservative and is suitable for single use only. rhuMAb HER2 will be added to 250 mL of 0.9% Sodium Chloride Injection, USP.

See the rhuMAb HER2 Investigator Brochure for more detailed information.

Placebo will be supplied by Genentech as a sterile excipient solution for IV administration. An appropriate volume of placebo will be added to 250 mL of 0.9% Sodium Chloride Injection, USP.

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5.2 *STORAGE REQUIREMENTS*

Vials of rhuMAb HER2 are shipped at a temperature ranging from 2°C to 8°C (36°F to 46°F) and must be placed in a refrigerator (same temperature range) 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 and colorless.

5.3 ADMINISTRATION AND DOSAGE

5.3.1 rhuMAb HER2 or Placebo

On Day 0, a 4 mg/kg loading dose of rhuMAb HER2 (or an equivalent amount of placebo) will be administered IV over a 90-minute period. Beginning on Day 7, patients will receive weekly administration of 2 mg/kg rhuMAb HER2 (or an equivalent amount of placebo) IV over a 90-minute period according to the randomization schedule. rhuMAb HER2 or placebo will be continued weekly until disease progression.

rhuMAb HER2 or placebo 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 rhuMAb HER2 or placebo administration.

5.3.2 *Chemotherapy*

Patients will receive one of two chemotherapy regimens in addition to rhuMAb HER2 or placebo: a) cyclophosphamide and doxorubicin, 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.

a. *Cyclophosphamide and Doxorubicin*

Cyclophosphamide and doxorubicin will be supplied by the pharmacy at the investigative site as Cytoxan® for Injection and

Adriamycin PFS®, respectively, *if available. Generic equivalents approved by the regulatory authorities in the country of administration will be allowed.* Cyclophosphamide and doxorubicin will be administered beginning on Day 1, then every 3 weeks on the day following administration of rhuMAb HER2 or placebo, for a total of six cycles.

Cyclophosphamide will be given at a dose of 600 mg/m^2 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.

Doxorubicin will be given at a dose of 60 mg/m^2 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 (also see Section 3)*

Patients who have received any anthracycline in the adjuvant setting may receive paclitaxel, supplied by the pharmacy as Taxol® for Injection Concentrate, beginning on Day 1, then every 3 weeks on the day following administration of rhuMAb HER2 or placebo, for a total of six cycles.

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

Paclitaxel will be given at a dose of 175 mg/m^2 over 3 hours by IV infusion. At the Week 17 tumor evaluation, if the patient is continuing to benefit from the therapy (see Section 3), and if there is no dose-limiting toxicity defined as WHO Grade 3 or 4

neuropathy, paclitaxel may be continued to a maximum of 10 cycles at the same dose every 3 weeks on the day following administration of either rhuMAb HER2 or placebo until disease progression or dose-limiting toxicity occurs.

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 F 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 or placebo) 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 pre-existing medical conditions 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).

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 between Days –14 and –2. The results of all tests listed below will be entered on the Case Report Form (CRF) provided.

- Complete medical history, including prior cancer history
- Complete physical examination
- Weight, height, body surface area (BSA)
- Karnofsky Performance Status (see Appendix D)
- New York Heart Association Classification of Functional Cardiac Capacity (see Appendix E)
- Vital signs (orthostatic)
- Pulmonary function (FEV_1 or PEFR)
- 12-lead electrocardiogram
- 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. An abdominal computerized tomography (CAT) scan should be performed if the patient has abnormal liver chemistries, abdominal pain, or a past abnormal abdominal CAT scan, ultrasound, or magnetic resonance imaging (MRI). A chest CAT 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)
- Hepatitis B surface antigen/hepatitis C virus (HBsAg/HCV)
- 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)

- Coagulation profile (prothrombin time [PT], partial thromboplastin time [PTT])
- Urinalysis
- Measurement of cardiac ejection fraction by echocardiogram or radionuclide angiography

6.2 STUDY EVALUATIONS (see Appendix A)

Day 0 (baseline) is the first day of rhuMAb HER2 or placebo infusion. All tests should be performed prior to administration of study medication.

6.2.1 Tests

a. Complete Physical Exam

Week 8 (1 week after the third cycle of chemotherapy), Week 17 (1 week after the sixth cycle of chemotherapy), Weeks 26, *36*, 52, and every 12 weeks thereafter; study termination

b. Clinical Assessment (includes adverse event review, concurrent medications, and symptom-directed physical examination, if appropriate)

Weekly, beginning on Day 0; study termination

c. Weight

Weekly beginning on Day 0; study termination

d. Karnofsky Performance Status

Weekly beginning on Day 0; study termination

e. *New York Heart Association Classification of Functional Cardiac Capacity (see Appendix E)*

Study Termination

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

Evaluate predose, at the end of the infusion, and 1 hour postdose

Weekly beginning on Day 0; study termination

g. 12-Lead Electrocardiogram

Week 17; study termination

h. Chest X-ray (AP and lateral)

Weeks 8, 17, 26, *36*, 52, and every 12 weeks thereafter; study termination

i. 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 CAT scans.

Patients having a complete or partial response (see Section 7) should have the radiographic study documenting that response repeated 4 weeks following the initial response determination.

Patients with symptoms suggestive of progressive disease may have tumor assessment studies done at times other than those described in the protocol at the investigator's discretion.

