Add 14

North Central Cancer Treatment Group

Phase III Trial of Doxorubicin and Cyclophosphamide (AC) Followed by Weekly Paclitaxel With or Without Trastuzumab as Adjuvant Treatment for Women with HER-2 Over-expressing or Amplified Node Positive or High-Risk Node Negative Breast Cancer

Intergroup

For any communications regarding this protocol,
please contact the protocol resource person on the following page.

Study Chairs

NCCTG: Edith A. Perez, M.D. (Research Base)*
Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
Update 2 507/538-0269
507/284-5280 (FAX)

Leila Kuttech, M.D. (NCCTG)

CALGB: Peter Kaufman, M.D.

ECOG: Nancy Davidson, M.D.

SWOG: Silvana Martino, D.O.

Add 14 NCIC CTG: Karen Gelmon, M.D.

Study Co-Chairs

NCCTG: Thomas M. Pisansky, M.D. (Radiation Therapy)
Richard J. Rodeheffer, M.D. (Cardiology)
Bernard J. Gersh, M.D. (Cardiology)
Add 13 Allan Jaffe, M.D. (Cardiology)
Daniel W. Visscher, M.D. (Pathology)

Statistician

Vera Suman, Ph.D. (507/284-8803)

DCTD Supplied Investigational Agents: *trastuzumab (NSC#688097, IND#6667)*

*Investigator having NCI responsibility for this protocol.

Document History	(Effective Date)	Document History	(Effective Date)
Addendum 1	May 19, 2000	Addendum 12	August 13, 2004
Addendum 2	July 28, 2000	Addendum 13	December 24, 2004
Addendum 3	January 26, 2001	Update 1	December 24, 2004
Addendum 4	April 27, 2001	Addendum 14	April 8, 2005
Addendum 5	September 7, 2001	Addendum 15	June 3, 2005
Addendum 6	September 7, 2001	Addendum 16	November 4, 2005
Addendum 7	January 11, 2002	Addendum 17	July 14, 2006
Addendum 8	July 19, 2002	Addendum 18	September 26, 2008
Addendum 9	September 3, 2002	Update 2	September 26, 2008
Addendum 10	May 2, 2003	Addendum 19	June 18, 2010
Addendum 11	December 12, 2003		

Study Participants	**Date Activated**
NCCTG	May 19, 2000
ECOG	August 10, 2000
CALGB	June 15, 2000
SWOG	July 1, 2000
NCIC	

NCI Version Date: 17May2010

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, forms completion	Barb Mulhern Phone: 507/538-0269 Fax: 507-538-0962 E-mail: mulhern.barbara@mayo.edu
Protocol document, consent form, regulatory issues	Lynn Flickinger Phone: 507/538-7034 Fax: 507/284-5280 E-mail: flickinger.lynn@mayo.edu
Adverse Events	Pat McNamara Serious Adverse Event Coordinator Phone: 507/266-3028 Fax: 507/284-9628 E-mail: mcnamara.patricia@mayo.edu
Pathology	Christy Maszk Phone: 507/266-8919 Fax: 507/538-0962 E-mail: maszk.christine@mayo.edu
Technical problems with electronic form entry (NCCTG members only)	Vicki Bryhn Phone: 507/266-5350 Fax: 507/538-0906 E-mail: bryhn.vicki@mayo.edu
Laboratory Advisors	Robert Jenkins, MD, PhD Wilma Lingle, PhD

