The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Intrinsic subtypes, PIK3CA mutation, and the degree of benefit from adjuvant trastuzumab in NSABP trial B-31

Pogue-Geile, et al

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NSABP PROTOCOL B-31

A RANDOMIZED TRIAL COMPARING THE SAFETY AND EFFICACY OF ADRIAMYCIN AND CYCLOPHOSPHAMIDE FOLLOWED BY TAXOL (AC→T) TO THAT OF ADRIAMYCIN AND CYCLOPHOSPHAMIDE FOLLOWED BY TAXOL PLUS HERCEPTIN (AC→T + H) IN NODE-POSITIVE BREAST CANCER PATIENTS WHO HAVE TUMORS THAT OVEREXPRESS HER2

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

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Statistician:	Jong-Hyeon Jeong, Ph.D.
Pathologist:	Soonmyoung Paik, M.D.

Herceptin IND 6667

STUDY DRUGS:		**SUPPLIED BY:**
Herceptin (rhuMAb HER2 or trastuzumab)	NSC #688097	Genentech, Inc. via the NCI
Adriamycin (doxorubicin)	NSC #123127	Commercial
Cyclophosphamide	NSC #26271	Commercial
Taxol (paclitaxel)	NSC #673089	Commercial
Tamoxifen	NSC #180973	Commercial

Version Date: April 6, 2010 (Replaces all other versions)

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NSABP PROTOCOL B-31

A RANDOMIZED TRIAL COMPARING THE SAFETY AND EFFICACY OF ADRIAMYCIN AND CYCLOPHOSPHAMIDE FOLLOWED BY TAXOL (AC→T) TO THAT OF ADRIAMYCIN AND CYCLOPHOSPHAMIDE FOLLOWED BY TAXOL PLUS HERCEPTIN (AC→T + H) IN NODE-POSITIVE BREAST CANCER PATIENTS WHO HAVE TUMORS THAT OVEREXPRESS HER2

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

Trial Activated: February 21, 2000

Protocol Revision Record

Original Version: February 8, 2000

Amendment #1: March 15, 2000
Sections Changed: Cover Page, Section 23.0, Appendix A, and the Consent Form

Amendment #2: May 22, 2000
Sections Changed: Cover Page, Table of Contents, Information Resources, Sections 6.1, 8.3.1, 8.6, 9.0, 16.2, 16.5, 21.4.6, 23.0 (Table 13), Appendix C1, Appendix F (addition), and the Consent Form

Amendment #3: April 23, 2001
Sections Changed: Cover Page, Table of Contents, Sections 1.0, 5.1.3, 5.1.7, 5.1.9, 5.4.11, 6.1, 7.0 (Table 2), 8.0, 8.3.1, 8.3.2, 9.0, 11.1.2, 11.1.4, 12.1.2, 12.1.4, 13.0, 13.4, 15.10.2, 16.2.2, 23.0 (Table 13),Appendix C1 (Table C1-A), and Appendix C2

Amendment #4: January 14, 2003
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Amendment #5: January 31, 2003
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Amendment #6:	May 16, 2003 *Sections Changed:* Cover Page, Table of Contents, Information Resources, Section 1.0, Schema, Sections 2.2, 2.4, 2.6, 2.10, 3.1, 3.2, 4.2.2, 5.1.4, 5.1.8, 5.1.9, 5.1.10, 5.1.11, 5.1.12, 5.1.13, 5.1.14, 5.2.2, 5.2.3, 5.4.2, 5.4.3, 5.4.4, 5.4.5, 6.1, 7.0 (Table 2), 8.0, 8.4, 9.0, 10.0, 11.1.3, 11.1.4, 11.2, 11.3, 12.1.3, 12.1.4, 12.2, 12.3.2 (Table 3),12.4, 12.5, 13.0, 15.0, 16.2 (text and Table 13), 18.0, 19.1, 19.3, 20.2, 20.6 (Table 14A), 20.7, 20.8 (Table 14C), 23.0 (Table 16), 24.2, 26.0, Appendix A, Appendix B1, Appendix B2, Appendix C1, Appendix E, and the Consent Form.
Amendment #7:	February 28, 2005 *Sections Changed:* Cover Page, Table of Contents, Information Resources, Section 1.0, Schema, Sections 2.5, 2.8, 2.11, 2.12, 3.1, 3.2, 4.2, 5.1.10, 6.1, 7.0, 11.2, 12.4, 13.3, 15.20.2, 15.22, 16.2, 16.2.2, 16.6, 17.0, 19.1.4, 20.3, 20.6, 20.8, 21.4.6, 21.5, 23.0, 24.1, 24.2, 24.5.1, 24.5.2, 24.5.3, 24.5.5, 24.5.6, 26.0, and the Consent Form.
Amendment #8:	March 28, 2005 *Sections Changed:* Cover Page and the Consent Form.
Amendment #9:	June 3, 2005 *Sections Changed:* Cover Page, Table of Contents, Sections 1.0, Schema, 2.5, 2.8, 2.9, 2.13, 3.0, 3.1, 3.2, 4.0, 5.0, 6.1, 6.2, 7.0, 11.0, 11.1, 11.2, 12.0, 12.2, 12.3, 12.3.2, 13.2, 13.3, 14.0, 15.0, 16.0, 16.2, 17.0, 18.1.3, 20.0, 21.4.1, 21.5, 22.0, 23.0, 24.0, 26.0, Appendices A, B2, E, and G.
Amendment #10:	July 18, 2005 *Sections Changed:* Cover Page, Information Resources, 1.0, 6.1.3, 12.2, 12.3.2, and Appendix H.
Amendment #11:	April 6, 2010 *Sections Changed:* Cover Page, Table of Contents, Sections 1.0, 3.0, 4.0, 6.0, 7.0, 22.0, 23.0, 24.0, and Appendices G and H.

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05/22/00, 4/23/01, 01/14/03, 05/16/03, 02/28/05, 06/03/05

INFORMATION RESOURCES *05/22/00, 01/14/03, 05/16/03, 02/28/05, 07/18/05*

NSABP Operations Center
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Questions concerning clinical aspects of the trial, eligibility, and dose modifications and delays

NSABP Operations Center
Clinical Coordinating Division
Phone: 1-800-477-7227
E-mail: ccd@nsabp.org

Questions/problems regarding IRB review & informed consent (see Appendix H)

NSABP Operations Center
Regulatory Affairs Division
Phone: (412) 330-4600
Fax: (412) 330-4661

NSABP Biostatistical Center
One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213
Phone: (412) 624-2666 General office fax: (412) 624-1082
http://www.nsabp.pitt.edu

Patient entry information (see Section 22.0)

NSABP Biostatistical Center
Patient Entry Coordinator
Phone: (412) 624-2666
Consult the Patient Entry Guidelines section in the Members' Area of the NSABP Web site.

Submission of expedited adverse event reports/questions concerning expedited adverse event reporting (see Section 20.0)

NSABP Biostatistical Center
Phone: (412) 383-2557
Fax: (412) 622-2113

Submission of tumor blocks (see Section 8.0)

NSABP Biostatistical Center
(When sending blocks, please indicate on the package "Pathology Specimens Enclosed.")

Submission of IRB approval

All IRB documents should be submitted to the CTSU Regulatory Office according to the directions found on the CTSU Web site at http://www.ctsu.org.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-888-823-5923
Fax: (215) 569-0206

Form M, Form PAC, and Form CR. Attach MUGA scan results and supporting documents. (see Sections 6.0, 16.2, and 23.0)

NSABP Biostatistical Center
Phone: (412) 624-2666
Fax: (412) 383-1133

Questions concerning data management/drug shipment

NSABP Biostatistical Center
Phone: (412) 624-2666

Submission of blood and serum samples (with Form BNK [B-31]) (see Appendix D)

NSABP Serum Bank:

Baylor College of Medicine Breast Center
NSABP Serum Bank
Room 0059
One Baylor Plaza
Houston, TX 77030
Phone: (713) 798-1647 Fax: (713) 798-1642

1.0 SUMMARY OF THE STUDY

04/06/10

Long-term cardiac follow-up: Additional follow-up to look at the long-term impact of trastuzumab on cardiac function and quality of life related to cardiac symptoms was initiated with Amendment #11. See Appendix G for full details and instructions.

06/03/05
07/18/05

Update: In April 2005, a pooled interim analysis of data from NSABP B-31 and NCCTG N9831 showed that the primary aim of prolonging disease-free survival by adding Herceptin to chemotherapy (4 cycles of AC followed by 4 cycles of Taxol) was achieved. Please see Section 2.13 for details. At the recommendation of the NSABP's independent Data Monitoring Committee, the B-31 study was closed to accrual on April 29, 2005. Patients who had not received Herceptin and who were enrolled in B-31 on or after April 26, 2004, were offered the opportunity to receive investigational Herceptin. All patients continue to be treated and followed according to the current version of the protocol.

03/25/03
05/16/03
02/28/05

This study will evaluate the worth of Herceptin in patients with node-positive breast tumors that overexpress the HER2 protein. This phase III randomized trial is being conducted in two stages. The first stage will evaluate cardiac safety and determine the toxicities of adding weekly Herceptin (H) to adjuvant Taxol following Adriamycin and cyclophosphamide (AC). The regimens employed in the first stage of the study consist of four cycles of Adriamycin* (A: 60 mg/m^2) and cyclophosphamide (C: 600 mg/m^2) followed by four cycles of Taxol (T: 175 mg/m^2) with or without weekly Herceptin (4 mg/kg loading dose; 2 mg/kg maintenance dose) for 1 year. In October of 2002, at the second planned interim analysis, the independent Data Monitoring Committee determined that the incidence of cardiac toxicity in the study arm (AC→T + H) remained within the boundaries set by the protocol and, therefore, accrual could continue without a hiatus pending results of the final cardiac safety analysis. The second stage of the study will increase patient accrual to allow, as a primary aim, an evaluation of the efficacy of adding Herceptin to chemotherapy in prolonging disease-free survival (DFS).

01/14/03
02/28/05
06/03/05

To qualify for this trial, patients must have node-positive primary breast cancer with HER2 overexpression, no evidence of metastatic disease, and must have undergone either lumpectomy or total mastectomy, plus axillary dissection. All patients treated with lumpectomy must receive breast irradiation after their assigned chemotherapy. Administration of postlumpectomy regional and postmastectomy locoregional irradiation will be at the discretion of the investigator but must be declared at the time of randomization. All women with tumors that are estrogen-receptor (ER)-positive and/or progesterone-receptor (PgR)-positive will receive hormonal therapy for a minimum of 5 years. Hormonal therapy must be initiated no sooner than 3 weeks but no later than 12 weeks following the last dose of chemotherapy. Patients will receive cytokines (G-CSF, GM-CSF, or pegfilgrastim) as secondary prophylaxis for bacterial infection. Following stratification by number of positive nodes, type of hormonal therapy, type of surgery with choice of radiotherapy, and Taxol schedule, patients will be randomized into one of the two treatment groups: either Group 1, AC→T; or Group 2, AC→T + H.

05/16/03

In response to recent data (see Section 2.10), which suggests administration of Taxol at shorter intervals than 3 weeks may improve the activity of the drug without increasing toxicity, Amendment #6 provides investigators with the option of employing weekly Taxol 80 mg/m^2 for 12 doses as an alternative to the schedule of 175 mg/m^2 every 3 weeks.

04/23/01
06/03/05

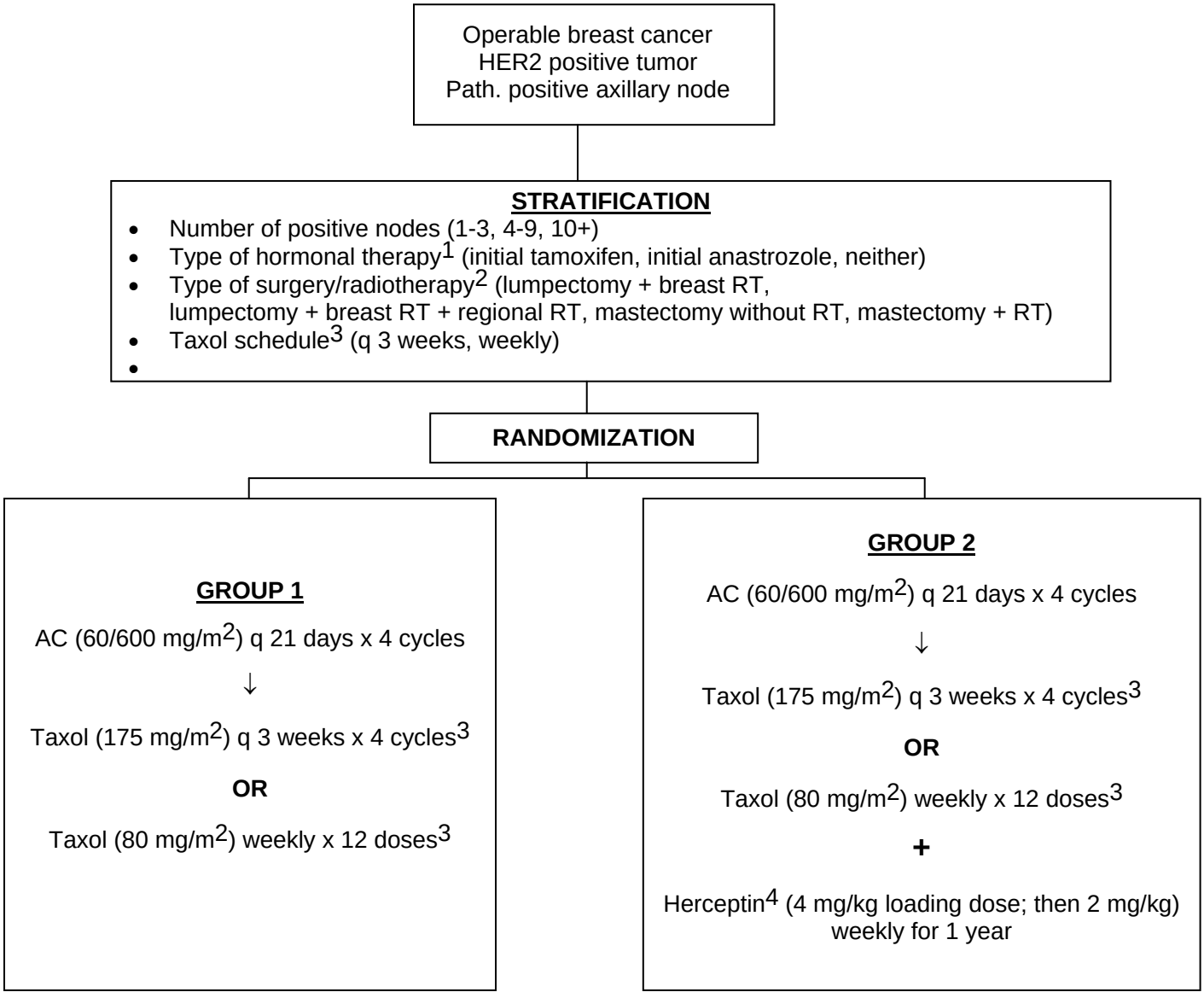
Close cardiac monitoring in the form of MUGA scans will be required for patients receiving Herceptin. See Section 6.0 for details on the MUGA schedules.

* Please note that in most cases throughout this protocol, doxorubicin will be referred to by one of its trade names, Adriamycin (or the letter A); however, other brands of doxorubicin may be used. In addition, in most cases, paclitaxel will be referred to by its trade name, Taxol.

The collection of tissue blocks and serum is an important part of this protocol. The tissue blocks and serum collection will be required at randomization and at the time of treatment failure, if it occurs. These specimens will be used for the following: 1) to determine whether expression of the phosphorylated receptor in the index tumor is prognostic for S and DFS in a population of patients with HER2-positive breast cancer; 2) to determine whether expression of the phosphorylated receptor in the index tumor is predictive of response to treatment with Herceptin, as indicated by the presence of a treatment-by-expression interaction with respect to S and DFS; 3) to determine whether the frequency of expression of the phosphorylated receptor in postrelapse tissues differs from the frequency of expression in index tumors, both in patients treated with Herceptin and in those patients not receiving Herceptin; 4) to determine, in a population of patients with HER2-positive breast cancer, whether higher levels of shed extracellular domain (ECD) or autoantibodies to HER2 measured in the serum prior to treatment are prognostic for S and DFS; 5) to determine whether higher levels of shed ECD or autoantibodies to HER2 are predictive of response to treatment with Herceptin, as indicated by the presence of treatment-by-covariate interactions with respect to S and DFS; 6) to determine, both in patients treated with Herceptin and in those patients not receiving Herceptin, whether levels of shed ECD or autoantibodies to HER2 are increased at the time of treatment failure relative to their pretreatment levels; 7) to determine whether the frequency of HER2 overexpression in postrelapse tissues of patients treated with Herceptin differs from the frequency in patients not treated with Herceptin; and 8) to determine, in this population of patients with HER2-positive breast cancer, the concordance of HER2 overexpression as measured by the following list of available assays: TAB250 (mAb-1), TAB250/pAb-1 cocktail, CB-11, HercepTest™ (DAKO), HER-2 FISH assay, array-based CGH; and to estimate the degree to which overexpression as measured by each of these assays is correlated with response to treatment with Herceptin.

Figure 1: B-31 SCHEMA *01/14/03, 05/16/03, 02/28/05, 06/03/05*

Note: The B-31 study was closed to accrual on April 29, 2005, and eligible Group 1 patients and Group 2 patients not receiving Herceptin for reasons other than cardiotoxicity were given the opportunity to receive investigational Herceptin. For details on the treatment regimens following the accrual closure, refer to Sections 11.0 and 12.0.



1 Hormonal therapy, starting no sooner than 3 weeks but no later than 12 weeks following the last dose of chemotherapy, will be given to all patients with ER-positive and/or PgR-positive tumors. Hormonal therapy should be administered for a minimum of 5 years. Total duration of tamoxifen should not exceed 5 years.

2 Radiation therapy, if planned by the investigator, must be designated at randomization and will be administered after the completion of all chemotherapy.

3 Investigators must select one of these two Taxol doses/schedules at the time of randomization.

4 The initiation of Herceptin is based on acceptable left ventricular function evaluation <u>following AC therapy</u>.

2.0 BACKGROUND

2.1 Rationale for the conduct of the study

In node-positive breast cancer patients, adjuvant chemotherapy has been shown to decrease recurrence rates and improve overall survival. Nevertheless, a subset of node-positive breast cancer patients develop tumor recurrence or metastases.

There has been a growing interest in the role of oncogenes in carcinogenesis. Oncogenes have been evaluated in terms of their prognostic significance for outcome and tumor responsiveness to chemotherapy, and they have been targeted for specific therapeutic intervention, e.g., the development of antibodies with antitumor activity.

One particular oncogene, HER2 (also referred to as erbB-2 or HER2/neu) on chromosome 17q21-22, plays a significant role in the biology of breast cancer. It codes for $p185^{HER2}$, a transmembrane growth factor receptor of the tyrosine kinase family, which is closely related to, but is distinct from, the epidermal growth factor receptor (EGFR). The amplification of HER2 oncogene and the overexpression of HER2 growth factor receptor $p185^{HER2}$ (which occurs in about 30% of breast cancer patients) correlates with poor disease-free survival (DFS) and overall survival (S).[1,2]

The murine monoclonal antibody (MAb 4D5) was created to act against the extracellular domain (ECD) of $p185^{HER2}$ with the intention of inhibiting the growth of tumors overexpressing this growth factor receptor.[3] MAb 4D5 was shown to have significant antiproliferative effects in human breast cancer cell lines and xenograft models that overexpress $p185^{HER2}$, but had no effect in tumors that did not overexpress the receptor. However, it was found that MAb 4D5 was immunogenic. In order to overcome this, a humanized version of MAb 4D5 was genetically engineered by inserting the complementarity-determining regions (CDRs) of MAb 4D5 into the framework of a consensus human immunoglobulin (IgG1).[4,5] The result, rhuMAb HER2 (generic name trastuzumab), was found to have three times greater affinity to the ECD of the HER2 receptor than does MAb 4D5, and to be capable of activating antibody-dependent cellular cytotoxicity against tumors. Moreover, rhuMAb HER2 was found to effectively inhibit the growth of $p185^{HER2}$ overexpressing breast cancer cells in vitro. Baselga et al[6] studied humanized MAb 4D5 given in combination with either Taxol or Adriamycin in xenograft models. Their experiment demonstrated superior tumor growth inhibition when the antibody was used with chemotherapy compared to chemotherapy or antibody alone; Taxol plus antibody showed a 93% growth inhibition; Adriamycin plus antibody showed a 70% growth inhibition; antibody alone showed a 35% growth inhibition; and chemotherapy with Taxol alone and Adriamycin alone showed a 35% and 27% inhibition, respectively.

RhuMAb HER2, or Herceptin (as the antibody will be called throughout this protocol), is produced by a genetically-engineered Chinese hamster ovary cell line that secretes the antibody in culture media. After the antibody is harvested from the culture media, it is purified using chromatographic and filtration techniques.

There are several possible mechanisms of action for Herceptin; one is that antibody-induced downregulation of $p185^{HER2}$ may result in reversing the malignant phenotype of tumors[7], or it may be that partial agonistic activity in activating the signal transduction pathway leads to the inhibition of tumor growth. Alternately, it is possible that Herceptin

may induce antibody-dependent cellular cytotoxicity. Also, downregulating HER2 may upregulate the p53 and p21 genes, which are associated with cell cycle arrest and apoptosis.[8] Not all HER2-overexpressing tumors have functional receptors so this subset of cells is somewhat antibody-resistant. It has been observed in vitro that the growth of breast cancer cells with high levels of phosphorylated $p185^{HER2}$ is most effectively slowed through inhibition by the antibody.[5]

2.2 Rationale for the use of Herceptin

A total of 48 patients whose tumors overexpressed HER2 were enrolled in three phase I studies (H0497g, H0452g, H0453) conducted with Herceptin. The doses studied ranged from 10 to 500 mg weekly. The half-life of Herceptin ranged from 1 day (at 10 mg dose) to 2-3 weeks (at doses of 250 to 500 mg). In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range 1 to 32 days) was observed. Between weeks 16 and 32, Herceptin reached a steady-state with a mean trough and peak concentrations of approximately 79 μg/ml and 123 μg/ml, respectively. No antibodies to Herceptin were detected throughout the study, and no significant laboratory abnormalities attributed to Herceptin were noted.

In a phase II clinical trial (Study H0649) of 222 women with previously treated metastatic breast cancer, Herceptin was given at 4 mg/kg intravenously to women whose tumors overexpressed $p185^{HER2}$ and subsequently at 2 mg/kg/week until disease progression. An overall response rate of 15% was reported in the 207 patients who were evaluable. The median duration of response was 8.5 months, and median survival time was 13 months. The response to the antibody was independent of the number of prior chemotherapy regimens received, the number of metastatic sites, performance status, the disease-free interval, and hormone-receptor status.[9] The most frequent adverse effects were fever, chills, chest pain, asthenia, diarrhea, dizziness, headache, nausea, vomiting, rash, and pain at the tumor site. Cardiac dysfunction occurred in 7% of patients, and in 5%, the cardiac dysfunction was regarded as severe [i.e., New York Heart Association (NYHA) classification III-IV]. Cardiac dysfunction included cardiomegaly, left-sided heart failure, congestive heart failure, and cardiomyopathy.

In a phase III randomized, controlled trial of patients with metastatic breast cancer (Study H0648), Herceptin was given as first-line treatment in combination with either Adriamycin or cyclophosphamide (AC) or Taxol. Patients who previously had received anthracycline adjuvant therapy received 6 cycles of Taxol ± weekly Herceptin until disease progression, while anthracycline-naive patients received 6 cycles of AC ± weekly Herceptin until disease progression. Among the 469 patients enrolled, the overall response rate was 45% for patients treated with chemotherapy (either AC or Taxol) plus Herceptin, vs 29% for patients treated with chemotherapy alone ($p<0.001$). The overall response rate for patients receiving AC + Herceptin was 50% vs an overall response rate of only 38% for patients receiving AC alone. The overall response rate for patients receiving Taxol + Herceptin was 38%, compared to a response rate of 15% for patients treated with Taxol alone. The combination of chemotherapy with Herceptin significantly prolonged the time-to-disease progression compared with chemotherapy alone. The median time-to-disease progression for patients who received Herceptin plus chemotherapy was 7.2 months, whereas in patients who received chemotherapy alone, the median time-to-disease progression was 4.5 months. The difference between the overall time-to-disease progression for the two treatment groups was statistically significant ($p<0.0001$; log rank test).[10] Cardiac dysfunction occurred in 7% of patients in the AC-

alone arm, in 28% of patients in the AC + Herceptin arm, in 1% of patients in the Taxol-alone arm, and in 11% of patients in the Taxol + Herceptin arm. Of patients experiencing cardiac dysfunction, a NYHA class III or IV dysfunction occurred in 19% of patients in the AC + Herceptin arm and in 0-4% in the remaining three arms.

In these phase II and III studies, cardiac dysfunction was defined by an independent Cardiac Review and Evaluation Committee (CREC) as any of the following:

- cardiomyopathy characterized by a fall in cardiac ejection fraction associated with abnormal myocardial wall motion that was either global or more severe in the septum;
- symptoms of congestive heart failure;
- signs of congestive heart failure, including but not limited to S3 gallop and/or tachycardia; or
- a decline in cardiac ejection fraction of at least 5 points to below 55% *with* signs and symptoms, or a fall in cardiac ejection fraction of at least 10 points to below 55% *without* signs and symptoms.

Patients in Study H0648 in whom disease progression occurred could participate in Study H0659, an open-label study in which the investigator could choose to continue Herceptin alone or to combine it with any chemotherapy. Of the 469 patients enrolled in H0648, 57 patients who had received AC alone subsequently received either single-agent Herceptin or Herceptin combined with a taxane. Cardiac dysfunction of any grade was noted in 3.5% (2/57) of these patients.[11]

Combining all the trials in which Herceptin was used alone or with chemotherapy, severe consequences or worsening clinical conditions as a result of cardiac dysfunction were observed in 1% of patients (14/977). Major clinical responses (complete and partial) were observed in patients with cardiac dysfunction; however, the risk of cardiac dysfunction appeared to be independent of responses to antitumor therapy. The results of the CREC review suggest that the nature of the cardiac dysfunction observed in these studies was similar to that seen in anthracycline-induced cardiomyopathy, and that the signs and symptoms of cardiac dysfunction almost always respond to treatment.

The mechanism underlying the cardiac toxicity seen in the Herceptin trials is not known. In the HER2 knockout mouse model, deletion of HER2 has been shown to result in abnormal development of the cardiac trabeculae.[12] Recently, HER2 and HER3 receptors have been found to be expressed by neonatal and adult ventricular myocytes in a rat model. Neuregulins, a family of locally acting peptide autocoids, important in the development of the central and peripheral nervous system, mediate their effects by binding to and signaling via the HER or erbB family of receptors. The neuregulin-erbB signaling system may play an important role in the proliferation, survival, and maturation of cardiomyocytes.[13] However, there are currently no human data available to explain the cardiac effect seen with Herceptin.

The long-term cardiac effects of Herceptin are also largely unknown. It is unknown whether Herceptin cardiotoxicity might follow an insidious pattern and show years of latency before causing cardiomyopathy. Therefore, it will be necessary to monitor for long-term cardiac events in women participating in the B-31 trial. For this reason, information on cardiovascular events (described in Section 19.2) will be collected during the course of this trial.

05/16/03

As noted above, if no excessive cardiotoxicity is demonstrated in the Herceptin arm of the trial during stage 1 of the study, the study will proceed to stage 2 in which the efficacy of adding Herceptin to chemotherapy will be evaluated. (See Section 24.0 for related statistical considerations.) In October of 2002, at the second planned interim analysis, the independent Data Monitoring Committee determined that the incidence of cardiac toxicity in the study arm (AC→T + H) remained within the boundaries set by the protocol and, therefore, accrual could continue without a hiatus pending results of the final cardiac safety analysis.

Adverse effects associated with Herceptin, other than cardiotoxicity, have been noted as generally mild to moderate in severity, and include fever, chills, and other constitutional symptoms, usually occurring with the first infusion. These symptoms have been uncommon with subsequent dosing and are treated with diphenhydramine hydrochloride, acetaminophen, and, rarely, meperidine. Pain, anorexia, diarrhea, insomnia, paresthesia, increased cough, pharyngitis, rhinitis, sinusitis, rash, upper respiratory tract and catheter infections, anemia, and leukopenia have been observed more frequently in the Herceptin-plus-chemotherapy group when compared with the chemotherapy-alone group. Adverse events commonly observed with standard systemic chemotherapy for breast cancer, such as leukopenia, mucositis, and alopecia, have been uncommon following administration of Herceptin as a single agent.

Herceptin appears to be nonimmunogenic. Among 977 patients participating in several safety trials involving Herceptin, only 1 patient developed neutralizing antibodies to the drug. This patient had no signs or symptoms of allergy while receiving Herceptin and discontinued treatment with Herceptin because of progressive metastatic breast cancer.

The biologic antitumor response seen with Herceptin warrants further study in the adjuvant setting. With careful cardiac monitoring as outlined in this protocol, NSABP Protocol B-31 will provide a unique opportunity to study the targeting of a molecular marker with a humoral agent in combination with chemotherapy. Its study in the adjuvant setting, where the tumor burden is least, may help pave the way for the development of HER2 cancer vaccines.

2.3 Rationale for including all node-positive patients

In NSABP Protocol B-15, a randomized trial comparing AC vs AC followed by CMF vs CMF in node-positive patients, a population of women aged ≤ 49 or age 50-59 with PgR ≤ 10 fmol were analyzed. Among the 1368 patients treated with either AC or AC followed by CMF who were assayed for HER2, survival was as follows [shown in Table 1 (unpublished data)]:

TABLE 1. Comparison of the effect of the number of positive nodes and HER2 status on DFS and S (in %): NSABP Protocol B-15, total number of patients = 1368

	1-3 positive nodes			4+ positive nodes		
	HER2-	HER2+	Overall	HER2-	HER2+	Overall
Survival						
Number	555	204	759	416	193	609
5-years	82%	74%	80%	61%	54%	59%
10-years	68%	63%	67%	46%	38%	43%
Disease-free Survival						
Number	555	204	759	416	193	609
5-years	69%	61%	67%	43%	35%	41%
10-years	55%	52%	54%	30%	27%	29%

NSABP Protocol B-31 will be open to all node-positive patients since, according to data from the B-15 study (Table 1), only 63% of patients who had 1 to 3 positive nodes and were HER2-positive survived at 10 years. While patients with ≥ 4 positive nodes whose tumors were HER2-positive had a worse overall survival (38%) compared to those with 1 to 3 positive nodes whose tumors were HER2-positive (63%), the absolute prognosis of patients with 1 to 3 positive nodes whose tumors were HER2-positive is not by any means favorable. The poor prognosis conferred by being HER2-positive in addition to being node-positive is sufficient to warrant testing alternative therapy and exposure to potential toxicities.

2.4 Rationale for using AC followed by Taxol as the control arm

It is reasonable to choose an anthracycline-based chemotherapy, such as AC, for the control arm since anthracycline-containing adjuvant therapy is considered standard therapy by many North American oncologists. In a retrospective study of 638 patients with node-positive, hormone receptor-negative breast cancer in NSABP Protocol B-11, patients whose tumors overexpressed HER2 by immunohistochemistry derived a preferential benefit for disease-free survival by receiving Adriamycin in the PAF (phenylalanine mustard, Adriamycin, fluorouracil) regimen compared to a non-Adriamycin-containing regimen, PF (phenylalanine, fluorouracil).[14] Another retrospective study was done in NSABP Protocol B-15, where node-positive women age 50-59 years old with PgR ≤ 10 fmol, and women age ≤ 49 years old, regardless of hormone receptor status, were randomized to AC alone vs AC followed by CMF vs CMF alone. A total of 599 (29%) out of 2034 stained sections were found to overexpress HER2. Those patients who received anthracycline and whose tumors also overexpressed

HER2 derived a nonstatistically significant benefit compared to those who received CMF.[15]

In the Intergroup study CALGB 9344, a study evaluating the use of adjuvant therapy in node-positive patients, Henderson et al reported a better 18-month DFS and overall S from the addition of sequential Taxol after AC, vs AC alone (90% vs 86% DFS, and 97% vs 95% S, respectively).[16] Muss et al reported their results from CALGB 8869 and noted that patients whose tumors overexpress HER2 benefit from higher doses of Adriamycin as defined in their study.[17] For NSABP Protocol B-31, the control arm of AC followed sequentially by Taxol was chosen because sequential therapy has the potential of better cytocidal effect by possibly eliminating anthracycline-resistant cancer clones. If the results of Henderson et al hold and if NSABP Protocol B-28, a randomized trial comparing AC alone vs AC followed by Taxol in node-positive tumors, also shows sequential therapy to be better, then it becomes reasonable to use AC followed by Taxol as the control arm and then test the role of the anti-HER2 antibody. In the Genentech trial H0648, more cardiotoxicity was seen with concurrent administration of AC + Herceptin compared to Taxol + Herceptin. Thus, testing the Herceptin antibody after AC is administered is potentially safer from a cardiotoxicity standpoint. In H0648, Taxol + Herceptin was considerably more active than Taxol alone in patients who had received prior anthracycline-based adjuvant therapy.

The dose of Taxol proposed in B-31 is 175mg/m^2 infused over 3 hours every 21 days for 4 cycles. This dose was chosen because it was used in the metastatic disease trial H0648 in combination with Herceptin. A schedule of weekly infusions for 1 year of Herceptin, beginning with the first course of Taxol, was chosen because maintenance therapy may be associated with enhanced tumor suppression, and a treatment duration greater than 52 weeks may result in decreased patient compliance. A weekly schedule should ensure a good antibody trough level, provide cytocidal effect, and eliminate tumor cell growth.

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In response to recent data, the protocol was modified as of Amendment #6 to give investigators the option of employing weekly Taxol 80 mg/m^2 for 12 doses as an alternative to every 3 week Taxol at 175 mg/m^2. (See Section 2.10 for the rationale for this change.)

2.5 Issues relating to hormonal therapy and HER2 overexpression

The questions of whether there is a significant biological interaction between HER2 overexpression and hormone receptor positivity, and how such interaction is affected by chemotherapy are important issues for clinical investigation. In vitro testing by Witters et al showed enhanced inhibition of cell proliferation when HER2 antibody 4D5 is combined with tamoxifen in BT474 human breast cancer, a cell line which overexpresses estrogen receptor (ER) and HER2.[18] However, the interaction between tamoxifen and Herceptin has not been studied adequately in the clinical setting.

In NSABP Protocol B-14, a randomized trial comparing placebo vs tamoxifen in patients with node-negative, ER-positive tumors, a retrospective analysis of HER2 status was done on 937 cases, which was 32% of the total randomized study population of 2892. Univariate analysis showed no significant difference in DFS or S when HER2-negative and HER2-positive patients were compared, either among patients treated with tamoxifen or patients treated with placebo.[19]

Elledge et al[20] conducted a retrospective study on 205 paraffin-embedded tumors of metastatic breast cancer which were ER-positive, HER2-positive, and previously treated only with tamoxifen (Southwest Oncology Group 8228). There was no significant correlation between HER2-positivity and response rate, DFS, or S.

There have been reports that HER2-positive tumors respond poorly to endocrine therapy. In a small study, Wright et al[21] examined 65 cases of metastatic breast cancer, 30 of which were ER-positive and 14 of which were HER2-positive. He noted that HER2 overexpression decreased the response rate to endocrine therapy from 48% (12/25) to 20% (1/5) in the ER-positive group. Among the patients with ER-negative tumors, HER2 overexpression reduced the response rate from 27% (7/26) to 0% (0/9). Definitive conclusions concerning the interaction between HER2 and endocrine therapy are difficult to make from these data, given that the number of patients with HER2 overexpressing tumors was small.

In the University of Naples GUN Trial (sponsored by the Gruppo Universitario Napoletano) reported by Bianco et al, 433 breast cancer patients were randomized to receive tamoxifen or no tamoxifen.[22] All premenopausal, node-positive women in the study received cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). At a median follow-up of 14 years, all patients, regardless of nodal or menopausal status, were shown to benefit from tamoxifen. A total of 245 patients (182 HER2-negative and 63 HER2-positive) were evaluated for a possible interaction between tamoxifen and HER2 overexpression. In this group of patients, tamoxifen seemed to improve DFS and S only in the HER2-negative patients and, paradoxically, worsened DFS and S in the HER2-positive patients. Unfortunately, many of these patients were ER-negative and little benefit from tamoxifen could be expected. With so few HER2-positive tumors involved, the study results suggest that further investigation of the possible interaction between HER2 and hormonal therapy is warranted.

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In the B-31 protocol, patients with tumors that are ER-positive and/or PgR-positive will receive hormonal therapy. See Sections 11.2 and 12.4 for details.

2.6 Rationale for conducting the trial in two stages

It is not known if a cumulative dose of 240 mg/m^2 of Adriamycin followed by concomitant Taxol and Herceptin will result in cardiotoxicity beyond what would occur if Adriamycin followed by Taxol were administered. This protocol is designed with a control arm without Herceptin so that differences in efficacy and cardiotoxicity can be assessed. The protocol will be conducted in two stages: 1) an evaluation of cardiac safety and 2) an evaluation of Herceptin efficacy in this combination. In the first stage, 500 patients in each arm will be closely monitored with MUGA scans prior to entry, following AC, and at 6 months, 9 months, and about 18 months. A temporary interruption following accrual of the first 1000 patients may occur in order to fully assess for cardiotoxicity. However, if it is determined that cardiotoxicity associated with the experimental regimen is within acceptable limits, then accrual of patients will continue (see Section 24.4.4 for details).

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In October 2002, the Data Monitoring Committee reviewed the results of the second interim cardiac safety analysis. Results indicated the difference in the rates of cardiac events between the control and investigational arms was within the limits specified in

Section 24.4.4, which allowed for continuation of accrual without a hiatus to the second stage of the study.

2.7 Concerns and changes regarding radiation therapy

It has been customary in NSABP adjuvant trials for patients to receive local breast irradiation after lumpectomy since this has been shown to lower the ipsilateral breast tumor recurrence rate significantly. It has also been the practice of the NSABP not to allow regional postlumpectomy radiation therapy or locoregional postmastectomy radiation therapy to be given in node-positive adjuvant trials. The meta-analysis performed by the Early Breast Cancer Trialists' Group, which analyzed data from all the randomized radiation trials begun before 1985, found a 67% reduction in rates of locoregional relapse ($p<0.001$) and a 6% reduction in mortality from breast cancer ($p=0.03$), but no improvement in overall survival.[23] Another overview of breast cancer trials where postoperative adjuvant radiotherapy was a randomized option after simple or radical mastectomy also showed no difference in survival at 10 years of follow-up in patients who had received or had not received postoperative radiotherapy.[24]

Recently, Overgaard et al reported a 14% survival difference (48% vs 34%) among 1708 node-positive breast cancer patients treated with chemotherapy plus postmastectomy chest wall and locoregional radiation compared to chemotherapy alone.[25] Ragaz et al also reported a survival advantage in a group of 318 women who received postmastectomy irradiation in addition to chemotherapy vs chemotherapy alone.[26] Based on these recent results, postmastectomy locoregional radiotherapy is now allowed for patients participating in NSABP node-positive trials, B-31 in particular, provided the investigator states this decision for stratification purposes prior to randomization.

In B-31, the possibility that there may be long-term cardiotoxic effects from Herceptin administration compounds the concern that radiation therapy to the chest may have a long-term cardiotoxic effect, particularly for women with left-sided breast lesions. However, Overgaard et al showed no evidence of a higher death rate among patients with left-sided tumors, after a median follow-up of almost 10 years.[25] Because of these concerns, *irradiation of any internal mammary nodes will be prohibited in this trial*. It is critical that the radiation guidelines in Appendix A, which detail proper technique and reflect the concern about heart irradiation in this trial, are followed in this protocol. It is currently very difficult to specify "existent and specified dose and volume of heart irradiated," since determining the irradiated volume of heart requires CT scan planning using complex computer programming. In this study, the NSABP will review the pertinent radiation therapy materials, including portal films (one set) and treatment position photographs, for the first 500 patients with left-sided lesions. (See Section 6.2 for cardiac safety related to radiation therapy.)

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2.8 Modification for chemotherapy and sequential vs. concurrent tamoxifen* administration

The issue of optimal administration of chemo-hormonal therapy has been a matter of debate for several years. Theoretical considerations have been put forward to justify either the combined administration of chemotherapy and tamoxifen or the sequential approach. The NSABP adopted the combined approach and continued with it based on the results from NSABP studies B-16 and B-20, where the concurrent administration of chemotherapy and tamoxifen was shown to be superior to tamoxifen alone. Other cooperative groups adopted the sequential administration of tamoxifen following completion of chemotherapy.

At the May 2002 meeting of the American Society of Clinical Oncology, results from three randomized trials addressing the question of optimal administration of chemo-hormonal therapy were reported.[26a, 26b, 26c] In all three trials the disease-free survival and overall survival (when reported) were not significantly different with the sequential administration when compared to the concurrent administration of chemotherapy and tamoxifen. In two of the trials, however, a non-significant trend favored the sequential approach. In all three studies, toxicity was similar between the concurrent and the sequential administration of tamoxifen and chemotherapy. Given these results, the NSABP amended the B-31 protocol (Amendment #4) to formally adopt the sequential administration of tamoxifen following completion of chemotherapy.

*(*At the discretion of the investigator, other hormonal therapeutic agents will be allowed in sequence with or as an alternative for tamoxifen therapy.)*

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2.9 Rationale for including anastrozole as adjuvant hormonal therapy for postmenopausal patients

The first results from the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial were presented by the ATAC Trialists' Group in *The Lancet*.[26d] This large, multinational, double-blind, placebo-controlled, randomized trial compared 5 years of tamoxifen with 5 years of anastrozole and with 5 years of the combination of anastrozole and tamoxifen in 9,366 postmenopausal women with hormone-receptor-positive or unknown hormone-receptor-status breast cancer. The primary study endpoints were disease-free survival and safety/tolerability. Secondary endpoints included the incidence of second non-breast cancer primaries, time to distant recurrence, and overall survival. The first analysis was scheduled to occur when there had been a total of 1056 events for the disease-free survival analysis. At the time of the study analysis there were 1079 events. The median follow-up was 33.3 months. There was a statistically significant improvement in disease-free survival favoring anastrozole compared to tamoxifen, with fewer events on anastrozole (hazard ratio 0.83, 95% CI: 0.71-0.96, p=0.013). The reduction in event rate was more prominent when receptor-positive patients were examined (hazard ratio 0.78, 95% CI: 0.65-0.93, p=0.005). There was no difference in disease-free survival between the tamoxifen group and the combination group (hazard ratio 1.02, 95% CI: 0.89-1.18, p=0.8). Several adverse events were significantly less frequent with anastrozole vs. tamoxifen such as hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, ischemic cerebrovascular events, and venous thromboembolic events. On the other hand, adverse events such as musculoskeletal disorders and fractures were significantly more common with anastrozole compared with tamoxifen.

The results of the ATAC trial and their potential impact as adjuvant therapy in postmenopausal patients with early-stage breast cancer were recently examined by a multidisciplinary panel of experts, which was commissioned by the American Society of Clinical Oncology to conduct a technology assessment on the adjuvant use of aromatase inhibitors and make recommendations to healthcare providers and patients.[26e] After reviewing the available evidence, with aromatase inhibitors and particularly the results of the ATAC trial, the panel recommended that the results of the ATAC trial should be considered preliminary, and that a 5-year course of tamoxifen should remain the standard of care for women with hormone-receptor-positive breast cancer. However, the panel went on to state that for patients who cannot tolerate tamoxifen or for whom tamoxifen is contraindicated (i.e., patients with prior history of a thromboembolic event), anastrozole is a reasonable alternative as adjuvant therapy.