Weeks 8, 17, 26, *36*, 52, and every 12 weeks thereafter; study termination

j. Laboratory Tests (see Appendices G and H)

- Serum pregnancy test (women of childbearing potential)

  Weeks 20 and 52; study termination

- Hematology (CBC with differential and platelet count)

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

  Weekly for the first 20 weeks and every 4 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)

  Weekly for the first 20 weeks and every 4 weeks thereafter; study termination

- Urinalysis

  Weekly for the first 20 weeks and every 4 weeks thereafter; study termination

k. Measurement of Cardiac Ejection Fraction by Echocardiogram or Radionuclide Angiography

   Week 16

   Note: *Patients receiving paclitaxel as the chemotherapy regimen will not undergo measurement of cardiac ejection fraction.*

l. EORTC Quality-of-Life Instrument *and Supplemental Questionnaire*

   Weeks 1 (Day 0), *8, 16, 24,* and every 12 weeks thereafter; study termination

m. Blood Concentration Measurements (to be performed on all patients):

   - Serum Pharmacokinetics of rhuMAb HER2

     Just prior to each dose and at the end of infusion of each dose of rhuMAb HER2 or placebo, 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 (see Appendix *I*).

     Weekly beginning on Day 0 for the first 8 weeks, and every 4 weeks thereafter; study termination

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

   - *Serum Antibodies to rhuMAb HER2 (see Appendix I)*

     Preinfusion antibody measurements will be obtained from the preinfusion pharmacokinetic sample.

     Weeks 1 (Day 0), 2, 4, 8, and every 4 weeks thereafter; study termination

   - Serum Shed Antigen Concentrations

     Three milliliters of blood (yielding approximately 1.5 mL of serum) will be drawn prior to infusion of rhuMAb HER2 or placebo at the times indicated for measurement of circulating

concentrations of shed antigen (extracellular domain of the receptor) and antibodies to rhuMAb HER2 (see Appendix *I*).

Weeks 1 (Day 0), 2, 4, *8,* and every 4 weeks thereafter; study termination

n. Blood Concentration Measurements (to be performed on *a minimum of* 10%–20% of *total* patients *in the study, but* at selected study sites only):

- Special Studies

  Eight milliliters of blood (yielding approximately *2.5* mL of serum and *1.5* mL of plasma) will be drawn prior to infusion of rhuMAb HER2 or placebo at the times indicated to better define the mechanism of action of rhuMAb HER2 (see Appendix *I*). (These studies will not represent efficacy parameters.)

  Weeks 1 (Day 0), 2, 4, 8, 12, 17, 26, *36*, 52, and every 12 weeks thereafter; study termination

o. 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*

Patients will be evaluated for adverse events 60 days after discontinuing study drug and will be followed for survival information every 2 months.

6.4 TOXICITY CRITERIA (see Appendix B)

WHO Recommendations for Grading of Acute and Subacute Toxicity will be used. All toxicities must be recorded on the Adverse Event CRF.

6.4.1 Toxicities during Infusion

If a Grade 3 or 4 toxicity occurs during an infusion of any study drug, the infusion must be immediately stopped. The patient must be monitored for a minimum of 1 hour after the infusion is stopped. If an outpatient, she must be admitted to the hospital for monitoring if the toxicity does not resolve during the hour.

6.4.2 Toxicities Postinfusion

If a Grade 3 or 4 toxicity occurs during the postinfusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first noticed. If an outpatient, she must be admitted to the hospital for monitoring if the toxicity does not resolve during the hour.

6.4.3 Toxicities at Study Discontinuation

All patients with Grade 3 or 4 toxicities existing at discontinuation of therapy should be followed until resolution.

7. RESPONSE CRITERIA

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.

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.

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.

7.1 RESPONSE EVALUATION COMMITTEE

The radiographs and/or photographs of all patients will be reviewed by the Response Evaluation Committee. 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.

All study sites must send copies of 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.

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
- Pharmacokinetic profile of rhuMAb HER2
- One-year survival

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. Time to progression is defined as time from the beginning of the treatment 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 versus placebo)*. The primary analysis will include all eligible patients (intent-to-treat) *and will be based on the pooled chemotherapy groups.*

A standard survival methodology such as Kaplan-Meier will be used to estimate the time to 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 versus +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), 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-square 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.

Survival will be measured from the beginning of the therapy 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. *The analysis will be stratified according to the therapeutic options chosen after discontinuation from this protocol.*

8.2.2 Subgroup Analysis

Two subgroups of patients will be considered: 1) those who received hormonal therapy for metastatic disease prior to study entry, and 2) those who did not. Response rates based on 1-year data, 1-year progression-free estimates, duration of response, and 1-year survival estimates will be calculated for these two subgroups.

8.2.3 Quality-of-Life Assessment

The quality-of-life questionnaire QLQ-C30, developed by the European Organization for Research and Treatment of Cancer (EORTC) with the module for breast cancer (BR23), will be used to evaluate the quality of life (*24*) (see Appendix *J*). 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 K) pertain to pharmacoeconomics and will be evaluated outside the scope of the protocol. They will be described and analyzed in a separate report.

8.2.4 Pharmacokinetic Profile

Pharmacokinetic profile data will be collected *on all patients* for assessment of predose (trough) and postdose (peak) serum concentrations of rhuMAb HER2.