Add 13, Update 2

Add 14

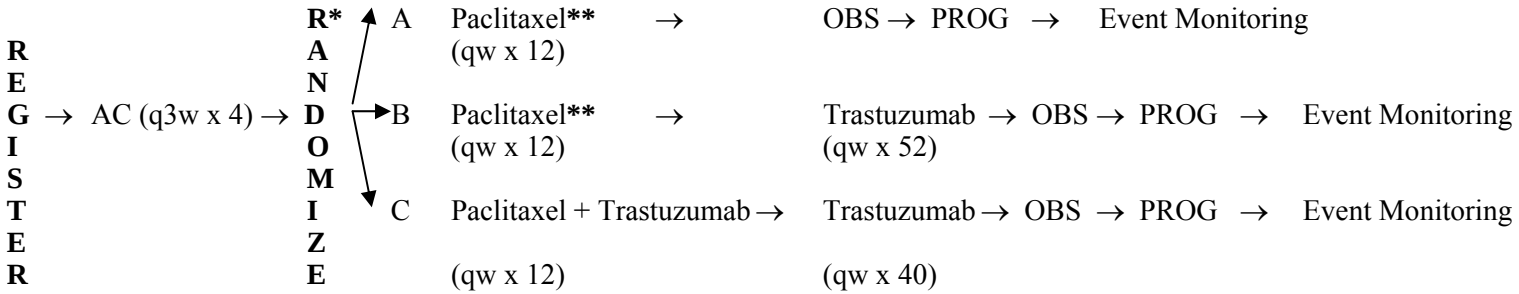
Add 16

*No waivers of eligibility per NCI

Index

Schema

Add 8,9



Add 7

AC = doxorubicin/cyclophosphamide

Add 7,8,15

* Patients will be randomized if their tumor specimen on central review is confirmed as HER-2 amplified by FISH or 3+ by HercepTest®. If not confirmed, the patient will not receive any further study treatment and will go to event-monitoring phase; further adjuvant therapy will be as per investigator's discretion and the patient will be followed for disease free survival and overall survival.

Blood samples for translational research are needed prior to treatment – See Sections 4.0 and 14.1.

****In April 2005, a joint interim analysis of the data from NSABP B-31 and NCCTG N9831 demonstrated that the addition of trastuzumab to paclitaxel following AC chemotherapy significantly prolonged DFS. Following consultations with the NCCTG DMC and NCI CTEP, patients randomized to Arm A who would complete or had completed paclitaxel on or after October 25, 2004, were offered the opportunity to receive trastuzumab (concurrently with paclitaxel, if patient was still receiving paclitaxel) and patients randomized to Arm B who were receiving paclitaxel on April 25, 2005 were offered the opportunity to receive trastuzumab concurrently with paclitaxel.**

Radiation to be initiated within 5 weeks of the completion of paclitaxel treatment.

Add 3,8,12

Premenopausal women: Tamoxifen (TAM), 20 mg daily for 5 years, will be initiated in premenopausal women with ER positive or PR positive tumors at the time of initiation of radiation or within 5 weeks of the completion of weekly paclitaxel treatment for patients not receiving radiation therapy. For patients who have received either TAM or raloxifene as chemoprevention before enrolling on this study, the use of TAM following weekly paclitaxel treatment will be at the physician's discretion (as per Breast Intergroup decision 5/00).

Add 12,13

Postmenopausal women with ER positive or PR positive tumors may receive any of the following at the investigator's discretion: 1) aromatase inhibitors (AI) (anastrozole 1 mg daily, letrozole 2.5 mg daily, or exemestane 25 mg daily) for 5 years, 2) TAM (20 mg daily) for 5 years, 3) TAM (20 mg daily) for 5 years followed by an AI for 5 years, or 4) sequential TAM/AI for a minimum of 5 years.

Generic name:	cyclophosphamide	Generic name:	doxorubicin
Brand name:	Cytoxan®	Brand name:	Adriamycin®
NCCTG abbreviation:	CTX	NCCTG abbreviation:	ADR
Available:	Commercial	Available:	Commercial
Generic name:	paclitaxel	Generic name:	trastuzumab
Brand name:	Taxol®	Brand name:	Herceptin®
NCCTG abbreviation:	TAXOL	NCCTG abbreviation:	HERCEP
Available:	Commercial	Available:	Supplied by NCI

1.0 Background

1.1 General Introduction:

Overall, the 10-year survival of patients diagnosed with Stage II breast cancer is approximately 50-66%, even with established adjuvant therapies such as CMF, AC, FAC, FEC, and tamoxifen (1). Methods to improve these results, incorporating novel therapeutics and new knowledge of the molecular basis of cancer, are of significant importance for the healthcare of these patients.

The HER-2 gene encodes a 185kDa transmembrane glycoprotein receptor with intrinsic tyrosine kinase activity. HER-2 has been proposed as a target for breast cancer therapy as it is overexpressed in 25-30% of human breast cancers, plays a role in the pathogenesis of the disease, and is associated with worse prognosis in patients with involved axillary lymph nodes and metastatic disease. Trastuzumab, a humanized monoclonal antibody that targets the HER-2 receptor, has been demonstrated to be active and fairly well tolerated in the treatment of HER-2 overexpressing metastatic breast cancer (MBC).

Paclitaxel is an anti-microtubule agent that has demonstrated high antitumor activity in patients with advanced breast cancer and has been demonstrated to enhance the efficacy of AC chemotherapy in patients with node positive breast cancer (2). Laboratory studies have demonstrated that trastuzumab markedly increases the antitumor effects of paclitaxel in HER-2 overexpressing breast cancer cells both in vitro and in human tumor xenographs in nude mice. Clinical studies (described below) have corroborated the increased antitumor effects of combination trastuzumab/paclitaxel versus paclitaxel alone in patients with MBC whose tumors overexpress HER-2. Preclinical data have provided conflicting results regarding additive versus synergistic interaction between paclitaxel and trastuzumab; the clinical interaction between these agents must be optimized considering a balance between antitumor activity and toxicity.