06/03/05 Based on the results of the ATAC trial and the American Society of Clinical Oncology Technology Assessment Panel recommendations, tamoxifen will continue as the adjuvant hormonal therapy of choice for this protocol. However, at the discretion of the investigator, anastrozole will be allowed in sequence with or as an alternative for tamoxifen therapy in postmenopausal patients.

05/16/03 2.10 **Rationale for allowing dose/schedule options for the administration of Taxol**

Since the activation of B-31, results of two randomized clinical trials suggested the activity of Taxol may be enhanced by administration of the drug at more frequent treatment intervals. A neoadjuvant trial conducted at MD Anderson Cancer Center randomized 258 patients with operable breast cancer to receive either 4 cycles of Taxol 225 mg/m^2 as a 24-hour continuous infusion every 3 weeks or a weekly Taxol regimen depending on clinical nodal status. Patients with clinically negative nodes received 80 mg/m^2 weekly for 12 doses, while those with clinically positive nodes received 150 mg/m^2 days 1, 8 and 15 on a 28-day cycle for a total of 4 cycles. Following completion of Taxol, all patients received 4 additional cycles of FAC (5-fluorouracil, Adriamycin, cyclophosphamide) and then underwent definitive surgery. The weekly regimens resulted in a pathologic complete response rate of 28.8% compared to a rate of 13.6% in patients who had received the every 3 week program ($p < 0.01$).[26f] Recently, the CALGB reported initial results from Trial 9741, a randomized study of dose dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as adjuvant treatment for node positive primary breast cancer. A 2 x 2 factoral design was used to evaluate whether chemotherapy administered at dose dense 2 week intervals would result in improved disease-free survival and overall survival relative to the standard 3 week schedule. The dose dense schedules improved 4-year disease-free survival from 75% to 82% (RR=0.74; p=0.010).[26g] These data are consistent with an improvement in outcome with more frequent dosing intervals of Taxol.

Data from metastatic disease trials available at the time of activation of B-31 had demonstrated weekly Taxol at 80–100 mg/m^2 was less toxic and at least as effective as every 3 week schedules.[26i] However, the NSABP elected to employ the every 3 week regimen for the initial cardiac safety portion of the trial since the only safety data on the combination of Herceptin and Taxol available at that time had employed the schedule of 175 mg/m^2 over 3 hours at 3 week intervals. The second planned interim cardiac safety analysis conducted after 600 evaluable patients had been followed for at least 6 months after initiation of Taxol indicated the addition of Herceptin to the every 3 week regimen of Taxol did not result in an absolute increase in protocol-specified cardiac events of

≥ 4%, so accrual has continued without a hiatus per protocol specifications (see Section 24.4.4).

Subsequent to activation of NSABP B-31, the North American Intergroup activated N9831, a Phase III trial of AC followed by weekly Taxol with or without Herceptin in women with HER-2 positive, node positive breast cancer. The design of the cardiac safety study developed by the NSABP for B-31 was also employed for N9831. The Intergroup trial has 3 arms: a control arm, a second arm in which Herceptin is initiated concurrently with Taxol, and a third arm in which Herceptin is initiated following completion of Taxol. While accrual to the combination arm was suspended by the NCCTG DMC for a period of time due to concerns about excessive cardiotoxicity, longer follow-up indicated the addition of Herceptin did not result in an increase in cardiotoxicity which exceeded the protocol parameters specified for N9831 and B-31.[26j] Since the cardiac safety program employed in both trials is identical, it is reasonable to assume the incidence of cardiotoxicity will not be substantially different between the every 3 week and weekly schedules. While the available data suggesting improved efficacy of more frequent dosing intervals of Taxol is not yet conclusive, it is appropriate to amend B-31 and allow investigators and their patients to choose between the every 3 week and the weekly schedules.

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2.11 Rationale for the pooled analysis of NCCTG N9831 and NSABP B-31

When Protocol B-31 was designed, there were data suggesting that use of a weekly Taxol schedule was feasible and justifiable both in terms of efficacy and reduced toxicity. However, experience from the metastatic setting regarding the concurrent administration of Taxol and Herceptin was, at that time, limited to the 3-week schedule. For this reason it was concluded that the 3 week Taxol schedule was appropriate for use in this study, despite the considerable potential advantages of weekly administration. However, since that time, additional information has become available confirming the desirability of the weekly schedule, including the CALGB 9741 and the CALB 9840 Intergroup trials that have suggested the efficacy of increasing dose-density.[26g,26k] In addition, experience to date in NCCTG N9831 suggests that the weekly schedule may be used in combination with adjuvant concurrent Herceptin while maintaining an acceptable level of cardiotoxicity. It was concluded that if Herceptin is eventually proven to be effective in the adjuvant setting, future use of the Taxol/Herceptin combination will rarely be based on the 3-week schedule. Accordingly, Amendment #6 was submitted in order to permit the use of the weekly schedule in NSABP B-31.

With this amendment, most patients in the concurrent Taxol/Herceptin therapy arms of NSABP B-31 and NCCTG N9831 will be treated identically. The leadership of both trials therefore concluded that the questions tested by NSABP B-31 and NCCTG N9831 (Arms A and C) are so similar that a joint analysis is both feasible and desirable, and indeed that a failure to analyze them jointly might result in inappropriately withholding definitive information with respect to the worth of 12 months treatment with Herceptin, when given following four cycles of AC therapy and begun concurrently with Taxol.

02/28/05 2.12 **Rationale for use of DFS as primary endpoint**

As initially proposed, DFS was the primary endpoint for NCCTG N9831 and S was the primary endpoint for NSABP B-31. In the joint analysis, DFS has been selected as primary endpoint for the following two reasons:

- Very strong evidence (~710 events) will be available for DFS about 24 months before a survival comparison can be reported; the appropriateness of withholding such information was debated. It was decided that this was not justified. Instead, a confirmatory S analysis has been scheduled without delaying the analysis of DFS.

- In addition, it is likely that DFS information will be reported from other trials prior to the time that the B-31 and N9831 trials will be able to reliably report survival data. It was concluded that the exclusion of mature NSABP/NCCTG DFS data from these early reports also would not be in the best interests of adjuvant patients who overexpress the HER2 receptor or amplify the HER2 gene.

06/03/05 2.13 **Results of the pooled interim analysis of NSABP B-31 and NCCTG N9831 data and actions following this analysis**

2.13.1 ***Results of the pooled interim analysis***

The first interim analysis of the pooled efficacy data was scheduled to occur following the reporting of 355 events. By March 15, 2005, 395 events had been reported in 3351 patients with follow-up from the two studies, triggering the first interim analysis. Median follow-up was 2.0 years (2.4 years on B-31, 1.5 years on N9831). There were 261 events reported on AC→T compared with 134 on AC→T+H. The hazard ratio for a first event is 0.48 (95% CI: 0.39 to 0.60; $2p= 3x10^{-12}$). The difference in absolute DFS at 3 years is 87%-75% = 12% (95% CI: 8% to 15%). At 4 years, the estimated benefit is 85%-67% = 18% (95% CI: 13% to 24%). The DFS comparison easily crossed the early stopping boundary 2p=0.001. The log-rank statistic differed from 0 by nearly 7 standard errors.[26l]

There were 92 deaths reported for patients on AC→T and 62 deaths for those on AC→T+H. The hazard ratio for mortality is 0.67 (95% CI: 0.48 to 0.93) and is statistically less than 1 (2p= 0.015). The difference in absolute survival at 3 years is 94.3%-91.7% = 2.5% (95% CI: 0.1% to 5.0%); at 4 years, the estimated benefit is 91.4%-86.6% = 4.8% (95% CI: 0.6% to 9.0%). Distant metastases were reported in 194 patients on the control arms and 96 patients on the investigational arms. The hazard ratio for first distant recurrence was 0.47 (95% CI: 0.37 to 0.60, $2p= 8x10^{-10}$). The difference in absolute DFS at 3 years was 90%-81% = 9% (95% CI: 6% to 12%) and at 4 years was 90%-74% = 16% (95% CI: 11% to 21%).[26l]

The important toxicity in these trials was cardiotoxicity with a rate of NYHA Class III/IV CHF of 3-4%. Age and post-AC LVEF values predicted for increased risk of CHF. Among women age 50 and older at randomization with post-AC LVEF values ranging from their institution's lower limit of normal to 54%, 9/47 (19%) developed CHF on NSABP B-31.[26l] Analyses for predictive factors for CHF on N9831 are in process.[26m]

The HERceptin Adjuvant (HERA) trial also recently reported results of an initial interim analysis which showed substantial improvement in DFS with the administration of trastuzumab following completion of chemotherapy. The three-arm trial randomized women who had HER-2 overexpressing breast cancer and who had completed at least 4 cycles of adjuvant chemotherapy to observation; 1 year of trastuzumab; or 2 years of trastuzumab. With a median follow-up of only 1 year, 2-year DFS was improved from 77.4% in the observation group to 85.8% (HR-0.54, 95% CI: 0.43-0.67) in the 1-year trastuzumab therapy group. Follow-up was too short to analyze the 2-year trastuzumab therapy group. Notably, the risk of NYHA Class III/IV CHF was only 0.5% in the trastuzumab group with the sequential approach.[26n]

2.13.2 *NSABP actions pursuant to pooled interim analysis*

On the basis of these results, accrual to B-31 was terminated, and investigators were instructed to notify patients of the results. Patients on the control arm randomized ***on or after April 26, 2004***, will be provided the opportunity to receive investigational trastuzumab concurrently with paclitaxel, if they meet the criteria for trastuzumab administration in B-31 and have not completed chemotherapy. If they have completed chemotherapy, they will be provided the opportunity to initiate trastuzumab sequentially for a year of therapy (see Section 12.3).

On the basis of the suggested increased risk of CHF in women age 50 or older with an LVEF <55%, initiation of investigational trastuzumab may be delayed in this group of women at the investigator's discretion (even though the women may have met the criteria to initiate trastuzumab concurrently with paclitaxel). If the B-31 criteria for concurrent therapy are not met, patients will be provided the opportunity to receive trastuzumab following completion of paclitaxel, if their LVEF remains in the normal range (see Section 12.3, Table 3B).

Finally, since the cardiac safety portion of the study is completed, patients who have not received or will not receive trastuzumab prior to recurrence will not be required to continue to undergo serial MUGA scans (see Section 6.1.1).

3.0 STUDY AIMS

04/06/10 *Note: Additional aims related to long-term cardiac follow-up were added to the study with Amendment #11. See Appendix G for further details.*

06/03/05 *Note: In April 2005, a pooled interim analysis of data from NSABP B-31 and NCCTG N9831 showed that the primary aim of prolonging disease-free survival by adding Herceptin to the chemotherapy regimen was achieved. See Section 2.13 for details. On April 29, 2005, the B-31 study was closed to accrual.*

3.1 Primary aims

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The primary aim of stage 1 of this trial is to compare the cardiotoxicity of four cycles of Adriamycin and cyclophosphamide (AC) followed by four cycles of Taxol, with that of the same chemotherapy regimen plus Herceptin, in patients with operable, histologically node-positive breast cancer which overexpresses the HER2 protein.

The primary aim of stage 2 of this trial is to determine whether four cycles of AC followed by four cycles of Taxol at 3 week intervals (or weekly for 12 doses) and weekly Herceptin for 1 year, with or without hormonal therapy for a minimum of 5 years, is more effective in prolonging DFS than four cycles of AC followed by four cycles of Taxol at 3 week intervals (or weekly for 12 doses), with or without hormonal therapy for a minimum of 5 years, in patients with operable, histologically node-positive breast cancer which overexpresses the HER2 protein.

3.2 Secondary aims

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A secondary aim of the trial is to determine whether four cycles of AC followed by four cycles of Taxol at 3 week intervals (or weekly for 12 doses) and weekly Herceptin for 1 year, with or without hormonal therapy for a minimum of 5 years, is more effective in prolonging S than four cycles of AC followed by four cycles of Taxol at 3 week intervals (or weekly for 12 doses), with or without hormonal therapy for a minimum of 5 years, in patients with operable, histologically node-positive breast cancer which overexpresses the HER2 protein.

Biological studies will be completed to address each of the following additional secondary aims:

- to determine whether expression of the phosphorylated receptor in the index tumor is prognostic for DFS and S in a population of patients with HER2-positive breast cancer;
- to determine whether expression of the phosphorylated receptor in the index tumor is predictive of response to treatment with Herceptin, as indicated by the presence of a treatment-by-expression interaction with respect to DFS and S;
- to determine whether the frequency of expression of the phosphorylated receptor in postrelapse tissues differs from the frequency of expression in index tumors, both in patients treated with Herceptin and in those patients not receiving Herceptin;
- to determine, in a population of patients with HER2-positive breast cancer, whether higher levels of shed ECD or autoantibodies to HER2 measured in the serum prior to treatment are prognostic for DFS and S;

- to determine whether higher levels of shed ECD or autoantibodies to HER2 are predictive of response to treatment with Herceptin, as indicated by the presence of treatment-by-covariate interactions with respect to DFS and S;
- to determine, both in patients treated with Herceptin and in those patients not receiving Herceptin, whether levels of shed ECD or autoantibodies to HER2 are increased at the time of treatment failure relative to their pretreatment levels;
- to determine whether the frequency of HER2 overexpression in postrelapse tissues of patients treated with Herceptin differs from the frequency in patients not treated with Herceptin; and
- to determine, in this population of patients with HER2-positive breast cancer, the concordance of HER2 overexpression as measured by the following list of available assays: TAB250 (mAb-1), TAB250/pAb-1 cocktail, CB-11, HercepTest™ (DAKO), HER-2 FISH assay, array-based CGH; and to estimate the degree to which overexpression as measured by each of these assays is correlated with response to treatment with Herceptin.

4.0 ENDPOINTS

04/06/10 *Note: Additional endpoints related to long-term cardiac follow-up were added to the study with Amendment #11. See Appendix G for further details.*

06/03/05 *Note: In April 2005, a pooled interim analysis of data from NSABP B-31 and NCCTG N9831 showed that the primary aim of prolonging disease-free survival by adding Herceptin to the chemotherapy regimen was achieved. See Section 2.13 for details. On April 29, 2005, the B-31 study was closed to accrual.*

4.1 Endpoints for evaluation of cardiac safety

The primary endpoints that will be used for statistical analysis in comparing the cardiac effects of the two treatment arms will be *cardiac death* and *cardiac events* as defined in Section 19.2.

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4.2 Endpoints for evaluation of efficacy

4.2.1 ***Primary endpoint***

The primary endpoint that will be used for statistical analysis of efficacy will be *disease-free survival.*

The following events are to be used in the analysis of disease-free survival:

- *Breast cancer recurrence*

  See Section 19.1 for definitions of local, regional, and distant recurrence.

- *Second primary cancer*

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  Any second primary cancer other than melanoma in situ, squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix, will be considered an event in the analysis of disease-free survival. Lobular carcinoma in situ of the breast (LCIS) is also *not* considered an event.

- *Death from any cause as first event*

  Defined as death from any cause in patients without a prior event (breast cancer recurrence or second primary cancer).

4.2.2 ***Secondary endpoint***

The secondary endpoint that will be used for statistical analysis of efficacy will be *survival*. The event to be used for survival analysis is death from any cause.

5.0 PATIENT ELIGIBILITY AND INELIGIBILITY

06/03/05 *Note: The B-31 study was closed to accrual on April 29, 2005. See Section 2.13 for details.*

5.1 Conditions for patient eligibility

Female patients who satisfy all of the following conditions are the only patients who will be eligible for this study:

5.1.1 The patient must consent to be in the study and must have signed an approved consent form conforming with federal and institutional guidelines.

5.1.2 The patient must have a life expectancy of at least 10 years, excluding her diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)

04/23/01

5.1.3 The interval between the last surgery for breast cancer treatment (lumpectomy, mastectomy, axillary dissection, or re-excision of lumpectomy margins) and randomization must be less than or equal to 84 days.

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5.1.4 All of the following staging criteria must be met:

- Primary tumor must be T_{1-3} by *clinical* and *pathologic* evaluation.
- Ipsilateral nodes must be cN_{0-1} by *clinical* evaluation.
- Ipsilateral nodes must be pN_1, pN_{2a}, or pN_{3a} by *pathologic* evaluation.
- M_0

See Appendix B1 for TNM nomenclature and description according to the AJCC Cancer Staging Manual, Sixth Edition.

5.1.5 Patients must have undergone either a total mastectomy and an axillary dissection or a lumpectomy and an axillary dissection. (See Section 5.2 regarding special eligibility criteria for lumpectomy patients.) Sentinel node biopsy is permitted, but must be followed by an axillary dissection.

5.1.6 The tumor must be invasive adenocarcinoma on histologic examination.

04/23/01

5.1.7 The tumor must be determined to be HER2-positive prior to randomization. Assays performed using fluorescent in situ hybridization (FISH) require gene amplification to be eligible. Assays using immunohistochemistry (IHC) must be performed at an NSABP-approved reference laboratory and require a strongly positive staining score (See Section 9.0).

05/16/03

5.1.8 Patients must have an analysis of both estrogen and progesterone receptors performed on the primary tumor prior to randomization (see Section 10.0). "Marginal," "borderline," etc., results (i.e., those not definitely negative) will also be considered positive regardless of the methodology used.

5.1.9 At the time of randomization, the patient must have had the following: history and physical exam, EKG, and PA and lateral chest x-ray within the past 3 months; and a bilateral mammogram (or unilateral if patient has had a mastectomy) and a pelvic exam (for women who have a uterus and who will be taking tamoxifen) within the past year.

04/23/01
01/14/03
05/16/03

05/16/03
02/28/05

5.1.10 Within 3 months prior to entry, the patient must have a baseline LVEF measured by MUGA scan equal to or greater than the lower limit of normal for the radiology facility. (If LVEF is > 75%, the investigator should consider having the LVEF determination reviewed prior to randomization. Following randomization, the LVEF determination may be *reviewed* up until the time of the post-AC MUGA. Please note that if a more accurate value is obtained from the review of the baseline MUGA, the corrected value must be submitted to the NSABP Biostatistical Center before the post-AC MUGA is performed.)

01/14/03
05/16/03

5.1.11 At the time of randomization:

- The postoperative absolute neutrophil count (ANC) must be $\geq 1500/mm^3$ (or $<1500/mm^3$ if, in the opinion of the investigator, this represents an ethnic or racial variation of normal).
- Postoperative platelet count must be $\geq 100,000/mm^3$. Significant underlying hematologic disorders must be excluded when the platelet count is above the upper limit of normal for the lab.
- There must be postoperative evidence of adequate hepatic function, i.e.,
  - total bilirubin must be ≤ ULN for the lab unless the patient has a chronic grade 1 bilirubin elevation (>ULN to ≤1.5 x ULN) due to Gilbert's disease or similar syndrome; and
  - alkaline phosphatase must be <2.5 times the ULN for the lab; and the SGOT [AST] must be <1.5 times the ULN for the lab.
- There must be postoperative evidence of adequate renal function (serum creatinine within or less than the institution's normal range).

05/16/03

5.1.12 Patients must have no clinical or radiologic evidence of metastatic disease. Suspicious findings must be confirmed as benign by radiologic evaluation or biopsy. A patient with skeletal pain is eligible for inclusion in the study if bone scan and/or roentgenological examination fails to disclose metastatic disease.

05/16/03

5.1.13 Patients with a history of *non-breast* malignancies are eligible if they have been disease-free for 5 or more years prior to randomization and are deemed by their physician to be at low risk for recurrence. Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: carcinoma in situ of the cervix, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.

05/16/03

5.1.14 Prior to randomization, the investigator must designate whether the patients who had a lumpectomy will receive local or locoregional radiation therapy. For patients who had a mastectomy, the investigator must designate whether or not the patient will receive radiation therapy. (Pre-randomization discussion and/or consultation with a radiation oncologist is encouraged.) Note: *Irradiation of any internal mammary nodes is prohibited in this trial.*

5.2 Special conditions for eligibility of lumpectomy patients: irradiation and surgery

Patients treated by lumpectomy and axillary node dissection to be followed by breast radiation therapy must meet all the eligibility criteria in Section 5.1 in addition to the following:

5.2.1 Generally, lumpectomy should be reserved for tumors <5 cm. However, at the investigator's discretion, patients treated with lumpectomy for tumors ≥ 5 cm are eligible.

05/16/03

5.2.2 The margins of the resected specimen must be histologically free of invasive tumor and DCIS as determined by the local pathologist. In patients in whom pathologic examination demonstrates tumor present at the line of resection, additional operative procedures may be performed to obtain clear margins. This is permissible even if axillary dissection has been performed. Patients in whom tumor is still present at the resected margin after re-excision(s) must undergo total mastectomy to be eligible.

05/16/03

5.2.3 Whole breast irradiation is required. Irradiation of regional lymph nodes is optional, *but partial breast irradiation and irradiation of any internal mammary nodes are prohibited in this trial*. Intent to irradiate the axilla or other regional node groups must be declared by the investigator prior to randomization for stratification purposes. Please see guidelines for radiotherapy in Appendix A.

5.3 Special conditions for eligibility of mastectomy patients: irradiation

The decision to use locoregional irradiation in patients who have undergone total mastectomy and axillary node dissection must be declared by the investigator prior to randomization for stratification purposes. Failure to adhere to the radiation therapy plan will be a protocol violation. Please see guidelines for radiotherapy in Appendix A, and also note that *irradiation of any internal mammary nodes is prohibited in this trial*.

5.4 Conditions for patient ineligibility

Male patients are not eligible for this study.

Patients with one or more of the following conditions or prior therapies are also ineligible for this study:

5.4.1 Bilateral malignancy or a mass or mammographic abnormality in the opposite breast suspicious for malignancy unless there is biopsy proof that the mass is not malignant.

05/16/03

5.4.2 Primary tumor staged as T_4 for any reason. (See Appendix B1 for TNM nomenclature and description.)

05/16/03

5.4.3 Nodes staged as *clinical* N_2 or N_3 for any reason and nodes staged as *pathologic* pN_{2b}, pN_{3b}, or pN_{3c}. (See Appendix B1 for TNM nomenclature and description.)

05/16/03

5.4.4 Prior history of breast cancer, including DCIS (patients with a history of LCIS are eligible).

05/16/03

5.4.5 Treatment including radiation therapy, chemotherapy, biotherapy, and/or hormonal therapy administered for the currently diagnosed breast cancer prior to randomization. The only exception is hormonal therapy, which may have been given for up to a total of 28 days anytime after diagnosis and before

randomization. In such a case, hormonal therapy must stop at or before randomization and be re-started if indicated following chemotherapy.

5.4.6 Prior anthracycline or taxane therapy for any malignancy.

5.4.7 Any sex hormonal therapy, e.g., birth control pills, ovarian hormonal replacement therapy, etc. (These patients are eligible only if this therapy is discontinued prior to randomization.)

5.4.8 Therapy with any hormonal agents such as raloxifene (Evista®), tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. (Patients are eligible only if these medications are discontinued prior to randomization. These medications are not permitted while on the study except for the use of tamoxifen as described in Sections 11.2 and 12.4.)

5.4.9 Nonmalignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude a patient from being subjected to any of the treatment options or would prevent prolonged follow-up.

5.4.10 Cardiac disease that would preclude the use of Adriamycin, Taxol or Herceptin. This includes:

04/23/01

Active cardiac disease:

- angina pectoris that requires the use of antianginal medication;
- cardiac arrhythmia requiring medication;
- severe conduction abnormality;
- clinically significant valvular disease;
- cardiomegaly on chest x-ray;
- ventricular hypertrophy on EKG; or
- patients with poorly controlled hypertension, i.e., diastolic greater than 100 mm/Hg. (Patients with hypertension who are well controlled on medication are eligible for entry.)

History of cardiac disease:

- myocardial infarction documented as a clinical diagnosis or by EKG or any other tests;
- documented congestive heart failure; or
- documented cardiomyopathy.

5.4.11 Psychiatric or addictive disorders that would preclude obtaining informed consent.

5.4.12 Pregnancy or lactation at the time of proposed randomization. This protocol excludes pregnant or lactating women based on the fetal toxicity of both tamoxifen and Taxol which are listed as Pregnancy Category D agents. Pregnant women who received tamoxifen have experienced fetal deaths, birth defects, spontaneous abortions, and vaginal bleeding. Women of reproductive potential must agree to use an effective barrier method of contraception. Hormonal birth control methods are not permitted.

5.4.13 Sensory/motor neuropathy ≥ grade 2, as defined by the NCI's Common Toxicity Criteria version 2.0.

5.4.14 Contraindications to corticosteroid use which, in the opinion of the investigator, would preclude participation in this study.

5.4.15 Concurrent treatment with other investigational agents.

5.4.16 Sensitivity to benzyl alcohol.

5.5 **Special conditions for ineligibility of lumpectomy patients: irradiation and surgery**

For patients treated by lumpectomy with axillary dissection, breast irradiation is required. Please see guidelines for radiation therapy in Appendix A.

In addition, the following patients will also be ineligible:

5.5.1 Patients with diffuse tumors (as demonstrated on mammography) that would not be considered surgically amenable to lumpectomy.

5.5.2 Patients treated with lumpectomy in whom there is another clinically dominant mass or mammographically suspicious abnormality within the ipsilateral breast remnant. Such a mass must be biopsied and demonstrated to be histologically benign prior to randomization or, if malignant, must be surgically removed with clear margins.

5.5.3 Patients in whom the margins of the resected specimen are involved with invasive tumor or ductal carcinoma in situ (DCIS). Additional surgical resections to obtain free margins are allowed. Patients in whom tumor is still present after the additional resection(s) must undergo mastectomy to be eligible.

6.0 CARDIAC SAFETY MONITORING

04/06/10 *Note: See Appendix G for additional cardiac monitoring for patients participating in the long-term cardiac follow-up initiated with Amendment #11.*

05/22/00 04/23/01 05/16/03 06/03/05 07/18/05

6.1 Cardiac safety related to chemotherapy and Herceptin

In an effort to ensure the cardiac safety of patients, there were five MUGA scans planned in stage 1 of the protocol. *At the time of Amendment #9, the MUGA scan schedule was revised to be based on the timing of initiation of investigational Herceptin.*

6.1.1 *MUGA schedules for patients who have received or will receive investigational Herceptin*

Depending on the timing of initiation of investigational Herceptin, patients must have MUGA scans according to one of the following two schedules. **However, MUGA scans are required only for patients who have received at least one dose of investigational Herceptin or who will be evaluated for initiation of investigational Herceptin.**

- Schedule A - MUGA scans at baseline (prior to study entry), 3 to 4 weeks after the last AC dose, ***and at 6, 9, and 18 months after randomization are required for:***
  - Group 1 and Group 2 patients who began investigational Herceptin on Day 1 of Taxol or at any point during Taxol; ***and***
  - Group 2 patients who began investigational Herceptin on Day 1 of Taxol, or at any point during Taxol, but discontinued Herceptin (for any reason); Schedule A should be followed regardless of whether Herceptin is or is not re-initiated.
- Schedule B - MUGA scans at baseline (prior to study entry), 3 to 4 weeks after the last AC dose, following Taxol but prior to initiation of investigational Herceptin, ***and at 3, 6, and 15 months from the first dose of investigational Herceptin for:***
  - Group 1 and Group 2 patients who began Herceptin at any time after completing Taxol. Refer to Section 12.3 (Table 3B) for LVEF requirements for initiation of Herceptin sequentially following Taxol.

6.1.2 *MUGA schedule for patients who never received and will not receive investigational Herceptin*

Routine MUGA scans are no longer required in asymptomatic patients.

6.1.3 *MUGA schedule for patients who never initiated Taxol*

Patients who never initiated Taxol may receive investigational Herceptin if initiation requirements are met. If the last dose of AC is within 3 months of the planned start date of Herceptin, ***follow LVEF initiation requirements on Table 3A and MUGA Schedule A***. ***(Initiation of Taxol is not required.)*** If the last

dose of AC is > 3 months from the planned start date of Herceptin, ***LVEF must be assessed within 3 months before Herceptin initiation and must be ≥ LLN. These patients will follow MUGA Schedule B.***

6.1.4 ***MUGA schedule for patients who receive commercial Herceptin***

If treatment is initiated with *commercial* Herceptin, subsequent evaluation of LVEF is at the investigator's discretion.

6.1.5 ***Important MUGA guidelines:***

- Investigators are strongly urged to schedule MUGA scans at the same radiology facility where the patient's baseline MUGA scan was done whenever possible.
- Appendix F contains recommended nuclear medicine guidelines for resting MUGA scan evaluations.
- **Rapid submission of MUGA scan form (Form M) with MUGA scan report attached is required**. Please fax all MUGA scan forms and reports as soon as possible within 14 days after the MUGA scan. Form M must be submitted for every MUGA scan done for any reason during the first 2 years on study. After 2 years, Form M must be submitted if a MUGA scan is done because the patient experiences symptoms of congestive heart failure. *Note: For patients having MUGA scans according to Schedule B (see Section 6.1.1), the 15-month MUGA is required even if this time point is more than 2 years after study entry.*
- MUGA scans and submission of Form M with the MUGA scan report are still required at the scheduled time points after the patient has had any of the following:
  - discontinuation of protocol therapy
  - congestive heart failure
  - breast cancer recurrence
  - second primary cancer

02/28/05
06/03/05

- When symptoms suggesting congestive heart failure or a definitive or probable cardiac death (see Section 19.2 for definition of probable cardiac death) occur, the Cardiac Report Form (Form CR) must be faxed to the NSABP Biostatistical Center (see Information Resources on page vi) within 14 days of learning of the symptoms or the death. Also fax Form M and MUGA scan report if applicable. (See Section 20.0 for additional adverse event reporting requirements.) ***Note: Submission of Form CR remains a study requirement for all B-31 patients, including patients who have received Herceptin (investigational or commercial supply) and patients who have not received any Herceptin.***

Stage 1 of the protocol will monitor cardiac safety closely. If it is determined that cardiotoxicity in the study arm is within acceptable limits, the number of required MUGA scans in both arms may be decreased. In October of 2002, the

independent Data Monitoring Committee determined that the incidence of cardiac toxicity in the study arm remained within the boundaries set by the protocol, and accrual to the study was permitted to continue without interruption.

Follow-up information in the form of a cardiac history questionnaire (Form CH) will be collected on all patients at baseline, every 6 months for 5 years, and then annually thereafter. The goal of this questionnaire is to keep track of medical conditions and cardiac procedures that may confound the analysis of the acute and long term cardiac effects of Herceptin.

06/03/05 6.2 **Cardiac safety related to radiation therapy**

This trial allows post-lumpectomy regional irradiation and post-mastectomy locoregional irradiation but prohibits the irradiation of internal mammary nodes because of the concern for possible additional cardiotoxicity from the combination of Herceptin and radiation therapy for Group 2 patients. To ensure that the radiation therapy delivered is in compliance with the radiation guidelines outlined in Appendix A and to ensure that the volume of the heart irradiated is minimal, a review of the treatment sheets, isodose breast contour, dosimetry, portal films *(as of Amendment #9, films are no longer required)*, and treatment position photographs *(as of Amendment #9, position photographs are no longer required)* of the first 500 patients with ***left-sided lesions*** who receive radiation therapy will be done centrally by the NSABP.

Investigators are requested to discuss cardiac toxicity concerns with their radiation oncologist to ensure careful planning of the ports for ***left-sided lesions***. Each radiation site is requested to submit the needed radiation materials within 4 weeks after completion of therapy to the NSABP Biostatistical Center. Central review of the radiation materials will be done promptly. If the radiation site is not in compliance with the guidelines, the radiation oncologist at the NSABP Operations Center or the Radiation Physics Center (whichever is pertinent) will contact the radiation site to discuss ways to improve the delivery of therapy.

The results of the radiation review will be correlated with the patient's clinical cardiac status and the results of her MUGA scans. Depending on this outcome, the review may be stopped or continued to include all the patients with left-sided lesions.

6.2.1 Materials listed below must be submitted to the NSABP Biostatistical Center ***within 4 weeks*** after completion of therapy for patients with ***right-sided lesion(s):***

- Form E1
- treatment sheets
- isodose breast contour
- dosimetry

06/03/05 6.2.2 Materials listed below must be submitted to the NSABP Biostatistical Center within 4 weeks after completion of therapy for patients with left-sided lesion(s):

- Form E1
- treatment sheets
- isodose breast contour
- dosimetry
- portal films (one set only) – *(not required following Amendment #9)*
- treatment position photographs – *(not required following Amendment #9)*

7.0 REQUIRED ENTRY AND FOLLOW-UP STUDIES (TABLE 2)

04/06/10 *Note: See Appendix G for additional requirements for patients participating in the long-term cardiac follow-up initiated with Amendment #11.*

06/03/05 *Note: The B-31 study was closed to accrual on April 29, 2005. See Section 2.13 for details.*

Table 2 lists: 1) all studies required to accurately stage trial patients prior to study entry, 2) all studies required during treatment, and 3) all studies required as part of long-term follow-up.

TABLE 2. Studies required *04/23/01, 01/14/03, 05/16/03, 02/28/05, 06/03/05*

Required studies[a]		Year 1 Through Year 5					Year 6+
	Prior to randomization	On day 1 prior to each chemotherapy dose	Every 12 weeks during Herceptin (following completion of Taxol)	All patients who plan to receive Herceptin: 3-4 weeks after last dose of AC; All patients who receive investigational Herceptin: schedule for additional MUGAs will depend on timing of Herceptin initiation. *See Section 6.0.*	Every 6 months[b]	Every 12 months[b]	Every 12 months[b]
Examinations							
History & Physical exam	X[c]	X[d]	X		X		X
Cardiac history	X				X		X
Pelvic exam[e]	X[f]					X[g]	X[g]
Hematologic studies							
CBC	X[h]	X	X		X		
Differential	X[h]	X	X		X		
Platelet count	X[h]	X	X		X		
Chemistries							
Serum Creatinine	X[h]	X[d]	X		X		
Bilirubin	X[h]	X[d]	X		X		
AST (SGOT)	X[h]	X[d]	X		X		
Alkaline Phosphatase	X[h]	X[d]	X		X		
X-rays, scans and other studies							
Chest (PA & Lat.)	X[c]				X[i,j]	X[i,j]	X[i,j]
Bone imaging[k]	X[i]					X[i]	X[i]
Bilateral Mammogram[l]	X[f]					X	X
MUGA[m]	X[c,n]			X[o]			
EKG	X[c]						
Serum collection[p]							
Tumor block collection[q]							

a History and physical examination, hematologic studies, chemistries, and appropriate diagnostic testing may be performed at more frequent intervals at the discretion of the investigator.

b From date of randomization.

c Within 3 months prior to randomization.

d For patients receiving weekly Taxol x 12 doses, the history & physical exam and chemistries should be performed before Taxol treatment weeks 1, 4, 7, and 10 are given. (Hematologic studies will be performed weekly.)

e Required only for women who have a uterus and who will be taking tamoxifen.

f Within 1 year prior to randomization.

g The first exam should be 12 months following the most recent exam prior to randomization and then every 12 months.

h Postoperative testing.

i Required only if symptoms are present.

j At any time a clinical diagnosis of CHF is confirmed.

k Bone scan and/or roentgenological exam may be performed.

l Unilateral for patients with mastectomy.

m MUGA scan is required. If possible, each patient should have all her MUGA scans performed at the same facility.

n If LVEF is > 75%, the investigator should consider having the LVEF reviewed prior to randomization. Following randomization, the LVEF may be *reviewed* up until the time of the post-AC MUGA. (Please note that if a more accurate value is obtained from review of the baseline MUGA, the corrected value must be submitted to the NSABP Biostatistical Center before the post-AC MUGA is performed.)

o Except for the MUGA scan at 3 to 4 weeks after the last AC dose, a repeat MUGA scan may be required after 4 weeks. See Table 13 for details. If a MUGA scan is done for any reason within the 30-day period before the date of any required MUGA, an additional MUGA does NOT need to be done at that time point. MUGA scans are still required at the scheduled time points after discontinuation of protocol therapy or protocol events, as outlined in Section 6.1.

p Required after randomization but before therapy. Also required at time of first recurrence/treatment failure.

q Tissue blocks of the index tumor and of the involved lymph node are both required and must be submitted within 30 days from randomization. Also required at time of first recurrence/treatment failure, if possible.

8.0 REQUIRED PATHOLOGY STUDIES (biomarker studies)

04/23/01
05/16/03

NSABP policy for B-31 mandates the collection and submission of tumor blocks and serum samples by NSABP institutions. However, individual patients may always refuse the collection, storage, and use of their tissues and serum by answering "No" to the appropriate questions in their B-31 consent form. These patients may still participate in the trial; however, tumor blocks and serum samples should **not** be submitted for patients who have answered "No" to the first three of the four questions (Questions #1, 2, and 3 as presented in the NSABP Sample Consent Form [Appendix H]). If the patient answered "Yes" to any of the three questions (Question #1, 2, or 3), a sample should be submitted. Non-submission of tumor blocks and/or serum samples will be a protocol violation unless a patient has not consented to the collection, use, and storage of her tissues.

NOTE: The tumor and blood specimens that will be collected in this study will be used for future studies as described in Section 8.0, as well as for other unspecified future research. The specimens procured will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used. Analysis of a patient's tumor pathology will not be reported to the patient or her physician and will not have any bearing on how she is treated and followed on the protocol.

Submitted slides and blocks are initially logged into the database at the NSABP Biostatistical Center. These samples are then stripped of patient identifiers except NSABP study numbers and forwarded to the NSABP Division of Pathology (refer to Information Resources, page vi), where they are assigned a code number for further processing and study. Serum samples are sent directly to the NSABP Serum Bank at the Baylor College of Medicine Breast Center and are stored with the NSABP study numbers and code numbers assigned by the Serum Bank.

8.1 Rationale for tissue block and serum collection

The following excerpt from the Report of the Breast Cancer Progress Review Group to the Advisory Committee to the Director of the NCI in September 1998, clearly states the rationale for the pathology studies planned for this protocol:

"How can we learn more about the biology of breast cancer for the purpose of predicting clinical course and predicting response to therapy?

As our therapies increase in sophistication, we will need improved methods of allocating patients to appropriate treatment. For example, adjuvant drug therapy improves disease free and overall survival of patients with early-stage breast cancer, but patients with an especially good prognosis may benefit so little from such treatment that it would be best that they not be so treated, especially if the treatments are toxic. Similarly, expensive or toxic chemoprevention should be applied only to women at high risk of developing the disease. Some drugs might work especially well in patients with tumors that have specific biochemical characteristics, and others—with a lesser chance of response—should be spared such therapy. Properly designed clinical trials should not only be able to demonstrate desirable therapeutic effects, but should facilitate an improved understanding of social vs biological determinants of clinical outcomes."[27]

Despite the encouraging results from the advanced-disease trials, it is clear that Herceptin does not cure all tumors that overexpress HER2 since, as a single agent, it showed a

response rate of only 15%. Even when combined with Adriamycin or Taxol, Herceptin results in a response rate of less than 60%. Although one cannot directly extrapolate these results to the adjuvant setting, it is reasonable to presume that only a subset of patients with HER2-overexpressing tumors will benefit from Herceptin, even when this agent is given together with chemotherapy. At the end of the B-31 trial, it will be important to gain insight into the potential markers, which are predictive for Herceptin efficacy.

While supportive data simply do not exist, there could be many potential reasons for the varying response rate of Herceptin:

- Since the predominant mechanism of cell killing with Herceptin may be through direct interaction with HER2 rather than indirect recruitment of immunologic mechanisms, Herceptin action may require the presence of the activated HER2 signaling mechanism. One study using an antibody directed against phosphorylated forms of the HER2 molecule demonstrated that less than 30% of the HER2 overexpressors have activated HER2.[28] Since HER2 essentially works as a co-receptor for other members of the Epidermal Growth Factor Receptor (EGFR) family of receptors (EGFR, HER3, and HER4), by functioning as a signal amplifier, the effect of Herceptin may be modulated by co-expression of any of them. In addition, an alternative splice (EGFRvIII) in the processing of the EGFR leading to an inframe 805 basepair (bp) deletion in the extracellular domain of the EGFR has been described. Preliminary data demonstrated that this variant has spontaneous tyrosine kinase activity. It has been shown by transfection that this variant can induce tumorigenicity in both 32D cells (which is unaffected by transfection with wild type EGFR) and in MCF-7 cells.[29] This variant is strongly augmented in its transforming activity when co-expressed with HER2 or HER4. Using antibodies which specifically recognize this variant in an immunostaining assay, it was demonstrated that in excess of 50% of breast cancers express the variant either alone or with co-expressed HER2. Alteration of other members of the EGFR family which heterodimerize with HER2,[30] or alteration of the components of the downstream signal transduction pathway such as GRB7,[31] could potentially influence the response to Herceptin.

- Assays for co-receptors and downstream signaling molecules will be performed using collected tissue blocks. However, due to the exponential development of new markers and technologies, it will be difficult to pinpoint specifically which markers will be examined when patient accrual ends. Potential methods that could be used at the end of this protocol are: 1) high throughput screening of chromosomal abnormalities using array-based Comparative Genomic Hybridization (CGH) methods,[32] 2) FISH for individual genes, 3) a Proteomics approach using protein chips based on multiple antibodies and chemicals,[33] and 4) immunohistochemistry for individual markers.

- Response to Herceptin may depend on the expression levels of HER2. Studies of Herceptin in advanced disease have been restricted to cases with high levels of overexpression determined by immunohistochemistry [2+ or 3+ as determined by immunohistochemistry using 4D5 and CB-11 antibodies (the Clinical Trial Assay (CTA) by Genentech)]. The response rate was higher in the 3+ than in the 2+ cases, suggesting that response to Herceptin may be governed by levels of HER2-expression. However, the assays were performed on formalin-fixed, paraffin-

embedded tumor sections, and it is questionable whether scoring based on paraffin sections represents a true quantitation of HER2 expression levels. In fact, when the DAKO HercepTest™ was compared to the CTA of the specimens that tested 3+ on the HercepTest™, 94% were observed to test at least 2+ on the CTA, including 82% which were observed to test 3+ on the CTA. Of specimens testing 2+ on the HercepTest™, only 34% were observed to test at least 2+ on the CTA, including 14% which were observed to test 3+ on the CTA. This means that, when a case is scored as 2+ according to the HercepTest™, there is a 66% chance that this case would have been classified as 1+ according to the CTA. This lack of standardization in the assay system and the lack of agreement in the scoring system emphasize the eventual need for a retrospective analysis of the B-31 specimens so that a direct head-to-head comparison of multiple assay methods can be conducted and the best assay method and scoring system for predicting a response to Herceptin can be determined. ***Since fresh-cut sections will be required to compare multiple assay methods (due to the rapid loss of some of the epitopes during the storage of cut sections) tissue block collection is mandatory for all institutions participating in this trial***. Collection of unstained sections would not provide adequate materials for a comparison study. However, individual patients may always refuse the collection, storage, and use of their tissues (by answering "no" to the corresponding consent questions in their B-31 consent form) and still participate in the trial.

- In cases with heterogenous expression of HER2, HER2-negative tumor cells could be selected during the Herceptin treatment. There could be a minor subset of cases in which tumor cells in axillary nodal metastases do not overexpress HER2 compared to the index tumor from which the assay was performed. In such cases, Herceptin might not benefit such patients. This possibility underscores the need to collect tissue blocks from the nodal metastases in this trial. The ideal duration of Herceptin administration is not known. An examination of the HER2 expression profile in treatment failure, such as ipsilateral breast tumor recurrence, distant metastases, or contralateral breast cancer, during Herceptin treatment vs after Herceptin treatment will provide insight as to whether continued treatment of more than 1 year with Herceptin is warranted in an adjuvant setting. If recurrences during Herceptin treatment are largely HER2-negative, whereas, recurrences after finishing Herceptin treatment are largely HER2-positive, an argument can be made to consider continued treatment with Herceptin. Therefore, collection of tissue blocks from ipsilateral breast tumor recurrence, distant metastases, and contralateral breast cancer will provide important information.