Standard pharmacokinetic methods will be applied to these data to determine the pharmacokinetics of rhuMAb HER2 in the presence of cyclophosphamide, doxorubicin, *and paclitaxel*.

8.2.5 Safety Analysis

All patients who receive at least one dose of either rhuMAb HER2 or placebo will be included in the safety analysis. Any incidence of adverse events will be recorded and classified according to body region and toxicity grade.

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 AND BLINDING

Patients will be randomized by telephone to either rhuMAb HER2 plus *chemotherapy* or placebo plus *chemotherapy. The chemotherapy regimen will be either* cyclophosphamide and doxorubicin *or paclitaxel, depending on whether or not the patient received anthracycline therapy in the adjuvant setting.* The randomization will be done in such a way that the two treatment arms will be balanced within each participating center, *within each chemotherapy regimen, and within the two types of metastatic* disease: visceral (e.g., liver or lung) versus superficial (e.g., skin, chest wall, and peripheral lymph node).

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 unblinded safety analyses will occur. The first* safety analysis will be performed after *60* patients complete two cycles *(6 weeks)* of therapy. *The timings of the additional analyses will be decided by the DSMB and will be based on the accrual rate.*

The sample size calculation is based on the assumption that the median time to progression on the standard therapy is 8 months. There are no known data from patients with HER2/*neu* overexpressing tumors that support this assumption. 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 logrank 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 (25). In the notation of Emerson and Fleming (25), 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 progression, interim and final, are planned during the study. The interim analysis is planned for 18 months after the accrual of the first 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 (26), 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 *placebo plus chemotherapy* arm is 8 months
- Median time to progression for the rhuMAb HER2 plus *chemotherapy* arm is 12 months (50% increase in time to progression)

- One-year accrual time
- 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 required total sample size is 450.

9. **ADVERSE EVENT REPORTING** (see also Section *6.4* and Appendix B)

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 for adverse events at each visit. Each adverse event, regardless of causality assessment, must be recorded on the appropriate Adverse Event Case Report Form (CRF). All toxicities (see Section *6.4*) must also be recorded.

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 should be reported to the contract research organization for this study (*Corning Besselaar, 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, or by direct telephone communication. A completed Serious Adverse Event Fax cover sheet and CRF should follow all telephone reports.

Study sites in the United States and Canada must contact:

Pat Devitt
Corning Besselaar, 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:

Fiona Ogborn
Corning Besselaar, Inc.
1D Roxborough Way
Maidenhead
Berkshire SL63UD
United Kingdom

Office Telephone: 01628-548-056
Cellular Telephone: 0374-971-535
Fax: 01628-824-508

Study sites in Australia and New Zealand must contact:

Victor Roberts
Corning Besselaar, Ltd.
51 Rawson Street, Suite 303
Epping NSW 2121
Australia

Office Telephone: 61-2-869-1811
Cellular Telephone (Australia): 0411-10-4509
(New Zealand): 61-411-10-4509
Fax: 2-868-5936

All patients with Grade 3 or 4 toxicities existing at discontinuation of therapy should be followed until resolution. *Patients will be contacted approximately 60 days after discontinuation of study drug for assessment of adverse events.*

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.

9.1 BREAKING THE STUDY BLIND

Only in the event of a serious adverse event that the investigator feels cannot be adequately treated without knowing the identity of the study medication may the medication code be broken by the investigator for

a particular patient. The investigator should consult with Corning Besselaar, Inc., prior to breaking the medication code.