We use these data to generate a new clinical study evaluating the sequencing of paclitaxel administration with trastuzumab as part of the adjuvant treatment of patients with node positive breast cancer whose tumors overexpress HER-2.

1.2 AC followed by paclitaxel as adjuvant therapy

The Intergroup has recently completed several trials evaluating new treatment approaches for patients with node positive breast cancer, which form the basis for this new proposed trial. Specifically, the United States Breast Intergroup study CALGB 9344 evaluated whether dose escalation of doxorubicin or the sequential addition of paclitaxel to patients receiving AC chemotherapy for resected node positive breast cancer improved outcomes (3). The study involved 3,170 women who were randomized to receive doxorubicin (A), 60, 75, or 90 mg/m^2, plus cyclophosphamide (C), 600 mg/m^2, followed three weeks later by paclitaxel (T), 175 mg/m^2 (3-hour infusion), or no paclitaxel. Four 3-week chemotherapy cycles were given; patients with estrogen-receptor-positive tumors also received tamoxifen following the completion of chemotherapy.

The study's primary objectives were 1) to determine if higher doses of doxorubicin used as an adjuvant with cyclophosphamide increased disease-free and overall survival; 2) to evaluate the impact of paclitaxel on disease-free survival independent of doxorubicin dose and as single agent after the completion of four cycles of AC; and 3) to assess toxicity. Eligibility criteria included patients with one or more positive lymph nodes whose tumors were T_1, T_2, T_3, and N_1, M_0, performance score 0-1, and adequate bone marrow and end-organ function.

The trial period was May 1994 to April 1997, and analysis of the data was conducted at the pre-planned time of 22 months (based on 453 recurrent breast cancers and 200 deaths). The results demonstrate that increasing doses of doxorubicin do not lead to improvements in disease-free or overall survival. However, paclitaxel added to AC chemotherapy significantly improving both disease-free and overall survival. Kaplan-Meier estimates of disease-free survival at 18 months were 90% in the group receiving paclitaxel, and 86% in the group who did not (p=0.0077). Overall survival at 18 months was 97% in the group receiving paclitaxel and 95% in the group who did not (p=0.0390). The use of paclitaxel resulted in a reduction in the annual odds of recurrence by 22.3% (p=0.0l) and a reduction in the annual odds of death by 21.2% (p=0.07). Therefore, this multicenter intergroup study, funded by the National Cancer Institute, found that paclitaxel offers a significant survival benefit when used sequentially with standard AC chemotherapy for patients with node-positive breast cancer.

With regards to toxicity, the incidence of ≥grade 3 cardiotoxicity was 6% for patients during or at post-chemotherapy follow-up. Differences in incidence of cardiotoxicity related to the dose of doxorubicin used or to the addition of paclitaxel were not observed. Additional grade 3/4 toxicity with paclitaxel treatment was generally mild, with a 39% incidence of neutropenia, 5% sensory neuropathy, 5% pain, and 2% infection.

1.3 Weekly Paclitaxel Schedule

The dose of single-agent paclitaxel proposed for this study is based on previous studies in the adjuvant and metastatic settings (2-9). The CALGB 9344 trial utilized paclitaxel at a dose of 175 mg/m^2 IV q3w x 4 (3).

A schedule of paclitaxel that has generated significant interest over the last two years is a dose of 80–100 mg/m^2 IV administered weekly. Clinical trials to date have demonstrated improved tolerability (compared to q3 week schedules of paclitaxel), in spite of higher dose intensity (7-9). Seidman et al reported the toxicity and efficacy of paclitaxel at an initial dose of 100 mg/m^2/week in 30 patients, treated at a single institution, who had received no more than one chemotherapy regimen for metastatic disease (7). The median delivered dose intensity was 91 mg/m^2/week. A response rate of 53% (95% CI, 34-72%) was observed, with a median response duration of 7.5 months and an overall 10% complete response rate. Therapy was well-tolerated, with a lack of cumulative neutropenia and manageable neurotoxicity. Peripheral neuropathy precluded dose escalation above 100 mg/m^2 and grade 3 neuropathy was observed in 2 of 21 patients at a paclitaxel dose of 100 mg/m^2/week.