- In some patients, high levels of shed ECD of HER2 could sequester or titrate out available Herceptin.[7] Measuring ECD in the serum at the time of randomization will provide insight as to whether ECD will act as a predictive marker for response to Herceptin. In addition, measuring ECD at the time of recurrence will provide insight as to whether ECD can be used as a surrogate for tissue HER2 levels at the time of recurrence.

- Patients with HER2 overexpressed tumors may demonstrate an autoimmune antibody response,[34] and their circulating autoantibodies may account for the tolerance to the antibody mediated cytotoxicity of Herceptin.

- Since Herceptin is a relatively big molecule, the bioavailability of Herceptin to tumor cells could be limited in a large tumor cell mass, which may not be a problem in the adjuvant setting since micrometastatic sites are targeted.

8.2 Tumor markers to be tested

The tissue blocks of the index tumor, index lymph node, and treatment failure site will undergo the following tests. Soon Paik, M.D., of the NSABP Division of Pathology will coordinate the conduction of the tests by the collaborating investigators shown below.

- Immunohistochemical assay to detect activated or phosphorylated HER2. (Michael DiGiovanna, M.D., David Stern, M.D., Ann Thor, M.D.)
- Immunostaining for molecules that are members of the EGFR family that can heterodimerize with HER2 and other downstream signal molecules like GRB7 and others. (Marc Lippman, M.D.)
- Array-based assays for chromosomal or gene copy abnormalities which will include the HER2 gene. Co-amplification or deletion of other genes could influence the biological behavior of tumor cells with HER2 overexpression. Array-based CGH will permit accurate quantitative examination of multiple abnormalities. (Craig Allred, M.D., Joe Gray, Ph.D., Soon Paik, M.D.)
- Any additional potentially predictive markers of response to Herceptin which may be discovered in the future.

8.3 Central assay for HER2 overexpression

The NSABP Division of Pathology will conduct a retrospective comparison study to determine the best assay methods for HER2 to predict a response to Herceptin. *The results of the central assay will not be given to the protocol investigators or patients, nor will the results have any bearing on how patients are treated and followed in the protocol*. The following assays will be compared, but this listing could change due to the rapid development of assay methodology and reagents: DAKO HercepTest™, TAB250 alone, TAB250/pAb-1 cocktail,[15] CB-11,[35] HER-2 FISH Assay,[36] and array-based CGH.[32] A total of 2700 cases will need to be screened with various methods, therefore, a high-density tissue microarray will be constructed using microsampling of collected tissue blocks without disruption of the diagnostic tissue.[37] Sections cut from the high-density tissue microarray will be used for the FISH assay, while individual sections will be used for immunohistochemistry. Staining results will be quantified based on both staining intensity and the percentage of positive cells, and the results will then be correlated with clinical outcome measures. The FISH results will be quantified as a continuous variable and correlated with clinical outcome measures as well as with immunostaining results. Assays will be performed by the following collaborating pathologists: Soon Paik, M.D., of the NSABP Division of Pathology; Craig Allred, M.D., of Baylor University; Ann Thor, M.D., of the Eastern Cooperative Oncology Group; and Lynn Dressler, M.S., and Lyndsay Harris, M.D., of the Cancer and Leukemia Group B (CALGB).

8.3.1 *Rationale for Continuing Quality Control of HER2 Assay*

04/23/01

Initially, this study allowed any IHC staining assays or FISH assays performed at the membership institutions or commercial laboratories to be accepted for eligibility determination. However, due to the lack of standardization and the

evolving technology of HER2 assays, there was a provision made that the first 100 tissue samples received would be assayed centrally. Initially, the central assays were to be HercepTest™ and the TAB250/pAb1 cocktail. However, due to new information published by Mass et al. (ASCO 2000, abstract 291), which showed that tumors determined to be HER2 positive by FISH had a better response to Herceptin than FISH negative tumors, the central assays were changed to HercepTest™ and FISH. There was also an initial provision that if more than 20 samples show negative testing with the central assay, the possibility of central HER2 testing for eligibility determination would be considered.

Results of this quality assessment on the first 104 samples received revealed that immunohistochemical staining performed by non-reference laboratories was not reliable; 19% to 35% would have been determined to be ineligible if assayed centrally using both the HercepTest™ and FISH. However, when the HercepTest™ was performed by a reference lab, there was a 96% concordance rate with the central assays. (See Section 9.0 for the definition of a reference lab. See Appendix C1 for details of the quality control results.)

04/23/01

8.3.2 ***Quality Control of HER2 Assays***

The tumor must be determined to be HER2 positive prior to randomization. Assays performed using FISH require gene amplification to be eligible. Assays using immunohistochemistry (IHC) must be performed by an NSABP-approved reference laboratory. (See Section 9.0) Assessment of the reproducibility of HER2 assays on tumor samples will continue to be monitored on the trial.

8.4 Tissue block submission

At least one tissue block representative of the index tumor and at least one tissue block of the involved lymph node is required and must be submitted after randomization. ***Non-submission of these two blocks will be a protocol violation unless a patient has not consented to the collection, use, and storage of her tissues.***

05/16/03

In other NSABP trials, unstained sections have been accepted as an alternative to paraffin-embedded blocks. However, because epitopes of HER2 protein that are recognized by immunostaining antibodies deteriorate rapidly after sectioning, ***tissue blocks instead of unstained sections must be collected in this study.*** (NOTE: A 2 mm core from both the tumor block and the node block, plus 30 unstained sections, may be submitted as an alternative to block submission.)

In addition to making over 30 serial sections from the tissue block, a few areas 0.6 mm in diameter will be sampled with a precision core needle to construct a high-density tissue array to facilitate the FISH assay for HER2 and its markers.

Ideally, one staff pathologist at each participating institution should supervise all pathology examinations. The tissue blocks and the institution's pathology report will be forwarded to the NSABP Biostatistical Center at the address indicated under Information Resources on page vi. Bubble wrap may melt into the blocks and destroy them; therefore, ***PLEASE DO NOT USE BUBBLE WRAP TO PAD YOUR SPECIMEN SHIPMENTS — USE PAPER INSTEAD***. Blocks will be stored at the NSABP

Division of Pathology and, if a clinical emergency arises, will be returned upon an institution's request.

8.5 Serum collection and submission

Baseline serum will be collected at the beginning of the study: 1) to measure the extracellular domain (ECD) level or the shed antigen and to examine whether high levels of ECD influence the response to Herceptin, and 2) to measure autoantibody level and to correlate it with outcome. Serum will be submitted to the NSABP Serum Bank at the address indicated under Information Resources (page vi), following the directions outlined in Appendix D.

8.6 Follow-up block and serum collection

05/22/00

Submission of tissue blocks is required at the time of first treatment failure (i.e., ipsilateral breast tumor recurrence, contralateral breast cancer, or a distant metastasis) if a biopsy is performed. This tissue block should be submitted to the NSABP Biostatistical Center.

Serum must be collected at the time of first treatment failure and submitted to the NSABP Serum Bank at the address indicated under Information Resources (page vi), following the directions outlined in Appendix D.

9.0 HER2 POSITIVITY AND ELIGIBILITY

04/23/01
01/14/03
05/16/03
02/28/05

In NSABP Protocol B-31, HER2 positivity as determined by protein overexpression using immunohistochemistry or by gene amplification using FISH will be accepted. The primary tumor should be used to determine HER2 positivity. However, patients whose HER2 status was determined using only tumor from a lymph node are eligible. DCIS components should not be counted in the determination of degree of staining.

- Assays using FISH must indicate the presence of gene amplification.

- Assays using immunohistochemistry (IHC) **must be performed by an NSABP-approved reference laboratory**. Results must indicate a score of 3+.

  A reference lab is defined as a laboratory that processed an average of 100 DAKO HercepTests™ per month during the last 6 months using FDA-approved methods. If a laboratory uses IHC antibodies other than the DAKO HercepTest™ **or** uses DAKO HercepTest™, but not FDA-approved methods, the director of the lab must contact the Director of the NSABP Division of Pathology. The Director of the NSABP Division of Pathology will determine if the lab qualifies as an NSABP-approved reference lab based on both information regarding specificity and sensitivity of the assays when compared to FISH and the number of assays performed per month. Please refer to the NSABP Web site for the B-31 reference lab list. For instructions on how to add a lab to the reference lab list, please contact the Clinical Coordinating Division (see page vi).

In cases where both IHC and FISH assays are done, either test would make the patient eligible as long as it fulfills eligibility criteria.

EXAMPLE 1: If DAKO HercepTest™ was 1+ or 2+ positive, but FISH assay shows gene amplification, then the patient is eligible.

EXAMPLE 2: If FISH assay shows no gene amplification but immunohistochemical assay by DAKO HercepTest™ was 3+, then the patient is eligible.

EXAMPLE 3: If FISH assay shows no gene amplification and immunohistochemical assay by DAKO HercepTest™ was 1+ or 2+ positive, then the patient is ineligible.

NSABP Form H2A must be completed and submitted to the Biostatistical Center prior to randomization. In addition, tissue block submission will be required for all participants who answered "yes" to Question #1 as presented in the NSABP Sample Consent Form (Appendix H) for this trial to confirm HER2 status in a retrospective fashion. See Section 8.0.

10.0 ESTROGEN (ER) AND PROGESTERONE (PGR) RECEPTORS

05/16/03

An analysis of estrogen and progesterone receptors performed on the primary tumor prior to randomization must be conducted for each participant in the study. ("Marginal" or "borderline" results [i.e., those not definitively negative] will be considered positive regardless of the methodology used for the analysis.) (See eligibility criterion in Section 5.1.8.)

06/03/05 11.0 **TREATMENT REGIMEN FOR GROUP 1 (AC→TAXOL ± HORMONAL THERAPY)**

Note: Group 1 patients enrolled in B-31 on or after April 26, 2004, and who meet the Herceptin initiation requirements (see Section 12.3) may receive investigational Herceptin. ***For patients who choose to receive Herceptin, Section 12.2 must be followed.***

11.1 **Chemotherapy (Group 1)**

Chemotherapy should start as soon as possible after randomization but no sooner than 2 weeks from the last surgical procedure (excluding placement of vascular access devices). Patients in Group 1 will receive:

11.1.1 ***Adriamycin followed immediately by cyclophosphamide (AC)***

- *Adriamycin 60 mg/m^2* IV push q 21 days for 4 cycles.
- *Cyclophosphamide 600 mg/m^2* IV over 30 minutes q 21 days for 4 cycles.

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11.1.2 ***MUGA scan 3 to 4 weeks after last dose of AC***

Three to four weeks after the last dose of AC, a MUGA scan must be done and the results submitted as soon as possible, within 14 days after the scan, to the NSABP Biostatistical Center using Form PAC and Form M. (For patients who never received and will not receive investigational Herceptin, MUGAs are no longer required. See Section 6.0.)

11.1.3 ***Premedication regimen for Taxol***

05/16/03

- For the q 3 week Taxol schedule: *dexamethasone 20 mg po, 12 and 6 hours before each Taxol administration*.

OR

For the weekly Taxol schedule: *dexamethasone 20 mg po, 12 and 6 hours before the first dose of Taxol.* If no hypersensitivity reaction occurs, convert to *dexamethasone 10 mg IV, completed 30 minutes before each subsequent Taxol administration*. (Note: at the investigator's discretion, dexamethasone may be tapered during the 12 weeks of Taxol.)

- For both the q 3 week and weekly Taxol schedules: *diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg or ranitidine 50 mg or famotidine 20 mg), initiated 60 minutes before Taxol administration.*

04/23/01
05/16/03

11.1.4 ***Taxol (as soon as possible following the post-AC MUGA and resolution of any AC-related toxicity)***

Note: The investigator must select one of the dose/schedule regimens listed below at the time of randomization. The selected dose/schedule must be given for all Taxol treatments, with the exception that patients on the q 3 week schedule who experience Taxol-related thrombocytopenia, diarrhea, stomatitis, neurologic toxicity, or myalgia/arthralgia (see Sections 15.4.2, 15.8, 15.10 and

15.11) may receive subsequent doses according to the weekly Taxol dose/schedule.

- *Taxol 175 mg/m^2* IV over 3 hours q 3 weeks for 4 cycles.

OR

Taxol 80 mg/m^2 IV over 1 hour weekly for 12 doses. (Taxol administration should be completed in 12 weeks if possible. If delays for medical or non-medical reasons occur, every effort should be made to administer all 12 doses of Taxol within 15 weeks after initiation of Taxol. No dose of Taxol may be given beyond the 15th week from the start of Taxol therapy.)

11.2 Hormonal therapy (Group 1)

01/14/03
05/16/03
02/28/05
06/03/05

Patients with tumors that are ER-positive and/or PgR-positive will receive hormonal therapy. Hormonal therapy must be initiated no sooner than 3 weeks but no later than 12 weeks following the last dose of chemotherapy. Hormonal therapy should be administered for a minimum of 5 years. Total duration of tamoxifen should not exceed 5 years.

Choice of the drug(s) to be used for hormonal therapy is at the physician's discretion. The dose and schedule of hormonal therapeutic agents should be consistent with the drug package insert instructions. Aromatase inhibitors should **not** be used unless the investigator is certain a patient is permanently postmenopausal following chemotherapy. Patients under the age of 45 are likely to recover ovarian function after chemotherapy, and the use of an aromatase inhibitor is strongly discouraged in this population.

Women who have received tamoxifen for breast cancer prevention may be treated with additional tamoxifen at the discretion of the investigator.

11.3 Radiation therapy (Group 1)

05/16/03

All women treated with lumpectomy will receive whole breast irradiation. Postmastectomy loco-regional irradiation or postlumpectomy regional irradiation will be administered according to the treatment plan indicated by the investigator prior to randomization. Please note that *partial breast irradiation and irradiation of any internal mammary nodes are prohibited in this trial*. Radiation will begin within 8 weeks after completion of all assigned chemotherapy. (Refer to Section 6.2 and Appendix A.)

06/03/05 12.0 **TREATMENT REGIMEN FOR GROUP 2 (AC→TAXOL + HERCEPTIN ± HORMONAL THERAPY)**

12.1 **Chemotherapy (Group 2)**

Chemotherapy should start as soon as possible after randomization but no sooner than 2 weeks from the last surgical procedure (excluding placement of vascular access devices). Patients in Group 2 will receive:

12.1.1 ***Adriamycin followed immediately by cyclophosphamide (AC)***

- *Adriamycin 60 mg/m²* IV push q 21 days for 4 cycles.
- *Cyclophosphamide 600 mg/m²* IV over 30 minutes q 21 days for 4 cycles.

04/23/01 06/03/05 12.1.2 ***MUGA scan 3 to 4 weeks after last dose of AC***

Three to four weeks after the last dose of AC, a MUGA scan must be done and *the results reviewed* and submitted as soon as possible, within 14 days after the scan, to the NSABP Biostatistical Center using Form PAC and Form M. (For patients who never received and will not receive investigational Herceptin, MUGAs are no longer required. See Section 6.0.)

05/16/03 12.1.3 ***Premedication regimen for Taxol***

- For the q 3 week Taxol schedule: *dexamethasone 20 mg po, 12 and 6 hours before each Taxol administration.*

OR

For the weekly Taxol schedule: *dexamethasone 20 mg po, 12 and 6 hours before the first dose of Taxol.* If no hypersensitivity reaction occurs, convert to *dexamethasone 10 mg IV, completed 30 minutes before each subsequent Taxol administration*. (Note: at the investigator's discretion, dexamethasone may be tapered during the 12 weeks of Taxol.)

- For both the q 3 week and weekly Taxol schedules: *diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg or ranitidine 50 mg or famotidine 20 mg), initiated 60 minutes before Taxol administration.*

04/23/01 05/16/03 12.1.4 ***Taxol (as soon as possible following review of post-AC MUGA and resolution of any AC-related toxicity)***

Note: The investigator must select one of the dose/schedule regimens listed below at the time of randomization. The selected dose/schedule must be given for all Taxol treatments, with the exception that patients on the q 3 week schedule who experience Taxol-related thrombocytopenia, diarrhea, stomatitis, neurologic toxicity, or myalgia/arthralgia (see Sections 15.4.2, 15.8, 15.10 and 15.11) may receive subsequent doses according to the dose/schedule.

- *Taxol 175 mg/m^2* IV over 3 hours q 3 weeks for 4 cycles.

  OR

  Taxol 80 mg/m^2 IV over 1 hour weekly for 12 doses. (Taxol administration should be completed in 12 weeks if possible. If delays for medical or non-medical reasons occur, every effort should be made to administer all 12 doses of Taxol within 15 weeks after initiation of Taxol. No dose of Taxol may be given beyond the 15th week from the start of Taxol therapy.)

- Administer Taxol prior to Herceptin.

06/03/05

12.1.5 ***Post-Taxol MUGA***

For patients who did not initiate Herceptin concurrently with Taxol but want to receive Herceptin, a MUGA scan must be done following Taxol but prior to initiation of investigational Herceptin (see Table 16).

05/16/03
06/03/05
07/18/05

12.2 Herceptin

Note: These instructions should be followed for Group 1 and Group 2 patients enrolled in B-31 on or after April 26, 2004, who choose to receive investigational Herceptin, and who meet the Herceptin initiation requirements described in Section 12.3.

Patients *who meet cardiac safety criteria (see Section 12.3)* will also receive Herceptin ***weekly*** for 1 year (beginning with the first dose of Taxol and ending 52 weeks after the first dose). Herceptin will be administered by intravenous infusion. *(Use of a vascular access device is at the physician's discretion.)* On the weeks Taxol is given, Herceptin will be given after Taxol.

- *Herceptin 4 mg/kg* IV, loading dose over 90 minutes, will be given on Day 1 of the first Taxol cycle. *Note: If a delay in Herceptin of more than 3 weeks occurs for any reason, a loading dose of 4 mg/kg IV over 90 minutes should be given as the first dose when Herceptin is re-initiated.*
- *Herceptin 2 mg/kg* IV, maintenance dose over 30 minutes, will be given every week for 51 weeks starting on day 8. *(Note: B-31 investigational Herceptin must be administered weekly. Administering Herceptin at a dose of 6 mg/kg every 3 weeks is NOT permitted.*)

At the time of Amendment #9, alternative instructions were provided for initiation of Herceptin following completion of Taxol (see Table 3B).

See Section 21.4.5 for further instructions.

06/03/05

12.3 Cardiac safety criteria for initiation of Herceptin

Note: These criteria also apply to Group 1 patients enrolled in B-31 on or after April 26, 2004, who wish to receive investigational Herceptin.

06/03/05

12.3.1 ***Symptomatic patients***

If a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia, while receiving AC, initiation of investigational Herceptin during Taxol or following Taxol is prohibited.

06/03/05
07/18/05

12.3.2 ***Asymptomatic patients***

At the time of Amendment #9, the LVEF requirements for initiation of Herceptin were revised. Following are two tables relevant to the initiation of investigational Herceptin in asymptomatic patients. ***Table 3A summarizes requirements for initiation of Herceptin during Taxol therapy. Table 3B summarizes requirements for initiation of Herceptin following Taxol therapy. For patients who never initiated Taxol, see Section 6.1.3.***

If a patient does not have significant symptoms related to LV dysfunction, initiation of Herceptin concurrently with Taxol (beginning at any point during Taxol) will depend on the absolute change in LVEF between baseline and 3 weeks after the last AC cycle (see Table 3A).

- HERCEPTIN SHOULD BE INITIATED IN AN ASYMPTOMATIC PATIENT IF: the LVEF increased or stayed the same; or b) the LVEF decreased by ≤ 15 percentage points but is still at or above the lower limit of normal for the radiology facility.

  Example: if the baseline LVEF is 65% and the post-AC LVEF is 60%, and the radiology facility's lower limit of normal is 60%, the patient will receive Herceptin.

- HERCEPTIN IS PROHIBITED DURING TAXOL IN AN ASYMPTOMATIC PATIENT IF: a) the LVEF decreased ≤ 15 percentage points and is below the lower limit of normal for the radiology facility; or b) the LVEF decreased by 16 percentage points or more (regardless of the lower limit of normal for the radiology facility). (See Table 3B.)

  Example: if the baseline LVEF is 65% and the post-AC LVEF is 55% and the radiology facility's lower limit of normal is 60%, the patient will ***not*** receive Herceptin.

  Example: if the baseline LVEF is 65% and the post-AC LVEF is 49%, the patient will ***not*** receive Herceptin.

TABLE 3A. Summary of post-AC LVEF requirements for initiation of Herceptin during Taxol protocol therapy in ***asymptomatic*** patients *05/16/03, 06/03/05*

Absolute change in LVEF between baseline and 3 weeks after last AC cycle	**Decision regarding initiation of Herceptin treatment**
Increase or no change	Initiate Herceptin with Taxol*****
Decrease of ≤ 15 percentage points, but at or above the radiology facility's lower limit of normal	Initiate Herceptin with Taxol*****
Decrease of ≤ 15 percentage points and below the radiology facility's lower limit of normal	Initiation of Herceptin with Taxol is prohibited; see Table 3B for LVEF requirements for initiation of investigational Herceptin following Taxol in asymptomatic patients
Decrease of 16 or more percentage points, (regardless of the radiology facility's lower limit of normal)	Initiation of Herceptin with Taxol is prohibited; see Table 3B for LVEF requirements for initiation of investigational Herceptin following Taxol in asymptomatic patients
***** For patients who were ≥ 50 years of age at study entry and the post-AC LVEF was at or above the lower limit of normal but < 55%, investigators may choose to administer Herceptin concurrently with Taxol or sequentially following Taxol. For instructions regarding the sequential treatment plan, see Table 3B.	

06/03/05
07/18/05

TABLE 3B. Summary of LVEF requirements for initiation of investigational Herceptin sequentially following Taxol protocol therapy in ***asymptomatic patients***

Note 1: Patients randomized before April 26, 2004, are NOT eligible to receive investigational Herceptin on NSABP B-31.

Note 2: For patients who never initiated Taxol, see Section 6.1.3.

Patient Status	Herceptin Administration Decision
Group 1 and Group 2 patients who have recently (within 4 weeks) completed Taxol, and the post-AC MUGA **did not** meet the Herceptin initiation requirements (as per Table 3A). Also for patients who were ≥ 50 years of age at study entry and who had a post-AC LVEF < 55% and who will receive investigational Herceptin sequentially following Taxol.	Initiation of investigational Herceptin is not permitted until the MUGA performed after Taxol has been evaluated. - If MUGA performed after Taxol is ≥ LLN, the patient may initiate investigational Herceptin which will continue until 52 weeks after the first dose of Herceptin.**a** - If MUGA performed after Taxol is < LLN, investigational Herceptin may not be initiated.**b**
Group 1 patients randomized on or after 4/26/04, who completed Taxol more than 4 weeks ago and *had a post-Taxol MUGA* ≥ LLN ***within the last 3 months.***[a,b]	Investigational Herceptin can be initiated and continued until 52 weeks after the ***first*** dose of Herceptin.
Group 1 patients randomized on or after 4/26/04, who completed Taxol more than 4 weeks ago and *had a post-Taxol MUGA* < LLN ***within the last 3 months***.[a,b]	Initiation of investigational Herceptin is not permitted until MUGA evaluation has been repeated. If repeat MUGA result is ≥ LLN, investigational Herceptin may be initiated.[a,b]
Group 2 patients randomized on or after 4/26/04, who completed Taxol, ***did not initiate investigational Herceptin*** for reasons other than protocol-specified cardiac-related toxicity, and *had a MUGA* ≥ LLN ***within the last 3 months***.[a,b,c]	Investigational Herceptin can be initiated and continued until 52 weeks after the first dose of Herceptin.
Group 2 patients randomized on or after 4/26/04, who completed Taxol, but ***permanently discontinued investigational Herceptin*** for reasons other than protocol-specified cardiac-related toxicity, and had a MUGA that was ≥ LLN ***within the last 3 months***.[a,b,c]	Investigational Herceptin can be re-initiated and continued until 52 weeks after the ***first*** dose of Herceptin *(not the date of re-initiation of Herceptin)*. If > 3 weeks have passed since last Herceptin dose, a loading dose of 4 mg/kg should be given initially.

a Patient must be asymptomatic; the decrease in LVEF from baseline does not have to be considered for initation of Herceptin following the completion of chemotherapy. All that is required is that the LVEF obtained following the completion of chemotherapy be ≥ LLN.

b If the most recent MUGA was < LLN, investigator may choose to re-evaluate LVEF with a repeat MUGA obtained at least 4 weeks from the previous scan. If LVEF on repeat MUGA scan is ≥ LLN, Herceptin may be initiated. (Also, refer to footnote a.)

c Patients who did not initiate Herceptin or ***who permanently discontinued Herceptin for protocol-specified cardiac-related toxicity may NOT receive investigational Herceptin.*** If the investigator discontinued Herceptin for cardiac-related reasons that did NOT meet protocol-specified criteria for discontinuation of Herceptin, the investigational Herceptin may be resumed if patient meets requirements on Table 3B.

12.4 Hormonal therapy (Group 2)

01/14/03
05/16/03
02/28/05
06/03/05

Patients with tumors that are ER-positive and/or PgR-positive will receive hormonal therapy. Hormonal therapy must be initiated no sooner than 3 weeks but no later than 12 weeks following the last dose of chemotherapy. Hormonal therapy should be administered for a minimum of 5 years. Total duration of tamoxifen should not exceed 5 years.

Choice of the drug(s) to be used for hormonal therapy is at the physician's discretion. The dose and schedule of hormonal therapeutic agents should be consistent with the drug package insert instructions. Aromatase inhibitors should **not** be used unless the investigator is certain a patient is permanently postmenopausal following chemotherapy. Patients under the age of 45 are likely to recover ovarian function after chemotherapy, and the use of an aromatase inhibitor is strongly discouraged in this population.

Women who have received tamoxifen for breast cancer prevention may be treated with additional tamoxifen at the discretion of the investigator.

05/16/03

12.5 Radiation therapy (Group 2)

All women treated with lumpectomy will receive whole breast irradiation. Postmastectomy loco-regional irradiation or postlumpectomy regional irradiation will be administered according to the treatment plan indicated by the investigator prior to randomization. Please note that *partial breast irradiation and irradiation of any internal mammary nodes are prohibited in this trial*. Radiation will begin within 8 weeks after completion of all assigned chemotherapy, and will overlap with Herceptin administration. (Refer to Section 6.2 and Appendix A for radiotherapy guidelines.)

13.0 DOSE DETERMINATIONS

05/16/03

13.1 Calculation of BSA and chemotherapy doses

Based on the patient's BSA, recommended chemotherapy doses will be provided by the NSABP at study entry. Re-calculation of BSA and dose is required if the patient has a ≥ 10 lb. weight change from baseline. The BSA and doses may also be re-calculated prior to each chemotherapy cycle at the investigator's discretion.

04/23/01
06/03/05

13.2 Rounding of chemotherapy doses

Rounding the doses of Adriamycin, cyclophosphamide, Taxol, and Herceptin is optional. If the treating physician decides to round the dose(s), follow these rules. (These rules also apply to dose modifications.)

- **Adriamycin** (60 mg/m^2 IV): should be rounded to the nearest mg.
- **Cyclophosphamide** (600 mg/m^2 IV): should be rounded to the nearest 25 mg.
- **Taxol** (175 mg/m^2 IV if given q 3 weeks or 80 mg/m^2 if given weekly x 12 doses): should be rounded to the nearest 5 mg.
- **Herceptin** (4 mg/kg IV loading dose; 2 mg/kg IV maintenance dose): should be rounded to the nearest mg.

  NOTE: If Herceptin is held for more than 3 weeks, when resumed, repeat the loading dose for the first dose, then return to the maintenance dose.

01/14/03
02/28/05
06/03/05

13.3 Hormonal therapy

The dose of the hormonal therapeutic agent(s) should be determined according to the drug package insert.

14.0 DOSE MODIFICATIONS AND DELAYS WITH AC THERAPY

14.1 Hematologic toxicity with AC

01/14/03
06/03/05

14.1.1 *Granulocytopenia with AC*

- Administration of AC will be delayed on day 1 if the granulocyte count is <1500.
- If a delay occurs, counts should be repeated at least weekly. When granulocytes are ≥ 1500, resume treatment at full dose with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support. Investigators should follow the prescribing recommendations in the cytokine drug package insert. All remaining cycles of AC will be administered with cytokine support.
- Administration of AC will also be delayed if granulocytes are <1500 on day 1, *despite cytokine administration during the previous cycle*. If the granulocyte count takes ≤ 1 week to recover to ≥ 1500, AC will be given at full dose at the next cycle. If the granulocyte count takes 2 to 3 weeks to recover to ≥ 1500, AC will be given with a dose reduction. (A: 50 mg/m^2 and C: 500 mg/m^2.) If the granulocyte count at 3 weeks is <1500 but is ≥ 1200, AC will be given with a dose reduction (A: 50 mg/m^2 and C: 500 mg/m^2.) If after the 3-week delay the granulocyte count remains <1200, the patient will be taken off AC therapy. When the granulocyte count returns to ≥ 1500, proceed with Taxol. If applicable, patients will proceed with Herceptin.
- Cytokine support is permitted but not required with Taxol, beginning with cycle 1.

06/03/05

14.1.2 *Thrombocytopenia with AC*

- The administration of AC will be delayed on day 1 if platelets are <75,000.
- If a delay occurs, counts should be repeated at least weekly. AC will be administered at the full dose when platelets are ≥ 75,000.
- If, after a 2-week delay, the platelet count is still <75,000, the patient will be taken off AC therapy. Proceed with Taxol when platelets are ≥ 75,000. If applicable, patients will proceed with Herceptin.
- A platelet count on day 1 of <25,000 will require a 25% reduction in *both* chemotherapeutic agents at the *next* cycle of AC. Drug administration will be resumed when the platelet count permits (platelets ≥ 75,000).
- Platelet transfusions and platelet colony-stimulating-factor may be given at the discretion of the investigator if clinically indicated.

01/14/03

14.2 Febrile neutropenia with AC (Table 4)

Patients who develop an episode of febrile neutropenia, defined as a fever ≥ 38.5°C (101.3°F) in the presence of neutropenia (granulocytes <1000), will have all remaining cycles of AC given at full dose, with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support.

If a second episode occurs in such patients, all remaining cycles will be given at full dose with cytokine support and ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice.

If a third episode occurs, the remaining cycle of AC will be dose-reduced to A: 50 mg/m^2 and C: 500 mg/m^2, and given with cytokine support and ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice.

TABLE 4. Management of AC cycles in patients who experience febrile neutropenia *01/14/03*

Febrile neutropenia			
Number of Events	AC dose (mg/m^2)	Prophylactic Cytokine support**a**	Prophylactic Ciprofloxacin HCl**b**
None	60/600	No	No
First event	60/600	Yes	No
Second event	60/600	Yes	Yes
Third event	50/500	Yes	Yes

a Prophylactic cytokine (G-CSF, GM-CSF, or pegfilgrastim). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

b Prophylactic ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice will be given for at least 7 days starting on day 5 of the next cycle(s).

01/14/03 14.3 **Grade 3 or 4 infection with AC (Table 5)**

- *Grade 3 (severe)*

  Patients who, during any cycle of chemotherapy, develop documented grade 3 (severe) infection, ***with or without neutropenia***, will have all remaining cycles of AC given at full dose, with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support and with prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

  If a second episode of grade 3 infection occurs in such patients, all remaining cycles of AC will be given at A: 50 mg/m^2 and C: 500 mg/m^2, with cytokine support and with prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

  If, despite the dose reduction, a third episode of grade 3 infection occurs, the remaining cycle of AC will be given at A: 40 mg/m^2 and C: 400 mg/m^2, with cytokine support and with prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

  If an episode of grade 3 infection occurs on any AC cycle, the investigator may use prophylactic cytokine support with all cycles of Taxol.

- *Grade 4 (life-threatening)*

  If the patient experiences a grade 4 infection, the investigator may discontinue AC therapy. If AC therapy is to be continued, follow the dose reduction guidelines for grade 3 infection.

TABLE 5. Management of AC cycles in patients who experience grade 3 infection *01/14/03*

Grade 3 infection (with or without neutropenia)			
Number of Events	AC dose (mg/m^2)	Prophylactic cytokine support[a]	Prophylactic Ciprofloxacin HC1[b]
None	60/600	No	No
First event	60/600	Yes	Yes
Second event	50/500	Yes	Yes
Third event	40/400	Yes	Yes

a Prophylactic cytokine (G-CSF, GM-CSF, or pegfilgrastim). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

b Prophylactic ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice will be given for at least 7 days starting on day 5 of the next cycle(s).

06/03/05 14.4 **Nausea/Vomiting with AC**

There are *no* dose reductions for nausea and/or vomiting.

Prophylactic antiemetics should be used at the discretion of the investigator.

Nausea and/or vomiting must decrease to ≤ grade 1 before administration of the next cycle. No more than a 2-week delay will be allowed for this recovery.

If the nausea and/or vomiting has not decreased to ≤ grade 1 after the 2-week delay, the patient will be taken off AC therapy. Proceed with Taxol. If applicable, patients will also proceed with Herceptin.

14.5 **Diarrhea and stomatitis with AC**

Antidiarrheal medication is at the physician's discretion.

Diarrhea must return to ≤ grade 1 and stomatitis must return to ≤ grade 1 before administration of the next cycle. No more than a 2-week delay will be permitted for this recovery. If after a 2-week delay the diarrhea and/or stomatitis have not resolved, AC therapy must be discontinued.

If the patient experiences grade 3 diarrhea and/or stomatitis that resolves by the end of the 2-week delay, the *remaining cycles* of AC must be administered with the following dose reductions:

- After the first episode of grade 3 diarrhea and/or stomatitis, decrease the Adriamycin dose to 50 mg/m^2 and the cyclophosphamide dose to 500 mg/m^2.
- If grade 3 diarrhea and/or stomatitis occur at reduced doses, decrease the Adriamycin to 40 mg/m^2 and the cyclophosphamide to 400 mg/m^2.
- If grade 3 diarrhea and/or stomatitis occur again, AC must be discontinued.

If the patient experiences grade 4 diarrhea and/or stomatitis, AC therapy must be discontinued.

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If AC therapy must be discontinued, proceed with Taxol when diarrhea and/or stomatitis have decreased to ≤ grade 1. If applicable, patients will also proceed with Herceptin.

02/28/05

14.6 Hepatic dysfunction with AC

A rising bilirubin, SGOT, or SGPT to a level ≥ grade 2 mandates the delay of AC therapy and a determination of the cause. If the rise is not due to metastatic disease and the levels return to < grade 2 within the 2-week delay, AC therapy should be resumed at full dose.

If the delay is longer than 2 weeks, notify the NSABP Clinical Coordinating Division to discuss further management. See Section 17.1 for a discussion of temporary discontinuation of tamoxifen due to hepatic toxicity.

14.7 Cardiotoxicity with AC

Patients should be monitored for signs and symptoms of congestive heart failure (CHF) (i.e., dypsnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.).

The presence of premature atrial or ventricular contractions without cardiac dysfunction, e.g., acute dysrhythmias that can occur during and shortly after Adriamycin infusion, are **not** an indication to permanently stop Adriamycin.

AC therapy must be discontinued when symptoms of heart failure are present and a diagnosis of CHF is confirmed. Further protocol therapy with Taxol will be at the discretion of the investigator. Herceptin will *not* be permitted in such instances.

If a patient has a myocardial infarction while on therapy, AC therapy must be discontinued, but Taxol may be given at the discretion of the investigator. Herceptin will *not* be permitted in such instances.

15.0 DOSE MODIFICATIONS AND DELAYS WITH TAXOL THERAPY

05/16/03

15.1 Treatment guidelines

15.1.1 When Taxol is administered on the q 3 week schedule, follow the instructions for dose modifications in Sections 15.4 through 15.11, 15.20, and 15.21.

When Taxol is administered on the weekly schedule, follow the instructions for dose modifications in Sections 15.12 through 15.21.

15.1.2 All Taxol treatments must be administered according to the dose/schedule selected at the time of randomization, with the exception that patients on the q 3 week schedule who experience Taxol-related thrombocytopenia, diarrhea, stomatitis, neurologic toxicity, or myalgia/arthralgia (see Sections 15.4.2, 15.8, 15.10 and 15.11) may receive subsequent doses according to the weekly Taxol dose/schedule.

15.1.3 For patients receiving the weekly Taxol schedule, Taxol should be completed in 12 weeks if possible.

If delays for medical or non-medical reasons occur, every effort should be made to administer all 12 doses of Taxol within 15 weeks after initiation of Taxol. No dose of Taxol may be given beyond the 15th week from the start of Taxol therapy.

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15.2 Initiation of Taxol therapy

Since AC and Taxol are substantially different in toxicity and mechanism of action, any toxicity that occurs during AC administration and resolves prior to Taxol administration does not require dose reduction or delay during Taxol therapy. In addition, a patient who discontinues AC therapy due to toxicity should still proceed with Taxol according to the protocol. The first Taxol dose should occur following the post-AC MUGA and after any AC-related toxicity has resolved. For patients who are to receive Herceptin, the post-AC MUGA report must be reviewed by the investigator before Herceptin is administered.

15.3 Taxol administration when Herceptin is delayed or discontinued

When Herceptin is delayed because of conditions related to LVEF, cardiac ischemia, or arrhythmia, Taxol administration may also be delayed at the investigator's discretion. If Herceptin is delayed for reasons other than those cited above, Taxol administration should continue.

When Herceptin is permanently discontinued because of conditions related to LVEF, cardiac ischemia, arrhythmia, or severe allergic reactions, Taxol administration may also be permanently discontinued at the investigator's discretion. If Herceptin is permanently discontinued for reasons other than those cited above, Taxol administration should continue.

05/16/03 15.4 **Hematologic toxicity with Taxol (q 3 week schedule)**

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15.4.1 ***Granulocytopenia with Taxol (q 3 week schedule)***

- The administration of Taxol will be delayed on day 1 if the granulocyte count is <1500.
- If a delay occurs, counts should be repeated at least weekly. When granulocytes are ≥ 1500, resume treatment at the full dose with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support. Investigators should follow the prescribing recommendations in the cytokine drug package insert. Do not administer cytokines within 24 hours of chemotherapy. All remaining cycles will be administered with cytokine support.
- Administration of Taxol will also be delayed if the granulocyte count is <1500 on day 1, *despite cytokine administration in the previous cycle.* If the granulocyte count takes ≤ 1 week to recover to ≥ 1500, Taxol will be given at full dose at the next cycle. If the granulocyte count takes 2 to 3 weeks to recover to ≥ 1500, Taxol will be given at the first dose reduction (T: 150 mg/m^2). If the granulocyte count at 3 weeks is < 1500 but is ≥ 1200, the patient can be treated with Taxol at a further dose reduction (T: 125 mg/m^2). If the granulocyte count after a 3-week delay remains < 1200, the patient will be taken off Taxol therapy. If applicable, patients will proceed with Herceptin.

06/03/05

15.4.2 ***Thrombocytopenia with Taxol (q 3 week schedule)***

- The administration of Taxol will be delayed on day 1 if platelets are < 75,000.
- If a delay occurs, counts should be repeated at least weekly.
- Taxol will be administered at full dose when platelets are ≥ 75,000.
- If, after a 2-week delay, the platelet count is still <75,000, the patient will be taken off Taxol therapy. If applicable, patients will proceed with Herceptin.
- A platelet count on day 1 of < 25,000 will require a reduction in Taxol dose to 150 mg/m^2 or consider converting to weekly Taxol at 80 mg/m^2 as an alternative to continuing the q 3 week regimen at a reduced dose. (A dose of Taxol given at 3 week intervals should be considered equivalent to 3 doses of Taxol given weekly.) Taxol administration will be resumed when the platelet count permits (platelets ≥ 75,000).
- Platelet transfusions may be given at the discretion of the investigator if clinically indicated.

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15.5 **Febrile neutropenia with Taxol (Table 6) (q 3 week schedule)**

Patients who, during a cycle of Taxol, develop an episode of febrile neutropenia, defined as fever ≥ 38.5° C (101.3°F) in the presence of neutropenia (granulocytes <1000), will have all remaining cycles of Taxol given at full dose, with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support.

If a second episode occurs in such patients, all remaining cycles of Taxol will be given at full dose with cytokine support and ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice.

If a third episode occurs, the remaining cycle of Taxol will be dose-reduced to 150 mg/m^2 and given with cytokine support and ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice.

TABLE 6. Management of Taxol cycles (q 3 week schedule) in patients who experience febrile neutropenia. *01/14/03 and 05/16/03*

Febrile neutropenia			
Number of Events	Taxol dose (mg/m^2)	Prophylactic Cytokine support**a**	Prophylactic ciprofloxacin HCl**b**
None	175	No	No
First event	175	Yes	No
Second event	175	Yes	Yes
Third event	150	Yes	Yes

a Prophylactic cytokine (G-CSF, GM-CSF, or pegfilgrastim). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

b Prophylactic ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice will be given for at least 7 days starting on day 5 of the next cycle(s).

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15.6 **Grade 3 or 4 infection with Taxol (Table 7) (q 3 week schedule)**

- *Grade 3 infection (severe)*

  Patients who develop documented grade 3 (severe) infection, ***with or without neutropenia,*** will have all remaining cycles of Taxol given at full dose, with cytokine (G-CSF, GM-CSF, or pegfilgrastim) support and prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

  If a second episode of grade 3 infection occurs in such patients, all remaining cycles of Taxol will be given at 150 mg/m^2 with cytokine support and with prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

  If, despite the dose reduction, a third episode of grade 3 infection occurs, the remaining cycle of Taxol will be given at 125 mg/m^2 with cytokine support and with prophylactic ciprofloxacin hydrochloride or antibiotic of choice.

- *Grade 4 infection (life-threatening)*

  If the patient experiences a grade 4 infection, the investigator may discontinue Taxol therapy. If Taxol therapy is to be continued, follow the dose reduction guidelines for grade 3 infection. When the patient has recovered, if applicable, patients will proceed with Herceptin.

TABLE 7. Management of Taxol cycles (q 3 week schedule) in patients who experience grade 3 infection *01/14/03*

Grade 3 infection (with or without neutropenia)			
Number of events	Taxol dose (mg/m^2)	Prophylactic cytokine support[a]	Prophylactic ciprofloxacin HCl[b]
None	175	No	No
First event	175	Yes	Yes
Second event	150	Yes	Yes
Third event	125	Yes	Yes

a Prophylactic cytokine (G-CSF, GM-CSF, or pegfilgrastim). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

b Prophylactic ciprofloxacin hydrochloride (500 mg po, bid) or antibiotic of choice will be given for at least 7 days starting on day 5 of the next cycle(s).

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15.7 Nausea/vomiting with Taxol (q 3 week schedule)

There are no dose reductions for nausea and/or vomiting. Prophylactic antiemetics may be used at the discretion of the investigator.

Nausea and/or vomiting must decrease to ≤ grade 1 before administration of the next cycle. No more than a 2-week delay will be allowed for this recovery. If the nausea and/or vomiting has not decreased to ≤ grade 1 after the 2-week delay, the patient will be taken off Taxol therapy. If applicable, patients will proceed with Herceptin.

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15.8 Diarrhea and stomatitis with Taxol (q 3 week schedule)

Antidiarrheal medication is at the physician's discretion.