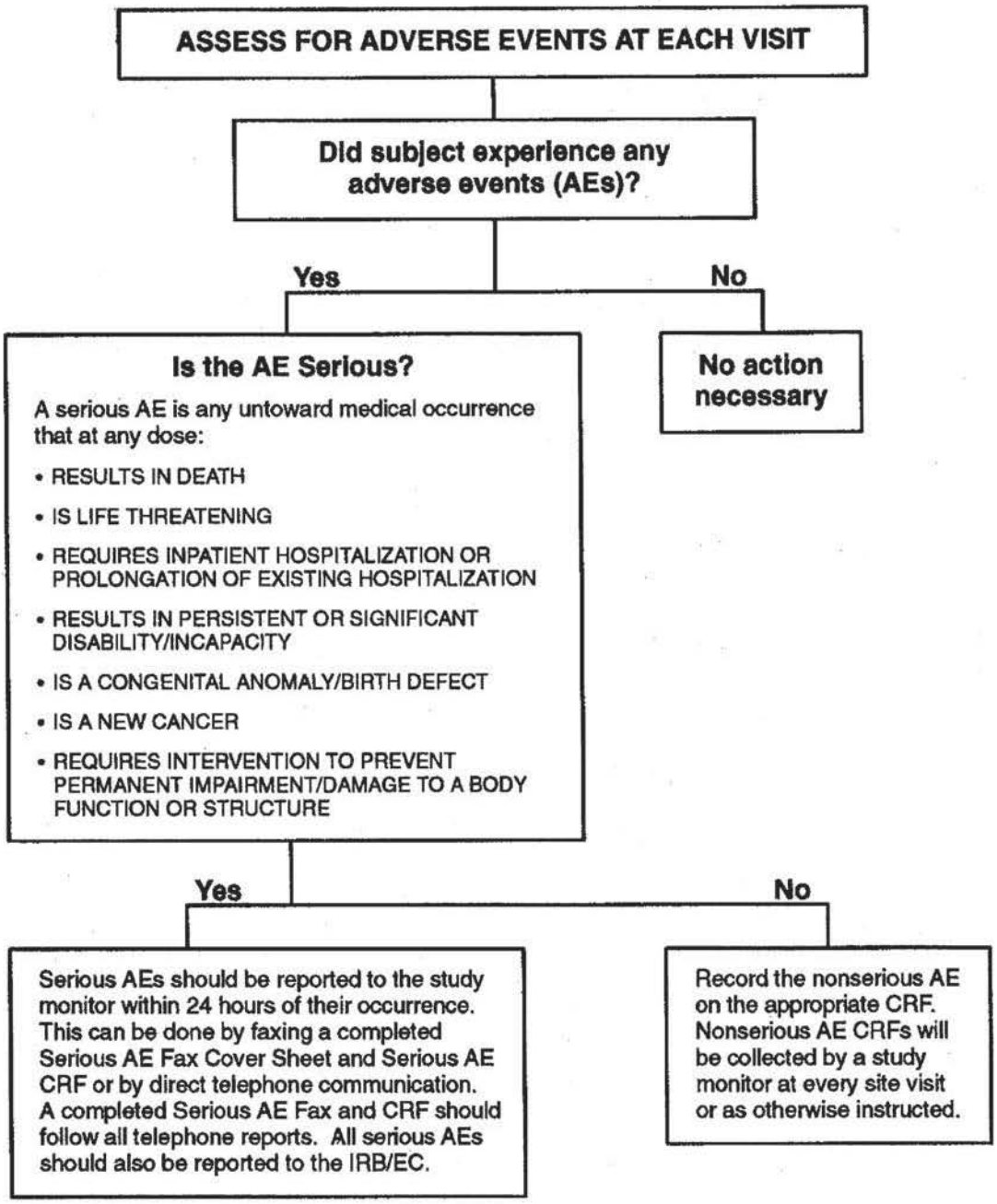
All unblinding cards will have a masked area that will conceal the identity of the drug and lot number. If an emergency occurs that requires immediate unblinding and the investigator cannot contact Corning Besselaar, Inc., the study drug treatment may be unblinded by scratching off the masked area of the card.

In all cases where unblinding occurs, a written explanation must be provided by the Principal Investigator on the patient's CRF.

Questions regarding unblinding must be directed to Corning Besselaar, Inc., as follows:

	During Business Hours			After Hours
	Contact			CBI, U.S.A.
Country	Name	Office Phone	Mobile Phone	Office Phone
Australia	Victor Roberts	61-2-869-1811	0411-10-4509	609-452-8550
Austria	Erika Dehne	49-89-921-0930	172-675-1526	609-452-8550
Belgium	Katia Verhamme	32-2773-2911	075-451-148	609-452-8550
Canada	Mark Russo, M.D.	609-452-4365	—	800-426-2813
Germany	Erika Dehne	49-89-921-0930	172-675-1526	609-452-8550
Netherlands	Katia Verhamme	32-2773-2911	075-451-148	609-452-8550
New Zealand	Victor Roberts	61-2-869-1811	61-411-10-4509	609-452-8550
Switzerland	Erika Dehne	49-89-921-0930	172-675-1526	609-452-8550
United Kingdom	Margaret O'Donoghue	0121-454-4955 or 01628-548-000	0850-739-780	609-452-8550
United States	Mark Russo, M.D.	609-452-4365	—	800-426-2813

Algorithm for Reporting Adverse Events during Clinical Trials



10. DISCONTINUATION

10.1 PATIENT DISCONTINUATION

Patients may be discontinued from therapy in the following instances:

- Intercurrent illness that would, in the judgment of the Principal Investigator, affect assessments of clinical status to a significant degree
- *Intolerable adverse experiences or toxicity as defined by the Principal Investigator*
- Disease progression
- Patient noncompliance, inability to comply with the treatment regimen, or request to withdraw
- Three consecutively missed rhuMAb HER2 or placebo infusions
- Immunotherapy, chemotherapy, hormonal therapy, or radiotherapy directed at the treatment of indicator lesions during the study period

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 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 the Declaration of Helsinki.

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. Food and Drug Administration (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
- Current laboratory certification of the laboratory doing analysis (if not Genentech), as well as current normal laboratory ranges for all laboratory tests
- 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, 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

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.