Perez et al. conducted a trial of paclitaxel 80 mg/m^2/week in 212 patients with metastatic breast cancer, using single agent intravenous dexamethasone (at decreasing doses of 20 mg/m^2 to 4 mg/m^2 depending on tolerability) in combination with diphenhydramine and an H-2 blocker as premedication. Preliminary data are available in the 1999 ASCO meeting book (8), and have been recently updated (9). Toxicity and efficacy data are available in 171 of the 212 patients enrolled, including approximately 2,800 weekly doses of paclitaxel. A wide range of patients with metastatic breast cancer were enrolled in this trial, including patients receiving first-line chemotherapy, second and third-line chemotherapy, patients who had received taxanes on a q3-week schedule and patients with disease progression after high-dose chemotherapy with stem cell transplantation. Only 2 episodes of febrile neutropenia have been documented, grade 3 myalgias have occurred in only 0.5% of patients, and grade 3 sensory neuropathy occurred in < 2% of patients by the twelfth week of therapy. Response data are compatible with a response rate of 33% in patients receiving this therapy as first-line therapy for metastatic disease, with evaluation ongoing. Overall, the conclusions of this trial include that this weekly paclitaxel regimen of 80 mg/m^2/week, administered as a one-hour infusion, has an excellent therapeutic ratio in metastatic breast cancer. These sequential multi-institutional trials suggest that the single-agent antitumor efficacy of weekly paclitaxel appears similar to the q3-week schedule of 175 mg/m^2 but with decreased toxicity. Thus, this adjuvant trial for patients receiving adjuvant chemotherapy for node positive Her-2 positive breast cancer (N9831), will utilize weekly (instead of q3w) paclitaxel for the 3 treatment arms. The dose of weekly paclitaxel will be 80 mg/m^2 IV administered over one hour.

Prospective cooperative group trials of weekly paclitaxel versus an every 3-week schedule are ongoing. The Intergroup trial E1199 is evaluating AC q3w x 4 followed by the two taxanes (paclitaxel or docetaxel) administered either weekly x 12 or q3w x 4 (10). The CALGB study 9840 is comparing weekly 80 mg/m^2 vs. q3w 175 mg/m^2 paclitaxel in the metastatic setting, with plans to include an evaluation of the addition of trastuzumab.

1.4 Trastuzumab (anti-HER-2 monoclonal antibody) in breast cancer

Data from six clinical trials utilizing trastuzumab in patients with breast cancer overexpressing HER-2 (by immunohistochemistry [IHC]) are available for review. All these trials have utilized trastuzumab as weekly intravenous infusions, either alone or in combination with different chemotherapeutic agents (11-16).

The study by Baselga et al. evaluated trastuzumab alone in patients with refractory breast cancer demonstrating excellent tolerability and an overall response rate of 11.6% (12). The study by Cobleigh et al. evaluated trastuzumab alone in 222 patients with refractory MBC (13). This trial again demonstrated excellent tolerability, an overall response rate of 15% (95% CI: 11-22%), a median duration of response of 9.1 months, and a median survival of 13 months for the entire group of patients. The phase III multi-national study reported by Slamon et al. evaluated chemotherapy (AC, EC [epirubicin/cyclophosphamide], or paclitaxel) ± trastuzumab in 469 patients receiving first-line chemotherapy for MBC, with the chemotherapy administered in q3w cycles (14). This trial demonstrated that trastuzumab improved the median time to progression

(7.6 vs. 4.6 months) and overall response (48% vs. 32%) compared to chemotherapy alone. An increased incidence of symptomatic cardiac toxicity was noted when trastuzumab was added to the anthracycline-based chemotherapy, AC or EC, 19% vs. 3%. On the other hand, severe cardiac toxicity was not significantly increased in the paclitaxel plus trastuzumab vs. paclitaxel alone treated patients (4% vs. 1%, respectively). Overall, the incidence of grade 1-4 cardiac toxicity was 1% for paclitaxel alone versus 11% for paclitaxel with concurrent trastuzumab treatment. Pegram et al. evaluated cisplatin plus trastuzumab in patients with refractory metastatic breast cancer yielding a response rate of 24% (15). Vogel et al reported preliminary data of a response rate of approximately 24% with trastuzumab as first-line treatment for metastatic disease (16).

These clinical trials highlight the potential impact of this novel anti-cancer agent in the management of patients with metastatic breast cancer who overexpress HER-2 (11). Further studies to optimize the utilization of trastuzumab as a single agent or in combination with other therapies are warranted both for patients with advanced or resected breast cancer. Prospective evaluation of cardiac tolerability to trastuzumab in combination with chemotherapy should be incorporated as part of these trials.