Diarrhea must return to ≤ grade 1 and stomatitis must return to ≤ grade 1 before administration of the next cycle. No more than a 2-week delay will be permitted for this recovery. If after a 2-week delay the diarrhea and/or stomatitis have not resolved, Taxol therapy must be discontinued.

If the patient experiences grade 3 diarrhea and/or stomatitis that resolves by the end of the 2-week delay, the *remaining cycles* of Taxol must be administered with the following dose reductions:

- After the first episode of grade 3 diarrhea and/or stomatitis, decrease the Taxol dose to 150 mg/m^2 or consider converting to weekly Taxol at 80 mg/m^2 as an alternative to continuing the q 3 week regimen at a reduced dose. (A dose of Taxol given at 3 week intervals should be considered equivalent to 3 doses of Taxol given weekly.)
- If grade 3 diarrhea and/or stomatitis occur at a reduced dose, decrease the Taxol dose to 125 mg/m^2.
- If grade 3 diarrhea and/or stomatitis occur again, Taxol must be discontinued.

If the patient experiences grade 4 diarrhea and/or stomatitis, Taxol therapy must be discontinued.

If Taxol therapy must be discontinued and, if applicable, patients will proceed with Herceptin.

05/16/03 15.9 **Hepatic dysfunction with Taxol (q 3 week schedule)**

06/03/05 15.9.1 ***SGOT (AST) or SGPT (ALT) or alkaline phosphatase increase (q 3 week schedule)***

Grade 1 (> ULN to 2.5 x ULN)

- No dose modification or delays in Taxol.
- Continue Herceptin (if applicable).

Grade 2 (> 2.5 to 5 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1. No more than a 2-week delay will be permitted. If after the 2-week delay the toxicity has not decreased to ≤ grade 1, Taxol must be discontinued. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.
- If toxicity has decreased to ≤ grade 1 by the end of the 2-week delay, decrease the dose of Taxol to 150 mg/m^2 for remaining cycles. If the dose was previously reduced to 150 mg/m^2, reduce it further to 125 mg/m^2. If the dose was previously reduced to 125 mg/m^2, discontinue Taxol. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.

Grade 3 (> 5 to 20 x ULN) **or** *grade 4* (> 20 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1. No more than a 2-week delay will be permitted. If after the 2-week delay the toxicity has not decreased to ≤ grade 1, Taxol must be discontinued. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.
- If toxicity has decreased to ≤ grade 1 by the end of the 2-week delay, decrease the Taxol dose to 150 mg/m^2 for remaining cycles. If the dose was previously reduced to 150 mg/m^2, reduce it further to 125 mg/m^2. If the dose was previously reduced to 125 mg/m2, discontinue Taxol.

06/03/05 15.9.2 ***Bilirubin increase (q 3 week schedule)***

Grade 1 (> ULN to 1.5 x ULN)

- No dose modifications or delays in Taxol.
- Continue Herceptin (if applicable).

Grade 2 (> 1.5 to 3 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1. No more than a 2-week delay will be permitted. If after the 2-week delay the toxicity has not decreased to ≤ grade 1, Taxol must be discontinued. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.

- If toxicity has decreased to ≤ grade 1 by the end of the 2-week delay, decrease the dose of Taxol to 150 mg/m^2 for remaining cycles. If the dose was previously reduced to 150 mg/m^2, reduce it further to 125 mg/m^2. If dose was previously reduced to 125 mg/m^2, discontinue Taxol. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.

Grade 3 (>3 to 10 x ULN) ***or*** *grade 4* (>10 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1. No more than a 2-week delay will be permitted. If after the 2-week delay the toxicity has not decreased to ≤ grade 1, Taxol must be discontinued. Herceptin should be resumed, if applicable, when toxicity returns to ≤ grade 1.
- If toxicity has decreased to ≤ grade 1 by the end of the 2-week delay, decrease the Taxol dose to 150 mg/m^2 for remaining cycles. If the dose was previously reduced to 150 mg/m^2, then decrease Taxol to 125 mg/m^2 for the remaining cycle. If the dose was previously reduced to 125 mg/m^2, discontinue Taxol for the remaining cycle.

05/16/03 15.10 **Neurologic (neurosensory, neuromotor) toxicity with Taxol (Table 8) (q 3 week schedule)**

The management of Taxol in patients who experience neurologic toxicity is summarized in Table 8.

TABLE 8. Management of Taxol cycles (q 3 week schedule) in patients who experience neurologic toxicity *05/16/03, 06/03/05*

Number of events	Grade 2	Grade 3**a,b**	Grade 4
	Taxol dose (mg/m^2)	Taxol dose (mg/m^2)	Taxol dose (mg/m^2)
None	175	175	175
First event	150	150	Discontinue Taxol therapy; Herceptin should be continued.
Second event	125	125	N/A
Third event	Discontinue Taxol therapy; Herceptin should be continued.	Discontinue Taxol therapy; Herceptin should be continued.	N/A

a For patients experiencing neurologic toxicity, investigators may consider converting to weekly Taxol at 80 mg/m^2 as an alternative to continuing the q 3 week regimen at a reduced dose. A dose of Taxol given at 3 week intervals should be considered equivalent to 3 doses of Taxol given weekly.

b Patients should return to ≤ grade 1 toxicity before retreatment. No more than 2 weeks will be allowed for this recovery. If after 2 weeks the toxicity has not returned to ≤ grade 1, the patient will be taken off Taxol therapy; if applicable, patients will proceed with Herceptin.

05/16/03 15.11 **Myalgia/arthralgia with Taxol (q 3 week schedule)**

Symptom management of myalgia and arthralgia, including anti-inflammatory medications, steroids, and narcotics, is at the physician's discretion. Myalgia/arthralgia must return to ≤ grade 1 before administering the next Taxol dose. No more than a 2-week delay will be permitted. If > grade 1 myalgia/arthralgia continues after the 2-week delay, Taxol must be discontinued. (Herceptin may be delayed during Taxol delays at the discretion of the investigator. Herceptin will be continued if Taxol is permanently discontinued.) Dose modification of Taxol is according to the following guidelines:

Grade 1 or 2

- No dose modification of Taxol.
- Administration of prophylactic steroids (prednisone 20 mg po, qd for 5 days beginning on the day Taxol is given), is at the discretion of the investigator.

Grade 3 or 4

- Administer prophylactic steroids as described for grade 1 or 2 event.
- Decrease Taxol dose to 150 mg/m^2 or consider converting to weekly Taxol at 80 mg/m^2 as an alternative to continuing the q 3 week regimen at a reduced dose. (A dose of Taxol given at 3 week intervals should be considered equivalent to 3 doses of Taxol given weekly.) If a second episode of grade 3 or 4 myalgia/arthralgia occurs, continue prophylactic steroids *and* decrease the dose to 125 mg/m^2. If a third episode of grade 3 or 4 myalgia/arthralgia occurs, discontinue Taxol therapy.

05/16/03 15.12 **Hematologic toxicity with Taxol (weekly schedule)**

15.12.1 ***Granulocytopenia with Taxol (weekly schedule)***

The administration of Taxol will be delayed if the granulocyte count is <1000/mm^3. When granulocytes are ≥ 1000, resume treatment at the full dose with cytokine (G-CSF or GM-CSF [do not use pegfilgrastim with this schedule]) support. Investigators should follow the prescribing recommendations in the cytokine drug package insert. *Do not administer cytokines within 24 hours of chemotherapy*. All remaining Taxol treatments will be administered with cytokine support.

15.12.2 ***Thrombocytopenia with Taxol (weekly schedule)***

- The administration of Taxol will be delayed if platelets are <75,000. Delay treatment until platelet count is ≥ 75,000/mm^3.
- A platelet count of < 25,000 will require a reduction in Taxol dose to 60 mg/m^2.
- Platelet transfusions may be given at the discretion of the investigator if clinically indicated.

05/16/03 15.13 **Febrile neutropenia with Taxol (Table 9) (weekly schedule)**

Patients who develop an episode of grade 3 or 4 febrile neutropenia, defined as fever ≥ 38.5° C (101.3°F) in the presence of neutropenia (granulocytes <1000), will have all

remaining Taxol given at full dose with cytokine (G-CSF or GM-CSF [do not use pegfilgrastim with this schedule]) support.

If a second episode occurs in such patients, all remaining Taxol will be given at 60 mg/m^2 with cytokine support as described above. If a third episode occurs, all remaining Taxol will be given at 45 mg/m^2 with cytokine support as described above. If a fourth episode occurs, discontinue Taxol.

TABLE 9. Management of Taxol (weekly schedule) in patients who experience febrile neutropenia *05/16/03*

Febrile neutropenia		
Number of Events	Taxol dose (mg/m^2)	Prophylactic cytokine support[a]
None	80	No
First event	80	Yes
Second event	60	Yes
Third event	45	Yes
Fourth event	Discontinue Taxol therapy; Herceptin should be continued.	N/A

a Prophylactic cytokine (G-CSF or GM-CSF [do not use pegfilgrastim with this schedule]). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

05/16/03
06/03/05

15.14 **Grade 3 or 4 infection with Taxol (Table 10) (weekly schedule)**

- *Grade 3 infection (severe)*

  Patients who develop documented grade 3 (severe) infection, ***with or without neutropenia***, will have all remaining Taxol given at full dose with cytokine (G-CSF or GM-CSF [do not use pegfilgrastim with this schedule]) support.

  If a second episode of grade 3 infection occurs in such patients, all remaining Taxol will be given at 60 mg/m^2 with cytokine support as described above. If a third episode occurs, all remaining Taxol will be given at 45 mg/m^2 with cytokine support as described above. If a third episode occurs, discontinue Taxol.

- *Grade 4 infection (life-threatening)*

  If the patient experiences a grade 4 infection, the investigator may discontinue Taxol therapy. If Taxol therapy is to be continued, follow the guidelines for grade 3 infection. When the patient has recovered, if applicable, patients will proceed with Herceptin.

TABLE 10. Management of Taxol (weekly schedule) in patients who experience grade 3 infection *05/16/03*

Grade 3 infection (with or without neutropenia)		
Number of events	Taxol dose (mg/m^2)	Prophylactic cytokine support[a]
None	80	No
First event	80	Yes
Second event	60	Yes
Third event	45	Yes
Fourth event	Discontinue Taxol therapy; Herceptin should be continued.	N/A

a Prophylactic cytokine (G-CSF or GM-CSF [do not use pegfilgrastim with this schedule]). Investigators should follow the prescribing recommendations in the cytokine drug package insert.

05/16/03

15.15 **Nausea/vomiting with Taxol (weekly schedule)**

There are *no* dose reductions for nausea and/or vomiting. Prophylactic antiemetics may be used at the discretion of the investigator.

Nausea and/or vomiting must decrease to ≤ grade 1 before administration of the next Taxol treatment.

05/16/03

15.16 **Diarrhea and stomatitis with Taxol (weekly schedule)**

Antidiarrheal medication is at the physician's discretion.

Diarrhea must return to ≤ grade 1 and stomatitis must return to ≤ grade 1 before administration of the next Taxol treatment. Following episodes of grade 3 or 4 diarrhea or stomatitis, remaining Taxol doses must be reduced to 60 mg/m^2. If grade 3 or 4 diarrhea and/or stomatitis occur at a reduced dose, decrease the Taxol dose to 45 mg/m^2.

05/16/03

15.17 **Hepatic dysfunction with Taxol (weekly schedule)**

06/03/05

15.17.1 ***SGOT (AST) or SGPT (ALT) or alkaline phosphatase increase (weekly schedule)***

Grade 1 (> ULN to 2.5 x ULN)

- No dose modification or delays in Taxol.
- Continue Herceptin (if applicable).

Grade 2 (> 2.5 to 5 x ULN) ***or*** *grade 3* (> 5 to 20 x ULN) ***or*** *grade 4* (> 20 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1; subsequent Taxol doses will be reduced to 60 mg/m^2.
- If a second episode occurs, reduce subsequent doses to 45 mg/m^2.

06/03/05

15.17.2 ***Bilirubin increase (weekly schedule)***

Grade 1 (> ULN to 1.5 x ULN)

- No dose modifications or delays in Taxol.
- Continue Herceptin (if applicable).

Grade 2 (> 1.5 to 3 x ULN) ***or*** *grade 3* (>3 to 10 x ULN) ***or*** *grade 4* (>10 x ULN)

- Delay Taxol *and* Herceptin until toxicity decreases to ≤ grade 1; subsequent Taxol doses will be reduced to 60 mg/m^2.
- If a second episode occurs, reduce subsequent doses to 45 mg/m^2.

05/16/03

15.18 **Neurologic (neurosensory, neuromotor) toxicity with Taxol (Table 11) (weekly schedule)**

The management of Taxol in patients who experience neurologic toxicity is summarized in Table 11.

TABLE 11. Management of Taxol (weekly schedule) in patients who experience neurologic toxicity *05/16/03, 06/03/05*

Number of events	Grade 2**a** or 3**a**	Grade 4
	Taxol dose (mg/m^2)	Taxol dose (mg/m^2)
None	80	80
First event	60	Discontinue Taxol therapy; Herceptin should be continued.
Second event	45	N/A
Third Event	Discontinue Taxol therapy; Herceptin should be continued.	N/A

a Patients should return to ≤ grade 1 toxicity before retreatment. No more than 2 weeks will be allowed for this recovery. If after 2 weeks the toxicity has not returned to ≤ grade 1, the patient will be taken off Taxol therapy; if applicable, proceed with Herceptin.

05/16/03

15.19 **Myalgia/arthralgia with Taxol (weekly schedule)**

Symptom management of myalgia and arthralgia, including anti-inflammatory medications, steroids, and narcotics, is at the physician's discretion. Myalgia/arthralgia must return to ≤ grade 1 before administering the next Taxol dose. No more than a 2-week delay will be permitted. If > grade 1 myalgia/arthralgia continues after the 2-week delay, Taxol must be discontinued. (Herceptin may be delayed during Taxol delays at the discretion of the investigator. Herceptin will be continued if Taxol is permanently discontinued.) Dose modification of Taxol is according to the following guidelines:

Grade 1 or 2

- No dose modification of Taxol.
- Administration of prophylactic steroids (prednisone 20 mg po, qd for 5 days beginning on the day Taxol is given), is at the discretion of the investigator.

Grade 3 or 4

- Administer prophylactic steroids as described for grade 1 or 2 event.
- Decrease Taxol dose to 60 mg/m^2. If a second episode of grade 3 or 4 myalgia/arthralgia occurs, continue prophylactic steroids and decrease the dose to 45 mg/m^2. If a third episode of grade 3 or 4 myalgia/arthralgia occurs, discontinue Taxol therapy.

05/16/03 15.20 **Cardiotoxicity with Taxol (q 3 week *and* weekly schedules)**

There will be no dose modifications for cardiotoxicity.

06/03/05 15.20.1 ***Asymptomatic decrease in LVEF***

A decline in LVEF is not expected with Taxol. However, for patients who have received at least one dose of Herceptin, MUGA scans must be done according to instructions in Section 6.0 and must be repeated based on instructions in Table 13. *As of Amendment #9, MUGA scans are no longer required for patients who have never received and will not receive investigational Herceptin. (Table 12 is no longer applicable and has been deleted.)* **For guidelines on performing MUGA scans for Group 1 and Group 2 patients receiving Herceptin, see Table 13.**

Table 12 (Guidelines for performing repeat MUGA scan for Group 1 patients who have an ***asymptomatic*** decrease in LVEF from baseline) **is no longer applicable and was deleted at the time of Amendment #9.**

Additional MUGA scans following a repeat MUGA and prior to the next scheduled MUGA scan may be performed at the investigator's discretion.

In cases where a delay in chemotherapy has occurred (during either AC or Taxol), and a MUGA scan is due at the 6-month period from randomization, the MUGA scan may be scheduled 3 weeks after the last Taxol dose. The 18-month MUGA must still be done at 18 months from randomization initiation regardless of any prior delays.

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15.20.2 ***Symptomatic decrease in LVEF***

If symptomatic congestive heart failure (CHF) occurs at a time when the patient is still taking Taxol, resumption of Taxol is at the investigator's discretion. The investigator must confirm a diagnosis of CHF either with a MUGA scan or echocardiogram. A chest x-ray is also required. All reports must be faxed with Form CR and Form M to the NSABP Biostatistical Center within 14 days of the MUGA scan. ***For all patients who have received Herceptin, the protocol-specified schedule for obtaining MUGA scans (see Section 6.0) should be followed even after the discontinuation of protocol therapy or occurrence of a cardiac event***. Any symptoms suggesting CHF (regardless of when they occur and even if the diagnosis of CHF is not confirmed) must be reported using Form CR.

15.20.3 ***Cardiac arrhythmia***

Asymptomatic, not requiring treatment (Grade 1)

- Interrupt or slow the Taxol infusion. Subsequent infusion for that cycle and future cycles should be done under continuous cardiac monitoring.

Symptomatic, but not requiring treatment (Grade 2)

- Hold Taxol *and* Herceptin (if patient is receiving Herceptin) and conduct cardiac evaluation. Resume Taxol and Herceptin at the discretion of the investigator.

Symptomatic and requiring treatment (Grade 3) or Life-threatening (Grade 4)

- Discontinue Taxol. Herceptin administration is *not* permitted.

05/16/03

15.21 **Hypersensitivity reactions with Taxol (q 3 week *and* weekly schedules)**

There will be no dose modifications for hypersensitivity reactions. Management of mild to moderate hypersensitivity reactions is at the discretion of the investigator. Severe reactions (Grade 3 or 4), such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate and permanent discontinuation of Taxol and aggressive symptom management. If a grade 3 or 4 hypersensitivity reaction occurs during or after Herceptin administration, following Taxol, both Herceptin and Taxol must be permanently discontinued.

02/28/05

15.22 **Interstitial pneumonitis/other pulmonary events**

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, delay Taxol therapy and perform a thorough evaluation. If pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to Taxol cannot be excluded), Taxol must be permanently discontinued.

06/03/05 16.0 **DELAYS IN HERCEPTIN ADMINISTRATION**

No dose modifications of Herceptin will be permitted on this trial.

Herceptin administration will stop at 1 year from its initiation, regardless of the number of doses the patient has received or missed.

If Herceptin is resumed following a delay of >3 weeks, a loading dose of 4 mg/kg IV over 90 minutes should be given as the first dose when Herceptin is re-initiated.

If a patient misses a Herceptin dose for any reason, the missed dose may be rescheduled for the same calendar week, but must ***not*** *be administered the following week (i.e., a patient may not be given 2 Herceptin doses in the same calendar week).*

16.1 **Herceptin administration when Taxol is delayed or discontinued**

When Taxol is delayed for any reason, Herceptin may also be missed, at the discretion of the investigator, provided that the Taxol delay is not more than 2 weeks. If the Taxol delay is more than 2 weeks, Herceptin may resume at the discretion of the investigator. If Taxol therapy is discontinued for any reason *other than cardiotoxicity, or severe hypersensitivity reactions that occurred when both Taxol and Herceptin were administered,* Herceptin therapy may continue.

05/16/03
06/03/05 16.2 **Considerations regarding cardiac dysfunction and Herceptin administration**

At the time of Amendment #9, the criteria for initiation of Herceptin were revised. See Section 12.3 (Tables 3A and 3B) for the current instructions. If Herceptin is initiated, a decision about whether to continue or discontinue it must then occur after the completion of all chemotherapy and while the patient is on Herceptin alone. Two goals must be considered in evaluating the benefits and risks of continuing Herceptin after chemotherapy is completed: 1) the protection of patients from serious myocardial toxicity and 2) the ability to assess the potential benefit of continuing Herceptin in patients with node-positive, HER2-positive breast cancer.The mechanism that underlies the cardiotoxicity observed with Herceptin is unknown. In addition, there are no data about the use of cardioprotective agents such as dexrazoxane (Zinecard®) with Herceptin. Therefore, *no cardioprotective drugs are permitted in this study.*

NOTE 1: In the sections that follow, definitions of cardiac toxicity are outlined to be used when making treatment decisions. The descriptions of left ventricular dysfunction are similar, but not exactly the same as defined by the NCI's Common Toxicity Criteria (version 2.0). Institutions will be required to *report* cardiac toxicity on Form AE in B-31 according to the Common Toxicity Criteria Guidelines; however, *treatment* should follow the directions outlined in the protocol.

NOTE 2: The baseline MUGA scan is the LVEF measured at randomization prior to receiving AC therapy. Individual patients should have their MUGA scans performed at the same radiology facility to eliminate variability between facilities.

02/28/05 NOTE 3: If the baseline LVEF is > 75%, the investigator should consider having the LVEF determination reviewed prior to randomization. (See eligibility Section 5.1.10 for additional details regarding the baseline LVEF.)

05/22/00 For a more detailed discussion of the assessment of cardiotoxicity and the decision to continue or stop Herceptin, please see Appendix E. Recommended nuclear medicine guidelines for resting MUGA scan evaluations are detailed in Appendix F.

16.2.1 ***Asymptomatic decrease in LVEF***

In asymptomatic patients, the decision to continue or stop Herceptin is made based upon two factors:

- the measured ejection fraction as it relates to the radiology facility's lower limit of normal, ***and***
- the change in ejection fraction from baseline.

Table 13 summarizes the management of Herceptin in patients who have an ***asymptomatic*** decrease in LVEF from baseline. Herceptin ***must*** be discontinued in patients who have a ***symptomatic*** decrease in LVEF (see Section 16.2.2).

Rules for interpreting and applying "repeat" MUGA scan results:

- Herceptin must be permanently discontinued when two consecutive -"hold" categories occur.
- Herceptin must be permanently discontinued when three intermittent "hold" categories occur. (At the investigator's discretion, Herceptin may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.)
- If LVEF is maintained at a "continue and repeat MUGA" or improves from a "hold" to a "continue and repeat MUGA" category, additional MUGA scans prior to the next scheduled MUGA scan will be at the investigator's discretion.

Table 13. Guidelines for performing MUGA scan and management of Herceptin in patients who have an ***asymptomatic*** decrease in LVEF from baseline

05/16/03 and 06/03/05

	Asymptomatic decrease in LVEF percentage points from baseline		
Relationship of LVEF to the lower limit of normal (LLN)	**Decrease of < 10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥ 16 percentage points**
Within radiology facility's normal limits	Continue Herceptin	Continue Herceptin	Continue Herceptin and repeat MUGA after 4 weeks
1 to 5 percentage points below the LLN	Continue Herceptin	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks
≥ 6 percentage points below the LLN	Continue Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks
NOTE 1: See Appendix E for examples of treatment decisions for asymptomatic patients with decreased LVEF.			
NOTE 2: If Herceptin is held or discontinued during therapy with Taxol, Taxol may be continued at the investigator's discretion.			
NOTE 3: Refer to the rules for interpreting and applying "repeat" MUGA scan results in Section 16.2.1 for important instructions.			

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16.2.2 ***Symptomatic decrease in LVEF:***

Please note that symptoms suggesting congestive heart failure (CHF) must be reported on Form CR (which must be faxed to the NSABP Biostatistical Center as soon as possible within 14 days) even if the diagnosis of CHF is not confirmed.

- *Congestive heart failure (Grade 3)*: Patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) Patients who develop these signs and symptoms must hold Herceptin. If CHF occurs while the patient is still on Taxol plus Herceptin, resumption of Taxol is at the investigator's discretion.

  The investigator must confirm the diagnosis of CHF either with a MUGA scan or echocardiogram. A chest x-ray is also required. Once the diagnosis of CHF is confirmed, Herceptin must be permanently discontinued and all reports must be faxed with Form CR and Form M to the NSABP Biostatistical Center within 14 days of the MUGA scan. ***The protocol-specified schedule (see Section 6.0) for obtaining MUGA scans should be followed even after the discontinuation of protocol therapy or occurrence of a cardiac event.***

- *Severe refractory CHF or requiring intubation (Grade 4)*: Discontinue Herceptin and submit Form CR.

16.2.3 ***Cardiac ischemia with Herceptin***

- *Non-specific T-wave flattening or changes (Grade 1):* Continue Herceptin with frequent monitoring.

- *Asymptomatic ST-and T-wave changes suggesting ischemia (Grade 2)*: Hold Herceptin and conduct cardiac evaluation. Based on this evaluation, Herceptin may be continued at the discretion of the investigator.

- *Angina without evidence of infarction (e.g., dynamic ischemic EKG changes, abnormal stress test, or cardiac angiography) (Grade 3)*: Discontinue Herceptin.

- *Acute myocardial infarction (Grade 4)*: Discontinue Herceptin.

16.2.4 ***Cardiac arrhythmia with Herceptin***

- *Asymptomatic; no treatment (Grade 1):* Continue Herceptin with careful monitoring, OR hold Herceptin (and Taxol if patient is receiving Taxol) and conduct cardiac evaluation. Based on that evaluation, Herceptin and Taxol or Herceptin alone may be continued or discontinued at the discretion of the investigator. If Herceptin is discontinued, Taxol may also be discontinued at the investigator's discretion.

- *Symptomatic; no treatment (Grade 2)*: Hold Herceptin (and Taxol if patient is receiving Taxol) and conduct cardiac evaluation. Based on that evaluation, Herceptin and Taxol or Herceptin alone may be continued or discontinued at the discretion of the investigator. If Herceptin is discontinued in this case, Taxol may also be discontinued at the investigator's discretion.

- *Symptomatic, requiring treatment (Grade 3):* Discontinue Herceptin. Taxol is not permitted.

- *Life-threatening (Grade 4)*: Discontinue Herceptin. Taxol is not permitted.

16.3 **Infusion-associated symptoms with Herceptin**

During the *first* infusion of Herceptin, a symptom complex consisting of fever and/or chills may occur. These symptoms, which are usually mild to moderate, may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These infusion-related symptoms occur infrequently during subsequent infusions. Treat fever and chills as follows. Management of other symptoms is at the physician's discretion.

16.3.1 ***Fever***

Grade 1 [38°C - 39°C (100.4°F - 102.2°F)] ***or***
Grade 2 [39.1°C- 40°C (102.3°F - 104°F)]

- Stop the infusion and give antipyretics. Once the temperature is < 38°C, resume the infusion at a slower rate.

Grade 3 [> 40°C (104°F) for < 24 hours] ***or***
Grade 4 [> 40°C (104°F) for > 24 hours]

- Immediately stop the Herceptin infusion.
- Give antipyretics.
- Monitor the patient for a minimum of 1 hour.
- If the patient's temperature drops to < 38°C within 3 hours, resume the infusion at a slower rate.
- If the fever does not resolve within 3 hours, inpatient monitoring is strongly recommended. Current Herceptin infusion must not be resumed. Subsequent administration of Herceptin is at the investigator's discretion.

16.3.2 ***Chills***

Chills may be treated with acetaminophen and/or diphenhydramine hydrochloride. Meperidine may also be used at the investigator's discretion.

16.4 **Diarrhea with Herceptin**

Patients are more likely to experience diarrhea following administration of Taxol and Herceptin. See Section 15.7 for management of diarrhea with Taxol. Treat as follows:

Grade 1 (increase of < 4 stools/day) ***or*** *Grade 2* (increase of 4-6 stools/day)

- Antidiarrheal medication is at the physician's discretion.

Grade 3 (increase of ≥ 7stools/day or need for parenteral support for dehydration)

- Herceptin must be stopped until the toxicity resolves to ≤ Grade 1. Antidiarrheal medication is at the physician's discretion.

Grade 4 (physiologic consequence requiring intensive care or hemodynamic collapse)

- Herceptin must be permanently discontinued.

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16.5 **Pulmonary/Hypersensitivity reaction with Herceptin**

Patients with underlying lung disease, such as bronchial asthma or chronic bronchitis, may be more susceptible to pulmonary reactions during or after infusion of Herceptin. Symptoms can include dyspnea, bronchospasm, Adult Respiratory Distress Syndrome (ARDS), and even death.

Grade 1 (transient rash, drug fever < 38°C or 100.4°F) ***or*** *Grade 2* (urticaria, drug fever ≥ 38°C or 100.4°F, and/or asymptomatic bronchospasm)

- Stop the infusion. Monitor the patient.

- Administer diphenhydramine hydrochloride. If toxicity resolves within 3 hours, treatment with Herceptin in the next cycle is allowed at a slower rate and under close observation. If toxicity does not resolve in 3 hours, overnight observation is recommended. Subsequent rechallenge with Herceptin is at the investigator's discretion.

Grade 3 (symptomatic bronchospasm requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema) ***or*** *Grade 4* (anaphylaxis)

- If a Grade 3 or 4 hypersensitivity reaction occurs during or after Herceptin administration following Taxol, Herceptin and Taxol must be permanently discontinued.

- If a Grade 3 or 4 hypersensitivity reaction occurs during or after Herceptin administration, without Taxol, Herceptin must be permanently discontinued.

02/28/05 16.6 **Interstitial pneumonitis/other pulmonary events**

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, delay Herceptin therapy and perform a thorough evaluation. If pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to Herceptin cannot be excluded), Herceptin must be permanently discontinued.

01/14/03 17.0 **DELAYS IN TAMOXIFEN* ADMINISTRATION**

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(*For patients who receive other hormonal therapy in sequence with or rather than tamoxifen, any decisions regarding the clinical management of the patient or dose delays will be at the discretion of the investigator.)

There will be no dose modifications for tamoxifen therapy. Temporary discontinuation of tamoxifen will be instituted in case of the following toxicities:

17.1 **Hepatic toxicity with tamoxifen**

If a grade 2 or greater elevation of SGOT or SGPT (> 2.5 x ULN) occurs at any time subsequent to the completion of the last cycle of all chemotherapy, the test should be repeated to ensure accuracy. If the value is confirmed, tamoxifen will be discontinued for at least 4 weeks. The patient should be evaluated carefully for other potential causes of the abnormality, including metastatic disease. The SGOT or SGPT test will be repeated at monthly intervals, or more frequently, depending on the severity of the abnormality noted. When the toxicity returns to ≤ grade 1, tamoxifen therapy may be resumed. Follow up testing will be performed 1 month after resuming tamoxifen, or sooner if indicated, to ensure that no further toxicity occurs with the rechallenge. When a grade 3 or 4 toxicity has occurred and is unequivocally related to tamoxifen, the decision to rechallenge the patient with tamoxifen after a return to grade 1 range must be done only after careful deliberation regarding potential risks and benefits.

If the toxicity returns, tamoxifen therapy must be permanently discontinued.

17.2 **Hematologic toxicity with tamoxifen**

If significant hematologic toxicity (leukopenia, granulocytopenia, thrombocytopenia) occurs at any time subsequent to the completion of the last cycle of all chemotherapy, testing should be repeated to ensure accuracy. If the value is confirmed, tamoxifen will be discontinued for at least 4 weeks. The patient should be evaluated carefully for other potential causes of the abnormality. Hematologic testing will be repeated at monthly intervals, or more frequently, depending on the severity of the abnormality noted. When blood counts improve to an acceptable level, tamoxifen therapy may be resumed. Follow up testing will be performed 1 month after resuming tamoxifen therapy, or sooner if indicated, to ensure that no further toxicity occurs with the rechallenge.

If significant toxicity returns, tamoxifen therapy must be permanently discontinued.

17.3 **Other serious toxicity with tamoxifen**

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If a serious toxicity occurs that is thought to be related to tamoxifen, tamoxifen may be discontinued at the discretion of the physician.

17.4 **Management of tamoxifen related side effects**

The following tamoxifen related side effects should be managed as indicated below:

- *Hot flashes:* Vitamin E, clonidine, Effexor® (venlafaxine hydrochloride), or phenobarbital/ergotamine tartrate/belladonna (Bellergal-S®) is permitted for treatment of hot flashes. Other nonhormonal therapies may be used at the investigator's discretion. Megestrol acetate (Megace®) and other hormonal therapies are not permitted.

- *Vaginal discharge:* Patients should be told to report unusual discharge so that infection can be ruled out. In the absence of pathogens, no treatment is indicated, and the problem is usually self limiting.

- *Menstrual irregularities, postmenopausal bleeding, and/or pelvic pain or pressure:* These may be early symptoms of endometrial cancer (for women with a uterus) and require immediate clinical examination and testing.

05/16/03 18.0 **NON-PROTOCOL THERAPY/POSTMENOPAUSAL MEDICAL MANAGEMENT**

18.1 **Non-protocol therapy**

The following categories of treatment, in addition to any cancer therapy other than that specified in the protocol, are prohibited until the time of development of first breast cancer recurrence, or second primary cancer.

18.1.1 ***Hormonal therapy***

Patients may ***not*** receive any of the following types of hormonal therapy:

- With the exception of tamoxifen, selective estrogen receptor modulators (SERMs) (e.g., raloxifene [Evista®]);
- Oral or parenteral sex hormones (e.g., birth control pills, hormone replacement therapy).

18.1.2 ***Radiation therapy***

- Patients may not receive any radiation therapy other than that specified in the protocol until the time of the first event.
- Internal mammary nodal irradiation is not permitted.
- Partial breast irradiation is not permitted.
- See Appendix A for details on radiation therapy.

06/03/05

18.1.3 ***Commercial Herceptin***

Since risks and benefits of initiation of Herceptin more than a year following initiation of adjuvant chemotherapy has not been evaluated, investigational Herceptin will not be offered to patients randomized prior to April 26, 2004. Administration of commercial Herceptin to these patients at investigator discretion should be recorded on Form F.

18.2 **Postmenopausal medical management**

18.2.1 ***Hormonal therapy***

Patients may receive hormonal therapy for the management of vaginal or urinary symptoms according to the following guidelines (refer to Section 18.1.1 for prohibited hormonal therapy):

- Low-dose estrogen in the form of a vaginal cream. (The dose of conjugated vaginal cream should not exceed 0.3 mg [or 1/8 of an applicator] three times each week.)
- Conjugated estrogen ring (Estring® or similar product)
- Vagifem® (or similar product)

18.2.2 *Management of osteoporosis*

- Osteoporosis assessment and interventions that should be included in the medical management for all postmenopausal women are strongly encouraged.
- In addition to weight bearing and resistance exercise and adequate dietary intake of calcium and vitamin D, the following are permitted:
  - calcium supplements
  - vitamin D
  - calcitonin (for example, Miacalcin®)
  - bisphosphonates (for example, Actonel®, Fosamax®)

19.0 DEFINITIONS AND DOCUMENTATION OF OUTCOME MEASURES

05/16/03

19.1 Breast and other cancer events

The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when both the clinical *and* laboratory findings meet "acceptable" criteria as defined below. Suspicious findings do not constitute criteria for breast cancer recurrence, nor are they an indication to alter protocol therapy. The following listing is offered as a guide. Further treatment after a breast cancer recurrence, second primary breast cancer, or other second primary cancer, will be at the discretion of the investigator.

Please submit a copy of the clinic or office note summarizing the work-up and treatment plan for the recurrence/second primary cancer.

19.1.1 ***Local recurrence***

- *In the ipsilateral breast (IBTR) after lumpectomy*

  Defined as evidence of tumor (except LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis.

  Acceptable: positive biopsy or cytology

- *Local recurrence (except IBTR)*

  Defined as evidence of tumor in any soft tissue or skin of the ipsilateral chest wall after mastectomy. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, posteriorly along the lateral edge to the latissimus dorsi, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence.

  Acceptable: positive biopsy or cytology

19.1.2 ***Regional recurrence***

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after operation.

Acceptable: positive biopsy or cytology

19.1.3 ***Distant recurrence***

Defined as evidence of tumor in all areas, with the exception of those described in Sections 19.1.1 and 19.1.2.

- *Skin, subcutaneous tissue, and lymph nodes (other than local or regional)*

  Acceptable: positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease

- *Bone marrow*

  Acceptable: positive cytology, aspirate, biopsy, or MRI scan

- *Lung*

  Acceptable: (i) positive cytology, aspirate, or biopsy or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases

  NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations, such as biopsy or needle aspiration, should be performed. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

- *Skeletal*

  Acceptable: (i) x ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis; (ii) biopsy proof of bone metastases; or (iii) bone scan that is clearly positive for bone metastases

  NOTE: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

- *Liver*

  Acceptable: (i) an abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases or (ii) liver biopsy confirmation of metastatic disease

  NOTE: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained to document stability or progression.

- *Central nervous system*

  Acceptable: (i) positive CT scan or MRI scan, usually in a patient with neurological symptoms or (ii) biopsy or cytology (for a diagnosis of meningeal involvement)

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19.1.4 ***Second primary cancer (breast or other cancer)***

Any second primary cancer other than melanoma in situ, squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix will be considered an event in the analysis of DFS. Lobular carcinoma in situ of the breast (LCIS) is also *not* considered an event. The diagnosis of a second primary cancer must be confirmed histologically whenever possible. Representative tissue blocks of only contralateral breast cancer should be submitted to the NSABP Biostatistical Center for review.

19.2 Cardiac events

There is a formal monitoring plan to assess the incidence of cardiac toxicity in both arms of Protocol B-31. The following definitions of cardiovascular events will be used (see Section 24.0 for details):

19.2.1 ***Cardiac left ventricular function***

A cardiac left ventricular function event will be considered to have occurred either in the study arm or the control arm if the following conditions are seen at any time on or after day 1 of cycle 5, but prior to the diagnosis of treatment failure or second primary cancer:

- A patient has been diagnosed with symptomatic congestive heart failure confirmed by MUGA scan or echocardiogram and chest x-ray.

19.2.2 ***Cardiac deaths***

- *Definite cardiac death:* Death due to congestive heart failure, myocardial infarction, or documented primary arrhythmia.

- *Probable cardiac death:* sudden death without documented etiology.

Submit Form CR for all cardiac deaths.

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19.3 Documentation requested following death

- Autopsy reports should be secured whenever possible and submitted to the NSABP Biostatistical Center.

- A copy of the death certificate should be forwarded to the Biostatistical Center if it is readily available or if it contains important cause-of-death information not documented elsewhere.

- Please submit the last clinic/office note before the death or the physician's note summarizing the death.

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20.0 ADVERSE EVENT REPORTING REQUIREMENTS

Please refer to Appendix E, "Information Basics for Adverse Event Reporting", for general information regarding adverse event reporting.

20.1 Definitions for adverse event reporting

- ***Investigational agent***

  The investigational agent in B-31 is ***trastuzumab***, which is being tested as adjuvant therapy for breast cancer.

- ***Commercial agents***

  The commercial agents in B-31 are ***cyclophosphamide, doxorubicin***, and ***paclitaxel***.

- ***Investigational combination therapy***

  This study includes both investigational and commercial agents. When an ***investigational agent*** (trastuzumab) is administered concurrently or sequentially with a ***commercial agent(s)*** (cyclophosphamide, doxorubicin, or paclitaxel) and an adverse event occurs that is expected for the commercial agents, but is not listed for the investigational agent(s), the adverse event should be considered expected for the combination. However, if based on clinical judgment, the investigator believes the adverse event is possibly, probably, or definitely related to the ***investigational agent*** rather than the ***commercial agent(s)***, the adverse event should then be considered unexpected for the combination.

20.2 Adverse event assessment

The NCI Common Toxicity Criteria (CTC) v2.0 must be used to identify the type and to grade the severity of adverse events.

20.3 Expedited reporting of adverse events

Expedited reporting methods

The NSABP follows procedures for centralized reporting of adverse events. Centralized reporting requires adverse events to be reported to the NSABP Biostatistical Center. The NSABP forwards reports to the appropriate regulatory agencies and pharmaceutical companies involved in the trial. Expedited reporting for B-31 utilizes the NCI's Adverse Event Expedited Reporting System (AdEERS). Submission requirements are as follows:

- **AdEERS 24-Hour Notification**: requires that an AdEERS 24-Hour notification is electronically submitted to the NSABP Lead Group within **24 hours** of learning of the event. Fax all available supporting documentation to the NSABP Biostatistical Center.

- **AdEERS 3 Calendar Day Report**: requires that a complete report is electronically submitted to the NSABP Lead Group within **3 calendar days** of submission of the AdEERS **24-Hour** notification. Fax to the NSABP Biostatistical Center all available supporting documentation not previously submitted with the 24-Hour notification.

- **AdEERS 5 Calendar Day Report**: requires that an expedited report is electronically submitted to the NSABP Lead Group within **5 calendar days** of learning of the event. NCI's guidelines for creating an AdEERS reports can be found at http://ctep.cancer.gov.

- The NSABP Biostatistical Center is identified in AdEERS as the NSABP Lead Group for NSABP protocols requiring AdEERS reporting. AdEERS reports must be submitted to the NSABP Lead Group using the AdEERS electronic web-based application located at http://ctep.cancer.gov. If web access is not available, the NCI Adverse Event Expedited Report-Multiple Agents template (located at http://ctep.cancer.gov) must be completed and faxed to the NSABP Biostatistical Center at **(412) 624-1082** within 24 hours for events requiring 24-Hour notification. If a complete report cannot be submitted within 24 hours, a preliminary report must be submitted within 24 hours and a complete report must be submitted within **3 calendar days** of learning of the event. Include all supporting documentation not previously submitted.

- **Supporting documentation**: Fax supporting documentation to **(412) 624-1082**. Include the patient's NSABP study number and AdEERS ticket number on each page of the supporting documentation.

- **Additional reporting obligations**: Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

20.4 Expedited adverse event reporting for investigational agents

For patients in Group 1 and Group 2 who have received at least one dose of trastuzumab, follow the expedited reporting requirements as outlined in Table 14A.

TABLE 14A. Phase 2 and 3 trials utilizing an agent under a CTEP IND: AdEERS expedited reporting requirements for adverse events that occur within 30 days[1] of the last dose of the ***investigational agent*** (trastuzumab)

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	24-Hour; 3 Calendar Days	5 Calendar Days

1 Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND (trastuzumab) require reporting as follows:

AdEERS 24-Hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

2 Although an AdEERS 24-Hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>3 calendar days</u> of the initial 24-hour report.
  - "5 calendar days" - A complete AdEERS report on the AE must be submitted within <u>5 calendar days</u> of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Please note that Table 14A is continued on the next page.

TABLE 14A. (continued)

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

a) Reports submitted via AdEERS 24-Hour notification are available for review by both the NCI and the NSABP after submission. All other AdEERS reports are first sent to the NSABP Lead Group and then are forwarded to the NCI. The timelines in the table above have been set so that the information can be forwarded to the NCI in a timely manner per the NCI/CTEP's guidelines.

b) On all reports, use the NCI protocol number, AdEERS ticket number, and the protocol-specific ID provided during the trial registration. **Fax supporting documentation to the NSABP Biostatistical Center**.

c) Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).

d) Refer to Section 20.1 for instructions regarding assignment of attribution and expectedness for ***Investigational Combination Therapy***.

e) AdEERS reporting is required for grade 2 unexpected adverse events and grade 3 unexpected adverse events without hospitalization **only** if the adverse event is possibly, probably or definitely related to the **investigational agent** (trastuzumab).

f) **Protocol-specific expedited reporting requirements**: Fax Form CR (cardiac event form) and supporting documentation to the dedicated fax number (see page vi) within 14 days of the event any time one or more of the following are experienced by a patient:

- Diagnosis of congestive heart failure (CHF) is confirmed or the patient exhibits significant symptoms of CHF even if not subsequently confirmed. Attach a copy of all pertinent documentation relative to the clinical diagnosis that was made (i.e., copy of MUGA scan report with Form M, echocardiogram report, chest x-ray, cardiology consult note, medical oncologist's progress note, history and physical, discharge summary).
- The patient had a definite or probable cardiac death. Attach pertinent documentation such as a copy of the death certificate, death summary, copy of MUGA scan report with Form M, echocardiogram report or consult note. If not immediately available, the death certificate may be submitted later, but should be sent as soon as possible.

g) **Protocol-specific expedited reporting exceptions:** For this study, the adverse events listed below, including hospitalizations for these events, **do not** require expedited reporting via AdEERS:

- Blood/Bone Marrow: grade 4 hemoglobin (Hgb), leukocytes (total WBC), neutrophils/granulocytes, and platelets. **These events are exclusions from expedited reporting only during chemotherapy. Beginning 30 days following the last dose of chemotherapy and when a patient is receiving trastuzamab alone, these grade 4 events should be reported in an expedited manner via AdEERS.**
- Constitutional: grade 2 sweating (diaphoresis), grade 2 weight gain
- Dermatology/Skin: grade 2 hair loss/alopecia, dry skin, nail changes, hyperpigmentation, hypopigmentation, pruritus, and urticaria (hives, welts, wheals); grade 2 and 3 wound-infectious and wound-non-infectious; grades 2, 3, and 4 radiation dermatitis (with or without hospitalization).
- Endocrine: grade 2 hot flashes/flushes
- Gastrointestinal: grade 2 dehydration, duodenal ulcer, flatulence, gastric ulcer, gastritis, mouth dryness, stomatitis/pharyngitis, and taste disturbance (dysgeusia); grade 2 and 3 constipation, ileus, and dyspepsia.
- Hemorrhage: grade 2 and 3 vaginal bleeding
- Infection/febrile neutropenia: grade 2 infection without neutropenia; grade 2 and 3 catheter-related infection.
- Metabolic: grade 2 and 3 hyperglycemia.
- Neurologic: grade 2 neuropathy- motor.
- Pain: grade 2 and 3 dysmenorrhea and dyspareunia.
- Renal/Genitourinary: grade 2 vaginitis (not due to infection); grade 2 and 3 urinary frequency/urgency.
- Sexual/Reproduction Function: grade 2 libido and vaginal dryness; grade 2 and 3 female sterility and irregular menses.