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APPENDIX A

Study Flowchart
H0648g

	Days –14 to –2 Preadmission	Wk 1 (Day 0)	Wk 1 (Day 1)	Weekly (beginning *Week 2*)	Week 8	Week 16	Week 17	Week 20	Every 4 weeks after Week 20	Week 26	Week *36*	Week 52	Every 12 weeks after Week 52	Study Termination	*Post-Treatment Follow-Up*
rhuMAb HER2 or Placebo Administration		x[a,b]		x[b]											
Cyclophosph./Doxorub. *or Paclitaxel* Administration			x[c]												
Complete Medical History	x														
Complete Physical Exam	x				x[b]		x[b,d]			x[b]	x[b]	x[b]	x[b]	x	
Clinical Assessment		x[b]		x[b]										x	
Weight, Height, BSA	x	x[b,e]		x[b,e]										x[e]	
Karnofsky Status	x	x[b]		x[b]										x	
NYHA Cardiac Classification	x													x	
Vital Signs	x	x[b,f]		x[b,f]										x	
FEV_1 or PEFR	x														
EKG (12-lead)	x						x[b,d]							x	
Chest X-ray (AP, Lateral)	x				x[b]		x[b,d]			x[b]	x[b]	x[b]	x[b]	x	
Tumor Assessment	x				x[b]		x[b,d]			x[b]	x[b]	x[b]	x[b]	x	
Serum Pregnancy Test	x[g]							x[b,g]				x[b,g]		x[g]	
HBsAg/HCV	x														
Hematology (CBC with Diff., Plts.)	x	x[b]		x[b]					x[b]					x	
Chemistry Panel	x	x[b]		x[b]					x[b]					x	
Coagulation Profile (PT, PTT)	x														
Urinalysis	x	x[b]		x[b]					x[b]					x	
Measurement of Cardiac Ejection Fraction	x					x[b,h]									

APPENDIX A (cont'd)

Study Flowchart
H0648g

	Days –14 to –2 Preadmission	Wk 1 (Day 0)	Wk 1 (Day 1)	Weekly (beginning *Week 2*)	Week 8	Week 16	Week 17	Week 20	Every 4 weeks after Week 20	Week 26	Week *36*	Week 52	Every 12 weeks after Week 52	Study Termination	*Post-Treatment Follow-Up*
EORTC Quality-of-Life *and Supplemental Questionnaire*		x[b,i]			*x*	*x*[i]								x	
Serum Pharmacokinetics		x[j]		x[j,k]										x	
Serum Ab to rhuMAb HER2		x[b,l]												x	
Serum Shed Antigen		x[b,l]												x	
Special Studies		x[b,m,n]												x[m]	
Adverse Events/Survival															*x*[o]

[a] Day 0 is the first day of rhuMAb HER2 or placebo administration. On Day 0, 4 mg/kg rhuMAb HER2 (or an equivalent amount of placebo) will be given; thereafter, 2 mg/kg will be given.

[b] All tests should be performed prior to study medication administration.

[c] *Either* cyclophosphamide and doxorubicin *or paclitaxel* will be administered every 3 weeks on the day following rhuMAb HER2 or placebo administration for six cycles: Weeks 1, 4, 7, 10, 13, and 16. *See Section 5.3.3 of the protocol for additional information on paclitaxel administration.*

[d] One week after the sixth cycle of chemotherapy treatment.

[e] *Weight only.*

[f] Vital signs will be checked preinfusion, at the end of the infusion, and 1 hour postinfusion.

[g] Women of childbearing potential.

[h] *Patients receiving paclitaxel as the chemotherapy regimen will not be measured.*

[i] Weeks 1 (Day 0), *8, 16, 24,* and every 12 weeks thereafter.

[j] Predose and at the end of infusion.

[k] Weekly for the first 8 weeks, then every 4 weeks thereafter.

[l] Predose at Weeks 1 (Day 0), 2, 4, *8,* and every 4 weeks thereafter.

[m] To be performed on *a minimum of* 10%–20% of patients at selected study sites only.

[n] Predose at Weeks 1 (Day 0), 2, 4, 8, 12, 17, 26, *36,* 52, and every 12 weeks thereafter.

[o] *Adverse events to be followed at 60 days; survival follow-up every 2 months.*

APPENDIX B

WHO Recommendations for Grading of Acute and Subacute Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic (Adults)					
Hemoglobin (g/dL)[a]	≥11.0	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
Leukocytes (WBC) (1000/mm^3)[a]	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
Granulocytes (1000/mm^3)[a]	≥2.0	1.5–1.9	1.0–1.4	0.5–0.9	<0.5
Platelets (1000/mm^3)[a]	≥100.0	75.0–99.0	50.0–74.0	25.0–49.0	<25.0
Hemorrhage	None	Petechiae	Mild Blood Loss	Gross Blood Loss	Debilitating Blood Loss
Gastrointestinal					
Bilirubin	≤1.25×N[b]	1.26–2.5×N[b]	2.6–5×N[b]	5.1–10×N[b]	>10×N[b]
AST/ALT	≤1.25×N[c]	1.26–2.5×N[c]	2.6–5×N[c]	5.1–10×N[c]	>10×N[c]
Alkaline Phosphatase	≤1.25×N[b]	1.26–2.5×N[b]	2.6–5×N[b]	5.1–10×N[b]	>10×N[b]
Oral	None	Soreness/Erythema	Erythema, Ulcers Can Eat Solids	Ulcers, Requires Liquid Diet Only	Alimentation Not Possible
Nausea/Vomiting	None	Nausea	Transient Vomiting	Vomiting Requiring Therapy	Intractable Vomiting
Diarrhea	None	Transient ≤2 days	Tolerable but >2 days	Intolerable Requiring Therapy	Hemorrhagic Dehydration
Renal, Bladder					
BUN or Blood Urea	≤1.25×N[b]	1.26–2.5×N[b]	2.6–5×N[b]	5–10×N[b]	>10×N[b]
Creatinine	≤1.25×N[b]	1.26–2.5×N[b]	2.6–5×N[b]	5–10×N[b]	>10×N[b]
Proteinuria (g/dL)[a]	None	1+, <0.3	2–3+, 0.3–1.0	4+, >1.0	Nephrotic Syndrome
Hematuria	None	Microscopic	Gross	Gross + Clots	Obstructive Uropathy
Pulmonary	None	Mild Symptoms	Exertional Dyspnea	Dyspnea (Rest)	Complete Bed Rest Required