Potential ways to optimize the therapeutic ratio of paclitaxel with trastuzumab include changing the classic q3w schedule of paclitaxel and/or using the trastuzumab with weekly paclitaxel. Seidman et al reported preliminary data of weekly paclitaxel and weekly trastuzumab for metastatic breast cancer in November 1998 (17) and these data have been presented at the 1999 ASCO meeting (18). As of May 1999, 60 patients with or without Her-2 overexpressing tumors have been enrolled and evaluated in this trial of weekly paclitaxel 90 mg/m^2 plus trastuzumab. Approximately 800 weekly infusions have been administered using dexamethasone 10 mg IV (with diphenhydramine and a histamine-2 blocker), and with cardiac ejection fractions measured by MUGA at scheduled intervals (0, 8 weeks, 16 weeks, then q3 months) from study entry. The preliminary response rate in this two-institution study is about 40-70%, accompanied by a favorable toxicity profile. Only 2 episodes of febrile neutropenia had occurred, with notable toxicities associated with chronic administration (>18 weeks) being cumulative neuropathy and steroid myopathy. The cardiac tolerability has been no worse and probably better than that reported in clinical trials of trastuzumab in combination with paclitaxel administered in the q3w schedule. Specifically, only one patient has developed symptomatic congestive heart failure (this patient had previously received doxorubicin at a cumulative dose of 615 mg/m^2). Therefore, these preliminary data are consistent with a favorable therapeutic ratio for paclitaxel and trastuzumab, both administered weekly, for patients with metastatic breast cancer. It is therefore appropriate to evaluate weekly paclitaxel in combination with trastuzumab in the adjuvant setting for patients with Her-2 overexpressing tumors.

An important question that remains to be answered is whether the paclitaxel and trastuzumab should be used concurrently or in sequence. Preclinical data have yielded conflicting results, but we hypothesize that at least the adverse toxicity results of this combination could be ameliorated by the sequential, instead of concurrent, use of these agents, without interfering with antitumor activity. The evaluation of the optimal way to incorporate trastuzumab as part of the treatment of patients with node positive breast cancer requires determining whether it should be added at all and whether it should be added concurrent with or sequential to the paclitaxel chemotherapy. These questions will be addressed in this proposed trial.

The appropriate duration of trastuzumab treatment in the adjuvant setting has not been previously evaluated. We have selected a twelve-month time period for this trial in a somewhat empirical manner, as a starting point for study. This is partly based on in vitro data demonstrating that longer exposure to this monoclonal antibody leads to greater antitumor activity.

Add 3

An extensive amount of follow-up data has been obtained from trials of weekly paclitaxel 80 mg/m^2 or weekly paclitaxel 90 mg/m^2 with trastuzumab documenting the safety of continued drug administration when the neutrophil count is > 800/uL (personal communication, Drs. EA Perez and AD Seidman).

Add 7

HER-2 expression can be determined by any acceptable method for registration. Centralized review of tumor HER-2 expression is now required for all registered patients. Patients with a strongly positive test result by central review (+3 by IHC or over amplification by FISH) will be eligible for randomization on this trial.

1.5

Add 1

Recent data indicates that amplification by FISH correlates very strongly with response to Herceptin® (personal communication, Robert Mass, M.D.). This relates to the trial of trastuzumab and combination studies of trastuzumab and chemotherapy. The single-agent trastuzumab trial results indicated a 5% response rate for patients who tumors were negative for FISH and 41% for those with positive FISH. Data from the combination trial demonstrated no improvement in response rate when trastuzumab was added to patients receiving chemotherapy whose tumors were FISH negative, but the response rate increased from 27% to 54% in the group of patients receiving chemotherapy whose tumors were FISH positive.

Add 8

1.6

Add 12,13

Data from the ATAC trial presented at the 2001 San Antonio Breast meeting (Baum M, oral presentation December 10, 2001) demonstrated a statistically significant improvement in disease-free survival for postmenopausal women receiving adjuvant anastrozole versus tamoxifen. The data also demonstrated significantly lower hot flashes for women receiving the aromatase inhibitor. Thus, we will modify trial to allow physicians to use their discretion regarding the use of tamoxifen or an aromatase inhibitor (anastrozole, letrozole, or exemestane) for postmenopausal women whose tumors are estrogen receptor positive. Physicians may also substitute an aromatase inhibitor for tamoxifen in postmenopausal women already on trial who are now receiving tamoxifen.

Add 12

As of Addendum 12, postmenopausal women who have received 2-3 years of tamoxifen may be switched to an aromatase inhibitor, as per investigator's discretion, based on the results of the IES trial (58). In this case, it is recommended that the total duration of adjuvant hormonal therapy is 5 years. The specific data of each hormonal therapy must be documented in the case report forms. Another hormonal option for postmenopausal women, based on the data from Goss et al is to use 5 years of tamoxifen followed by 5 years of the aromatase inhibitor (59). Thus, a variety of options are currently available as considered to be standard of practice in postmenopausal women in 2004 (based on randomized clinical trials). All of them will be allowed as women participate in N9831: 5 years of tamoxifen, 5 years of an aromatase inhibitor, 5 years of sequential tamoxifen-aromatase inhibitor, or 5 years of tamoxifen followed by 5 years of an aromatase inhibitor. In other words, the specific duration and type of adjuvant post-chemotherapy hormonal therapy will be left at the investigator's discretion (documentation of the agents and dates of use will be required).