20.5 Expedited adverse event reporting requirements for commercial agents:

For all patients in Group 1 and Group 2 who have **not** received at least one dose of trastuzumab, follow the expedited reporting requirements as outlined in Table 14B.

TABLE 14B. AdEERS expedited reporting requirements for adverse events that occur within 30 days of the last dose of study therapy with a ***commercial agent*** (cyclophosphamide, doxorubicin, and paclitaxel)

Attribution	**Grade 2**	**Grade 3**		**Grade 4[b]**		**Grade 5[a,b]**		**Protocol-Specific Requirements/ Exceptions**
	Unexpected	*Unexpected*	*Expected*	*Unexpected*	*Expected*	*Unexpected*	*Expected*	-See footnote **(c)** for other requirements -See footnote **(d)** for special ***requirements***
Unrelated or Unlikely				AdEERS		AdEERS	AdEERS	
Possible, Probable, Definite		AdEERS if hospitalized		AdEERS-24 and AdEERS		AdEERS-24 and AdEERS		

AdEERS-24: Indicates an AdEERS 24-Hour notification must be electronically submitted to the NCI and to the NSABP Lead Group *within 24 hours* of learning of the event.

AdEERS: Indicates a complete expedited report must be electronically submitted to the NSABP Lead Group *within 5 calendar days* of learning of the event.

Hospitalization: Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).

All Reports: On all reports, use the NCI protocol number, AdEERS ticket number, and the protocol-specific patient ID provided during trial registration. ***Fax supporting documentation to the NSABP Biostatistical Center.***

a All deaths within 30 days of the last dose of study therapy require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. **Although an AdEERS 24-Hour notification is not required for death clearly related to progressive disease, a complete AdEERS report is required as outlined in the table.**

b Adverse events that occur greater than 30 days after the last dose of study therapy with attribution of possible, probable or definite to study therapy require reporting as follows:

- AdEERS 24-Hour notification followed by a complete AdEERS report within 5 calendar days of learning of the event for:
  - grade 4 unexpected events
  - grade 5 unexpected events
- AdEERS 5-calendar day report for:
  - grade 5 expected events

c Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment.

d **Protocol-specific expedited reporting requirements:** Fax Form CR (cardiac event form) and supporting documentation to the dedicated fax number (see page vi) within 14 days of the event any time one or more of the following are experienced by a patient:

- Diagnosis of congestive heart failure (CHF) is confirmed or the patient exhibits significant symptoms of CHF even if not subsequently confirmed. Attach a copy of all pertinent documentation relative to the clinical diagnosis that was made (i.e., copy of MUGA scan report with Form M, echocardiogram report, chest x-ray, cardiology consult note, medical oncologist's progress note, history and physical, discharge summary).
- The patient had a definite or probable cardiac death. Attach pertinent documentation such as a copy of the death certificate, death summary, copy of MUGA scan report with Form M, echocardiogram report or consult note. If not immediately available, the death certificate may be submitted later, but should be sent as soon as possible.

20.6 Reporting secondary AML/MDS/ALL

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP).

Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- complete NCI/CTEP Secondary AML/MDS Report Form;
- copy of the pathology report confirming the AML/MDS/ALL; and
- copy of the cytogenetics report (if available).

Submit the information to the NSABP Biostatistical Center. The NSABP will submit the form and any accompanying reports to the IDB of the NCI.

Note: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report Form must be submitted for the most recent trial. The NSABP must also be provided with a copy of the report even if the NSABP study was not the patient's most recent trial.

20.7 **Pregnancy occurring while patient is on protocol therapy**

If the patient becomes pregnant while receiving protocol therapy, discontinue therapy and contact the NSABP Clinical Coordinating Division immediately for instructions (see Information Resources on page vi).

20.8 **Routine reporting of adverse events**

Table 14C. Routine adverse event reporting requirements for all B-31 patients.

Expectedness and attribution to both Herceptin and chemotherapy							
Attribution	**Grade 2**		**Grade 3-4**		**Grade 5[a]**		**Special Routine Reporting Requirements**
	Unexpected	*Expected*	*Unexpected*	*Expected*	*Unexpected*	*Expected*	
Unrelated, Unlikely			Form AE	Form AE	Form AE	Form AE	See footnote **(c)** for special requirements
Possible, Probable, or Definite	Form AE	Form AE	Form AE Form F	Form AE	Form AE Form F	Form AE Form F	

Form AE: Mail Form AE to the NSABP Biostatistical Center as follows: at the end of each chemotherapy report period[b] (all patients); every 3 months during Herceptin after chemotherapy is completed (patients who initiate Herceptin); and 3 months after completion of chemotherapy (patients who do not initiate Herceptin) or chemotherapy and Herceptin (patients who initiate Herceptin). Attach supporting documentation for all grade 3, 4, and 5 adverse events if documentation has not previously been submitted for that adverse event.

Form F: Report any adverse event that occurs more **than 3 months after the last cycle of chemotherapy (patients who do not initiate Herceptin) or of chemotherapy and Herceptin (patients who initiate Herceptin)** that is severe (grade 3 or greater), unexpected, and possibly related to the protocol therapy. Report **all** deaths on Form F. Attach supporting documentation.

Hospitalization: Mail supporting documentation for any adverse events which precipitate a hospitalization ≥ 24 hours.

a This includes all deaths within 30 days of the last dose of protocol therapy, regardless of attribution. Any death that occurs more than 30 days after the last dose of protocol therapy and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b For chemotherapy given on a q 3 week schedule, the report period is defined as the time from the administration of a chemotherapy dose up to the administration of the next dose. For Taxol given on a weekly schedule, the report period includes 3 doses of chemotherapy; if there are no delays, this will result in routine AE reporting at the end of Taxol weeks 3, 6, 9, and 12. (See instructions on Form AE.)

c Special routine reporting requirements: Report on Form AE and provide supporting documentation for the following adverse events ***regardless of attribution and expectedness:***

- Cardiovasular General: grade 2 cardiac left ventricular dysfunction
- Pulmonary: grade 2 dyspnea

20.9 **Reporting second primary malignancies**

Report all second primary malignancies (including AML/MDS/ALL) on the NSABP follow-up form (Form F). Attach supporting documentation that confirms the second primary cancer diagnosis.

21.0 DRUG INFORMATION

21.1 Adriamycin (generic name: doxorubicin)

Adriamycin should be obtained from commercial sources. Please refer to the current FDA approved package insert provided with the medication or the *Physician's Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing, and storage of the drug.

21.2 Cyclophosphamide (intravenous form)

Cyclophosphamide should be obtained from commercial sources. Please refer to the current FDA approved package insert provided with the medication or the *Physician's Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing, and storage of the drug.

21.3 Taxol (generic name: paclitaxel)

Taxol should be obtained from commercial sources. Please refer to the current FDA-approved package insert provided with the medication or the *Physician's Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing, and storage of the drug.

21.4 Herceptin (generic name: trastuzumab) [NSC#688097] [IND 6667]

Herceptin is a recombinant DNA-derived humanized monoclonal antibody produced by a genetically engineered Chinese hamster ovarian cell line that secretes the antibody into the culture medium. The antibody is then harvested from the culture medium and purified using chromatographic and filtration techniques. The product is verified for purity, identity, and potency that meets FDA standards.

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21.4.1 *Procurement*

Note: Investigational Herceptin must only be used for Group 2 patients and Group 1 patients who are eligible for and choose to receive B-31 investigational Herceptin. At the investigator's discretion, patients who do not meet the criteria for initiation of investigational Herceptin may be given a commercial supply of Herceptin.

Investigational Herceptin will be supplied free of charge by Genentech, Inc., through the Division of Cancer Treatment and Diagnosis (DCTD), NCI, for this protocol.

Herceptin (NSC #688097) may be requested by the principal investigator (or his/her authorized designee[s]) for Protocol NSABP B-31 at each participating institution. Completed Clinical Drug Requests (NIH-986) should be submitted to the Pharmaceutical Management Branch (PMB) by fax to (301) 480-4612 or mailed to:

Pharmaceutical Management Branch
CTEP, DCTD, NCI
6130 Executive Boulevard
Executive Plaza North, Room 7149
Rockville, MD 20852

For questions call (301) 496-5725.

PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Herceptin may not be used outside the scope of this protocol, nor can Herceptin be transferred or licensed to any party not participating in the clinical study.

Drug inventory records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from the DCTD, using the NCI Drug Accountability Record Form. (Refer to the NCI Investigator's Handbook for procedures for Drug Accountability and Storage.) The Drug Accountability record (DAR) should be maintained on a milligram-by-milligram basis. Hence, the quantity dispensed, received, and the balance should be reflected by milligrams, not by vial(s). Each vial will potentially contain overfill. Overfill can be added back into the drug balance on the DAR by completing a separate line item with a "date", "overfill", and "mg". Reconstituted vials that have expired should be discarded appropriately, and documented on the DAR.

21.4.2 ***Shipping***

Vials of Herceptin are shipped at room temperature by overnight express delivery ***Monday through Thursday***, and must be placed in a 2° C - 8° C (36° F - 46° F) refrigerator immediately upon receipt to ensure optimal retention of physical and biochemical integrity.

21.4.3 ***Storage***

Vials of freeze-dried Herceptin and the reconstituted formulation of Herceptin must be stored in a 2° C - 8° C (36° F - 46° F) refrigerator. **DO NOT FREEZE**. Expiration dates on individual vials must be strictly adhered to. The reconstituted formulation (440 mg vial) is designed for multiple use. Unused reconstituted drug may be stored for 28 days.

21.4.4 ***Reconstitution***

Herceptin will be supplied for use as a freeze-dried preparation at a nominal content of 440 mg per vial for intravenous administration. The study drug is formulated in histidine, trehalose, and polysorbate 20.

Each vial is reconstituted with 20 ml of Bacteriostatic Water for Injection (BWI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. After adding the diluent, gently swirl the vial to dissolve the lyophilized Herceptin. The reconstituted solution contains 21 mg/mL Herceptin and will be added to 250 mL of 0.9% sodium chloride, USP **DO NOT USE DEXTROSE 5% SOLUTION**. Gently invert the IV bag to mix the solution. Herceptin may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). **DO NOT SHAKE**. Vigorous handling of solutions of Herceptin results in aggregation of the protein and may create cloudy solutions. Reconstituted Herceptin should be clear to slightly opalescent and colorless to pale yellow.

21.4.5 ***Administration***

Patients will receive Herceptin administered by intravenous infusion via a vascular access device 4 mg/kg loading dose on day 1 of the first Taxol cycle, followed by 2 mg/kg weekly for 1 year from its initiation.

The initial dose of Herceptin will be infused over a 90-minute period. If this first dose is well tolerated, subsequent infusion periods may be shortened to 30 minutes. **DO NOT ADMINISTER AS IV PUSH OR BOLUS**.

Because Herceptin is a protein, local and/or systemic allergic manifestations are possible, e.g., rash, pruritus, urticaria, anaphylactoid signs and symptoms, or anaphylaxis. **DO NOT ADMINISTER TO PATIENTS WITH KNOWN SENSITIVITY TO BENZYL ALCOHOL**. Do NOT mix or dilute Herceptin with other drugs.

Patients must remain under medical supervision for 1 hour following completion of the initial dose of Herceptin. If no adverse events occur with the first infusion, the postinfusion observation period for the second infusion may be shortened to 30 minutes and can be eliminated with subsequent infusions.

TABLE 15. Herceptin infusion time and postinfusion observation period

Infusion	Herceptin dose	Infusion time (minutes)	Observation period (minutes)
First	4 mg/kg	90	60
Second	2 mg/kg	30	30*
Third and subsequent	2 mg/kg	30	None required*

* If no adverse events occur with the first infusion.

05/22/00

21.4.6 ***Adverse effects***

- *Important safety warning regarding hypersensitivity, infusion reaction, and pulmonary adverse events*

  Herceptin postmarketing reports describe patient experiences in the metastatic setting that were more severe than those experienced during clinical trials. These serious adverse events, which resulted in fatal outcomes, can be categorized as: 1) hypersensitivity reactions including anaphylaxis; 2) infusion reactions; and 3) pulmonary events including adult respiratory distress syndrome. Specific adverse events included urticaria, bronchospasm, angioedema, hypotension, dyspnea, wheezing, pleural effusions, pulmonary infiltrates, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia requiring supplemental oxygen or ventilatory support, and anaphylaxis. These events were most likely to occur during the first infusion or within 12 hours following the infusion; however, some events occurred more than 24 hours following the infusion. Although most patients having fatal outcomes had pre-existing pulmonary involvement, it is not known if patients receiving adjuvant therapy will experience these adverse events. Careful patient monitoring during and following the first infusion of Herceptin is very important.

- *Hypersensitivity*

  Refer to the ***important safety warning*** at the beginning of the adverse effects section (Section 21.4.6).

  In the arm of Genentech's clinical trial H0648 in which Herceptin was combined with Taxol (91 patients), 35 cases of rash, 1 case of urticaria, and 10 cases of allergic reaction were reported. Only 2 of these cases were deemed related to Herceptin. In the arm in which Herceptin was combined with AC (143 patients), 38 cases of rash, 2 cases of urticaria, and 7 cases of allergic reaction were reported. Only 1 of these cases was deemed related to Herceptin.[10]

- *Infusion-related reactions*

  Refer to the ***important safety warning*** at the beginning of the adverse effects section (Section 21.4.6).

  Fever and chills during the first infusion are the most common adverse events. These symptoms were observed in about 40% of patients and were usually mild-to-moderate in severity. The infusion-associated symptom complex can also include nausea, vomiting, rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. These symptoms occurred infrequently with subsequent Herceptin infusions.

02/28/05

- *Pulmonary reactions*

  There have been rare reports of severe pulmonary reactions leading to death associated with Herceptin treatment. Such reactions may include bronchospasm, hypoxia, pulmonary infiltrate, adult respiratory distress syndrome (ARDS), pneumonitis/fibrosis, non-cardiogenic pulmonary edema, and pleural effusion. These reactions may or may not occur as sequelae of infusion reactions. Symptomatic lung disease at baseline or extensive pulmonary metastases increase the risk for development of a severe pulmonary reaction, although rare incidents of pneumonitis and ARDS with fatal outcome have also been reported in the adjuvant setting in patients treated with a combination of Herceptin and paclitaxel followed by Herceptin alone.

  Refer to the ***important safety warning*** at the beginning of the adverse effects section (Section 21.4.6).

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- *Cardiac events*

  – CARDIOMYOPATHY: This appears to be the most serious adverse effect of Herceptin administration. Signs and symptoms of cardiac dysfunction include dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, and reduced ejection fraction. Congestive heart failure may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The risk of cardiac dysfunction may be increased in geriatric patients.[10]

  – MYOCARDIAL INFARCTION/MYOCARDIAL ISCHEMIA: As of January 2003, there were 12 events of myocardial infarction/myocardial ischemia in 11 patients reported in Genentech's global database. Four events were spontaneously reported adverse drug reactions and 8 events were reported as serious adverse events in clinical trials. One clinical trial patient experienced 2 episodes of myocardial infarction during study enrollment. Of the clinical trial adverse events, 3 were assessed as related, 2 were unknown, and 3 were not related. Two clinical trial adverse events culminated in fatal outcomes. Based on the review of available data, Genentech could not establish or exclude the possibility of a cause and effect relationship between the administration of Herceptin and the occurrence of myocardial infarction/myocardial ischemia. Continuous collection of data from ongoing clinical trials as well as the postmarketing setting will allow for monitoring of these events in various settings and with various chemotherapy regimens.

- *Anemia and leukopenia*

  Anemia and leukopenia, secondary to Herceptin plus chemotherapy, may be increased.

- *Diarrhea*

  An increased incidence of mild to moderate diarrhea was observed in patients receiving Herceptin and chemotherapy.

- *Infection*

  There may be an increased incidence of primarily mild upper respiratory infections and vascular access catheter infections.

  Please refer to the current Physician's Desk Reference for further information about other adverse effects of Herceptin.

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21.5 **Hormonal therapy**

Hormonal therapeutic agents should be obtained from commercial sources. Please refer to the current FDA approved package insert provided with the medication or the *Physician's Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing, and storage of the drug.

22.0 PATIENT ENTRY PROCEDURES

04/06/10 *Note: See Appendix G for instructions related to participation in the additional long-term cardiac follow-up initiated with Amendment #11 and Appendix H for consent form addendum #2 related to Amendment #11.*

06/03/05 *Note: The B-31 study was closed to accrual on April 29, 2005. See Section 2.13 for details.*

22.1 Patient consent form

Before the patient is entered, the consent form (see Appendix H), including any addenda, must be signed and dated by the patient and a witness. **In addition, *before entry*, a copy of the signed, witnessed, and dated consent form must be faxed to the NSABP Biostatistical Center**.

22.2 Entry

Entry of patients to treatment groups will be accomplished by **faxing** the necessary information to the NSABP Biostatistical Center Patient Entry Area at **(412) 383 2065**. The following must be faxed to ensure proper execution of patient entry:

- a ***completed*** Form A (Entry and Eligibility Form) with any necessary attachments;
- a properly signed and dated consent form;
- *04/23/01* Form H2A with lab report attached;
- estrogen/progesterone lab report; and
- Form M and MUGA scan (baseline MUGA scan results)

In addition to verifying the above materials, the NSABP Biostatistical Center will verify that the institution has a current IRB approval for the study. Entry will *not* take place if the IRB approval is not current for the institution with IRB oversight responsibility.

The entry material must be received by the Biostatistical Center's fax (412) 383-2065 by **4:00 p.m. EST, Monday Friday, excluding holidays**, for same-day registrations. Those received after that time will be faxed back the next business day. **This process could involve some unavoidable delays**. Therefore, it is necessary to plan adequate time between the patient entry process and scheduling the onset of the patient's treatment.

22.3 Patient study number and treatment schedule

After all of your faxed eligibility criteria have been completed, you will receive the following via fax: 1) the patient's nine-digit study number; 2) the treatment assignment and schedule; and 3) the initial BSA and drug dose. See Section 13.0 for instructions regarding recalculation of doses for subsequent cycles.

23.0 REQUIRED RECORDS

04/06/10 *Note: See Appendix G for additional instructions related to the additional long-term cardiac follow-up initiated with Amendment #11.*

06/03/05 *Note: The B-31 study was closed to accrual on April 29, 2005. See Section 2.13 for details.*

TABLE 16. Required forms and materials *05/22/00, 04/23/01, 01/14/03, 05/16/03, 02/28/05, 06/03/05*

Form/material	Description	Submission
Pre-entry		
Consent form (B-31)	Signed/dated informed consent	Prior to randomization.
Form A (B-31)	Registration form	
Form M with MUGA scan report	MUGA scan results (baseline)	
Form H2A with HER2 assay report	Results of HER2 determination	
Entry		
Form CH-B	Baseline cardiac history	Within 30 days of randomization
Form D-1 (B-31)	Pathology report form	Submit as a single packet within 30 days of randomization
Dictated Operative Report	Typed operative report(s) (attached to Form D-1)	
Dictated Pathology Report	Typed pathology report(s) (attached to Form D-1)	
Form BLT (B-31) with tissue blocks	Tissue block transmittal form	
Pathology Blocks	Tissue block for primary tumor	
	Tissue block for involved lymph node	
Form BNK (B-31) with serum specimens (send to Serum Bank [address on page vi] not to the Biostatistical Center.)	Serum specimens (with transmittal form)	Required after randomization (prior to beginning therapy) and at time of first treatment failure.
Treatment		
Form AC (B-31)	Treatment form for AC therapy	Submit this form when AC has ended or if the patient did not begin AC.
Form TAX (B-31)	Treatment form for Taxol therapy	Submit this form when Taxol has ended or if the patient did not begin Taxol.
Form HT (B-31)	Hormonal therapy treatment form	If tamoxifen or anastrozole is specified on Form A, submit Form HT after the last dose of hormonal therapy or if hormonal therapy did not begin.
Form HER (B-31)	Treatment form for all Group 2 patients and Group 1 patients who receive investigational Herceptin. (Report treatment with commercial Herceptin on Form F.)	Every 3 months.
Form PAC	Post-AC cardiac status *(when applicable)*	When post-AC MUGA is done (see Section 6.1.1), fax to (412) 383-1133 within 14 days after the MUGA scan.
Form M with MUGA scan report	MUGA scan results (both treatment groups) *(when applicable)*	
Form PT	Post-Taxol cardiac status *(when applicable)*	When post-Taxol MUGA is done (see Section 6.1.1), fax to (412) 383-1133 within 14 days after the MUGA scan documenting LVEF for initiation of Herceptin sequentially following Taxol.
Form M with MUGA scan report	MUGA scan results *(when applicable)*	
Form CR (B-31)	Cardiac event report for both treatment groups (see Section 6.1.4)	Fax to (412) 383-1133 within 14 days of learning of symptoms suggesting congestive heart failure, definite cardiac death, or probable cardiac death. (See instructions at top of form.)
Form AE (B-31)	Routine reporting form for adverse events as specified in Table 14C.	At the end of each report period, as defined in the instructions for completing and submitting Form AE (see page 2 of Form AE).

TABLE 16. (cont.) Required forms and materials *03/15/00, 05/22/00, 05/16/03, 02/28/05, 06/03/05*

Form/material	Description	Submission
Radiation therapy		
Form E-1 (B-31)	Radiation therapy report	Form E-1 is required for all B-31 patients. If a B-31 patient does not receive radiation therapy, submit Form E-1 within 90 days of randomization. If the patient receives radiation therapy, submit all radiation therapy materials as one packet within 4 weeks of completion of radiation therapy.
Radiation Daily Treatment Sheets	Treatment prescription and daily record sheet	
Isodose Breast Contour	Isodose distribution for treatment plan & a breast contour	
Dosimetry	Copies of dosimetry calculations	
Portal Films (only 1 set) (required for ***left-sided lesions only***)	Copies of field verification films (portal film)	As of Amendment #9, submission of portal films and position photographs is no longer required.
Treatment Position Photographs (required for ***left-sided lesions only***)	Photographs of patient in treatment position with field margins	
Follow-up		
Form M with MUGA scan report	MUGA scan results	Fax to (412) 383-1133 within 14 days after MUGA scan during the first 2 years on study and anytime a MUGA scan is performed for patients exhibiting symptoms of CHF (see instructions at top of form). *Note: For patients having MUGA scans according to Schedule B (see Section 6.1.1), the 15-month MUGA and Form M are required even if this time point is more than 2 years after study entry.*
Form CR (B-31) with Form M and MUGA scan report (if applicable)	Cardiac event report (both treatment groups).	Fax to (412) 383-1133 within 14 days of learning of symptoms suggesting congestive heart failure, definite cardiac death, or probable cardiac death. (See instructions at top of form.)
Form F	Follow-up form; see Table 14C for reporting requirements for late adverse events.	Every 6 months from the date of randomization for first 5 years and every 12 months thereafter (with attached documentation when indicated).
Form CH-F	Follow-up cardiac history form	With Form F every 6 months from the date of randomization for the first 5 years and every 12 months thereafter.
Form BNK (B-31) with serum specimens (send to Serum Bank [address on page vi] not to the Biostatistical Center)	Serum specimens (with transmittal form)	Required at time of first treatment failure.
Form BLT (B-31) with tissue block	Tissue block at time of first treatment failure (if failed organ/tissue site is biopsied)	Submit within 30 days of first treatment failure (if failed organ/tissue site is biopsied).
NSABP Biostatistical Center One Sterling Plaza 201 North Craig Street Pittsburgh, PA 15213 Phone: (412) 624-2666 Fax: (412) 624-1082		

24.0 STATISTICAL CONSIDERATIONS

04/06/10

Note: See Appendix G for statistical considerations related to the additional long-term cardiac follow-up initiated with Amendment #11.

06/03/05

Note: The B-31 study was closed to accrual on April 29, 2005. Please see Section 2.13 for details.

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24.1 Overview of the study design

Patients will be accrued in two stages. In the first stage, 1000 patients will be randomized to either the experimental arm (AC→Taxol + Herceptin) or the control arm (AC→Taxol). The primary goal of the first stage of the study is the assessment of left ventricular dysfunction on the experimental arm as compared to the control arm. Allowance is made for the possibility of early stopping following the assessment of either 200, 600 or 1000 patients, if excessive cardiotoxicity is observed on the experimental arm.

Assuming that an acceptable level of cardiotoxicity is observed following the first stage of accrual, the second stage will be initiated to accrue an additional 1700 patients. The primary goal of the second stage of the study is to obtain a sufficient number of patients which, in combination with those patients previously accrued, will allow an assessment of disease-free survival (DFS) and survival on the experimental arm with adequate power to detect a 25% decrease in event rate and mortality rate relative to the control arm.

Except as noted below, the second stage of the study will not be initiated until all patients accrued in the first stage have been followed for at least 6 months beyond day 1 of cycle 5, and have been fully assessed for cardiotoxicity. This may necessitate a temporary interruption in accrual lasting approximately 9 months.

[**Note**: The independent Data Monitoring Committee (DMC) that monitors all NSABP treatment trials met on October 11, 2002, and reviewed the overall data from the study along with the planned second interim cardiac safety analysis. Based on their review, they notified the NSABP that the accrual hiatus was not necessary, and that the trial should proceed immediately with accrual to stage two. The DMC noted the difference in protocol-defined cardiac events observed at the time of their review was no more than 4% between the control and investigational arms, which was the difference initially anticipated.]

24.2 Stratification factors

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Assignment of treatment to patients will be balanced with respect to number of positive nodes (1-3,4-9,10+), administration of hormonal therapy* (initial tamoxifen, initial anastrozole, neither), surgery/radiotherapy (lumpectomy + breast irradiation, lumpectomy + breast irradiation + regional irradiation, mastectomy without irradiation, mastectomy + irradiation) and institution, using a biased-coin minimization algorithm.[38]

(*At the investigator's discretion, anastrozole may be used in sequence with or substituted for tamoxifen therapy for postmenopausal patients.)

Beginning with the adoption of Amendment #6 dated 05/16/03, treatment assignments will also be balanced with respect to the intention to administer weekly or three-weekly Taxol, as specified at the time of randomization.

24.3 Accrual estimates

We expect initial accrual to the cardiac safety assessment stage of the study to be relatively slow. If levels of cardiotoxicity are acceptable in the first stage, and the efficacy assessment stage is opened, it is expected that enrollment rates will increase.

We project an accrual rate of 40 patients per month during the cardiac safety stage, and 75 patients per month in the subsequent efficacy assessment stage. This implies a time interval of 25 months to complete accrual to the first stage and 23 months for the second stage. Allowing for the possibility of a temporary interruption of accrual between the two stages, the sample size target of 2700 patients will be achieved in 4 years, 9 months.

24.4 Stage 1: Cardiac safety monitoring plan

In accordance with the NCI's Data Monitoring Committee's (DMC) policy the DMC will be kept apprised of all relevant efficacy and safety data from this and related clinical trials. The leadership of the NSABP and the North Central Cancer Treatment Group's (NCCTG) adjuvant Herceptin trials have agreed to share all relevant cardiotoxicity data with their respective DMCs.

A group sequential monitoring plan will be implemented to monitor the incidence of cardiac toxicity in patients treated with Herceptin, relative to the rate observed on the control arm. In addition to the DMC, a Cardiac Advisory Panel (CAP), which consists of two cardiologists and a medical oncologist, was established at the inception of this trial. The CAP helped to formulate the cardiac guidelines and will also help provide medical expertise and oversight on difficult cardiac issues that may arise.

01/14/03

24.4.1 *Evaluable patients*

Patients in either arm of the study will be considered evaluable for the cardiotoxicity analysis if:

- they have completed the AC phase of treatment;

  AND

- they have received an acceptable post-AC cardiotoxicity evaluation as defined in Section 12.3 of this protocol. [That is, their post-AC cardiotoxicity evaluation must be such that they would be eligible to begin treatment with Herceptin, if they were assigned to the experimental arm. This requires that 1) they exhibit no significant symptoms related to LV dysfunction, cardiac ischemia or arrhythmia while receiving AC, 2) they have not experienced a $\geq$ 16 percentage point drop in resting LVEF measured relative to their pre-AC baseline evaluation, and 3) they have not experienced a $\leq$ 15 percentage point drop in LVEF measured relative to their pre-AC baseline, to a level below the radiology facility's lower limit of normal];

  AND

- they have begun post-AC therapy (i.e., have received any Herceptin [with or without Taxol] in the treatment arm, ***or any*** Taxol in the control arm).

  Patients who fail to complete the required post-AC cardiotoxicity evaluation prior to beginning post-AC therapy will be considered evaluable for cardiotoxicity analysis.

24.4.2 ***Events to be included in the cardiac safety analysis***

Specific definitions of those events to be monitored in the cardiac safety analysis are given in Section 19.2. That is, the endpoint to be followed in the group sequential cardiac safety monitoring plan is the total frequency of events of the following 3 types:

- Cardiac left ventricular function: Occurrence of symptomatic congestive heart failure with any objective finding (e.g., rales, S3, elevated jugular venous pressure) confirmed by MUGA scan or echocardiogram and chest x-ray;

- Definite cardiac death: Death due to congestive heart failure, myocardial infarction, or documented primary arrhythmia;

- Probable cardiac death: Sudden death without documented etiology.

A cardiac event will be included in the formal statistical analysis comparing patients who receive Herceptin to those who receive only Taxol if the event occurs at any time following day 1 of cycle 5, but prior to the diagnosis of treatment failure or second primary cancer.

24.4.3 ***Monitoring plan***

Three formal statistical comparisons will be made at the following intervals:

- *Comparison #1*: after 100 evaluable patients in each arm (200 total) have been followed for at least 6 months beyond day 1 of cycle 5, and have received their second post-Taxol MUGA;

- *Comparison #2*: after 300 evaluable patients in each arm (600 total) have been followed for at least 6 months beyond day 1 of cycle 5, and have received their second post-Taxol MUGA;

- *Comparison #3*: after 500 evaluable patients in each arm (1000 total) have been followed for at least 6 months beyond day 1 of cycle 5, and have received their second post-Taxol MUGA.

Define p_0 = probability that a control patient will experience a cardiac event, p_H = probability that a Herceptin-treated patient will experience a cardiac event, and $\Delta = p_H - p_0$. We estimate that p_0 will be approximately 1%. (On Protocol B-28 as of 11/02/99, 0.4% of patients assigned to the AC→Taxol arm have experienced cardiac events meeting the above definition, following the initiation

of their treatment with Taxol. We anticipate a slightly greater incidence of reported events on the control arm of B-31 due to an increased level of scrutiny.)

Based on data from Study H0648, it is believed that the increase in cardiac event rate (Δ) in the B-31 trial will be approximately 4%. This hypothesized increase of 4% is considered acceptable by the Cardiac Advisory Panel, but higher rates are considered unacceptable. This motivates the following proposed monitoring rules:

At each interim analysis, the following hypothesis test is performed:

Test H_0: $\Delta = 4\%$ vs H_A: $\Delta > 4\%$ at the nominal one-sided level of significance $\alpha = .05$. If H_0 is rejected in favor of H_A: $\Delta > 4\%$, accrual will be terminated pending re-evaluation of trial feasibility. Otherwise, accrual continues.

Table 17 shows the probability that accrual will be terminated during the cardiac monitoring stage of the study. This probability is tabled as a function of the true increase (Δ) in cardiac event probability due to the administration of Herceptin. Column 1 gives "what-if" values for Δ, column 2 lists the corresponding probability that accrual will be terminated on or before the completion of the cardiac monitoring stage, and columns 3-5 break down this probability into probabilities of termination following the first, second, or third interim analysis. In these calculations, the nuisance parameter p_0 was assumed to equal 1%.

- Example 1: If the rate of cardiac events on the control arm were 1% and the rate on the treatment arm were 5% (so that $\Delta = 4\%$), there is a .12 chance that accrual will be terminated on or before the end of the cardiac monitoring stage of the trial. The probability that this will happen after the first interim analysis is .06, after the second analysis .04, and after the third and final analysis, .02.

- Example 2: If $\Delta = 3\%$, there is only a .03 probability of early termination.

- Example 3: If $\Delta = 7\%$, the probability of early termination is .85. However, even in this case the trial is likely to proceed to the second or possibly even the third interim analysis before accrual is terminated (the probability of termination following the first look is .34).

01/14/03

24.4.4 *Temporary interruption in accrual following accrual of the 1000th patient*

[Note: Please refer to the notation made in Section 24.1 regarding the status of the hiatus.]

Since patients will not become evaluable for cardiotoxicity until they have completed 6 months treatment beyond day 1 of cycle 5 and have completed their second post-Taxol MUGA, there will be a lag of approximately 9 months between the accrual of the 1000th patient and the final cardiac analysis. This consideration necessitates an accrual hiatus separating the cardiac monitoring stage of the study (accrual of the first 1000 patients), and the subsequent efficacy evaluation stage (accrual of the final 1700 patients). Thus, accrual will be temporarily interrupted after the accrual of the 1000th patient until the data are

sufficiently mature to complete the third interim cardiotoxicity analysis. At this point, assuming that this analysis does not lead to the termination of accrual according to the rules described in Section 24.4.3, accrual to the second stage of the study will begin.

An exception will be made if, at the time of the second interim cardiotoxicity analysis, the difference in *observed* cardiotoxicity event rates between the experimental and control arms is less than 4%. In this case, accrual will not be interrupted after the enrollment of the 1000th patient. Even so, the third analysis will still be completed when there is sufficient follow-up to do so. In the unlikely event that the third analysis leads to the rejection of the hypothesis H_0: $\Delta = 4\%$ in favor of H_A: $\Delta > 4\%$, accrual will be terminated at that time.

This exception is reasonable, because it is highly unlikely that events will occur in such a way that the difference in observed rates is less than 4% over the first 600 patients, and yet differences which are statistically significantly greater than 4% are obtained based on all 1000 patients. In fact, it can be shown that for each of the possible states of nature summarized in Table 17, the probability of this occurrence is never greater than .004.

24.4.5 ***Analysis of late events***

Cardiac events may occur at any time following day 1 of cycle 5. Since at any interim analysis, some patients will have been followed for only 6 months beyond this point in time, the question arises as to how to treat events which occur after an interim analysis is completed. Such events will be included in all subsequent analyses, but once completed, interim analyses will not be repeated.

24.4.6 ***Derivation of Table 17***

Table 17 is based on simulation of the joint sampling distributions of statistics of the form

$$Z_j = (X_{Hj} - X_{0j} - n_j\Delta_0)/\{\sqrt{n_j} \bullet \tilde{\sigma}_0\} \text{ , } j = 1,2,3$$

where j is the number of the interim analysis, n_j is the number of evaluable patients on either arm as of that time (total sample size=$2n_j$), X_{0j} is the number of observed events on the control arm, X_{Hj} is the number of observed events on the treatment arm, Δ_0 is the value of Δ under the null hypothesis,

$$\tilde{\sigma}_0 = \{\tilde{p}_0 (1 - \tilde{p}_0) + (\tilde{p}_0 + \Delta_0)(1 - \tilde{p}_0 - \Delta_0)\}^{1/2}$$

is the estimated variance of $(X_{Hj} - X_{0j} - n_j\Delta_0)/\sqrt{n_j}$ under the null hypothesis, and $\tilde{p}_0$ is the maximum likelihood estimator of p_0, subject to the constraint that $\Delta = \Delta_0$.

Each entry in Table 17 is based on 40,000 simulated replications of the interim analysis plan. The tabulated results are in surprisingly good agreement with asymptotic results obtained by numerical integration using the techniques of Armitage.[39]

The probabilities in Table 17 are essentially independent of the unknown nuisance parameter p_0 only in the null case ($\Delta = \Delta_0 = 4\%$). The value $p_0 = 1\%$ was used in constructing the table. If the true value of p_0 is materially greater than this, the monitoring plan will be somewhat less powerful in detecting values of $\Delta > 4\%$. To illustrate, if $p_0 = 1.5\%$ and $\Delta = 7\%$, the probability that the hypothesis H_0:$\Delta = 4\%$ will be rejected at one of the three interim analyses is 0.81.

24.5 Analysis of treatment efficacy data

24.5.1 *Efficacy endpoints*

02/28/05

The primary endpoint for analysis of clinical efficacy is DFS. A later confirmatory analysis of survival (S) will also take place. The survival endpoint is defined as death from any cause. DFS events are local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral breast cancer, other second primary cancer (excluding melanoma in situ, squamous or basal cell carcinoma of the skin, carcinoma *in situ* of the cervix or lobular carcinoma *in situ* of the breast), and death from any cause prior to recurrence or second primary.

24.5.2 *Original statistical analyses (modified 02/28/05 per Section 24.5.6)*

01/14/03
02/28/05

Definitive analysis will take place following the 480th death (total on both arms), and will be based on the intent-to-treat principle, with all patients analyzed as randomized. An eligibles-only analysis will also be completed, and any substantive discrepancies between the results of this analysis and the intent-to-treat analysis will be fully investigated.

Differences in S and DFS between the control arm and the experimental arm will be assessed by stratified log-rank tests, controlling for number of positive nodes, administration of hormonal therapy*, surgery, and radiotherapy. Two-sided .05-level tests will be used.

(*At the investigator's discretion, anastrozole may be used in sequence with or substituted for tamoxifen therapy for postmenopausal patients.)

Cox models will be used to estimate and to control for the effect of additional prognostic variables (strength of HER2 expression according to centralized assay, receptor status, clinical tumor size, age). Wald tests will be used to assess the prognostic importance of each variable, and treatment-by-covariate interactions will be tested by adding interaction terms one at a time to the models. Sample size may be inadequate to support detailed subgroup analyses. Such subgroup analyses will be carried out only in the event that preliminary tests of treatment-by-covariate interactions are statistically significant ($\alpha \leq .05$ for treatment-by-HER2 interaction, $\alpha \leq .01$ for other treatment-by-covariate interactions). Patient and tumor characteristics, eligibility and follow-up rates, and treatment acceptance rates will be tabled for comparison between treatment arms. Kaplan-Meier curves will be computed for both S and DFS. Ninety-five percent confidence intervals will be constructed for relative risks, 5-year S and DFS, and for absolute differences in 5-year S and DFS between treatments. A site-of-first- treatment-failure table will be constructed to summarize local,

regional, and distant failures; contralateral disease; non-breast second primary cancers; and deaths prior to recurrence or second primary cancer.

02/28/05

24.5.3 ***Original statistical power of the survival comparison (modified 02/28/05 per Section 24.5.6)***

We consider a 25% reduction in annual mortality rate due to the addition of Herceptin to be clinically significant, and require that the power for detecting this S difference be at least 0.80, using a two-sided test with Type I error rate = 0.05. We also suppose that the observed reduction in mortality may be attenuated by compliance issues. Specifically, we assume that 5% of patients who are randomized to the experimental arm will fail to begin treatment with Herceptin, and an additional 10% will discontinue their Herceptin therapy uniformly over the 1-year course. Under an assumption that log-hazard ratio is proportional to the amount of Herceptin actually received, these noncompliance assumptions attenuate a 25% percent reduction in mortality rate to a 22.8% reduction. Under a proportional hazards assumption, deferring the definitive analysis until the occurrence of 480 deaths gives a power of 80% against the attenuated relative risk.

To assist in interpretation, Table 18 shows the relationship between a 25% mortality reduction and absolute S improvement at 5 years. This relationship depends on the 5-year S on the control arm. While it is usually the case that S on the control arm can be reasonably estimated from historical data, such is not the case here, since: 1) the efficacy of the sequential addition of Taxol to AC chemotherapy is not yet established, although preliminary results from CALGB study 9344[16] give some guidance; 2) it is uncertain to what degree the patient population will self-select due to uncertainties concerning the cardiotoxicity of Herceptin; and 3) the prognostic significance of HER2 overexpression in the adjuvant setting is uncertain, particularly in light of recent evidence that HER2 overexpression may be a marker of preferential sensitivity to doxorubicin.[14, 17, 35, 40] However, based on considerations described in Section 24.5.4, it is probable that 5-year S on the control arm of this study will fall between 70% and 80%, in which case a 25% reduction in mortality rate would correspond to a 5% or 6% absolute improvement in 5-year S.

At the point in time that a total of 480 deaths have been reported, we project that about 834 first events (treatment failures, second primaries, deaths prior to treatment failure or first event) will also have been reported. Based on this figure, the logrank comparison of DFS will have 80% power to detect a 17.6% decrease in hazard rate due to treatment with Herceptin, relative to the control arm.

24.5.4 ***Baseline hazard rates***

The population of patients eligible for this trial is identical to that of NSABP Protocol B-25, with the additional requirement that patients are required to overexpress HER2. Thus, the HER2-positive subset of the B-25 patient population provides a rational basis for estimation of hazard rates on the B-31 control arm, (apart from the potential benefit of sequential Taxol when added to AC). While HER2 overexpression has not yet been assayed in the B-25

population, it is possible to indirectly estimate the percentage of this population who were HER2-positive, as well as their 5-year S, by using mathematical models derived from 638 patients assayed for HER2 in protocol B-11 and 2034 patients assayed for HER2 in Protocol B-15. Analysis of S in both B-11 and B-15 indicated that while HER2 overexpression was strongly prognostic in patients treated with regimens not containing doxorubicin, it was only moderately prognostic in patients who were treated with doxorubicin-based regimens (PAF in B-11, AC or AC→CMF in B-15). In fact, among patients treated with doxorubicin, HER2 overexpression conferred no worse a prognosis when the analysis also accounted for other prognostic factors that were themselves strongly associated with HER2 overexpression. These factors included negative ER- and/or PgR-receptor status, 4+ positive nodes, and to a lesser degree, large tumor size.[15,40] Similar findings have been reported in other analyses, in particular that of CALGB trial 8869[17,35], which reported the first evidence suggesting HER2 overexpression conferred responsiveness of breast cancer to adequate doses of doxorubicin-based chemotherapy in the adjuvant setting.