APPENDIX B (cont'd)

WHO Recommendations for Grading of Acute and Subacute Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Fever	None	Fever <38°C	Fever 38°C–40°C	Fever >40°C	Fever with Hypotension
Allergic	None	Edema	Bronchospasm, No Parenteral Therapy Needed	Bronchospasm, No Parenteral Therapy Needed	Anaphylaxis
Cutaneous	None	Erythema	Dry Desquamation Vesiculation, Pruritus	Moist Desquamation Ulceration	Exfoliative Dermatitis, Necrosis Requiring Surgical Intervention
Hair	None	Minimal Hair Loss	Moderate, Patchy Alopecia	Complete Alopecia, but Reversible	Nonreversible Alopecia
Infection (Specific Site)	None	Minor Infection	Moderate Infection	Major Infection	Major Infection with Hypotension
Cardiac					
Rhythm	None	Sinus Tachycardia >110 BPM at Rest	Unifocal Premature Ventricular Contraction (PVC), Atrial Arrythmia	Multifocal PVC	Ventricular Tachycardia
Function	None	Asymptomatic, but Abnormal Cardiac Sign	Transient Symptomatic Dysfunction No Therapy Required	Symptomatic Dysfunction Responsive to Therapy	Symptomatic Dysfunction Nonresponsive to Therapy
Pericarditis	None	Asymptomatic Effusion	Symptomatic, No Tap Required	Tamponade, Tap Required	Tamponade, Surgery Required

APPENDIX B (cont'd)

WHO Recommendations for Grading of Acute and Subacute Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neurotoxicity					
State of Consciousness	Alert	Transient Lethargy	Somnolent <50% of Waking Hours	Somnolent ≥50% of Waking Hours	Coma
Peripheral	None	Paresthesias and/or Decreased Tendon Reflexes	Severe Paresthesias and/or Mild Weakness	Intolerable Paresthesias and/or Marked Motor Loss	Paralysis
Constipation[d]	None	Mild	Moderate	Abdominal Distention	Distention and Vomiting
Pain[e]	None	Mild	Moderate	Severe	Intractable

Source: Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.

[a] Equivalent values in SI units are given below.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic					
Hemoglobin (mmol/L)	≥6.8	5.9–6.7	5.0–5.8	4.0–4.9	<4.0
Leukocytes (WBC) (10^9/L)	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
Granulocytes (10^9/L)	≥2.0	1.5–1.9	1.0–1.4	0.5–0.9	<0.5
Platelets (10^9/L)	100	75–99	50–74	25–49	<25
Renal, Bladder					
Proteinuria (g/L)	None	1+, <3.0	2–3+, 3.0–10.0	4+, >10.0	Nephrotic Syndrome

[b] N = Upper limit of normal.

[c] N = Upper limit of normal or baseline.

[d] Constipation does not include constipation resulting from narcotics.

[e] Only treatment-related pain is considered, not disease-related pain. The use of narcotics may be helpful in grading pain, depending upon the tolerance level of the patient.

APPENDIX C

Determination of HER2 Overexpression

To be eligible for the trial, the patient must have a tumor that overexpresses the HER2 receptor as determined by Roche Biomedical Laboratories (RBL) in Research Triangle Park, North Carolina. RBL will perform immunohistochemistry 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 will be reported by RBL as indeterminate, 0, 1+, 2+, or 3+. For study eligibility purposes, the determination of HER2 overexpression will be limited to the first set of adequate slides reviewed.

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

APPENDIX D

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 E

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest[a]	Physical Ability to Work[b]
I	None	None	None	Full-time
II	Only moderate	Slight	Usually only slight or occasional	Usually full-time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part-time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

[a] To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

[b] At accustomed occupation or usual tasks.

Reference: Bruce RA. Evaluation of functional capacity and exercise tolerance of cardiac. Mod Concepts Cardiovasc Dis 1956;25:321–2. (Modified from New York Heart Association, 1953).

APPENDIX F

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 G

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

PT and PTT

Urinalysis

Serum Pregnancy Test

HBsAg and HCV

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
Corning Besselaar, Inc.
210 Carnegie
Princeton, NJ 08540-6233

Office Telephone:
(800) 621-8901, extension 4293

Europe:
Fiona Ogborn
Corning Besselaar, Inc.
1D Roxborough Way
Maidenhead
Berkshire SL63UD
United Kingdom

Office Telephone:
01628-548-056

APPENDIX H

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	*Urinalysis*
Serum Chemistry Panel	*Serum Pregnancy Test*
PT and PTT	*HBsAg and HCV*

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*

Victor Roberts
Corning Besselaar, Ltd.
51 Rawson Street, Suite 303
Epping NSW 2121
Australia
Office Telephone: 61-2-869-1811
Cellular Telephone: 0411-10-4509 (Australia)
61-411-10-4509 (New Zealand)

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APPENDIX I

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 *and Antibodies to rhuMAb HER2* (to be conducted by Genentech)
Note: These measurements will be performed on all patients.