Add 13

Add 12

Based on options available regarding hormonal therapy of premenopausal women with hormonally responsive breast cancer, this N9831 trial also allows ovarian function suppression (ablation) at investigator's discretion, either as part of SOFT or TEXT or outside of these studies, for premenopausal women with hormonally positive tumors. This is another type of hormonal adjuvant therapy that would need to be documented in the case report forms.

Add 10

1.7 Rationale for including high-risk node-negative patients.

The prognosis of certain subsets of women with node negative breast cancer based on HER-2 status and age is described in several publications (44, 45-52).

Allred et al (48) assessed the impact of HER-2 expression on the disease free survival (DFS) of women with node-negative breast cancer. In the group of patients with small (< 3 cm) ER-positive breast tumors, DFS was significantly decreased for those with Her-2 positive disease relative to those with HER-2 negative disease. The 5-year DFS rate was 80% for those with small HER-2 negative disease and 41% for those with small HER-2 positive disease. Among patients with high-risk node-negative disease (that is, patients with ER-negative or ER-positive and ≥ 3 cm tumors), the 4-year DFS rate as 78%.

The effect of HER-2 amplification on clinical outcome of women with node negative breast cancer was assessed by Andrulis and colleagues (49). This study found that a patient with HER-2 amplified tumor had a greater than two-fold increase in the risk of recurrence compared to those with HER-2 non-amplified tumors. The 3-year DFS rate was 90% for those with Her-2 non-amplified tumors and 80% for those with HER-2 amplified tumors. This trial also found age to be an important prognostic factor. Moreover, they found that patients younger than 35 have more than double the risk of recurrence compared to those above the age of 55 (consistent with the data from the St. Gallen conference in 1998 and 2000) (50).

The effect of HER-2 amplification on the prognosis of patients with node negative breast cancer was evaluated by Press and colleagues (50). This study also showed a doubling in the risk of recurrence for patients with HER-2 amplified tumors relative to HER-2 non-amplified tumors. The 4-year DFS rate was approximately 90% for HER-2 non-amplified tumors and 70% for those with HER-2 gene amplified tumors (50).

Presently, there are two international adjuvant trials that allow enrollment of patients with node negative, HER-2 positive breast cancer, BCIRG 006 and the HERA trial (53,54). The criteria for high-risk node negative disease are more liberal than we are proposing to use of this study. The BCIRG 006 trial (53) allows patients with at least one of the following factors: tumor size >2 cm; hormonal receptor status negative; histological and/or nuclear grade 2-3; or age <35 years (53). The primary aim of this clinical trial is to compare and contrast the DFS of patients who receive AC → TH to patients who receive TCH to patients who receive AC → T. It is assumed that the distribution of nodal disease will be such that 20% will be N-, 50% N1-3+, and 30% N4+. The overall 5-year DFS among the patients randomized to AC followed by T using a stratified randomization scheme with nodal status as the strata factor is assumed to be about 55%.

The criteria for high risk node negative breast cancer on the HERA trial is node negative, HER-2 positive breast cancer of any size, grade, or hormonal receptor status (54). The primary aim of this clinical trial is to determine the impact of Herceptin® on DFS of women with high risk node negative disease or node positive disease who have completed adjuvant chemotherapy. Patients are randomized to receive either no Herceptin®, 1 year of Herceptin®, or 2 years of Herceptin®. The sample size of this trial is based on the assumption that 5-year DFS rate of those randomized to the no Herceptin® arm is 60%.

Add 16

1.8 Rationale for banking tissue, serum and DNA

Add 11

Recent developments have demonstrated the value and feasibility of analysis of serum and paraffin-embedded tissues to identify tumor markers and predictors of disease progression (55-57). Banking of serum samples at the time of enrollment and upon disease recurrence will allow for future proteomic analysis that may identify predictors of recurrence and/or may lead to a means of proteomic pattern diagnostics (56). New methods of extracting RNA greatly extend the ability to analyze gene expression in formalin-fixed paraffin embedded tissues (57). In addition, construction of tissue microarrays, in which cores from up to 200 tumors are arrayed in a single block, permits rapid and efficient immunohistochemical analysis. To take advantage of these new technological developments, serum and tissue cores from patients enrolled in this study will be banked. Three tissue cores from each patient will be incorporated into tissue mircorarrays and one core will be set aside for future RNA extraction for gene expression studies. Banked biospecimens from women enrolled in this trial will constitute an invaluable resource that can be used for proteomic analysis of serum, for gene expression studies, and for immunohistochemistry and other histological studies. Use of these specimens will be accessed via IRB-approved protocols. Studies using this resource have the potential to further the understanding of the biology of response to the therapies used in the trial and to determine patient/tumor profiles indicative of either good or poor response to the treatment arms.