Under the assumption that HER2 expression is not prognostic in the B-25 patient population when differences in relevant predictors (hormone-receptor status, nodal status, tumor size) are controlled for, it can be shown under reasonable assumptions that

$$\sum S(5,X_i) \bullet w(X_i) / \sum w(X_i)$$

is a consistent estimator for the 5-year S of the HER2-positive subset, where X_i is a vector of prognostic covariates (other than HER2 overexpression) associated with the i^{th} patient in the B-25 cohort, S(5,x) is the 5-year S of that subpopulation having covariate vector x, and w(x) is the probability that a patient having covariate vector x also overexpresses HER2. To apply this estimator, S(5,x) was estimated by fitting a proportional hazards model to the B-25 cohort; w(x) was estimated by fitting logistic regression models to pooled data from Protocol B-11 and B-15, and was then used to assign probabilities of HER2 overexpression to each patient in the B-25 cohort. Using this indirect method, it was estimated that about 28% of the B-25 population overexpress HER2, and the 5-year S of this subset is about 73%.

An estimate of 73% for the 5-year S on the B-31 control arm would therefore be appropriate under two assumptions: 1) the B-31 patient population will resemble that subset of the B-25 population which was HER2-positive, and 2) the sequential addition of Taxol to AC will add no additional benefit. In fact, for reasons already described, it is probable that at least the initial cohort of patients accrued to B-31 will be somewhat riskier, suggesting that 5-year S on the control arm might be several percent lower than this estimate. Conversely, preliminary reports of CALGB Protocol 9344 suggest that the sequential addition of Taxol to AC may confer a reduction in mortality rate estimated at 26%[8], in which case, a baseline 5-year S of 73% would be improved to about 79%. Thus, reasonable scenarios may be constructed yielding baseline 5-year S ranging from about 70% to about 80%.

In order to estimate the accrual needed to support the power requirements of Section 24.5.3 with a feasible amount of follow-up time, it is prudent to select a conservative estimate for the baseline mortality rate. Therefore, we have chosen an estimate of 4.7 deaths per 100 patient-years, corresponding to a 5-year S estimate of 79%. Based on this estimate, the requirement for 480 deaths prior to analysis, and the accrual rate estimates summarized in Section 24.3, a total accrual of 2700 patients will allow the definitive analysis to occur approximately 7 years, 6 months after study initiation, or about 2 years, 9 months after the completion of accrual. If the population attracted to this trial is riskier than indicated by our estimate of mortality rate, or if an interruption of accrual is not required between the two stages of the trial, then definitive analysis will occur more rapidly.

02/28/05 24.5.5 ***Original interim analyses of outcome (modified 02/28/05 per Section 24.5.6)***

Interim analyses of outcome will be based on the S endpoint. Four interim analyses are scheduled prior to the definitive analysis, after 96, 192, 288 and 384 deaths. Asymmetric stopping boundaries will be employed. The upper boundaries correspond to z-scores of 3.02, 2.97, 2.92, 2.86 and 2.00 respectively. The lower boundaries correspond to z-scores of -1.76, -1.17, -0.72, -0.32 and 0.84. The upper boundaries are based on the O'Brien-Harrington-Fleming method[42], corresponding to a one-sided $\alpha = 0.025$ test of the hypothesis that the relative risk is 1, against the hypothesis that the relative risk is less than 1. The lower boundaries are derived from a one-sided lower O'Brien-Harrington-Fleming boundary for a test of the hypothesis that the relative risk is 0.772 (22.8% reduction in mortality rate), against the hypothesis that it exceeds this amount. Because these analyses must be timed to coincide with the semiannual meetings of the NSABP DMC, in practice the numbers of deaths at each interim analysis will differ slightly from the figures given above. If significant deviations are necessary, the nominal levels of significance will be adjusted by alpha-spending.[43]

TABLE 17. Cardiac safety monitoring stage (Probability that accrual will be terminated as a function of the increase $\Delta = p_H - p_0$ in the probability of a cardiac event due to the administration of Herceptin).

Pr{ H_0: Δ=4% is rejected in favor of H_A :Δ > 4%}				
Increase in cardiac event rate (Δ)	**Probability that accrual will be terminated***	**After 100 patients per arm***	**After 300 patients per arm***	**After 500 patients per arm***
0%	.00	.00	.00	.00
1%	.00	.00	.00	.00
2%	.00	.00	.00	.00
3%	.03	.02	.01	.00
4%	.12	.06	.04	.02
5%	.34	.13	.13	.09
6%	.63	.22	.24	.17
7%	.85	.34	.34	.17
8%	.95	.46	.37	.12
9%	.99	.57	.35	.06
10%	.997	.67	.30	.03
*Probability calculations assumed that p_0 = 1%.				

TABLE 18. Effect of a 25% reduction in rate of mortality on survival at 5 years

Survival on control arm	**Survival on experimental arm**	**Absolute improvement**
70%	76.5%	6.5%
75%	80.6%	5.6%
80%	84.6%	4.6%

02/28/05

24.5.6 ***Statistical analysis plan modified to accommodate a joint efficacy analysis of NCCTG 9831 and NSABP B-31***

This section modifies the original statistical analysis plan described in Sections 24.5.2, 24.5.3 and 24.5.5.

A joint analysis of efficacy data from NCCTG N9831 and NSABP B-31 will be performed to test the benefit of twelve months' treatment with Herceptin following administration of AC and begun concurrently with Taxol. Both Arms of the NSABP Protocol will be included in this analysis, but only NCCTG N9831Arm A (AC->T) and Arm C (AC->T+H, with H beginning on day 1 of the first Taxol cycle and ending 12 months later) will be included. Arm B (AC->T->H) is to be omitted since NSABP B-31 does not investigate this sequential schedule. Also, NCCTG patients accrued from 2/1/2002 to 9/3/2002 will be excluded from the control Arm A, since accrual to Arm C was suspended during that time.

DFS will be the primary endpoint. A later confirmatory analysis of S is also scheduled as a secondary endpoint. Analyses of both endpoints will be based on one-sided tests at the 0.025 level of significance.***** Unless there is early stopping, the definitive analysis of DFS will take place after 710 events have been reported, aggregated over both trials. The definitive analysis of S will occur after the report of the 710th death. In this case, the DFS analysis will be reported approximately 24 months before the data are mature enough to perform the definitive analysis of S.

For both DFS and S, the comparison of control (AC→T) to treatment (AC→T+H) will be based on a stratified log-rank test, where the strata take into account differences between studies (NCCTG vs. NSABP), differences in the intended Taxol schedule and dose (q 3 weeks vs. weekly, as declared at the time of randomization), pathologic nodal status (0, 1-3, 4-9, 10+ positive nodes) and hormone receptor status (ER and PR negative, ER and/or PR positive). The following table shows these strata; due to the design of the two studies, certain cells will be empty, i.e. there are no node-negative patients in NSABP B-31, and no patients receive q 3 weekly Taxol on NCCTG N9831. These null cells are blackened in the table.

TABLE 19. Strata for joint analysis

		Hormone Receptor Status							
		ER and PR Negative				ER and/or PR Positive			
		Number of Positive Nodes				Number of Positive Nodes			
Protocol	Taxol Schedule	0	1-3	4-9	10+	0	1-3	4-9	10+
NCCTG	Q3w								
	Weekly								
NSABP	Q3w								
	Weekly								

The primary analyses will be based on the intent-to-treat principle, i.e. all patients will be analyzed according to their randomly assigned treatments. All randomized patients will be included except those NCCTG patients accrued after the institution of centralized HER2 testing who were found to be HER2-negative by central review.****** Exclusion of these patients is consistent with the intent-to-treat principle and can result in no bias, since the pathologic specimens required for blinded central review are obtained prior to randomization, even though they may not be assayed for several weeks thereafter. Also, the NCCTG randomization process assigns patients to treatment after disregarding earlier patients who have been found to be HER2 negative by central laboratory testing and reference laboratory testing. Therefore, no treatment imbalances can result from the exclusion of these patients.

As secondary analyses, DFS and S stratified log rank tests will be restricted to include only those patients meeting all of the following conditions:

- Patients must be eligible and have received at least one cycle of AC;
- Patients must be alive and disease-free at the time of their post-AC MUGA or ECHO scan;
- Patients' post-AC MUGA or ECHO and clinical cardiac assessment must be adequate to permit treatment with Herceptin according to the treatment rules common to both protocols (see Section 12.3 of the NSABP Protocol);
- Patients must have begun post-AC therapy (i.e. have received any Herceptin with or without Taxol on the treatment Arms, or any Taxol on the control Arms); and
- Patients must not have been found to be HER2-negative on central review.

In these secondary analyses, time to event will be measured from the date of the post-AC MUGA rather than the date of randomization. If any substantive differences are seen between the primary and secondary analyses, these will be fully described and discussed in the manuscript in which the analyses are reported.

Additional DFS and S secondary analyses will be done to ensure that results are not confounded by any imbalances of patient or tumor characteristics. These analyses will be based on Cox models controlling for the effect of the stratification factors listed above, as well as the effects of additional covariates including pathologic tumor size (≤ 2 cm, 2.1 + cm), tumor grade (SBR/Elston: low, intermediate, high), age at randomization (≤ 49, ≥ 50), surgical treatment and radiotherapy (L+XRT, M-XRT, M+XRT).

DFS and S will be summarized with Kaplan-Meier curves. Ninety-five percent confidence intervals will be reported for relative risks, for DFS and S at the 5-year point, and for absolute benefit as defined by differences in DFS and S. A site-of-first-event table will be constructed, breaking down first events into the following categories: local-regional recurrence, distant recurrence, contralateral breast cancer, other second primary cancer, or death prior to cancer recurrence.

Poolability of Patient Cohorts: Define the following patient subgroups:

C_1 = the cohort of NSABP B-31 patients electing to receive q 3 weekly Taxol;

C_2 = the cohort of NSABP B-31 patients electing to receive weekly Taxol;

C_3 = the cohort of NCCTG N9831 patients, all assigned to receive weekly Taxol.

We will estimate the effect of Herceptin within each of the patient subgroups $C_1, C_2, C_3, C_1 + C_2, C_2 + C_3$, and $C_1 + C_2 + C_3$, even in the absence of statistically significant interactions. The estimated treatment effects (in terms of hazard ratios and their confidence intervals) for the various subgroups will be displayed in a forest plot,[43a] and will be compared between subgroups.

Because interpretation of these subgroup comparisons is difficult in the absence of a statistically significant interaction test to control for the inflated type I error rate inherent in multiple testing, we will perform a 0.05-level omnibus test of heterogeneity of hazard ratios across and , using a Cox model which includes terms representing treatment (Herceptin vs not), subgroup membership, and the two degrees of freedom for Herceptin-by-subgroup interaction. The Cox model will also contain terms to control for hormone receptor status and pathological nodal status.

Furthermore, the presence of minor non-qualitative interactions do not necessarily proscribe a pooled analysis, and the apriori probability of clinically meaningful interactions between Herceptin effect and either protocol or Taxol schedule is, in our opinion, rather remote. Thus, in interpreting the subgroup treatment comparisons with a view towards assessing the "poolability" of the data, we will be primarily interested in confirming that the effect of Herceptin is qualitatively similar across groups.

As additional exploratory analyses, we will use Cox models to screen at the 0.01 level for statistically significant treatment-by-covariate interactions for the following set of covariates: hormone receptor expression (ER and PR Negative vs. ER and/or PR Positive), nodal status (0,1-3,4-9,10+), pathologic tumor size (≤ 2 cm., 2.1+ cm.), tumor grade (SBR/Elston: low, intermediate, high), age at randomization (≤ 50, ≥ 51), surgical treatment and radiotherapy (L+XRT, M-XRT, M+XRT).

Power Considerations We wished to power the analyses to be able to detect a 25% decrease in event rate (for DFS) or rate of mortality (for S), each with probability 0.90. We also wished to attenuate this target efficacy to account for the following two factors:

- To date, approximately 9% of patients have failed to begin treatment with Herceptin (the majority of these cases are due to the occurrence of asymptomatic drops in LVEF following four courses of AC, which preclude the initiation of Herceptin per protocol).

- Not all patients truly overexpress or amplify HER2 . Following early centralized assessments of the reproducibility of HER2 determinations in both the NCCTG and NSABP trials, requirements for HER2 testing to establish eligibility were tightened in both trials.[43b,43c] In NCCTG N9831, central testing is now required to establish eligibility. In NSABP B-31, IHC tests must now be completed at approved laboratories. These amendments appear to have significantly improved assay reproducibility[43d], so that assuming a 95% proportion of true HER2-positive patients in either trial is probably somewhat conservative.

If 91% of all patients randomized to receive Herceptin actually receive it, and 95% of these are HER2 positive, and if patients who do not receive Herceptin or who are not HER2 positive achieve no benefit, then a 25% reduction in risk is attenuated to (0.91)*(0.95)*25% = 21.6%. To achieve 90% power against this alternative, while maintaining a 0.025 level of significance, requires that final analysis be deferred until the 710th event is reported.

Timing of Analyses As of 11/24/2004, accrual to NSABP B-31 was 1955 patients, and accrual to Arms A and C of NCCTG N9831 was 1779 patients. In total 205 events and 81 deaths have been reported on NSABP B-31, and 133 events and 52 deaths have been reported on Arms A and C of NCCTG N9831. (The following calculations of time to analysis are based only on numbers of events and deaths aggregated over treatment arms; as yet no interim analyses of outcome have taken place in either trial.) Based on accrual figures from 5/2004 through 10/2004, it is assumed that accrual to B-31 will continue at the rate of 38 patients per month and that accrual to N9831 will continue at the rate of 58 per month (Arms A and C), until the respective trial accrual goals are met (2700 for NSABP B-31, 2200 for NCCTG N9831 Arms A and C).

For DFS, we assume an event rate of 0.089 per year, corresponding to a 5-year DFS of 64% in the control arm. For S, we assume a mortality rate of 0.047 per year, corresponding to a 79% 5-year survival (see NSABP Protocol Section 24.5.4 for justification). Further, we conservatively assume that no events or deaths will occur in the first 6 months post-randomization, since historically failure and death rates are low immediately following surgery. Under these assumptions, the 710th event is predicted to occur around 12/2005. Allowing 6 months for events to be reported and the database locked, we predict that the DFS analysis should occur around 6/2006. Similarly, the 710th death is predicted to occur around 12/2007. Allowing 6 months for deaths to be reported and the database locked, we predict that the S analysis will occur around 6/2008.

Interim Analyses: The first interim analysis of DFS will take place as soon as possible following the report of the 355th event in both trials combined. Subsequent interim analyses will be presented semiannually to coincide with scheduled meetings of the NSABP Data Monitoring Committee. At each interim analysis, consideration will be given to stopping the trials early and reporting results if the hypothesis of equivalence is rejected (in favor of the hypothesis that Herceptin increases DFS) at the nominal one-sided 0.0005 level. Consideration will be given to stopping the trials for futility if, at any interim analysis the standardized log-rank statistic is negative (that is, if the event rate among patients receiving Herceptin exceeds that among control patients[43e]). If the interim

analysis boundary is not crossed prior to the report of the 710th event, the method of alpha-spending will be used to determine the nominal level of the final test in such a way that the overall type I error rate (i.e. the probability that the treatment arm is declared superior to the control at any analysis, given no true difference) is exactly 0.025 (one-sided).

24.6 Statistical analysis of adverse events

Frequencies of all adverse events will be tabulated by treatment, toxicity type and grade. Cumulative incidence functions will be estimated for the occurrence of LV dysfunction on either treatment arm, as defined in Section 19.2. Ninety-five percent confidence intervals for the proportion of patients experiencing LV dysfunction will be computed as follows: i) during treatment with four courses of standard AC chemotherapy, up to 12 weeks post day 1; (ii) during and after treatment with four cycles of Taxol chemotherapy, at 6 months, 15 months, and 5 years post day 1 of cycle 5; and (iii) during and after treatment with four cycles of Taxol chemotherapy and Herceptin, at 6 months, 15 months, and 5 years post day 1 of cycle 5. Ninety-five percent confidence intervals for between-arm differences in the proportion of patients experiencing LV dysfunction will be computed at 6 months, 15 months, and 5 years post day 1 of cycle 5.

24.7 Statistical analysis of biological studies

24.7.1 *Phosphorylated receptor*

Analyses will be carried out to determine whether expression of the phosphorylated receptor in the index tumor is prognostic for DFS and S, and whether expression of the phosphorylated receptor is predictive of response to treatment with Herceptin. Cox proportional hazards models will be fit to DFS and S data, each containing a term representing treatment (AC→Taxol, AC→Taxol + Herceptin), a term representing expression of the phosphorylated receptor in the index tumor (no, yes), and a cross-product term representing their interaction. A Wald test will be used to test the hypothesis that expression of phosphorylated receptor is predictive of response to treatment with Herceptin (expression-by-treatment interaction). Ninety-five percent confidence intervals will be calculated for the proportional reduction in hazard rate due to treatment with Herceptin, both among expressors and nonexpressors of the phosphorylated receptor. Similarly, ninety-five percent confidence intervals will be calculated for the proportional increase in hazard rate associated with expression of the phosphorylated receptor, both for patients receiving and not receiving treatment with Herceptin. Analyses will be carried out both ignoring and adjusting for other prognostic patient and tumor characteristics (nodal status, tumor size, hormone-receptor status, age).

McNeymar's test will be used to determine whether the frequency with which the phosphorylated receptor is expressed in postrelapse tissues differs from the frequency of expression in the index tumor, both in patients treated with Herceptin and in those not receiving Herceptin. Between-treatment comparisons will be made of the proportion of patients gaining and losing expression on relapse.

24.7.2 ***Baseline levels of shed ECD or autoantibodies to HER2***

Analyses will be carried out to determine whether these markers are prognostic for DFS and S, and whether they are predictive of response to treatment with Herceptin. Cox proportional hazards models will be used in a fashion analogous to that described in Section 24.7.1. In these models, quantitative levels of shed ECD will be dichotomized above and below the median. Presence or absence of autoantibodies to HER2 at baseline and at relapse will be compared as in 24.7.1. Within either treatment arm, quantitative levels of shed ECD will be compared between baseline and relapse using the signed-rand test, and treatment comparisons will be based on rand-sum tests of baseline-relapse differences.

24.7.3 ***Frequency of HER2 overexpression in postrelapse tissues***

The frequency with which HER2 expression is lost at relapse may differ in patients treated and not treated with Herceptin. Fisher's exact test will be used to compare the frequency of expression between the two treatment arms in postrelapse tissues.

24.7.4 ***Correlation of HER2 assays***

HER2 overexpression will be correlated in centralized application of the following assays: TAB250 (mAb-1), TAB250/pAb-1 cocktail, CB-11, HercepTest™ (DAKO), HER-2 FISH assay, and array-based CGH. Assay results will also be correlated with DFS and S to determine whether the degree of overexpression is either prognostic or predictive of treatment response in this highly selected population.

24.8 Issues relating to racial and ethnic differences

Possible racial and ethnic variation in response to the treatments under consideration is of most concern in African-Americans. Many researchers have noted less favorable survival rates for African-American breast cancer patients compared to Caucasians.[44, 45] This has been attributed to many factors, including more advanced disease at the time of treatment[46], social and economic factors[47], or specific tumor characteristics such as ER positivity.[48, 49] Although, in general, outcomes tend to be less favorable for African-Americans, significant interaction between race and treatment response has not been reported, suggesting that, when treatment efficacy is noted, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.[50, 51]

Potential for the enrollment of minority patients in this protocol is enhanced by the NSABP's recognition of the importance of increasing minority accrual, and to this end, we provide opportunities for greater participation by underrepresented racial and ethnic groups. In similar NSABP studies, the racial/ethnic composition for the study population has been approximately 87% white; < 1% American Indian or Alaskan Native; 2% Asian or Pacific Islander; 8% black, not of Hispanic origin; 3% Hispanic; and < 1% other.

We anticipate that this distribution will be maintained for Protocol B-31, and that the racial and ethnic composition of the 2700 patient group (all of whom will be female, since male patients are not eligible for the study) will be as follows:

TABLE 20. Expected racial and ethnic composition of NSABP B-31

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Total	–	54	216	81	2349	–	2700

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.
Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes China, India, Japan, Korea, the Philippine Islands and Samoa.
Black, not of Hispanic Origin: A person having origins in any of the black racial groups of Africa.
Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin regardless of race.
White, not of Hispanic Origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

The prognostic effect of race/ethnicity will be evaluated using statistical models. Because of sample size limitations, we will not be able to compare effects separately for the different cultural or racial groups.

25.0 PUBLICATION INFORMATION

01/14/03

The agent, Herceptin, used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between Genentech, Inc. and the NCI Division of Cancer Treatment, Diagnosis and Centers. Therefore, the following obligations/guidelines apply to the use of Herceptin in this study:

Genentech data for Herceptin is confidential and proprietary to Genentech and should be maintained as such by the investigators. The NCI encourages investigators to make data from clinical trials fully available to Genentech for review at the appropriate time (see Section 24.4). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Genentech and not to other parties. When Genentech wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate Group Chair of Genentech's wish to contact them. Any data provided to Genentech must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC). Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Genentech for advisory review and comment prior to submission for publication. Genentech will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to the company's intellectual property rights are protected. Copies of abstracts should be provided to Genentech for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

National Cancer Institute
Regulatory Affairs Branch
6130 Executive Boulevard
Executive Plaza North, Room 7111
Rockville, MD 20852
Fax: (301) 402-1584

The Regulatory Affairs Branch will then distribute them to Genentech. For details, see the NCI-*Cooperative Group-Industry Relationship Guidelines,* which discusses each of these points in detail.

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GUIDELINES FOR RADIOTHERAPY FOR NSABP B-31 ONLY

05/16/03
06/03/05

Whole breast irradiation following lumpectomy is mandatory for all patients entered into NSABP breast cancer protocols.

Patients in NSABP B-31 are permitted to receive regional node irradiation following lumpectomy. Patients who undergo mastectomy are allowed to have chest wall irradiation and/or regional node irradiation. *Please note that in this protocol, partial breast irradiation and irradiation of any internal mammary nodes are prohibited.*

Radiotherapy will be administered following completion of chemotherapy. Patients receiving Herceptin will receive radiotherapy and Herceptin concurrently.

1.0 RADIOTHERAPY AFTER LUMPECTOMY

05/16/03

1.1 Whole breast irradiation following lumpectomy

Whole breast irradiation following lumpectomy is mandatory. It is the intent of radiation therapy to treat the entire breast: tissue, skin, and the lumpectomy scar.

When lumpectomy and axillary node dissection are performed through separate incisions, the axillary dissection incision does not need to be irradiated. If the axillary dissection incision is continuous with that of the lumpectomy, no special attempt needs to be made to irradiate that portion of the scar which is beyond the breast tissue.

1.2 Breast field bondaries

The irradiation boundaries are as follows.

- The medial border lies along the mid-sternal line.
- The lateral border usually lies along the mid-axillary line. However, the lateral border should be placed to ensure coverage of the entire breast. Therefore, this border may be moved more anteriorly if possible, thus decreasing the amount of irradiated lung. If the lumpectomy incision extends posteriorly to this line, the lateral border may, within limits, be moved posteriorly to include the entire scar. The extent to which the lateral border may be moved posteriorly should be guided by the amount of lung tissue which would be irradiated if this border is parallel, that is, opposed to the medial border. If the irradiated slice of lung tissue exceeds a width of 3 cm, the lateral border should be left at the mid-axillary line, and the surgical incision beyond this line should be treated by superficial radiotherapy or electrons. For patients with small breasts, the lateral borders may be moved anterior to the mid-axillary line and still include the entire breast.
- For left-sided lesions, it is important to limit, as much as possible, the amount of heart in the irradiated volume.
- The inferior border of the tangential field is at a level about 1 to 2 cm below the inframammary fold. The entire breast is to be included, and for patients with pendulous breasts, the inferior border may be several centimeters below the actual inframammary fold.

- The superior border is usually located along the horizontal line which bisects the sternomanubrial junction. If necessary, this border may be moved superiorly to ensure that both the entire breast and the tail of the breast are included.

1.3 **Angle of the tangential fields**

The central axes of the medial and lateral fields lie on the same line, but each field may be angled anteriorly 5º to prevent diversions into the lungs. Exposure to the heart should be blocked as much as possible, while still ensuring irradiation of the entire breast.

1.4 **Localization films**

Localization films should be taken in the treatment position with the therapeutic beam. If more than a 3-cm thickness of lung tissue is included in the beam (taking into account magnification), adjustments should be made in the medial and lateral portals **if possible** to try to reduce the thickness of lung tissue in the beam.

03/15/00

1.5 **Time and dose of breast radiotherapy**

Patients will receive radiation therapy following completion of all chemotherapy. *Radiation therapy must be started no later than 8 weeks following the completion of all chemotherapy in order to prevent variation on the protocol*. Patients will receive a dose of 5,000 - 5,040 cGy in 25 - 28 fractions at 180 - 200 cGy/day. This dose is calculated at a depth of 2/3 the distance between the skin overlying the breast and the base of the tangential fields at mid-separation. Both fields will be treated daily.

1.6 **Treatment modality**

Breast irradiation will be administered with Cobalt-60 or linear accelerator x-rays with a minimum energy of 4MV.

The extent to which bolus should be used is determined by details of the treatment situation. Plastic blocking trays may enhance the skin dose. Bolus may be added to reach the desired skin reaction (i.e., dry desquamation and erythema).

2.0 USE OF BOOSTS

A boost to the operative area is permitted following whole breast irradiation. The type of external beam boost used is left to the discretion of the radiation oncologist. Electrons, ortho-voltage x-rays, super-voltage x-rays, and interstitial implants (high and low dose rate) are permitted.

The dose of irradiation administered as a boost to the operative area is also left to the discretion of the radiation oncologist. We recommend that this boost dose be 1,000 cGy in 5 fractions.

3.0 OPTIONAL REGIONAL NODAL IRRADIATION FOLLOWING LUMPECTOMY

Irradiation of the supraclavicular and axillary nodal areas is optional. One or both of these areas may be irradiated. Irradiation of regional nodal areas is left to the discretion of the participating clinicians. Recommended dosage for treatment of the regional nodal sites is 4,500 - 5,000 cGy at 180 - 200 cGy/day. *Please note that in this trial, irradiation of any internal mammary nodes is prohibited.*

4.0 OPTIONAL RADIOTHERAPY AFTER MASTECTOMY

In B-31, radiotherapy will be administered after the completion of all chemotherapy; however, such radiotherapy is optional.

4.1 Chest wall irradiation after mastectomy

Node-positive patients are permitted to receive chest wall irradiation in a recommended dose of 5,000 - 5,040 cGy in daily fractions of 180 - 200 cGy. We suggest that either parallel opposed tangential fields using x-ray (photon beams) or a direct *en face* electron beam of appropriate energy be employed. Whenever an electron beam with an energy greater than 6 Mev is employed, ultrasound or CT scan determination of the chest wall thickness is recommended. The electron beam energy should be determined to ensure that the pleural surface is at, or below, the 80% isodose line.

For tangential beam irradiation, every attempt should be made to insure that less than a 3-cm thickness of lung tissue is within the irradiated volume. The point of dose determination is the same as for breast irradiation, a point 2/3 the distance between the skin overlying the chest wall and the base of the tangential field at mid-separation. The use of bolus is left to the discretion of the treating radiation oncologist to achieve a target dose to the skin surface of 4,500 - 5,000 cGy.

4.2 Boost to the mastectomy incision area

A boost to the mastectomy incision area in addition to chest wall irradiation is permitted, though optional. When used, we recommend that the boost area include the entire mastectomy incision, with a 3-cm border superiorly and inferiorly for transverse incisions, and a 3-cm border medially and laterally for vertical incisions. A dose of 1,000 cGy in 5 fractions is recommended. It may be administered either by reduced radiation using superficial radiotherapy or an electron beam.

5.0 REGIONAL NODE IRRADIATION FOLLOWING MASTECTOMY

Treatment of the supraclavicular region and axilla in patients undergoing mastectomy is permitted, but optional. One or both of these areas may be irradiated. Irradiation of the regional nodal areas is at the discretion of the participating clinicians. We strongly suggest that the axilla not be irradiated if $\geq$ 10 nodes have been removed in the axillary dissection. Recommended dosage for treatment of regional nodal sites is 4,500 - 5,000 cGy at 180 - 200 cGy/day. When regional node irradiation is used in patients receiving chest wall irradiation following mastectomy, the treating radiation oncologist should be careful about the abutment of adjacent fields so that there are neither extreme "hot spots" nor "cold spots."

Please note that in this trial, irradiation of any internal mammary nodes is prohibited.

06/03/05 6.0 **MATERIALS TO BE SUBMITTED FOLLOWING RADIOTHERAPY**

The treating radiation oncologist will submit a completed Form E1 to report the sites irradiated. Daily treatment sheets and dosimetry calculations (including isodose curves for breast irradiation) are also required. Prior to Amendment #9, submission of portal films (one set, only) and treatment position photographs was required for all patients with ***left-sided lesions***. (Following Amendment #9, submission of portal films and position photographs is no longer required.)

TNM nomenclature for breast cancer

05/16/03

Primary Tumor (T)

T_0 No evidence of primary tumor
T_{is} Carcinoma in situ
T_1 ≤2 cm
- T_{1mic} ≤0.1 cm
- T_{1a} > 0.1 cm but not > 0.5 cm
- T_{1b} > 0.5 cm but not > 1.0 cm
- T_{1c} > 1.0 cm but not > 2.0 cm

T_2 > 2 cm- but not > 5 cm
T_3 > 5 cm
T_4 Any size, with direct extension to chest wall or skin (only as described below)
- T_{4a} Extension to chest wall (excluding pectoral muscle)
- T_{4b} Edema (including peau d'orange) or ulceration of skin or presence of satellite skin nodules (confined to the same breast)
- T_{4c} Both T_{4a} and T_{4b}
- T_{4d} Inflammatory carcinoma

Important notes:

Inflammatory Carcinoma
Inflammatory carinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass. These clinical findings should involve the majority of the skin of the breast. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings. In addition to the clinical picture, however, a biopsy is still necessary to demonstrate cancer either within the dermal lymphatics or in breast parenchyma itself.

Skin of Breast
Dimpling of the skin, nipple retraction, or any other skin change, except those described under T_{4b} and T_{4d} may occur in T_1, T_2, or T_3 without changing classification.

Regional Lymph Nodes (N)

Clinical

N_0 No regional lymph node metastasis
N_1 Metastasis to movable ipsilateral axillary lymph node or nodes
N_2 Metastasis to ipsilateral axillary lymph nodes fixed or matted to one another or to other structures; or in clinically apparent* ipsilateral mammary nodes in the absence of clinically evident axillary lymph node metastasis
- N_{2a} Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
- N_{2b} Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis

N_3 Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.
- N_{3a} Metastasis in ipsilateral infraclavicular lymph node(s)
- N_{3b} Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- N_{3c} Metastasis in ipsilateral supraclavicular lymph node(s)

Pathologic

pN_1 Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**

- pN_{1mi} Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
- pN_{1a} Metastasis in 1 to 3 axillary lymph nodes
- pN_{1b} Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
- pN_{1c} Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN_{3b} to reflect increased tumor burden)

pN_2 Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis.

- pN_{2a} Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
- pN_{2b} Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

pN_3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

- pN_{3a} Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
- pN_{3b} Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
- pN_{3c} Metastasis in ipsilateral supraclavicular lymph nodes

Distant Metastasis (M)

M_0 No distant metastasis

M_1 Distant metastasis, including metastasis to ipsilateral Supraclavicular lymph node or nodes

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

**Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Stages of primary breast cancer *05/16/03, 06/03/05*

	T	***N***	***M***
Stage 0	T_{is}	N_0	M_0
Stage I	T_{1*}	N_0	M_0
Stage IIA	T_0 T_{1*} T_2	N_1 N_1 N_0	M_0 M_0 M_0
Stage IIB	T_2 T_3	N_1 N_0	M_0 M_0
Stage IIIA	T_0 T_{1*} T_2 T_3	N_2 N_2 N_2 N_1,N_2	M_0 M_0 M_0 M_0
Stage IIIB	T_4	Any N	M_0
Stage IIIC	Any T	N_3	M_0
Stage IV	Any T	Any N	M_1

*T_1 includes T_{1mic}.

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HER2 Quality Control Results *04/23/01 and 05/16/03*

Central HER2 testing was performed using HercepTest™ and FISH on the first 104 tissue samples received by the NSABP for B-31. This testing was done to determine the reliability of the results being submitted by member institutions. The results of this initial quality assessment are detailed in Table C1-A.

Table C1-A. HER2 Quality Control Results of First 104 Tissue Samples

Test Used for eligibility	Type of Lab Used	Central HercepTest™		Central FISH		Negative by both Central Assays
		0-2+	3+	Not Amplified	Amplified	
HercepTest™ 3+ (n=80)	Non-reference lab* n = 52	10 (19%)	42 (81%)	12 (23%)	40 (77%)	10 (19%)
	Reference lab* n = 28	1 (4%)	27 (96%)	1 (4%)	27 (96%)	1 (4%)
Other Antibodies ≥ 33% stain positive (n=24)	Non-reference lab n = 23	11 (48%)	12 (52%)	9 (39%)	14 (61%)	8 (35%)
	Reference lab n = 1	0	1	0	1	0
Total=104						

* See Section 9.0 for the definition of a reference lab.

This table shows two apparent trends:

1. If a 3+ HercepTest™ used to establish patient eligibility was done in a reference laboratory, it almost always was confirmed as 3+ on central HercepTest™ assay, and was almost always amplified by FISH: only 1/28 (4%) of such cases failed to be confirmed as positive by both central HercepTest™ and FISH. On the other hand, HercepTest™ assays done at non-reference laboratories often could not be confirmed centrally by either HercepTest™ or FISH: 10/52 (19%) of such assays were judged to be negative by both central assays.

2. If IHC assays other than the HercepTest™ were used at non-reference laboratories to establish patient eligibility, the results often could not be confirmed centrally: 8/23 (35%) of such assays were judged centrally to be negative by both HercepTest™ and FISH. Immunohistochemical assays other than the HercepTest™ were rarely done at reference laboratories.

Based on the above results, eligibility changes were implemented with Amendment #3. In order to ascertain the success of these changes, 240 cases enrolled after Protocol Amendment #3 were centrally reviewed by the NSABP Division of Pathology using Vysis® PathVysion™ FISH assay. The results are summarized in Table C1-B. The results show clear improvement of HER2 assay quality after the protocol amendment with an overall false positive rate of only 3%. Therefore, we conclude that the revised eligibility criterion has been effective in assuring the quality of the assay used to identify patients entering into B-31.

Table C1-B. Central review of 240 cases enrolled after B-31 Protocol Amendment #3

Original assay used	No gene amplification	Assay failure*	Total
FISH	6/132 (4.5%)	1	133
IHC	2/104 (2%)	3	107
Total	8/236 (3%)	4	240

* No hybridization signal seen

04/23/01 [TEXT DELETION]

PROCEDURE FOR COLLECTING, PROCESSING AND SHIPPING BLOOD AND SERUM SPECIMENS

A. SUPPLIES, EQUIPMENT AND FACILITIES

The following supplies will be provided to each clinical site by the NSABP Serum Bank:	**The clinical sites must have on hand the following supplies and equipment:**
• 10 ml evacuated red-top vacutainer tubes (3) • 10 ml yellow-top vacutainer tube (1) (containing 3 ml ACD) • 7 ml polypropylene Sarstedt sample vials (3) • Polyfoam container including ziplock bag, foam pad, absorbent pad, and U-Tek refrigerant cold packs • patient identification labels • preprinted airbills for specimen shipments (supply provided at time of study start-up) • corrugated cardboard boxes - must be used with each shipment • diagnostic lab packs	• disposable gloves • alcohol swabs • sterile gauze pads or cotton swabs • 21-gauge vacutainer needle, 1-1/2" (multiple-sampling) • pipets and pipeting system • vacutainer holder • tourniquet • refrigerator or ice bucket with crushed ice • centrifuge capable of accommodating 10-ml vacutainer tubes • needle disposal containers • biohazard containers • waterproof black markers • Ziplock bags • package tape • NSABP Form BNK (specimen documentation form)

For problems with supplies or requests for additional supplies, please contact the NSABP Serum Bank at the telephone number provided under Information Resources, page vi.

B. TIMING OF SPECIMEN COLLECTIONS

Blood specimens are to be collected at the following time points:

- Sample 1: Baseline (after randomization, prior to treatment).
- Sample 2: At time of treatment failure (i.e., ipsilateral breast tumor recurrence, contralateral breast cancer and distant metastases. Second primary cancer other than breast cancer is not required.

C. SAMPLE COLLECTION PROCEDURES

Four vacutainer tubes of blood are to be drawn for these specimens. Tubes will be provided by the NSABP Serum Bank for this purpose.

Procedures:

Please refer to your institutional policies and procedures for drawing blood specimens. The following are specific procedures related to the collection of specimens for transport to the NSABP Serum Bank.

1. Assemble the vacutainer tubes and vials required for the collection. These include:
   - Three 10 ml red top vacutainer tubes (plain, without silica or polymer)
   - One 10 ml yellow top ACD vacutainer tube
   - Three 7 ml polypropylene Sarstedt sample vials

2. Label the above tubes and vials with patient identification labels provided by the NSABP Serum Bank.

3. Completely fill the three red top vacutainer tubes and the yellow top ACD vacutainer tube with blood, according to your institutional procedure for blood specimen collection.

4. Place the yellow top tube on ice or in the refrigerator.

5. Place the three red top tubes upright in the test tube rack; allow to sit at room temperature for approximately 1 hour for clot to form before the tubes are centrifuged. The blood from patients with abnormal clotting due to disease or from those receiving anticoagulant therapy will require a longer time for complete clot formation. *Do not refrigerate tubes before centrifugation.*

6. If using a refrigerated centrifuge, set temperature of centrifuge to 25 C°. Balance centrifuge carriers containing the vacutainer tubes using a top loading balance. Fill a fourth reusable tube with distilled water to serve as a balance tube. Make sure that tubes are properly seated in the carriers.

7. Load the carriers onto the centrifuge rotor. If either a swinging bucket rotor or a fixed angle bucket rotor is used, centrifuge tubes at 1000 1200 g for 15 minutes. *Do not exceed 1300 g in a fixed angle bucket rotor or 2200 g in a swinging head bucket rotor when centrifuging glass vacutainer tubes.*

8. While tubes are being centrifuged, sort the empty labeled Sarstedt vials in a row of a test tube rack.

9. Allow the centrifuge to come to a complete stop. Carefully open the centrifuge, taking care to avert your face from the opening. (Avoid inhaling escaping air.) Inspect carriers for tube breakage. Remove carriers from centrifuge and place on table. Carefully remove vacutainer tubes from carriers and sort into the test tube rack, matching each red top tube with the appropriately labeled Sarstedt vial.

10. Pick up the first red top tube, verifying identification against the labeled Sarstedt vial. Hold the tube so the stopper is pointing away from your face. Gently pry the stopper out,

using a pulling force with the forefinger and a pushing force with the thumb. Discard stopper in a biohazard container.

11. Using a transfer pipet, carefully transfer serum from the first tube into the Sarstedt vial. The clot/serum interface will be very tight so that serum can be carefully pipetted off to within a few millimeters of the interface. Remove as much of the serum as possible. Cap the Sarstedt vial and return it to the test tube rack. Discard the tube with remaining clot and the transfer pipet into a biohazard container. Repeat this procedure with the two additional red top tubes.

12. The yellow top tube does not require any processing before shipping.

D. SHIPPING PROCEDURES

Both serum and blood specimens must be shipped the same day as collected to the NSABP Serum Bank. To ensure the integrity of the specimens, the mailers must contain a refrigerant pack to maintain a cool temperature during shipping.

Polyfoam containers are provided with a foam insert to cushion the vials/tubes. Cold packs are provided; these must be frozen at -20 C° overnight before shipping. One cold pack must be placed in the lid of the polyfoam container; the polyfoam container lid is designed to accommodate this. The vials/tubes must be placed in a Ziplock bag before inclusion in the polyfoam container. Be sure that the bag is securely closed before placing in the polyfoam container. Absorbent pads are provided that can be cut to fit to fill up any empty space remaining in the polyfoam container. The polyfoam container ***must*** be sealed completely, placed inside a cardboard box ***and*** then in a diagnostic lab pack, or it ***will not*** be accepted for shipment. A completed Form BNK must be included in the polyfoam container.

An account has been established with an overnight carrier for priority "Overnight Air Shipment" of specimens to this laboratory. **Clinics should ship on Monday through Thursday** so that shipments do not arrive on the weekend.

As shipments are received in this laboratory, the mailers will be opened, emptied, and returned with the cold packs to the clinic from which they were sent. Shipping containers will be returned by surface mail and may require a week to arrive at the clinic from which they were sent.

Since over the course of the study, overnight carriers may vary and the specific details required for specimen shipment could change, the NSABP Serum Bank will provide more detailed instructions with specimen kits when they are shipped to the institutions. Please review those instructions carefully before mailing specimens.

Stepwise Procedures:

1. Place a frozen U Tek cold pack in the cover of the insulated polyfoam container. Place the foam pad in the other cover of the polyfoam container.

2. Carefully place the three Sarstedt vials in a Ziplock bag; wipe any moisture from the outside of the yellow top tube and place this in the Ziplock bag. Seal the bag and place in the polyfoam container next to the ice pack. (The tube should be "sandwiched" between the refrigerant pack and the foam pad.)

3. Fill any dead space in the polyfoam container with the absorbent pad; it may be necessary to cut the pad to fit. ***Complete the NSABP Form BNK and enclose in the polyfoam container.*** Seal the polyfoam container. Place the polyfoam container inside the

cardboard box and seal the cardboard box. Place the cardboard box inside the diagnostic lab pack. Close the lab pack and seal.

4. Fill out the overnight carrier airbill shipment form; check all information for accuracy.

5. Arrange for priority overnight shipping. Specify that these are diagnostic specimens.

6. Ship the package immediately. Please note that blood and serum should be shipped on Monday through Thursdays only so that delivery is made to the NSABP Specimen Bank on a weekday.

CANADIAN SITES PLEASE NOTE: If you are shipping on a Thursday, please contact the NSABP Serum Bank by fax at the fax number provided under Information Resources on page vi and provide the tracking number of your shipment. Serum Bank personnel can then arrange for Saturday delivery if your shipment is delayed in Customs and does not arrive on Friday as scheduled.

Shipments should be sent to the address under Information Resources on page vi using the preprinted airbills.

EVALUATION OF CARDIAC TOXICITY

05/16/03
06/03/05

To evaluate the benefits and risks of continuing Herceptin after chemotherapy is completed, two goals must be balanced: 1) the protection of patients from serious myocardial toxicity and 2) the ability to assess the potential benefit of continuing Herceptin in patients with node-positive, HER2-positive breast cancer.

The following are guidelines and requirements:

- Make every effort to schedule each patient's MUGA scan at the same radiology facility throughout the study.

- It is required that a MUGA scan be performed and not substituted with an echocardiogram. (Echocardiograms may be done in addition to MUGA scans.)

- There are several conditions wherein a repeat MUGA scan 4 weeks later is required. Please refer to Sections 15.20.1 and 16.2.

In some patients, anthracycline-induced myocardial dysfunction may occur months after Adriamycin is discontinued. Therefore, it is important to monitor myocardial function throughout the study in the control group as well as in the Herceptin-treated group to determine whether, and to what degree, there may be additional myocardial toxicity associated with Herceptin in the adjuvant setting.

When making the decision to continue or stop Herceptin in an asymptomatic patient, both the *change in the patient's LVEF from baseline* **and** *the relationship of the patient's LVEF to the LLN for the facility* must be considered. The ejection fraction in one patient may be a grade 0 toxicity while the same ejection fraction in another patient may be a grade 2 toxicity, depending on the baseline ejection fractions of the two patients. Conversely, two patients with the same grade of toxicity as determined by change from their baseline ejection fraction may have very different measured ejection fractions.