1. Specimen Requirements

   The investigators will supply *the appropriate laboratory* with serum samples taken prior to and within 1 hour after the end of the 90-minute infusion of rhuMAb HER2 in accordance with the protocol.

   Serum collected preinfusion will be used for both pharmacokinetic and antibody measurements at Weeks 1 (Day 0), 2, 4, and every 4 weeks thereafter and at study termination. Additionally, at Weeks 3, 5, 6, and 7 serum for the pharmacokinetic measurements will be collected.

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 Shed Antigen Concentrations (to be conducted by RBL)
Note: These measurements will be performed on all patients.

1. Specimen Requirements

The investigators will supply *the appropriate laboratory* with serum samples taken prior to the start of the 90-minute infusion of rhuMAb HER2 in accordance with the protocol.

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.

C. Special Studies (to be conducted by Genentech)
Note: These measurements will be performed on *a minimum of* 10%–20% of *total* patients *in the study, but* 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 90-minute infusion of rhuMAb HER2 in accordance with the protocol.

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
Corning Besselaar, Inc.
Office Telephone:
(800) 621-8901, extension 4293

Europe:
Fiona Ogborn
Corning Besselaar, Inc.
Office Telephone:
01628-548-056

Australia and New Zealand:
Victor Roberts
Corning Besselaar, Ltd.
Office Telephone: 61-2-869-1811
Cellular Telephone (Australia): 0411-10-4509
(New Zealand): 61-411-10-4509

APPENDIX J

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 the past week:	Not at All	A Little	Quite 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

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

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 the past week:	Not at All	A Little	Quite a Bit	Very 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 K

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

Please go on to the next page

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)

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)

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

Please go on to the next page

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

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SAMPLE INFORMED CONSENT
(U.S.)

A PHASE III, MULTINATIONAL, DOUBLE-BLIND STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) PLUS CHEMOTHERAPY COMPARED WITH PLACEBO PLUS CHEMOTHERAPY IN PATIENTS WITH HER2/*neu* OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER

(Protocol H0648g)

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 has been confirmed by biopsy and 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), an electrocardiogram, a chest X-ray, laboratory blood tests, a pulmonary (lung) function test, and a pregnancy test, if

appropriate. If you are pregnant or nursing, you will be 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. placebo (an inactive ingredient) plus either cyclophosphamide and doxorubicin or paclitaxel

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.

Neither you nor your doctor will know which treatment you will receive. A dose of four milligrams of rhuMAb HER2 (or an equivalent amount of placebo) 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 the first week. Once a week thereafter, you will receive an intravenous dose of two milligrams of rhuMAb HER2 or placebo for every kilogram you weigh. Either cyclophosphamide and doxorubicin or paclitaxel will be given intravenously every 3 weeks for a total of 15 weeks. You will receive medications to minimize nausea and vomiting caused by the chemotherapy. After you complete the 15-week chemotherapy regimen, you will continue to receive weekly infusions of either rhuMAb HER2 or placebo according to the initial randomization for the duration of your participation in the study.

If you received paclitaxel as the chemotherapy and if, at the Week 17 tumor assessment, your tumor has decreased in size, you may continue to receive paclitaxel every 3 weeks for no more than 10 treatments.

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 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

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_____ Initials

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.

One year after enrollment of the last patient, if you were randomized to rhuMAb HER2 and your medical condition is still appropriate for continued rhuMAb HER2 therapy (in the opinion of your doctor and the Sponsor), you will be eligible to continue rhuMAb HER2 therapy in an open-label extension program. If you were randomized to placebo you will be followed for your health status until your tumor grows or the study ends.

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 administration of rhuMAb HER2 in a few patients. Diarrhea, vomiting, and worsening of previously existing neuropathy (a disease of the nerves in the arms or legs) have also been reported as possible effects of rhuMAb HER2 therapy.

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_____ Initials

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.

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 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 blood clot). Heart damage (occasionally fatal) may occur with doxorubicin therapy, but usually at a total dosage higher than the dose that will be used in this study. 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.

Patients are required to use effective contraception while in this study.

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_____ Initials

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 (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.

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_____ Initials

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.

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_____ 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

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_____ Initials

PATIENT INFORMATION SHEET

A PHASE III, MULTINATIONAL, DOUBLE-BLIND STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) PLUS CHEMOTHERAPY COMPARED WITH PLACEBO PLUS CHEMOTHERAPY IN PATIENTS WITH HER2/*neu* OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER

(Protocol H0648g)

PURPOSE

This clinical research study will evaluate a new experimental drug called rhuMAb HER2. This drug is an antibody to cancer cells. The study will include administration of this antibody in combination with either cyclophosphamide and doxorubicin (two chemotherapy drugs commonly used as treatment for breast cancer) or paclitaxel (another chemotherapy agent) if you have previously received doxorubicin. The purpose of the study is to determine if the addition of the antibody to the chemotherapy may be more effective in controlling tumor growth. Approximately 450 patients will participate in this clinical research study worldwide.

PROCEDURES

The study design requires that half the patients will receive the new drug and half will receive placebo (an inactive substance). Neither you nor your doctor will know which treatment you are receiving. If you agree to participate, your treatment will include the standard chemotherapy given intravenously (into your bloodstream) every third week for 15 weeks. If you have received doxorubucin 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. You will also receive a weekly infusion of either the new drug or the placebo for 15 weeks, then weekly thereafter until the study ends. The 90-minute infusion is followed by an additional hour of monitoring.