Due to the increased role that genomics plays in cancer treatment efficacy and tolerability, combined with the strong scientific and clinical relevance of this study exploring targeted therapy for early breast cancer, DNA samples collected from blood will be banked for planned and future studies, including studies related to breast cancer diagnosis and efficacy/tolerability of treatment. This proposal is consistent with NCCTG/ Intergroup/NCI policy to maximize the understanding of breast cancer biology through appropriate collection of pertinent specimens for current and future studies.

Add 8,13

1.9a Summary

This proposed study in women with node positive or node negative, HER-2 *neu* positive breast cancer will compare the efficacy and toxicity of adjuvant AC every 3 weeks x 4 followed by paclitaxel administered weekly x 12 alone to this regimen with trastuzumab to be started concurrent with paclitaxel followed by trastuzumab for 9 months and to this regimen with trastuzumab started after the completion of paclitaxel and continuing for 12 months. Patients scheduled to receive radiotherapy and/or tamoxifen (TAM) or an aromatase inhibitor will start those treatments within five weeks after the completion of paclitaxel treatment. With the development of new methods for proteomics and gene expression, we propose to bank tissue (in the form of paraffin-embedded tissue microarrays) and sera for future IRB-approved translational studies that may facilitate identification of serum and tissue markers to predict response to the treatments used in this study. This may be especially critical for identifying which patients would benefit from trastuzumab as well as gaining an understanding for the biological basis for response.

Add 11

Add 11,13

1.9b Determining the Effect AC, Paclitaxel, and Trastuzumab on Cardiac Serum Markers

The combination chemotherapy of anthracyclines and taxanes has a well-established role in improving antitumor efficacy and survival in patients with invasive breast cancer. Doxorubicin cumulative doses of greater than 550 mg/m^2, older ages, and a tri-weekly bolus schedule have been found to be associated with higher risk of cardiomyopathy (60,61). A doxorubicin dose as low as 240-300 mg/m^2, including our own work at the North Central Cancer Treatment Group (NCCTG) has been associated with decreases in LVEF and in other studies even congestive heart failure (CHF) (62,63). Infusion of this agent has resulted in changes in cardiac conduction, leading to arrhythmias that are not always clinically apparent.

Herceptin® (trastuzumab) is a humanized monoclonal antibody that blocks the HER2 growth factor receptor $p185^{HER2}$. This receptor is over-expressed or amplified in about 20% to 30% of breast cancer patients and has been found to correlate with poor survival (64,65). In a pivotal phase III study of patients with HER-2+metastatic breast cancer, trastuzumab was shown to improve response rate, time to disease progression and survival when added to standard chemotherapy. In the same study, trastuzumab was associated with an increased rate of cardiac dysfunction. The rate of New York Heart Association Class III-IV cardiac dysfunction was 16% with trastuzumab plus AC, 3% with AC alone, 2% with trastuzumab plus paclitaxel, and 1% with paclitaxel alone (66). The effects of trastuzumab on cardiac function warrant study to define the mechanism and potential mediators of these adverse effects.

Studying cardiac function, including circulating markers, is one step towards providing a better understanding of the problem of cardiac toxicity associated with these agents in patients with invasive breast cancer. The Intergroup study N9831 provides a unique opportunity to study questions of cardiac tolerability in a uniformly evaluated group of patients receiving anthracycline/cyclophosphamide followed by paclitaxel with or without trastuzumab. Although pilot studies have begun to prospectively evaluate circulating markers, the ongoing trial N9831 is a large trial evaluating chemotherapy with or without trastuzumab in the adjuvant setting (without potentially confounding cardiac effects of metastatic disease) where all patients undergo ejection fraction determinations at fixed time points and careful clinical cardiac monitoring. Thus, this trial provides an excellent opportunity for evaluation of circulating markers that may be predictors of cardiac injury.

1.9b1 Rationale for measuring circulating (serum and plasma) markers that may reflect cardiac injury

There is very limited information on the mechanism of trastuzumab's cardiotoxicity. Xenograft data show the HER2 signaling pathway to be an essential component for activation of the myocyte survival pathway during biomechanical stress (63). In humans, the cardiotoxic effect from trastuzumab appears to be that of cardiomyopathy. The treatment and potential for reversing of this cardiomyopathy is a field of active investigation.