Patients should be monitored for signs and symptoms of congestive heart failure (CHF) (i.e., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.). Patients who develop these signs and symptoms must permanently discontinue Herceptin.

NOTE 1: In the sections that follow, definitions of cardiac toxicity are outlined to be used when making treatment decisions. They are similar, but not exactly the same as, the definitions of cardiac toxicity as defined by the NCI's Common Toxicity Criteria (version 2.0). Institutions will be required to report cardiac toxicity on Protocol B-31 according to the Common Toxicity Criteria Guidelines.

NOTE 2: Rules for interpreting and applying "repeat" MUGA scan results.

- Herceptin must be permanently discontinued when 2 consecutive "hold" categories occur.
- Herceptin must be permanently discontinued when 3 intermittent "hold" categories occur. (At the investigator's discretion, Herceptin may also be permanently discontinued prior to the occurrence of 3 intermittent "hold" categories).
- If LVEF is maintained at a "continue and repeat MUGA" or improves from a "hold" to a "continue and repeat MUGA" category, additional MUGA scans prior to the next scheduled MUGA scan will be at the investigator's discretion.

Examples of Left Ventricular Function Changes (Measured by decreases in percentage points of the MUGA compared to baseline MUGA results)

05/16/03 ***Conditions that allow continuation of Herceptin without requiring a repeat MUGA after 4 weeks.*** **(Refer to Table 13.)**

1. Asymptomatic decrease in resting LVEF of less than 10% and within the radiology facility's normal limits: continue Herceptin with careful patient assessment.

   For example:

Radiology facility's lower limit of normal	50
Baseline MUGA	60
LVEF during Herceptin drops to	55
Treatment decision	Continue Herceptin

   Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

2. Asymptomatic decrease in resting LVEF of less than 10% and LVEF is 1 to 5% below the radiology facility's lower limit of normal (LLN): continue Herceptin with careful patient assessment.

   For example:

Radiology facility's LLN	55
Baseline MUGA	55
LVEF during Herceptin drops to	50
Treatment decision	Continue Herceptin

   Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

3. Asymptomatic decrease in resting LVEF of 10-15% and LVEF is within the radiology facility's normal limits: continue Herceptin with careful patient assessment.

   For example:

Radiology facility's LLN	50
Baseline MUGA	65
LVEF during Herceptin drops to	50
Treatment decision	Continue Herceptin

   Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

Conditions that allow continuation of Herceptin but require a repeat MUGA after 4 weeks. **(Refer to Table 13.)**

4. Asymptomatic decrease in resting LVEF less than 10% and LVEF is $\geq$ 6% below the lower limit of normal: continue Herceptin and repeat MUGA after 4 weeks. If the repeat MUGA continues to show the decrease of less than 10% from baseline and the LVEF $\geq$ 6% below the lower limit of normal, continue Herceptin.

For example:	
Radiology facility's LLN	50
Baseline MUGA	50
LVEF during Herceptin drops to	41
Treatment decision	Continue Herceptin
Repeat MUGA after 4 weeks	41
Treatment decision	Continue Herceptin

Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

05/16/03 ***Conditions that require holding Herceptin and a repeat MUGA after 4 weeks.*** **(Refer to Table 13.)**

5. Asymptomatic decrease in resting LVEF of 10-15% and LVEF is below the lower limit of normal: hold Herceptin and repeat the MUGA after 4 weeks.

For example:	
Radiology facility's LLN	50
Baseline MUGA	50
LVEF during Herceptin drops to	40
Treatment decision	Hold Herceptin
Repeat LVEF after 4 weeks	45
Treatment decision	Continue Herceptin

Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

6. Asymptomatic decrease in resting LVEF that requires two consecutive holds: permanently discontinue Herceptin.

For example:	
Radiology facility's LLN	50
Baseline MUGA	50
LVEF during Herceptin drops to	40
Treatment decision	Hold Herceptin
Repeat LVEF after 4 weeks	40
Treatment decision	Permanently discontinue Herceptin because 2 consecutive "holds" have occurred

Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

7. Asymptomatic decrease in resting LVEF of 10-15% and LVEF is below the lower limit of normal: hold Herceptin and repeat the MUGA after 4 weeks. This repeat MUGA is within the acceptable parameters to continue Herceptin. Six weeks later, a discretionary MUGA shows an asymptomatic decrease in resting LVEF and requires another hold category. The repeat MUGA shows that the patient can continue Herceptin. Six weeks later another discretionary MUGA shows an asymptomatic decrease in resting LVEF that requires holding Herceptin. Three intermittent "hold" categories have occurred, and therefore, Herceptin must be permanently discontinued.

For example:	
Radiology facility's LLN	50
Baseline MUGA	55

LVEF during Herceptin drops to	45
Treatment decision	Hold Herceptin
Repeat LVEF after 4 weeks	50
Treatment decision	Continue Herceptin
6 weeks later a discretionary MUGA is done and the LVEF drops to	35
Treatment decision	Hold Herceptin
Repeat LVEF after 4 weeks	50
Treatment decision	Continue Herceptin
6 weeks later a discretionary MUGA is done and the LVEF drops to	35
Treatment decision	Permanently discontinue Herceptin because 3 intermittent "holds" have occurred.

Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

8. Asymptomatic decrease in resting LVEF of ≥ 16% and LVEF is within normal limits: hold Herceptin and repeat MUGA after 4 weeks.

For example:	
Radiology facility's LLN	50
Baseline MUGA	70
LVEF during Herceptin drops to	50
Treatment decision	Hold Herceptin
Repeat MUGA after 4 weeks	55
Treatment decision	Continue Herceptin

Further monitoring until the next scheduled MUGA scan will be at the investigator's discretion.

05/22/00

NSABP Protocol B-31
Nuclear Medicine Guidelines for Resting MUGA Scan Evaluations
Adapted from the
Society of Nuclear Medicine Procedure Guideline
For Gated Equilibrium Radionuclide Ventriculography

(for unedited guidelines see www.snm.org/policy/new_guidelines_1.html)

I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of gated equilibrium radionuclide ventriculography.

II. Background Information and Definitions

Gated cardiac blood-pool imaging or multigated acquisition (MUGA) is a procedure in which the patient's blood is radiolabeled and ECG-gated cardiac scintigraphy is obtained. Single or multiple measurements of left and/or right ventricular function are made. Data are collected from several hundred cardiac cycles to generate an image set of the beating heart that is presented as a single, composite cardiac cycle. The method can be used to assess (a) regional and global wall motion, (b) cardiac chamber size and morphology and (c) ventricular systolic and diastolic function, including left and right ventricular ejection fractions.

III. Procedure

A. Patient Preparation

No special preparation is required for a resting MUGA. A fasting state is generally preferred. It is not necessary to withhold any medications. The electrodes used for cardiac gating must be placed securely to the skin in order to ensure an optimal ECG signal.

B. Information Pertinent to Performing the Procedure

An adequate history and cardiovascular examination should be obtained prior to diagnostic evaluation. Specific areas to be reviewed include the indication(s) for testing, medications, symptomatology, cardiac risk factors, and prior cardiac procedures (diagnostic or therapeutic). The patient's cardiac rhythm should be noted, as marked heart rate variability may limit the ability to both perform and interpret the MUGA.

C. Precautions

1. It is mandatory that the OSHA guidelines for safe handling of human blood products be followed at all times when techniques labeling autologous red blood cells are used.
2. When an in vitro method is used for radiolabeling autologous red blood, a fail-safe policy and procedure must be in place and implemented to assure that misadministration of labeled cells to the wrong patient is prevented.

D. Radiopharmaceuticals

For the adult, the usual administered activity is 555–1110 MBq (15–30 mCi) of autologous red blood cells labeled with Tc-99m preferably using in vitro techniques. The largest absorbed radiation dose to an organ is to the heart (about 0.02 mSv/MBq). Tc-99m labeled red blood cells distribute within the blood-pool with an estimated volume of distribution of approximately 4–7% of body weight. The estimated biological half-life

is approximately 24–30 hr. Approximately 25% of the administered dose is excreted in the urine in the first 24 hr. A stannous pyrophosphate preparation is typically used in most red cell labeling techniques.

Labeling is least consistent with the in vivo, intermediate with the modified in vivo and most consistent with the in vitro method. The in vitro method is, therefore, preferred. Tc-99m radiolabeled human serum albumin (HSA) is an alternative to radiolabeled red blood cells.

Radiation Dosimetry for Adults

Radiopharmaceutical	**Administered Activity MBq (mCi)**	**Organ Receiving the Largest Radiation Dose+ mGy (rad)**	**Effective Dose+ mSv (rem)**
Tc-99m labeled RBCs*	555 – 1110 i.v. (15 – 30)	0.023 Heart (0.085)	0.0085 (0.031)
Tc-99m Albumin**	370 – 740 i.v. (10 – 20)	0.020 Heart (0.074)	0.0079 (0.029)

+ Per MBq (per mCi)
*ICRP 53, page 210
**ICRP 53, page 173

E. Image Acquisition for Rest Study

1. Instrumentation

Acquisition is performed by a gamma camera interfaced to a dedicated computer. Images are acquired with either a low energy all purpose (LEAP) or high resolution parallel hole collimator. An appropriate ECG gating device should interface with the acquisition computer. The simultaneity of the gating device's R-wave trigger and the patient's QRS complex should be verified prior to initiation of the study. An appropriate R-R interval beat acceptance window should be selected to account for heart rate variability and ectopy. Systolic function determinations are less susceptible to heart rate variability than diastolic function measurements. "List" mode acquisition is useful for making a composite cardiac cycle from a heterogenous population of beats.

2. Acquisition Parameters

A minimum of 16 frames per R-R interval are required for an accurate assessment of ventricular wall motion and assessment of ejection fraction. Images should be acquired such that the heart occupies approximately 50% of the usable field of view. Typical acquisitions are for a total of 3 – 7 million counts. Supine imaging is performed in a minimum of three views to visualize all wall segments of the left ventricle. The left anterior oblique acquisition (LAO) is obtained at 45° or at an angle which allows the best separation of the right and left ventricles (best septal or best separation view). An anterior acquisition is obtained in a straight (0°) anterior projection or at an angle approximately 45° less than the "best septal" view. The lateral acquisition is obtained as a left cross-table lateral or at an angle that is approximately 45°greater than the best septal view. A 70° LAO acquisition may be used instead of a left cross-table lateral

view. Left posterior oblique (LPO) or right anterior oblique (RAO) acquisitions may be of additional benefit. A slant hole collimator may be used for angulation in the caudal-cephalic plane to help separate the ventricles from the atria.

F. Processing

The cine loop should be reviewed for adequacy of counting statistics, appropriate ECG gating, adequacy of radiopharmaceutical labeling, and positioning of the heart. A subjective visual assessment of left ventricular systolic function should be performed prior to calculation of LVEF. Regions of interest (ROI) should be created, either manually by the operator or automatically by the computer, so that all activity from the left ventricle is encompassed by the ROI. The ROI used for background correction should be free of activity from the spleen or descending aorta. Other ventricular systolic and diastolic parameters may be generated. Discrepancies between the calculated LVEF and qualitative left ventricular systolic function should be resolved by reprocessing when necessary. Ventricular volumes may be calculated using either count-based or geometric methods. Calculation of the stroke volume ratio may be helpful in patients suspected of valvular disease. Spatial and temporal filtering may be used, if desired, to enhance visual appearance of the images. Parametric images (e.g. phase/ amplitude images) may be generated.

G. Interpretation Criteria

1. Cardiac Morphology

The morphology, orientation and sizes of the cardiac chambers and great vessels should be subjectively evaluated and reported. The thickness of the pericardial silhouette and the ventricular wall may also be subjectively evaluated and reported. When measured, absolute ventricular volumes may also be included.

2. Systolic Ventricular Function

Global left ventricular function should be assessed qualitatively and compared to the calculated ejection fraction. Discrepancies should be resolved by reprocessing when necessary. All left ventricular segments should be assessed for regional function using cinematic display of each view. Abnormalities of contraction should be described using the conventional terms of hypokinesia, akinesia and dyskinesia. Systematic reporting may be aided by standardized recording forms. Parametric images such as phase and amplitude images may be useful in evaluating regional variations in the timing and magnitude of contraction, identifying valve planes and in the identification of conduction abnormalities. The pattern of left ventricular diastolic function may be qualitatively evaluated and supported by quantitative measurements.

3. Comparison to Previous Studies

Results should be compared to any previous studies by direct comparison of the cinematic displays of the two studies, whenever possible. Discrepancies should be resolved by reprocessing when necessary.

H. Reporting

1. Procedures and Materials

Reporting of method of ECG gating (forward only, buffered beat averaging), beat acceptance/rejection and underlying cardiac rhythm. Report type and dose of radiolabelling (Tc-99m RBCs—in vivo, modified in vivo, in vitro; Tc-99m HSA) and views obtained.

2. Findings
   a. Cardiac Morphology
      Comments on size of various cardiac chamber, ventricular wall thickness and pericardial silhouette.

   b. Systolic Function
      i. Report global left ventricular ejection fraction (LVEF)
      ii. Report regional LV wall motion

I. Quality Control
Please refer to the *Society of Nuclear Medicine Procedure Guideline for General Imaging.*

J. Sources of Error
1. RBC Labeling
   Certain medications (e.g. heparin) and disease processes (e.g. chronic renal failure) will decrease labeling efficiency and reduce the target-to-background ratio.
2. Patient Positioning
   The ejection fraction may be inaccurately calculated by inadequate separation of the left ventricle from other cardiac structures.
3. Gating Errors
   A poor ECG signal, or one in which complexes other than the QRS complex are dominant, may result in spurious gating and data that is not interpretable. Care should be taken to ensure that the QRS complex is the triggering signal.
4. Heart Rate Variability
   Significant heart rate variability may compromise the determination of diastolic filling indices.
5. Image Statistics
   Inadequate counts/frame may compromise image interpretation as well as decrease the statistical reliability of quantitative measurements.
6. Processing Errors
   Inclusion of non-ventricular activity or exclusion of ventricular activity from ventricular ROIs may cause underestimation or overestimation of the ejection fraction. Inclusion of structures such as the spleen or the descending aorta in the background ROI may alter the left ventricular ejection fraction.

IV. Concise Bibliography

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NSABP B-31 LONG-TERM CARDIAC FOLLOW-UP

1.0 OVERVIEW OF LONG-TERM CARDIAC FOLLOW-UP DESIGN

The goal for the NSABP B-31 long-term cardiac follow-up is to collect additional data to evaluate the long-term impact of trastuzumab on cardiac function and quality of life (QOL) related to cardiac function by evaluating B-31 patients who were treated with sequential AC→paclitaxel with and without trastuzumab according to their assigned therapy.

2.0 BACKGROUND

2.1 Rationale for the long-term cardiac follow-up design

Trastuzumab given concurrently with or following adjuvant chemotherapy has been shown to improve disease-free survival (DFS) and overall survival (OS) in early-stage HER2-positive breast cancer.[G1-5] Results of four large Phase III trials evaluating the role of trastuzumab incorporated into standard anthracycline-based adjuvant chemotherapy regimens in women with HER2-positive breast cancer have demonstrated a consistent 30-50% reduction in hazard for DFS events 3-4 years following randomization along with a 35-40% reduction in risk for mortality.[G3-5] These remarkable benefits were achieved without a substantial increase in toxicity, with the notable exception of low rates of NYHA Class III or IV congestive heart failure (CHF) ranging from 1.9-3.8%, and lesser degrees of left ventricular dysfunction resulting in early discontinuation of trastuzumab.[G4,G6-8]

In the B-31 treatment trial, patients with HER2-positive, node-positive breast cancer were randomized to receive chemotherapy alone consisting of four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) (AC) every 3 weeks followed by paclitaxel administered once every 3 weeks for four cycles at 175 mg/m^2 or weekly for 12 doses at 80 mg/m^2 depending on investigator choice, or to receive chemotherapy plus weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg) for 52 weeks starting with the first paclitaxel dose.[G1]

The North Central Cancer Treatment Group (NCCTG) N9831 trial compared three regimens: AC followed by weekly paclitaxel (Arm A); AC followed by paclitaxel followed by trastuzumab (Arm B); or AC followed by paclitaxel plus trastuzumab followed by trastuzumab alone (Arm C).[G1,G5]

The combined analysis of NSABP B-31 and NCCTG N9831 demonstrated a significant improvement in DFS for the addition of trastuzumab. With a median follow-up of 3 years, the addition of trastuzumab to this chemotherapy regimen reduced disease recurrence by 52% (HR 0.48; 95% CI 0.41-0.57; p<0.00001) and the risk of death by 35% (HR 0.65; 95% CI 0.51-0.84; p=0.0007) relative to chemotherapy alone.[G5]

A prospectively defined cardiac safety study was an important component of NSABP B-31. The 3-year cumulative incidence of protocol-defined cardiac events (CHF with NYHA Class III/IV symptoms or definite or probable cardiac death) was 4.1% in the experimental arm vs. 0.8% in the control arm.[G6] Trastuzumab had to be discontinued before completion of 1 year of therapy in 15.5% of patients due to asymptomatic or symptomatic cardiac dysfunction. The 5-year cumulative incidence of protocol-defined cardiac events remained stable at 3.8% in the experimental arm.[G7] Substantial recovery in left ventricular ejection fraction (LVEF) was noted among patients who developed a cardiac event while receiving trastuzumab. Among 33 patients with a confirmed cardiac event and a minimum of 6 months of follow-up, 12 still had an LVEF of

< 50%, five remained symptomatic, and 20 had received medication for CHF in the previous 6 months.

A modest increase in risk of a cardiac event was associated with age over 50, as well as use of anti-hypertensive medications. A baseline LVEF between 50-54% appeared to substantially increase risk for a cardiac event.[G7] Based on these data, a continuous model for prediction of risk for NYHA Class III/IV CHF was developed to support a more individualized assessment of cardiac risk for the regimen employed in B-31. It would be of clinical benefit to also develop a predictive model for less severe long-term cardiac dysfunction.

NCCTG N9831 employed the same definition of a cardiac event as B-31. Reported 3-year cumulative incidence rates of cardiac events were 0.3% for Arm A (n=664), 2.8% for Arm B (n=710), and 3.3% for Arm C (n=570).[G8] Factors associated with increased risk of a cardiac event in patients receiving trastuzumab included age ≥ 60, previous or current use of antihypertensive medication, and a baseline LVEF < 55% but above the lower limit of normal.

The Herceptin Adjuvant (HERA) trial reported results comparing one year of trastuzumab treatment (n=1703) with observation alone (n=1698) after standard neoadjuvant or adjuvant chemotherapy. The majority of patients (94%) received anthracycline-based regimens prior to randomization. After a median follow-up of two years, the group of women treated with trastuzumab following chemotherapy had a significant improvement in DFS (HR 0.64; 95% CI 0.54-0.76; p<0.0001) and OS (HR 0.66; 95% CI 0.47-0.91; p<0.0115) compared to women treated with chemotherapy alone.[G2,G4]

The HERA trial reported that the incidence of severe CHF was very low but slightly increased in the trastuzumab arm (0.60 vs. 0.00; 95% CI for difference in incidence, 0.20% to 0.99%). The incidence of symptomatic CHF was also higher in the trastuzumab arm (2.15 vs. 0.12; 95% CI for difference in incidence, 1.29% to 2.77%). Significant LVEF drop, defined as an absolute decline from baseline of ≥ 10% to below 50% was significantly higher in the trastuzumab group (3.04% vs. 0.53%; 95% CI for difference in incidence, 1.59% to 3.43%).[G9]

The fourth adjuvant therapy trastuzumab trial, the Breast Cancer International Research Group (BCIRG) 006 trial, included three arms. In Arm 1, patients received AC for four cycles followed by docetaxel for four cycles (AC→T). Arm 2 consisted of the same chemotherapy with the addition of trastuzumab initiated with docetaxel and continued for one year (AC→TH). In Arm 3, patients were treated with the combination of docetaxel and carboplatin for six cycles concurrently with trastuzumab, which was continued for 1 year.

In BCIRG 006, the DFS HR for the investigational anthracycline-based chemotherapy regimen relative to the chemotherapy alone was 0.64 (0.53-0.78); p<0.001. The non-anthracycline arm consisting of trastuzumab, docetaxel, and carboplatin (TCH) reported a HR for DFS of 0.75 (0.63-0.90; p=0.04) relative to the control regimen of AC followed by docetaxel. There was also an improvement in OS for the patients who received trastuzumab compared to the control regimen with a HR for AC→TH vs. AC→T of 0.63 (95% CI 0.48-0.81; p<0.001) and a HR for TCH vs. AC→T of 0.77 (95% CI 0.60-0.99; p=0.038). Grade 3 or grade 4 CHF (symptomatic) were reported in 7/1,050 patients in the AC→T arm, 21/1,068 patients in the AC→TH arm, and 4/1,056 patients in the TCH arm.[G3]

The Finland Herceptin (FinHer) study randomly assigned 1,010 patients with node-positive or high-risk node-negative breast cancer to receive three cycles of vinorelbine or docetaxel followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide. The 232 patients with

HER2-overexpressing tumors were further randomly assigned to receive either nine weekly doses of trastuzumab or observation with the first three cycles of chemotherapy. Women who received trastuzumab tended to have an improvement in 5-year distant DFS (83% vs. 73%; HR 0.65; 95% CI 0.38-1.12; p=0.12). In the subset of patients with HER2-positive disease, one patient (0.9%) who received trastuzumab and two patients (1.7%) who received chemotherapy only were diagnosed with heart failure. During the 5-year follow-up, median LVEF (65%) did not decline in patients treated with trastuzumab.[G10]

While the incidence of severe cardiac toxicity was low enough to allow completion of the adjuvant trastuzumab trials, which employed standard anthracycline-based chemotherapy regimens and demonstrated the remarkable effectiveness of trastuzumab, important questions regarding long-term cardiac effects need to be addressed. In NSABP B-31, MUGA scans were performed at baseline and at 3, 6, 9, and 18 months after randomization. Cardiac history update forms are being collected every 6 months for the first 5 years on study and submitted annually thereafter in order to identify possible late cardiac morbidity. However, the B-31 study has not included collection of long-term data for QOL and LVEF assessment. One late LVEF assessment by MUGA scan between 5 and 10 years after entry in patients who remain free of DFS events has been added in Amendment #11. Patients will be asked to complete one questionnaire that includes several QOL instruments with respect to symptoms associated with underlying cardiac disease, as well as provide an update on chronic medications and comorbid conditions, which may increase risk for cardiac disease or produce symptoms similar to those of cardiac disease.

The population for the additional follow-up will consist of patients from the NSABP B-31 study who were eligible for B-31, had 18-month MUGA scan results submitted, and remain disease-free. The primary outcome of the long-term cardiac follow-up will be a MUGA scan LVEF measurement obtained during a 5- to 10-year window from baseline. In the HERA trial, a significant LVEF decline was defined as an absolute drop of at least 10 percentage points from baseline to a LVEF below 50%. This endpoint defined an early group of patients who began therapy with normal cardiac function and no apparent cardiac history but developed a substantial decrement in their LVEF. A review of the NSABP B-31 data using this definition demonstrated that the proportion of patients in the AC→T group with significant LVEF declines at 18 months was about 0.04. The primary aim of the long-term cardiac follow-up addressed in Amendment #11 will be to compare the proportions of patients with late significant LVEF declines from baseline in the AC→T group relative to the AC→TH group.

From the NSABP B-31 data, substantial recovery in LVEF was noted in patients who developed substantial declines in LVEF while receiving trastuzumab. However, at 18 months, there was a 4% absolute increase in incidence of LVEF declines of at least 10 percentage points from baseline to below 50% in the group who had received trastuzumab. Sufficient follow-up is now available for this population to formally evaluate the data after 6-7 years of follow-up. The LVEF assessment performed at 5 to 10 years will address whether trastuzumab is associated with a higher incidence of persistent significant LVEF declines. We will collect information on cardiac medication history, comorbid conditions, and patient-reported outcomes (PROs). Previous data focused on physicians' reporting of patients' symptoms. For this assessment, the focus will be on patients’ reporting of their symptoms and QOL. These data will be able to address if milder degrees of LVEF dysfunction are associated with impairment in physical function.

2.2 **Rationale for assessing long-term QOL and cardiac-related symptoms**

Little is known about the long term and late effects of potentially cardiotoxic adjuvant chemotherapy on the QOL and symptoms experienced by breast cancer survivors. With the growing number of breast cancer survivors, as well as their advancing age, prior treatment exposures as well as coincident comorbid disease may contribute to objective and subjective impact on physical functioning and overall well-being. While anthracycline chemotherapy has known toxicity in terms of the risk for diminished ejection fraction and overt CHF acutely and chronically,[G11,G12] little is known about the late effects of trastuzumab therapy, thus prompting this long-term follow-up. Although objective assessments of cardiac function and cardiac-related medical morbidity can be obtained through clinical examinations, more subtle changes in physical functioning and symptoms may not be apparent in such assessments. Increasingly, PROs have been added to the assessment of the late effects of cancer treatments, with measurement of symptoms and QOL seen as key components.[G13]

Anthracycline-based regimens have been accepted as a standard of care for the adjuvant therapy of women with breast cancer for some time, yet little is known about the late effects of this therapy. How the addition of trastuzumab may interact with the risk for late cardiac effects is unknown. A cross-sectional follow-up study of a cohort of patients treated with cyclophosphamide, methotrexate, and 5-FU (CMF) or cyclophosphamide, doxorubicin, and 5-FU (CAF) five to eight years earlier in Southwest Oncology Group (SWOG) 8897, showed a statistically significant reduction in mean LVEF among the women who received CAF relative to CMF. However, there was no difference in the rate of women with LVEF below normal.[G14] These results suggest adjuvant therapy with anthracyclines may result in some decrease in LVEF in a portion of individuals receiving the therapy, but this decrement rarely results in clinical CHF. The addition of trastuzumab to anthracycline-based adjuvant therapy may increase the risk for both a decline in ejection fraction (a strict objective measure of decreased cardiac function), especially in those previously identified at high risk (those over 55 years at exposure, with hypertension, lower post-AC ejection fraction); however, how this plays out over the long-term is not known. Furthermore, the assessments used in the B-31 trial did not assess diastolic dysfunction, which may be an early sign of cardiac dysfunction which may lead to dyspnea and fatigue, among other symptoms.

To date, studies evaluating the potential impact of such decrements on long-term functional status and exercise tolerance have not been conducted in breast cancer survivors, with or without trastuzumab exposure. In a large observational cohort study of disease-free breast cancer survivors initially treated in the mid-1990s, Ganz and colleagues found a significantly lower self-reported physical functioning score (ability to do vigorous physical activities such as running, lifting heavy objects, and participating in strenuous sports) three and seven years after surgery among those women who received adjuvant systemic therapy relative to women who did not.[G15,G16] This observation has generated the hypothesis that subclinical decrements in ejection fraction associated with anthracycline therapy may have contributed to patient-reported difficulties in the ability to do vigorous physical activities. However, specific treatment information was not linked to the PROs collected in this study, nor were patients randomly assigned to adjuvant therapy. The extent to which the addition of trastuzumab may add to long-term changes in physical functioning is unknown, but the B-31 trial provides an ideal sample of long-term survivors to explore this question. Given the randomization to therapy and the detailed historic data in the B-31 database on cardiac history, medical events, and serial cardiac ejection fraction monitoring, the B-31 survivors in long-term follow-up may provide invaluable information on whether or not contemporary adjuvant therapy contributes to any decrement in QOL in breast cancer survivors, and whether or not women experience significant

symptoms that are in need of effective management, independent of whether or not their cardiac ejection fraction appears normal.

3.0 OBJECTIVES

3.1 Primary objective

To determine the long-term effect of trastuzumab on cardiac function by determining ejection fraction, as measured by MUGA scan, in disease-free survivors who received B-31 therapy and are available for clinical assessment.

3.2 Secondary objectives

- To determine the long-term effect of B-31 assigned treatments on cardiac performance and QOL in disease-free survivors who received B-31 therapy.
- To describe late comorbid health problems (cardiac and non-cardiac) in disease-free survivors who received B-31 therapy.
- To develop a predictive model to examine risk factors for unfavorable late cardiac effects (cardiac performance and QOL) in disease-free survivors who received B-31 therapy.

4.0 PATIENT POPULATION FOR THE LONG-TERM CARDIAC FOLLOW-UP

B-31 patients who meet the criteria listed below must be offered participation in Amendment #11 long-term cardiac follow-up assessments. (Refer to the Coordinator Online section of the Members' Area of the NSABP Web site for the site-specific listing of eligible patients.)

- The patient must have had her 18-month MUGA scan performed and the LVEF reported to the NSABP Biostatistical Center.
- The patient must be disease-free, i.e., she must not have had any local, regional, or distant recurrences or second primary cancer diagnosis since B-31 study entry.
- The patient must have only received the B-31 therapy to which she was randomized, i.e. she must **NOT** have been treated with trastuzumab subsequent to completion of her assigned B-31 therapy.
- The patient must have provided written informed consent (see Consent Addendum #2 in Appendix H) for the long-term cardiac follow-up outlined in this appendix.

5.0 SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Assessments

Within 15 months after the site receives IRB approval for Amendment #11, all eligible patients who have consented to participate in the long-term cardiac follow-up described in Consent Addendum #2 (part of B-31 Amendment #11) will be asked to do the following **within 2 months after signing the consent form addendum**:

- Complete one Quality of Life/Patient Reported Outcome (QOL/PRO) questionnaire
  - Measurement of cardiac-related PROs will include the MOS-SF-36,[G17] the Duke Activity Status Index (DASI),[G18, G19] a brief cardiac symptom scale, and a review of comorbid conditions and chronic health problems.[G20] The questionnaire will be administered on one occasion and should take about 30 minutes for the patient to complete.
  - It is preferred, but not required, that the questionnaire be completed before the LVEF assessment.
  - The QOL/PRO questionnaire will be available in English, Spanish, and French.

- Undergo one LVEF assessment by MUGA scan. Echocardiogram may not be substituted.

5.2 **Related data submission**

The following data will be submitted to the NSABP Biostatistical Center:

- Updated cardiac-related information (Form CH-F)
- LVEF measured by MUGA scan (Form M)
- QOL/PRO questionnaire or Form QMD (if the questionnaire was not completed)
- Contact information

5.3 **Summary of requirements for the long-term cardiac follow-up**

Long-term cardiac follow-up requirements included in Amendment #11	**Prior to completing any Amendment #11 requirements**	**Within 2 months after the patient signs Consent Form Addendum #2[a]**	**About 5 years after first QOL/PRO completed**
Obtain local IRB approval for B-31 Amendment #11 (includes Consent Form Addendum #2)	X		
Confirm patient meets requirements for participation in the long-term cardiac follow-up assessments (Amendment #11)	X[b]		
Obtain patient signature on Consent Form Addendum #2	X (within 15 months after local IRB approval for the B-31 Amendment #11)		
Submit the signed/dated Consent Form Addendum #2 to the NSABP Biostatisical Center	X (prior to submitting data)		
Provide the QOL/PRO questionnaire to the patient for completion		X	
LVEF assessment by MUGA scan (Form M)		X	
Assessment needed for completion of the cardiac-related co-morbid conditions and other pertinent medical history (Form CH-F)		X[c]	
Submit required data and the QOL/PRO questionnaire to the NSABP Biostatisical Center		X	
Submit patient contact information form for patients who have consented to be contacted by the NSABP Headquarters staff in 5 years		X[d]	
Completion/submission of QOL/PRO questionnaire by patient who consented to be contacted by the NSABP Headquarters staff in the future			X

a All assessments and data submission should be completed **within 18 months after local IRB approval** of B-31 Amendment #11.

b A list of patients who are eligible for the long-term cardiac follow-up will be provided by the NSABP Biostatistical Center in the Coordinator Online section of the Members' Area of the NSABP Web site. If a patient does not meet the requirements in Section 4.0 of this appendix, but was included on the list of eligible patients posted by the NSABP Biostatistical Center, the site must submit any necessary data form(s) and required documentation for unreported events or other change in patient status.

c If an additional Form CH-F was completed as part of the patient's annual B-31 follow-up within 2 months of completion of the QOL/PRO questionnaire, Form CH-F does **not** need to be completed.

d See Section 6.0.

6.0 PROPOSAL FOR FUTURE QOL/PRO ASSESSMENT

The consent form addendum associated with the long-term cardiac follow-up (B-31 Amendment #11 - Consent Form Addendum #2) asks patients to consent to future contact by NSABP Headquarters staff for consideration of a second long-term QOL/PRO assessment about 5 years after the assessment that will be performed as part of Amendment #11. This approach would facilitate patient recruitment for the second assessment and avoid the need for additional B-31 local IRB submissions and patient contact by local research staff. Patients who consent to future contact will be asked to provide, in addition to their own contact information, the contact information for two individuals, preferably other than a spouse or partner, who could contact the patient. The NSABP Headquarters staff will maintain the contact information. Periodically, a mailing will be sent to the patient requesting confirmation or updates of the contact information.

About 5 years after the first QOL/PRO assessment is completed as part of this long-term cardiac follow-up study, the NSABP Headquarters staff will mail a letter and the QOL/PRO questionnaire to consenting patients. Patients will be asked to complete the questionnaire, which will be similar in content and format to the first questionnaire, and return it directly to the NSABP Biostatistical Center. If the completed questionnaire is not received by the NSABP staff after 4 weeks, a second letter and questionnaire will be mailed to the patient. If the questionnaire is not received after an additional 4 weeks, the NSABP Headquarters staff will attempt to contact the patient or her secondary contacts by phone to verify the mailing address or change in status. If a patient is unable to complete a written questionnaire, arrangements will be made for the NSABP Headquarters staff to administer the questionnaire by phone.

7.0 STATISTICAL CONSIDERATIONS

Hypotheses:

1. There will be no difference in the proportions of patients with an absolute decline in LVEF assessed 5-10 years after study entry of at least 10% from baseline to below 50% between women treated with trastuzumab compared to those who did not receive trastuzumab, controlling for various covariates.
2. There will be no difference in QOL and PROs between women treated with trastuzumab compared to those without, controlling for various covariates.
3. Some of the baseline characteristics including age at randomization, baseline blood pressure, baseline LVEF, 18-month LVEF, left-sided radiation therapy, and the current physical function component of the SF-36 will be significant predictors for the magnitude of decline in LVEF.

Patient population and sample size:

The population of this study will consist of patients from the NSABP B-31 study who were eligible for the B-31 study, had 18-month MUGA scan results submitted, and remain disease-free. About 400 patients in the AC→T arm who did not cross over to trastuzumab after the disclosure of the B-31 study results remain disease-free, and about 800 patients remain disease-free in the AC→TH arm. With the expectation that 75% of the eligible patients would participate in the study, the sample size will be 900 patients total, 300 from the AC→T arm and 600 from the AC→TH arm.

Analyses:

The primary outcome of the study will be a MUGA scan LVEF measurement obtained during a 5- to 10-year window from baseline. The primary aim of the study is to compare the proportions of patients who experience significant LVEF declines from baseline, defined as an absolute decline of at least 10% to below 50%. From the NSABP B-31 data, it was observed that the proportion of patients in the AC→T group (control) with significant LVEF declines at 18 months was about 0.04. Assuming the unbalanced total sample size of at least 900, the probability of the proportion of patients in the AC→TH arm being 0.085 (0.045 difference between the two groups) would be about 80% (power) at a two-sided significance level of 0.05.

A secondary aim is to compare the proportions of patients with LVEF values below 40% between the two groups among patients whose LVEF values were above 50% at 18 months. A two-sample *z*-test with the unpooled variance[G21] will be used to test any difference in the proportions of significant drops of LVEF values between the two groups.

The QOL outcomes will be the Duke Activity Status Index and the physical functioning component from the MOS-SF-36 survey. The differences between treatment groups in the mean values of these measurements will be assessed using the *z*-test. In addition, the association of each of these QOL measurements with the likelihood of having experienced a significant drop in LVEF, as defined in B-31, will be evaluated using logistic regression that includes adjustment for treatment, age, and other host factors that may be confounders, including left-sided breast irradiation.

Logistic regression modeling will also be utilized to model the probability of experiencing a significant drop in LVEF among long-term survivors. Variables that will be considered for evaluation include age at randomization, baseline blood pressure (performed prior to randomization), baseline LVEF (performed prior to randomization), 18-month LVEF, the baseline physical function component of the SF-36 (completed as part of Amendment #11), and others.

8.0 APPENDIX G REFERENCES

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NSABP PROTOCOL B-31

06/03/05 Sample Consent Form Version: 05/16/03
07/18/05 Sample Consent Addendum #1 (Options A, B, and C) Version: 07/18/05

Note regarding Consent Addendum #1*: B-31 was closed to accrual on April 29, 2005, following a pooled interim analysis of data from NSABP B-31 and NCCTG N9831, which showed that the primary aim of prolonging disease-free survival was achieved.* ***Updated consent items from Amendments #7, 8, 9, and 10 are provided in the consent form addendum #1, and have NOT been included in the main study consent form****.*

All patients must sign and date the IRB-approved consent addendum #1 (option A, B, or C) that applies to them as described below:

- **Option A:** Group 1 patients who were randomized on or after April 26, 2004.
- **Option B:** Group 1 patients who were randomized before April 26, 2004.
- **Option C:** Group 2 patients.

04/06/10 Sample Consent Addendum #2 Version: 04/06/10
To be attached to Protocol Version: 04/06/10

Note regarding Consent Addendum #2: An IRB-approved Consent Addendum #2 for cardiac follow-up must be provided to all patients treated according to their randomized B-31 therapy who had the 18-month MUGA and who remain disease-free. See Appendix G for additional information regarding cardiac follow-up.

Instructions to Local Institutional Review Boards
Regarding Local IRB Review of Multicenter Clinical Trials

01/14/03
02/28/05

The NSABP understands and agrees with the position of the Office for Human Research Protections (OHRP – formerly OPRR) that "only the local IRB is familiar with the particular circumstances of its research setting and is in a position to weigh critical considerations like state and local laws, professional and community standards, institutional policies, and the needs of differing patient or subject populations." In order to conform to OHRP guidelines regarding local IRB review of multicenter clinical trials (effective November 9, 1992), and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial.

The protocol and sample provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the sample consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. Also, the NSABP Operations Center requires that, similarly, they also be notified of substantive changes in the consent form section regarding consent to collect and store samples for possible future testing. Of primary concern are text changes that could potentially impact the future usage of the banked samples. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. The investigator is responsible for forwarding copies of such IRB approved changes with their justifications to the NSABP Operations Center Regulatory Affairs Division (see page vi) immediately following such IRB approved changes. It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff and government agencies.

NSABP SAMPLE CONSENT

Consent Form
for
Chemotherapy Treatment with or without Herceptin for
Breast Cancer Patients who have Positive Axillary Nodes and
Tumors that Overexpress HER2

Why have I been asked to take part in this research study?

You have been asked to take part in this study because the breast cancer tumor you have has an overactive gene called HER2. This gene produces a substance called HER2 growth factor receptor, which is known to make cancer grow faster. A new drug, Herceptin (also called trastuzumab), has been shown to slow down such growth.

It is up to you to decide whether or not to take part in this study. Please read this entire consent form and take your time to make your decision. We encourage you to talk to your doctor, your family, and/or your friends before you decide.

Who is conducting the study?

If you decide to join this study, you will be taking part in a clinical trial being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). Clinical trials are studies designed to find better ways to treat diseases like cancer.

(The NSABP institution must supply appropriate information about who is conducting the trial locally.)

Why is this research study being done?

There are a number of reasons this study is being done:

- This study is being done to find out if adding Herceptin to standard chemotherapy (drugs given to fight cancer) will help prevent your cancer from coming back. Herceptin is an antibody, a substance which helps your immune system kill cancer cells.
- This study is also being done to check the side effects of chemotherapy when given with Herceptin. At present, we do not know whether the possible benefits of Herceptin outweigh its potential risks when it is taken together with chemotherapy.

- Another goal of this study is to conduct tests to help us learn more about how breast cancer works in the body so we can design better treatments for patients.
- The final reason for doing the study is that the U.S. Food and Drug Administration (FDA) and the Health Products and Food Branch (HPFB) in Canada have approved the use of Herceptin for treating cancer that has spread to other organs. Its use in patients with early-stage breast cancer like yours must be tested further.

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How many people will take part in the study?

About 2700 women from many cancer treatment centers will take part in this study.

What is involved in the study?

Before you begin the study. To find out if you can join the study, you will need to have the following exams and medical tests. If you have had some of them recently, your doctor may decide not to repeat them:

- physical exam
- pelvic exam (if you have a uterus)
- mammogram
- blood tests
- chest x-ray
- bone scan (optional)
- MUGA scan (a test to see how well your heart works)
- Electrocardiogram (EKG)

These exams and tests are part of standard good medical care even if you do not join the study. However, if you do join the study, the MUGA scan will be done more often to check your heart. These tests are mostly done on an outpatient basis at your doctor's office, clinic, or in a hospital.

During the study. If the tests and exams show that you can be in the study, you will be randomly assigned (randomized) to one of two treatment groups: Group 1 or Group 2. This means a computer program will put you into Group 1 or Group 2 by chance. Neither you nor your doctor will choose which group you are in. You will have an equal chance of being placed in either of the two groups.

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05/16/03

If you are in Group 1, you will receive three chemotherapy drugs that are widely used in breast cancer treatment: *doxorubicin* (brand name Adriamycin), *cyclophosphamide* (brand name Cytoxan) and *paclitaxel* (brand name Taxol). Once every 21 days, for 4 visits, you will be given the doxorubicin and cyclophosphamide through a vein in your arm. This will take about 1 or 2 hours each time. When you have finished all four treatments, you will begin receiving paclitaxel. You will receive paclitaxel either once every 21 days for 4 visits or you will receive a lower dose of paclitaxel once every week for 12 visits. Your doctor will decide which of these schedules is best for you. If you receive paclitaxel on the every 21 day schedule, this will take about 3 ½ hours each time. If you receive paclitaxel on the weekly schedule, this will take about 1 ½ hours each time. If your tumor has a positive estrogen and/or progesterone (ER/PgR)

hormone receptor test, you will take *tamoxifen* (brand name Nolvadex) by mouth once a day for 5 years, once your chemotherapy has ended. Based on your medical history and if you are postmenopausal, your doctor may choose to prescribe another drug called *anastrozole* (brand name Arimidex) instead of tamoxifen. Anastrozole, like tamoxifen, has been shown to be effective in preventing cancer from returning.

01/14/03

If you are in Group 2, you will receive the same chemotherapy as in Group 1 and you will also receive Herceptin. You will start Herceptin on the same day as your first paclitaxel treatment, and you will continue to receive the Herceptin weekly for 1 year. Your doctor will talk with you about having a temporary tube put into a vein in your chest or arm so that you can receive this drug, and your chemotherapy, more easily. The first time you receive Herceptin, it will take about 1 ½ hours; after that, it will take about ½ hour each time.

If your tumor has a positive estrogen and/or progesterone (ER/PgR) hormone receptor test, you will take *tamoxifen* (brand name Nolvadex) by mouth once a day for 5 years, once your chemotherapy has ended. Based on your medical history and if you are postmenopausal, your doctor may choose to prescribe another drug called anastrozole (brand name Arimidex) instead of tamoxifen. Anastrozole, like tamoxifen, has been shown to be effective in preventing cancer from returning.