If you received paclitaxel as the chemotherapy and if, at the Week 17 tumor assessment, your tumor has decreased in size, you may continue to receive paclitaxel every 3 weeks for no more than 10 treatments.

The study will involve close monitoring of your health status. Monitoring will include a medical history, physical examination, chest X-ray, and heart (electrocardiogram) and lung function tests. Additional testing will include blood tests, a pregnancy test (if appropriate), and X-rays or scans to check the tumor. You are agreeing to allow the use of your samples for any scientific purpose. Your doctor will explain the procedure for skin biopsies, should they be needed. Occasionally, your doctor will ask you to complete questionnaires about the quality of your life.

The duration of your participation will depend on how your cancer responds to treatment. If your tumor grows or if the side effects are severe, the treatment will stop. At the end of the study, if you received the antibody and your disease is stable, you may be eligible to continue receiving the antibody. Your doctor will discuss the possible options available to you for further treatment. If your tumor grows, you will be contacted approximately every 2 months to follow up on your health status.

POSSIBLE RISKS AND DISCOMFORTS

The most common side effects of the chemotherapy drugs are nausea and vomiting, for which anti-nausea medication is available. In addition, hair loss, inflammation of the lining of the mouth, and a decrease in white blood cells (which fight infection) and platelets (which help blood clot) have been observed. Chemotherapy drugs have caused fetal abnormalities.

Heart damage may occur with doxorubicin therapy, but usually only when given at doses much higher than those used in this study. Cyclophosphamide may cause sterility and cessation of menstrual periods.

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.

Patients who have taken rhuMAb HER2 have experienced side effects such as mild fever, and some pain at the tumor site. Patients also experienced diarrhea, vomiting, and worsening of previously existing neuropathy (a disease of the nerves in the arms or legs). The long-term side effects of rhuMAb HER2 are unknown. Since the effect of rhuMAb HER2 on the reproductive system or developing fetus is unknown, if you are of childbearing potential you must use effective contraception while participating in this study.

The possible side effects from the use of an intravenous catheter may include bleeding or infection. There is a small but possible health risk of radiation exposure from X-rays.

You will receive any relevant new information that becomes available during the study.

POTENTIAL BENEFITS

The growth of your tumor may be controlled, or you may receive little or no benefit from the combination of chemotherapy and this experimental drug. Information from this study may be useful in the treatment of other patients with breast cancer.

ALTERNATIVE TREATMENT

Other standard treatments, such as other chemotherapy or radiation therapy, are available for anyone who does not wish to take part in this study.

CONFIDENTIALITY

Your medical records and any information obtained during the study are subject to inspection by the U.S. Food and Drug Administration, other relevant national drug regulatory authorities, and the Sponsor or their authorized representative. Your personal information is strictly confidential and will not be publicly available. Your doctor will be informed that you are taking part in this study.

TERMINATION OF PATIENT PARTICIPATION

Your participation in this study is voluntary. You may choose not to take part in this study or you may withdraw at any time without prejudice or loss of benefits. If you withdraw from this study due to an adverse experience, you should inform your doctor. Your doctor may stop your treatment and participation in this study for medical reasons. In addition, the Sponsor of this research study may find it necessary to limit or stop your treatment or participation, or stop the study at any time.

RESEARCH-RELATED INJURIES

If you suffer from any medical problem resulting directly from administration of the study drug in accordance with the protocol, the Sponsor will provide reimbursement for reasonable costs of medical treatment. Reimbursement is available only for costs not covered by your medical or hospital insurance or by third party or government programs providing such coverage. Information on compensation and study-related injury is available upon request.

QUESTIONS

If you experience any medical problems that you think may be related to receiving the study drug, or have questions about the research, compensation, or your rights as a participant in the study, please contact Dr. _____ at _____ or his or her associates at _____.

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INFORMED CONSENT

I have read and understood the above information. My doctor has explained the requirements of this study to me. I have had an opportunity to ask and receive answers to all of my questions. I have had sufficient time to consider my participation in this study. While I am a patient in the study, I agree to follow the instructions of the doctor and to call the doctor immediately if I become ill or experience any side effects. I understand that I can withdraw my consent at any time without affecting my future treatment. I have been given a copy of the Patient Information Sheet and this Informed Consent.

_____

Patient Name (print)

_____ _____

Patient Signature Date

I have explained the requirements of the study and have obtained written consent from the patient prior to her participation in this study.

_____

Investigator Name (print)

_____ _____

Investigator Signature Date

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Investigator's Signature for Protocol Amendment

A PHASE III, MULTINATIONAL, DOUBLE-BLIND STUDY OF RECOMBINANT HUMANIZED ANTI-p185^{HER2} MONOCLONAL ANTIBODY (rhuMAb HER2) PLUS CHEMOTHERAPY COMPARED WITH PLACEBO PLUS CHEMOTHERAPY IN PATIENTS WITH HER2/*neu* OVEREXPRESSION WHO HAVE NOT RECEIVED CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER

(Protocol H0648g-A1)

I have read Amendment 1 to the above-named protocol and agree to abide by all provisions of the amendment.

Protocol Number: H0648g-A1

Investigator's Name: _____

Date: _____

Signature: _____

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

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