01/14/03
05/16/03

Summary of treatment. You will be randomized into one of these two groups:

<table>
<tr><th>Group 1
(standard treatment)</th><th>Group 2
(test treatment)</th></tr>
<tr><td><u>doxorubicin</u> and <u>cyclophosphamide</u>

every 3 weeks for four visits (3 months)

Followed by</td><td><u>doxorubicin</u> and <u>cyclophosphamide</u>

every 3 weeks for four visits (3 months)

Followed by</td></tr>
<tr><td rowspan="2"><u>Paclitaxel</u>

every 3 weeks for four visits (3 months)
or
every week for 12 visits (3 months)</td><td><u>Paclitaxel</u>

every 3 weeks for four visits (3 months)
or
every week for 12 visits (3 months)
AND</td></tr>
<tr><td><u>Herceptin</u>

every week for 1 year</td></tr>
<tr><td colspan="2">Other treatments: If your tumor has a positive estrogen and/or progesterone (ER/PgR) hormone receptor test, you will take tamoxifen or anastrozole by mouth once a day for 5 years, once your chemotherapy has ended. You may also need to have radiation therapy after your chemotherapy is completed. Your doctor will talk to you about this.</td></tr>
</table>

Everyone in the study will receive the following drugs before the paclitaxel to prevent a possible allergic reaction: dexamethasone; diphenhydramine; and either cimetidine, ranitidine, or famotidine. Also, you may be given an antibiotic between your chemotherapy treatments and/or other drugs to help prevent infections. Tell your doctor or nurse if you are taking any drugs other than those you receive in this study. They need to make sure that any drugs you are already taking will not cause problems with your study treatment.

For both Groups 1 and 2: Before and during your treatment, you will have a test called a MUGA (MultiGated cardiac blood pool) scan to check your heart for possible side effects from the therapy you are receiving. MUGA scans will be done at the start of the study and at 3, 6, 9, and 18 months. If your MUGA scan is abnormal, you may have to repeat the scan in 4 weeks.

For those in Group 2: If after the first 3 months of chemotherapy you have signs of early heart damage, you will not be given Herceptin, but you may still receive paclitaxel. We expect that about 5% of patients assigned to Group 2 will **not** receive Herceptin because of their MUGA scan results. Also, if the NSABP receives new information at any time that shows receiving Herceptin may be harmful to you, you may be asked to stop taking the drug, even if you do not have symptoms.

05/16/03

After the chemotherapy: At the end of your chemotherapy treatment, if you had a lumpectomy you will receive radiation therapy to your breast. For Group 2 patients, you will get radiation therapy for about 5 to 6 weeks while you are on Herceptin. If your doctor wants you to have radiation therapy to areas other than your breast, you and your doctor will need to decide this before you begin the study. If you had a mastectomy and your doctor recommends radiation therapy, you and your doctor will need to decide this before you begin the study.

After all of your treatment is finished, your doctor will ask you to come in for a follow-up physical exam and blood tests every 6 months. You must have a pelvic exam (only if you have a uterus), a mammogram, and if you have symptoms, a chest x-ray and/or a bone scan, every year for 5 years from the time you begin the study.

How long will I be in the study?

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Depending on which group you are assigned to, your treatment will last either about 6 months (Group 1) or about 15 months (Group 2). You will take tamoxifen or anastrozole for 5 years. We would like to keep track of your medical condition for the rest of your life to look at the long-term effects of the study. However, your doctor may take you off the study drugs if one of the following happens:

- the study treatment does not work for your cancer;
- you develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications;
- your health gets worse;

- you are unable to meet the requirements of the study (for example, you cannot take the medicine as prescribed or cannot return for follow-up visits); or
- new information about the study drugs or other treatments for breast cancer becomes available.

In addition, your participation in this study may be ended because the NSABP finds it must limit or stop the study.

You can stop taking part at any time. If you decide to stop, you should talk to your study doctor first.

What are the risks to me from being in the study?

There are risks involved in taking the drugs in this study, and there may be side effects. Most of these are listed here, but they will vary from person to person. *There may be other side effects that we cannot predict*. Your doctor may give you other medications to prevent or reduce some side effects.

Many side effects go away shortly after the drugs are stopped, but in some cases, side effects may be serious, long lasting, and/or life-threatening. Talk with your study doctor about this. If you want to read more about these study drugs, please ask your doctor or pharmacist for more information.

During the study, we will do blood tests to see if the amount of some of the drugs you are receiving during your chemotherapy should be changed or delayed. The tests will also help monitor any side effects you may have. You will not need to be hospitalized unless you have serious side effects.

Side effects of doxorubicin, cyclophosphamide, and paclitaxel chemotherapy:

Likely side effects:

- Nausea
- Vomiting
- Diarrhea
- Complete or partial hair loss
- Fever
- Fluid retention (bloating or swelling)
- Allergic reaction (including itching, hives, flushing, shortness of breath, wheezing, chest tightness, skin rashes, fever, chills, muscle stiffening)
- Numbness, tingling, prickling, and burning in your hands and feet, which may extend to your arms and legs
- Headache
- Mood changes
- Constipation
- Red-colored urine (not blood)
- Feeling tired
- Pain in muscles or joints
- Skin and nail discoloration
- Sores in mouth and/or throat
- Lowered white blood cell count (may lead to infection)
- Lowered red blood cell count (may lead to anemia, tiredness, shortness of breath)
- Infection
- Weight gain/loss
- Loss of appetite
- Irregular or permanent stopping of menstrual cycle (periods)
- Inability to get pregnant
- Time away from work

Possible side effects: darkening of soles of the feet or palms of the hands; skin damage (due to leakage of drug); changes in blood test results that indicate possible liver injury; damage to kidneys; stomach or back pain; blood in your urine; low sodium; low blood pressure; hardening of the walls of the veins; uric acid in the blood; eye problems; changes in taste; and lowered platelet counts (may lead to bleeding or bruising). Changes in your heart rhythm may also occur, but usually these go away on their own.

03/15/00 *Rare but serious* side effects you may have include: liver failure, acute leukemia (cancer of the blood cells), other cancers, chest pain, or heart damage or failure. Rarely, a group of symptoms may occur which include a blister-like rash, which may be severe; fever; inflammation of the eyes; and redness, swelling, and painful sores on your lips and in your mouth. If you have this group of symptoms, it is likely that you will need IV fluids and medicines, and you may need to be hospitalized. If you have ever had radiation treatments, redness and soreness may develop in the treated areas.

01/14/03 If you get an infection or if your white blood cell counts become very low, you will need to take a shot of a blood-cell stimulating drug, such as G-CSF (brand name Neupogen), GM-CSF (brand name Sargramostim), or pegfilgrastim (brand name Neulasta) to fight infections. If this happens, we will teach you to give yourself this shot, or we can teach a friend or relative to give it to you. Depending on which drug you are given, it may be prescribed as a daily shot or as one shot with each cycle of chemotherapy. Some patients experience bone pain with these drugs. If this happens to you, let your doctor know.

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01/31/03 *Side effects related to Herceptin:* You are ***likely*** to have chills, fever, and diarrhea when you receive the first dose of Herceptin. It is unlikely that you will have these symptoms with the rest of the doses. You may ***possibly*** have an infection; chest pain; shortness of breath; feelings of weakness; dizziness; headache; nausea; vomiting; lack of appetite; hard time sleeping; burning, tickling, or tingling (especially in the hands and feet); swelling in the hands or feet; low blood pressure; muscle stiffening; a cough or a cold; inflammation of the throat; runny nose; sinus trouble; low red or white blood cell counts; and rash. You *may* develop serious heart trouble, including damage to or weakening of the heart muscle. This makes it hard for the heart to pump blood and may lead to congestive heart failure or stroke, which can result in death. Heart attacks, which can be fatal, have occurred in patients after they began taking Herceptin. There is a chance of developing shortness of breath, or a drop in blood pressure with the use of Herceptin. Rarely, these reactions can be severe or life threatening. A few deaths have occurred in patients with breast cancer, particularly in those who already have lung disease and shortness of breath. There is also a rare chance of acute leukemia (cancer of the blood cells) with the combination of chemotherapy and Herceptin or that Herceptin may be associated with kidney problems.

Side effects related to tamoxifen: If you are taking tamoxifen, you are ***likely*** to have hot flashes and/or vaginal discharge. In addition, you may ***possibly*** experience constipation or pain with intercourse, or problems controlling your bladder when you cough or sneeze. ***Rare but serious*** side effects include: uterine cancer or abnormal non-cancer cell growth in the pelvic area that can cause pain or bleeding; eye problems (including cataracts, a clouding of the lens inside the eye); liver cancer or changes in blood tests that show possible liver damage; stroke; and blood clots in areas such as the legs, the eyes, or the lungs that could be life-threatening.

01/14/03 *Side effects related to anastrozole*: If you are postmenopausal and taking anastrozole instead of tamoxifen, you are likely to have hot flashes, nausea, back pain, headache, weakness or decreased energy, or shortness of breath. In addition, it is possible you will experience gastrointestinal upset (constipation, diarrhea, vomiting, loss of appetite), dizziness, dry mouth, cough, skin rash, joint pain/stiffness, increased cholesterol levels, osteoporosis (thinning of the bones), swelling of the hands and feet, or sore throat. Rare but serious side effects of anastrozole include blood clots in areas such as the lungs, the legs, or the eyes that could be life-threatening.

You are at risk for any of these side effects for as long as you are receiving treatment as part of this study. There may be other side effects that we cannot predict. You should discuss risks and side effects with the researcher ***(insert name and phone number here)*** or with your regular doctor.

Risks related to pregnancy: If you are pregnant, you should not participate in this study. You should not become pregnant if you decide to take part because the drugs can affect an unborn baby. Ask about counseling and more information about preventing pregnancy if this applies to you. Also, you should not nurse your baby while on this study. Some of the drugs used in the study may make you unable to have children in the future.

Are there benefits to taking part in this study?

There may or may not be direct medical benefit to you from your taking part in this study. All of the drugs used in this study have been given to women with breast cancer, but it is not known if the potential benefits of adding Herceptin to standard chemotherapy outweigh the risks. We hope the information learned from this study will help future patients with breast cancer. We also hope that the treatment you receive in this study may help prevent your breast cancer from coming back. Herceptin is provided free of charge by Genentech, Inc., through the National Cancer Institute (NCI).

01/14/03 **What other treatment options are there?**

Instead of being in this study, you can decide:

- to take chemotherapy with these or other drugs used for treating breast cancer;
- to take hormonal therapy with tamoxifen or other drugs known to be effective for treating breast cancer;
- to have radiation therapy;
- to have some combination of the above three options; or
- to receive no treatment.

These options are available to you at this center or other centers, even if you do not take part in this study. Please talk with your doctor about all your options before you enter the study.

How will information about me be kept private?

05/22/00 We will try to keep your personal information as private as we can. We cannot guarantee total privacy. Your personal information may be disclosed if required by law. Your research records will include your medical history, results of your blood tests and exams, reports from your surgery and treatment, reports of your office visits, your MUGA scans, and your mammogram films and reports. Some of the information collected as part of the research will also be included in your medical records. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include:

- the NSABP;
- Genentech, Inc., which is supplying the drug Herceptin free of charge through the NCI;
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and

01/14/03

- government agencies, including the NCI, the FDA, the Office for Human Research Protections (OHRP), and the Canadian Health Products and Food Branch (HPFB). These agencies may review the research to see that it is being done safely and correctly.

What are the costs?

01/14/03 Herceptin will be provided free of charge by Genentech through the NCI. Doxorubicin, cyclophosphamide, paclitaxel, tamoxifen, and anastrozole will not be provided for free with this study.

Taking part in this study may lead to added costs for you or for your insurance company from the extra tests needed. Once you start receiving chemotherapy, the required MUGA scans will be paid for by Genentech, Inc. Your doctor may want you to have more MUGA scans or other tests in addition to those required by the study. You or your insurance company may be billed for these extra tests. Please ask about any added costs or health insurance problems. If you are injured or become ill from taking part in this study, emergency medical treatment is available and will be provided at the usual charge. No funds have been set aside to pay you in case you

are injured. You or your insurance company will be charged for medical care and/or hospitalization.

You will not be paid for taking part in this study. If during the study, the Herceptin is no longer provided free of charge by Genentech, Inc., you may have to pay for the amount of drug needed to complete the study. However, we do not expect this will happen.

Do I have to be part of the study?

You may choose either to take part or not to take part in this research study. If you have any questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

What are my rights as a study participant?

Even after you agree to take part in this study, you may withdraw at any time. Before you withdraw, you should talk to one of the researchers or nurses involved. This will allow them to inform you of any medical problems that could result from stopping your treatment. You can choose to withdraw one of two ways. In the first, you can stop your study treatment, but still allow the study doctor to follow your care. In the second, you can stop your study treatment and not have any further contact with the study staff. Either way, there will be no penalty to you. Your decision will not affect your medical treatment, or your relationship with those treating you or with this institution. If you withdraw from the study, you will still be offered all available care that suits your needs and medical condition.

The Data Monitoring Committee, an independent group of experts, will be reviewing the data from this research on an ongoing basis. If any important new information about the study develops that may affect your health, welfare, or willingness to stay on the study, your doctor will tell you. You may be asked to sign another consent form at that time.

Who can I call if I have questions or problems?

For questions about the study or a research-related injury, contact ***(insert investigator's name)*** at ***(insert phone number)***. For questions about your rights as a research participant, call ***(insert name and phone number of Institutional Review Board or Patient Representative)***.

What about use of my blood and tissue for research?

Recommended special tests for the B-31 study: The NSABP will be sent some of the blood and tissue samples that are taken from you during the study but are not used for other tests. These samples will be used to confirm that your tumor has the overactive HER2 gene. They will also be used for other tests to help us learn more about the biology of breast cancer to design better treatments for patients. At this time, we plan to test for markers of the activity of the HER2 gene. Since they will provide important information for the goals of the study we strongly urge

you to allow your samples to be tested for these markers as part of this study. In circling "yes" to question #1 of this consent form, you will be agreeing to have your samples checked for these markers. If you would like a list of the markers, please ask one of the study staff.

(A) The blood and tissue samples will be given only to researchers approved by the NSABP. Any research study using your samples must also be approved by an IRB. The research that is done with your blood and tissue samples is not designed to specifically help you. It might help

people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your blood and tissue samples will not affect your care.

(B) The possible benefits of research from your blood and tissue samples include learning more about what causes cancer, how to prevent it, and how to treat it. The greatest risk is the release of information from your health records. The NSABP will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood or tissue samples collected and stored by the NSABP.

The tests described under "Recommended special tests in the B-31 study" are strongly recommended for *all* patients entered in the trial. Please answer the following question by circling "yes" or "no" below.

1. Do you agree to have special tests for the HER2 gene and its activity performed on your samples?

   YES NO

Optional tests for future studies: There may be some blood or tissue that is not used up in the tests which are to be done as part of the B-31 study. If you agree, some of your samples will also be kept and may be used in future research to learn more about cancer and other diseases.

The choice to let the NSABP keep the blood and tissue samples for future research is up to you.

No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood and tissue samples can be kept for future research that is not part of this trial, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want the NSABP to use your blood and tissue samples and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the NSABP decides to destroy them.

The same information listed for (A) and for (B) under the *"Recommended Tests for the B-31 Study"* applies to the samples to be used for future research.

In the future, people who do research with your blood and tissue samples may need to know more about your health. While the NSABP may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue samples are used for genetic research (about diseases that are passed on in families). Even if your blood and tissue samples are used for this kind of research, the results will not be told to you and will not be put in your health records.

Your blood and tissue samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future, but you will not get paid.

Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or nurse. No matter what

you decide to do about ***the storage and future use*** of your blood and tissue samples, you may still take part in the B-31 study.

By signing this form, you are agreeing that:

2. Your blood and tissue samples may be kept by the NSABP for use in future research (not related to the special tests required for the B-31 study) to learn about, prevent, detect, or treat cancer.

   YES NO

3. Your blood and tissue samples may be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   YES NO

4. Your study doctor (or someone he or she chooses) may contact you in the future to ask you to take part in more research.

   YES NO

Where can I get more information about cancer and its treatment?

01/14/03

You can call the Cancer Information Service at 1-800-4-CANCER or visit the National Cancer Institute's Cancer Trials Web Site at http://www.cancer.gov/clinical_trials. You can also visit the NSABP Web Site at http://www.nsabp.pitt.edu. If you would like additional information about the drugs used in this trial and their side effects, you should ask your doctor or pharmacist.

You can also get information from the doctor in charge of your medical care in this study.

(NSABP institutions may insert or attach a list of materials that they can provide locally to patients regarding clinical trials, drug information, the institution/investigator, and/or the NSABP.)

You will get a copy of this form.

Signatures

I agree to take part in this research study.

_____	_____
Date	Patient's Signature
_____	_____
Date	Signature of Person Conducting the Informed Consent Discussion

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NSABP SAMPLE CONSENT FORM ADDENDUM #1

(<u>Option A</u>: Group 1 patients who were randomized on or after April 26, 2004)

Consent Form Addendum #1
for
A Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol (AC→T) to that of Adriamycin and Cyclophosphamide Followed by Taxol plus Herceptin (AC→T + H) in Node-Positive Breast Cancer Patients who have Tumors that Overexpress HER2

When you entered the NSABP B-31 study, the NSABP promised to tell you about new information that might affect the therapy you are receiving as part of this study. Recently, you received new information about the positive results of adding the drug Herceptin (trastuzumab) to chemotherapy in the treatment of your type of breast cancer. This consent form includes this information and new information about possible changes in your treatment plan. Also, this form provides you with new risk information about the B-31 study.

Information about the results of NSABP B-31:

In April 2005, data from the B-31 study were analyzed along with the data from another similar national trial (NCCTG N9831) conducted by the North Central Cancer Treatment Group (NCCTG). Both studies examined the value of receiving 1 year of Herceptin that started at the same time as the chemotherapy drug paclitaxel (Taxol). You are one of several thousand women who were enrolled in these studies, which began in 2000.

Each of the committees responsible for protecting the interests of women enrolled in these studies has reviewed these results independently. Both recommended to the National Cancer Institute (NCI), the organization responsible for these studies, that all study participants and their doctors be told the results. The NCI, the NSABP, and the NCCTG have agreed with this recommendation, and the results were made public on April 25, 2005. The committees also recommended closing the two studies to further accrual, which means that no more women were able to join the studies after the end of April 2005.

The data from these studies showed very positive results. The studies showed that by the time of the committees' review, Herceptin had improved the chance of being alive and free of cancer by 52%. This means that these studies showed that when Herceptin is given with chemotherapy, breast cancer returns much less often than it does when chemotherapy is given without Herceptin.

Information about possible changes in your study therapy:

You joined the B-31 study on or after April 26, 2004. At that time, you were randomized to ***Group 1***, which means that you were selected by chance to receive chemotherapy ***without Herceptin*****.** You may still be receiving chemotherapy (AC or paclitaxel), or you may have completed your chemotherapy within the past six months. Because of the positive results of the B-31 study, we are providing you with the option of receiving Herceptin. If you choose to receive Herceptin, you will follow the treatment plan below:

Treatment Plan
doxorubicin and cyclophosphamide *(Adriamycin)* *(Cytoxan)* *(AC)* every 3 weeks for four visits (3 months) ***Followed by*** paclitaxel *(Taxol)* every 3 weeks for four visits (3 months) ***or*** every week for 12 visits (3 months) ***AND*** trastuzumab *(Herceptin)* every week for 1 year given either during Taxol or following completion of Taxol

You will start Herceptin either during your paclitaxel treatment or after you have completed paclitaxel, and you will continue to receive Herceptin weekly for 1 year. Your doctor will talk with you about the possibility of having a temporary tube put into a vein in your chest or arm so that you can receive your therapy more easily. The first time you receive Herceptin, it will take about 90 minutes. After that, it will take about 30 minutes each time.

If you have not already made your decision about receiving Herceptin, you should discuss this with your study doctor. Your decision should be made ***as soon as possible*** because it may be important that you begin the Herceptin while you are still receiving chemotherapy or as soon as possible after completing your chemotherapy. Our current information shows that giving Herceptin in this timeframe is effective. Early results of another study call the HERA trial have shown that giving Herceptin after chemotherapy also improved a woman's chance of being alive

and free of cancer. This means that you should still benefit from receiving Herceptin, even if the Herceptin is started or restarted ***after*** you have completed chemotherapy.

Herceptin will be provided free of charge by Genentech, Inc., the company that makes Herceptin. You must **begin** Herceptin by December 30, 2005, in order to receive Herceptin free of charge through this study. You will receive enough Herceptin to complete 1 year of therapy. There may be costs which are not covered by the study such as co-pays and doctor's fees. These will be the responsibility of you and/or your insurance company.

If you decide to receive Herceptin, your study doctor will confirm that you meet the requirements to begin Herceptin therapy. If the result of your most recent MUGA scan is within the range required by the study, you will be able to begin Herceptin. After reviewing your tests and exams, your doctor could advise you that adding Herceptin to your treatment plan at this time is not in your best interest.

You will continue to have all of the tests and exams as outlined in the B-31 study consent form that you signed when you entered the study. However, there are two possible changes discussed below:

- The schedule of MUGA scans may differ from the original schedule depending on when you begin Herceptin.
  - If you begin Herceptin ***immediately after AC chemotherapy or during paclitaxel therapy***, you will have MUGA scans 3-4 weeks after completing AC and at 6, 9, and 18 months after you joined the study.
  - If you begin Herceptin ***after you complete all of your chemotherapy***, you will have a MUGA scan 3-4 weeks after completing AC. You may also have a MUGA scan following paclitaxel therapy before starting Herceptin, and then at 3, 6, and 15 months after starting Herceptin.
  - If you do not receive any Herceptin, the MUGA scans initially required by the study no longer need to be done.
- You also will have physical exams and blood tests done about every 3 months while you receive Herceptin after chemotherapy.

Although we have told you about these important initial results, the B-31 study is not over. Your study doctor will still follow your progress as described to you in the consent form that you signed when you joined the study.

Your doctor may advise you to stop Herceptin if one of the following happens:

- you develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications;
- new information becomes available about Herceptin or about other treatments for preventing breast cancer recurrence;
- your doctor determines it is no longer in your best interest to continue Herceptin.

New information about hormonal therapy in the NSABP B-31 study:

As described in the consent form you signed when you joined the study, if your tumor has a positive estrogen and/or progesterone (ER/PgR) hormone receptor test, you will receive hormonal therapy for 5 years. When the B-31 study was planned, 5 years of tamoxifen was considered standard hormonal therapy. Tamoxifen was the only hormonal therapy allowed in this study. In 2003, another hormonal drug, anastrozole, was added as an option. Recent results from two large research studies have shown that similar hormonal therapy drugs can be used in postmenopausal women. One study also showed that some women may benefit from taking hormonal therapy for longer than 5 years. The NSABP has changed the B-31 study to allow your doctor to choose the hormonal therapy that is best for you. Your doctor can also choose how long you should take the hormonal therapy. Your doctor will discuss the choices and the risks and side effects of hormonal therapy with you.

New information about the risks on NSABP B-31:

The information listed below is new risk information relating to the drugs in this study. There are other risks that are not described here. These were listed in the consent form that you signed when you joined the study. You should discuss these risks with your study doctor.

- *New side effect related to paclitaxel (Taxol)*: There have been rare cases of severe lung problems in patients who received paclitaxel.

- *New side effects related to Herceptin (trastuzumab)*: You may possibly have tiredness; diarrhea; pain in the stomach, joints, or muscles; sores in the mouth; a rapid heart rate; or wheezing with the use of Herceptin. There is a rare chance of changes in blood test results that may indicate possible liver injury.

  There have been rare cases of severe lung problems which may be bad enough to cause low levels of oxygen in the blood and can be life threatening. Some patients with this problem died. Most of the cases occurred in patients who had other lung problems such as spread of their cancer to the lungs. However, some cases occurred in patients who did not have spread of cancer to their lungs.

New information about possible increased risk for heart problems for some women receiving Herceptin:

The NSABP has continued to study the B-31 data and has recently learned that ***some*** women may be at increased risk for heart problems with Herceptin. The women we have identified as having this increased risk of heart problems include those:

- who were 50 years of age or older at the time they joined the study; ***and***
- who had a MUGA scan after completing Adriamycin and cyclophosphamide that showed a test result that was at the low end of normal (less than 55%); ***and***
- who received Herceptin at the same time as paclitaxel.

This new information suggests that, if you were 50 years old or older when you joined the study ***and*** your MUGA scan result was at the lower end of normal, it may be safer to receive Herceptin ***after*** you complete paclitaxel therapy. However, Herceptin may work best when given with paclitaxel. If the items noted above apply to you, you will need to discuss this with your study doctor to decide how you will continue your study therapy. The timing of Herceptin therapy may be changed depending on what you and your doctor decide. If you have already begun receiving Herceptin along with paclitaxel, your doctor may advise you to stop Herceptin until after you finish paclitaxel. Or, you and your doctor may decide that you should continue to receive Herceptin at the same time as your paclitaxel.

- If you make the decision to delay receiving Herceptin, you will be able to begin or restart Herceptin therapy after you finish all your paclitaxel, as long as the result of the MUGA scan done after finishing your paclitaxel is in the normal range.
- If the result of the MUGA scan that you have after finishing your paclitaxel is not in the normal range, you will not be able to begin or restart Herceptin. Your study doctor may schedule a follow-up MUGA scan (waiting at least 4 weeks after your last MUGA scan) to see if your heart function returns to the normal range. If your heart function does return to the normal range, you may be able to begin or restart Herceptin at that time. If your heart function does not return to the normal range, you will not be able to receive Herceptin through the B-31 study.
- If you made the decision to begin or continue to receive Herceptin therapy ***along with paclitaxel,*** your treatment will continue as described earlier in this consent form.

Signature (You must sign and date <u>only one</u> option below.)

Option 1:

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

I choose ***to receive or to continue to receive Herceptin*** as provided by Genentech, Inc., as part of the B-31 study. I understand that I must meet all study requirements to start or continue Herceptin therapy.

_____ _____

Date Patient's Signature

_____ _____

Date Signature of person conducting the informed consent discussion

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Option 2:

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

I choose ***<u>not</u> to receive Herceptin*** as provided by Genentech, Inc., as part of the B-31 study.

_____ _____

Date Patient's Signature

_____ _____

Date Signature of person conducting the informed consent discussion

NSABP SAMPLE CONSENT FORM ADDENDUM #1

(Option B: Group 1 patients who were randomized before April 26, 2004)

Consent Form Addendum #1
for
A Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol (AC→T) to that of Adriamycin and Cyclophosphamide Followed by Taxol plus Herceptin (AC→T + H) in Node-Positive Breast Cancer Patients who have Tumors that Overexpress HER2

When you entered the NSABP B-31 study, the NSABP promised to tell you about new information that might affect the therapy you are receiving as part of this study. Recently, you received new information about the positive results of adding the drug Herceptin (trastuzumab) to chemotherapy in the treatment of your type of breast cancer. This consent form includes that information and new risk information about the B-31 study.

Information about the results of NSABP B-31:

In April 2005, data from the B-31 study were analyzed along with the data from another similar national trial (NCCTG N9831) conducted by the North Central Cancer Treatment Group (NCCTG). Both studies examined the value of receiving 1 year of Herceptin starting at the same time as the chemotherapy drug paclitaxel (Taxol). You are one of several thousand women who were enrolled in these studies, which began in 2000.

Each of the committees responsible for protecting the interests of women enrolled in these studies has reviewed these results independently. Both recommended to the National Cancer Institute (NCI), the organization responsible for these studies, that all study participants and their doctors be told the results. The NCI, the NSABP, and the NCCTG agreed with this recommendation, and the results were made public on April 25, 2005. The committees also recommended closing the two studies to further accrual, which means that no more women were able to join the studies after the end of April 2005.

The data from these studies showed very positive results. The studies showed that by the time of the committees' review, Herceptin had improved the chance of being alive and free of cancer by 52%. This means that these studies showed that when Herceptin is given with chemotherapy, breast cancer returns much less often than it does when chemotherapy is given without Herceptin.

Information about your continued B-31 study therapy:

When you joined the NSABP study, you were randomized to ***Group 1***, which means you were selected by chance to receive chemotherapy ***without Herceptin***.

The NSABP and the NCCTG study results were based on patients who either received the Herceptin *along with their chemotherapy* or patients *who started receiving Herceptin within weeks after completing chemotherapy.* You joined the study before April 26, 2004. Currently, we do not have enough information to know whether receiving Herceptin at this point would be in your best interest. It is very important that you talk with your doctor about this.

After considering this point, if you and your doctor decide that you want to receive Herceptin, you may do so. However, the Herceptin will not be provided through the B-31 study. You and/or your health plan/insurance company will have to pay for the Herceptin. As with any drug, there may be side effects as a result of receiving Herceptin. If you decide to receive Herceptin, you should talk with your doctor about the side effects.

If you do not receive Herceptin, the MUGA scans initially required by the study no longer need to be done.

Although we have told you about these important initial results, the B-31 study is not over. You will continue to follow the ***Group 1*** treatment and follow-up plan. Your study doctor will still follow your progress with physical exams and blood tests as described in the consent form that you signed when you joined in the study.

New information about hormonal therapy on NSABP B-31:

As described in the consent form you signed when you joined the study, if your tumor has a positive estrogen and/or progesterone (ER/PgR) hormone receptor test, you will receive hormonal therapy for 5 years. When the B-31 study was planned, 5 years of tamoxifen was considered standard hormonal therapy. Tamoxifen was the only hormonal therapy allowed in this study. In 2003, another hormonal drug, anastrozole, was added as an option. Recent results from two large research studies have shown that similar hormonal therapy drugs can be used in postmenopausal women. One study also showed that some women may benefit from taking hormonal therapy for longer than 5 years. The NSABP has changed the B-31 study to allow your doctor to choose the hormonal therapy that is best for you. Your doctor can also choose how long you should take the hormonal therapy. Your doctor will discuss the choices and the risks and side effects of hormonal therapy with you.

New information about the risks on NSABP B-31:

The information listed below is new risk information relating to paclitaxel. There are other risks that are not described here. These were listed in the consent form that you signed when you joined the study. You should discuss these risks with your study doctor.

- *New side effect related to paclitaxel (Taxol)*: There have been rare cases of severe lung problems in patients who received paclitaxel.

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

_____ _____

Date Patient's Signature

_____ _____

Date Signature of person conducting the informed consent discussion

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NSABP SAMPLE CONSENT FORM ADDENDUM #1

(Option C: Group 2 patients)

Consent Form Addendum #1
for
A Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol (AC→T) to that of Adriamycin and Cyclophosphamide Followed by Taxol plus Herceptin (AC→T + H) in Node-Positive Breast Cancer Patients who have Tumors that Overexpress HER2

When you entered the NSABP B-31 study, the NSABP promised to tell you about new information that might affect the therapy you are receiving as part of this study. Recently, you received new information about the positive results of adding the drug Herceptin (trastuzumab) to chemotherapy in the treatment of your type of breast cancer. This consent form includes that information and new information about possible changes in your treatment. Also, this form provides you with new risk information about the B-31 study.

Information about the results of NSABP B-31:

In April 2005, data from the B-31 study were analyzed along with the data from another similar national trial (NCCTG N9831) conducted by the North Central Cancer Treatment Group (NCCTG). Both studies examined the value of receiving 1 year of Herceptin starting at the same time as the chemotherapy drug paclitaxel (Taxol). You are one of several thousand women who were enrolled in these studies, which began in 2000.

Each of the committees responsible for protecting the interests of women enrolled in these studies has reviewed these results independently. Both recommended to the National Cancer Institute (NCI), the organization responsible for these studies, that all study participants and their doctors be told the results. The NCI, the NSABP, and the NCCTG agreed with this recommendation, and the results were made public on April 25, 2005. The committees also recommended closing the two studies to further accrual, which means that no more women were able to join the studies after the end of April 2005.

The data from these studies showed very positive results. The studies showed that by the time of the committees' review, Herceptin had improved the chance of being alive and free of cancer by 52%. This means that these studies showed that when Herceptin is given with chemotherapy, breast cancer returns much less often than it does when chemotherapy is given without Herceptin.

Information about your continued B-31 study therapy:

When you joined the B-31 study, you were randomized to ***Group 2*** which means that you were selected by chance to receive chemotherapy ***with Herceptin***. You may have already completed your Herceptin therapy on NSABP B-31. However, if you have not, we are providing information about how the positive results of the B-31 study may affect your Herceptin therapy. At this time, you:

- may currently be receiving Herceptin; or
- may not have started Herceptin therapy; or
- may have stopped Herceptin before completing 1 full year of therapy.

07/18/05 If you are currently receiving Herceptin, you will still be given enough Herceptin to complete one full year of therapy. If you have not started Herceptin, or if you started Herceptin but stopped and now you want to restart Herceptin therapy, your study doctor will confirm that you meet study requirements to start or restart Herceptin therapy. One of these requirements is that you must have joined the study on or after April 26, 2004. It is very important that you talk with your doctor about your treatment options. If your study tests show that you meet requirements, you will be given enough Herceptin to complete 1 full year of therapy (starting on the date of your very first Herceptin dose). After reviewing your tests and exams, your doctor could advise you that starting or restarting Herceptin at this time is not in your best interest.

Herceptin will be provided free of charge by Genentech, Inc., the company that makes Herceptin. You must **begin** Herceptin by December 30, 2005, in order to receive Herceptin free of charge through this study. If you start Herceptin therapy by this date, you will be provided enough Herceptin for a full year of therapy. There may be costs which are not covered by the study such as co-pays and doctor's fees. These will be the responsibility of you and/or your insurance company.

You will continue to have all of the tests and exams as outlined in the B-31 study consent form that you signed when you entered the study. However, the schedule of MUGA scans may differ from the original schedule depending on when you begin Herceptin.

- If you began or will begin Herceptin ***immediately after AC chemotherapy or during paclitaxel therapy***, you will have MUGA scans 3-4 weeks after completing AC and at 6, 9, and 18 months after you joined the study.
- If you began or will begin Herceptin ***after you complete all of your chemotherapy***, you will have a MUGA scan 3-4 weeks after completing AC. You may also have a MUGA scan following paclitaxel therapy before starting Herceptin, and then at 3, 6, and 15 months after starting Herceptin.
- If you have not and will not receive any Herceptin, the MUGA scans initially required by the study no longer need to be done.

Although we have told you about these important initial results, the B-31 study is not over. Your study doctor will still follow your progress as described to you in the consent form that you signed when you joined the study.

New information about possible increased risk for heart problems for some women receiving Herceptin:

The NSABP has continued to study the B-31 data and has recently learned that ***some*** women may be at increased risk for heart problems with Herceptin. The women we have identified as having this increased risk of heart problems include those:

- who were 50 years of age or older at the time they joined the study; ***and***
- who had a MUGA scan after completing Adriamycin and cyclophosphamide that showed a test result that was at the low end of normal (less than 55%); ***and***
- who received Herceptin at the same time as paclitaxel.

This new information suggests that, if you were 50 years old or older when you joined the study ***and*** your MUGA scan result was at the lower end of normal, it may be safer to receive Herceptin ***after*** you complete paclitaxel therapy. However, Herceptin may work best when given with paclitaxel. If the items noted above apply to you, you will need to discuss this with your study doctor to decide how you will continue your study therapy. The timing of Herceptin therapy may be changed depending on what you and your doctor decide. If you have already begun receiving Herceptin along with paclitaxel, your doctor may advise you to stop Herceptin until after you finish paclitaxel. Or, you and your doctor may decide that you should continue to receive Herceptin at the same time as your paclitaxel.

- If you make the decision to delay or temporarily stop receiving Herceptin, you will be able to begin or restart Herceptin therapy, as long as the result of your MUGA scan done after you complete paclitaxel is in the normal range.
- If the result of your MUGA scan done after you complete paclitaxel is not within the normal range, you will not be able to begin or restart Herceptin. Your study doctor may schedule a follow-up MUGA scan (waiting at least 4 weeks after the last MUGA scan) to see if your heart function returns to the normal range. If your heart function does return to the normal range, you may be able to begin or restart Herceptin at that time. If your heart function does not return to the normal range, you will not be able to receive Herceptin through the B-31 study.
- If you made the decision to begin or continue to receive Herceptin therapy ***along with paclitaxel***, your treatment will continue on a regular basis just as it did previously on this study.

Your doctor may advise you to stop Herceptin if one of the following events happens:

- you develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications;
- new information becomes available about Herceptin or about other treatments for preventing breast cancer recurrence;
- your doctor determines that it is no longer in your best interest to continue Herceptin.

New information about hormonal therapy in the NSABP B-31 study:

As described in the consent form you signed when you joined the study, if your tumor has a positive estrogen and/or progesterone (ER/PgR) hormone receptor test, you will receive hormonal therapy for 5 years. When the B-31 study was planned, 5 years of tamoxifen was considered standard hormonal therapy. Tamoxifen was the only hormonal therapy allowed in this study. In 2003, another hormonal drug, anastrozole, was added as an option. Recent results from two large research studies have shown that similar hormonal therapy drugs can be used in postmenopausal women. One study also showed that some women may benefit from taking hormonal therapy for longer than 5 years. The NSABP has changed the B-31 study to allow your doctor to choose the hormonal therapy that is best for you. Your doctor can also choose how long you should take the hormonal therapy. Your doctor will discuss the choices and the risks and side effects of hormonal therapy with you.

New information about the risks on NSABP B-31:

The information listed below is new risk information relating to the drugs in this study. There are other risks that are not described here. These were listed in the consent form that you signed when you joined the study. You should discuss these risks with your study doctor.

- *New side effect related to paclitaxel (Taxol)*: There have been rare cases of severe lung problems in patients who received paclitaxel.

- *New side effects related to Herceptin (trastuzumab)*: You may possibly have tiredness; diarrhea; pain in the stomach, joints, or muscles; sores in the mouth; a rapid heart rate; or wheezing with the use of Herceptin. There is a rare chance of changes in blood test results that may indicate possible liver injury.

  There have been rare cases of severe lung problems which may be bad enough to cause low levels of oxygen in the blood and can be life threatening. Some patients with this problem died. Most of the cases occurred in patients who had other lung problems, such as spread of their cancer to the lungs. However, some cases occurred in patients who did not have spread of cancer to their lungs.

Signature (You must sign and date <u>only one</u> option below.)

Option 1:

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

I choose ***to receive or to continue to receive Herceptin*** as provided by Genentech, Inc., as part of the B-31 study. I understand that I must meet all study requirements to start or continue Herceptin therapy.

_____ _____
Date Patient's Signature

_____ _____
Date Signature of person conducting the informed consent discussion

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Option 2:

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

I choose ***<u>not</u> to receive Herceptin*** as provided by Genentech, Inc., as part of the B-31 study.

_____ _____
Date Patient's Signature

_____ _____
Date Signature of person conducting the informed consent discussion

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07/18/05

Option 3:

I have read this consent form or it has been read to me. I understand the new information and have had my questions answered. A copy of this form has been provided to me.

I have ***completed*** Herceptin therapy as part of the B-31 study or I am ***not eligible*** to receive Herceptin as provided by Genentech, Inc., at this time.

_____ _____
Date Patient's Signature

_____ _____
Date Signature of person conducting the informed consent discussion

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NSABP SAMPLE CONSENT FORM ADDENDUM #2

Consent Form Addendum #2
for
A Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol (AC→T) to that of Adriamycin and Cyclophosphamide Followed by Taxol plus Herceptin (AC→T + H) in Node-Positive Breast Cancer Patients who have Tumors that Overexpress HER2

Additional follow-up is being added to the NSABP B-31 study to learn more about the long-term effects of the B-31 therapies. You are being asked to take part in this additional follow-up because you received treatment for your breast cancer as a participant in the B-31 study and because your cancer has not returned. If you have any questions, you can ask the study doctor for more information.

Information about additions to your B-31 follow-up schedule:

We would like to find out more information about how Herceptin affects the heart over time. We will use questionnaires that assess quality of life and a current re-evaluation of your heart function with a MUGA scan. We expect that this the new information will help to understand whether heart function affects quality of life after taking Herceptin. Specifically, we are interested in learning about potential effects of past B-31 treatments on your physical and emotional functioning. You will be asked to complete questionnaires that ask how you feel and your symptoms and your current physical activities. We will compare the information from women who received Herceptin in the B-31 study with women who did not receive Herceptin to see if Herceptin affects the heart over time and whether that affects how you are functioning.

You will continue to have all of the tests and exams as outlined in the B-31 study consent form that you signed when you joined the study. In addition, within about 2 months after you sign this consent form, we would like you to do the following:

- You will be asked to complete a questionnaire about symptoms you may be having and about your quality of life. We want to learn about your opinion of how your life is affected by the study treatment and its side effects. This quality of life questionnaire will ask you about how you are feeling physically and emotionally. We also want to learn how well you are able to carry out your day-to-day activities, and whether you have any other medical conditions that may affect your health and quality of life. The questionnaire will take about 30 minutes of your time to complete. If any questions make you feel uncomfortable or you do not wish to answer them, you may skip those questions and not give an answer. Your individual questionnaire answers will not be used in published reports or articles.
- You will be asked to have a MUGA scan (to check your heart function). It is a good idea to drink some fluids on the day of your MUGA scan before getting the test to make sure you are not dehydrated since dehydration can cause an inaccurate reading. Your doctor will go over the results of the MUGA scan with you. The cost of this MUGA scan will not be charged to you or to your insurance.

Your study doctor will also provide the NSABP with updated information on medical conditions related to your heart function.

By signing this consent form, you are agreeing to take part in the additional cardiac follow-up research described above as part of the B-31 study. Participation in the additional cardiac follow-up research is voluntary. If you choose not to take part, it will not affect your care or the schedule of the tests and exams outlined in the B-31 study consent form that you signed when you joined the study.

Information about optional contact in 5 years to complete an additional quality of life questionnaire:

In addition to the changes in follow-up described above, the NSABP Headquarters staff would like to ask your permission to contact you again in about 5 years from now to complete a second questionnaire about your quality of life. All contact regarding this questionnaire will come directly from the NSABP Headquarters staff and not from your local doctor or medical center. You will be asked to give the contact information for yourself and two people who would always be able to reach you. The NSABP Headquarters staff will contact you by mail several times during the next 5 years to make sure that the contact information you gave has stayed the same. Your contact information will be provided to the NSABP Headquarters located in Pittsburgh, Pennsylvania, where it will be kept in a secure location.

The NSABP Headquarters staff will contact you by mail in about 5 years. You will receive a questionnaire and a letter with instructions. You will complete the questionnaire and mail it back to the NSABP in Pittsburgh. The NSABP will pay the postage.

If you are unable to complete a written questionnaire, the NSABP Headquarters staff will make arrangements for you to complete the questionnaire by phone, if you would like to do so.

If the NSABP does not receive your completed questionnaire, the NSABP staff will send you a reminder by mail. If your questionnaire has still not arrived, the NSABP staff will try to contact you by phone to check if you received the letter and questionnaire. If you cannot be reached, the NSABP staff may try to locate you by contacting the people you named as a contact or your B-31 study doctor. If you move within the next 5 years, please let your study doctor know.

We will keep your contact information and your questionnaire as private as we can. We cannot guarantee that information in the questionnaire may not be seen during the mailing process.

The contact in 5 years to complete a second quality of life questionnaire is optional. Remember, no matter what you decide about the contact for quality of life follow-up in 5 years, you may still take part in the NSABP B-31 cardiac follow-up research. Please read the sentence below and think about your choice. After reading the sentence, circle "yes" or "no." If you have questions, please talk to your doctor or health care team member.

The NSABP Headquarters staff may contact me in about 5 years to complete another questionnaire about my quality of life.

YES NO

Signatures

I have read this consent form or it has been read to me. I understand this information and have had my questions answered. A copy of this form has been provided to me. By signing this consent form, I choose ***to take part in the additional cardiac follow-up*** as part of the B-31 study.

_____	_____
Date	Patient's signature
	_____
	Print patient's name
_____	_____
Date	Signature of person conducting the informed consent discussion
	_____
	Print name of person conducting the informed consent discussion

[Additional signature lines may be added as required by local policies or regulations.]