In the study of doxorubicin cardiotoxicity in the 1970s, endomyocardial biopsy was found to provide information that was both sensitive and specific; however, the technique's invasive nature limits widespread application. Other measures to assess myocardial function include evaluation of ejection fraction (EF) via MUGA scans and ECHOs. However, variability in techniques and interpretation make these tests imperfect regarding early cardiac injury. Thus, and as it has happened in the setting of unstable angina and chest pain, it will be important to evaluate whether the risk of clinically relevant cardiotoxicity (or significant decreases of EF) can be predicted using circulating blood markers such as the troponins and others. This approach has already been shown to have some predictive accuracy in a small study from Milan using multiple regimens of therapy (67). It is likely to be far more sensitive than imaging since most measures of ventricular performance are sensitive to loading conditions and only become abnormal after the ability of adaptive mechanisms to compensate have been overcome.

Patients participating in NCCTG N9831 Intergroup trial are undergoing prospective evaluation of cardiac function using ECHOs or MUGAs. We propose to extend the prospective evaluation of cardiac function by also studying the potential role of early markers of cardiac injury in a subset of patients participating in this large adjuvant trial. This information would not only be helpful for patients in this study, but also to the thousands of women receiving anthracyclines, paclitaxel or trastuzumab as treatment for breast cancer.

1.9b2 Rationale for the type of circulating markers to evaluate

Serum and plasma cardiac markers that reflect myocardial function will be measured at established intervals in a subset of patients enrolled on N9831. As the myocardium undergoes volume or pressure stress, cardiac myocytes release measurable substances that may or may not correlate with patient characteristics, echocardiographic findings, and clinical signs and symptoms.

1.9b21 Rationale for measuring BNP

Natriuretic peptides (NPs) are a group of structurally similar but genetically distinct peptides that have diverse actions in cardiovascular, renal and endocrine homeostasis. NPs can also be elevated in patients with renal failure, pulmonary hypertension, arterial hypertension, and liver cirrhosis (68). Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are cardiac hormones while C-type natriuretic peptide (CNP) is of endothelial origin (69). NPs are synthesized as prohormones. The C-terminal endocrinologically active peptide and the N-terminal prohormone fragments are found in plasma (68). The amino-terminal fragment of pro-brain natriuretic peptide (NT-BNP) is a hormone formed from proBNP. Its function is largely still undefined, but when compared with active BNP, the former may be a more sensitive marker of cardiac overload and decompensation (70,71).

Both ANP and BNP are stress-induced hormones and exert almost identical biological function. BNP differs from ANP in the sense that BNP is secreted predominantly in the ventricle, and its synthesis, secretion and clearance differs from ANP (72). BNP promotes natriuresis and diuresis, acts as a vasodilator, and antagonizes the vasoconstrictor effect of the renin-angiotensin-aldosterone system (73). The BNP level is known to increase in heart failure (74,75,76) and correlates with LV systolic and diastolic dysfunction parameters (77,78). Increased levels of BNP predict cardiac morbidity and mortality (74,78-79). In some cases, it is predictive in both asymptomatic as well as symptomatic patients (80-83). In cases of post myocardial infarction, BNP levels have been found to be a strong independent predictor of left ventricular function, heart failure, and death (84).

Measuring BNP levels has been suggested as a useful screening test to select patients for further cardiac investigation. In one study, it was found to have a sensitivity of 77% and specificity of 87% in patients with known systolic dysfunction (78). In another study conducted by

Friedl et al., the sensitivity and specificity of resting levels of BNP as a marker for asymptomatic left ventricular dysfunction were only 58% and 76% respectively (85). More recent data strongly support the concept and particularly the negative predictive accuracy of BNP (86,87).

However, the role of BNP in patients receiving adjuvant chemotherapy or trastuzumab is unknown.

1.9b22 Rationale for measuring TnT, TnI, and TNF-α

Troponins are regulatory proteins that have cardiac-specific isoforms. Both cTnT and cTnI are substantially greater sensitivity than CKMB for the detection of cardiac injury and have nearly perfect cardiac specificity (88). The cardiac troponins increase in patients with CHF and its levels are greater as the severity of the disease increases (89-91). They are also usually elevated in patients with latent and progressive myocardial damage including those at risk for cardiac events (92-94). In patients who had undergone surgery, elevated TnT detected myocardial ischemia and predicted cardiac events within 6 months (95). Because troponin is so sensitive, it is frequently elevated in patients with subtle forms of cardiac injury (96). Prognosis of such subtle elevations such as those seen in renal failure often require up to 2 years to manifest their prognostic importance (97).

The use of troponin markers to assess the use of chemotherapeutic agents was started initially be Missov (98). Using an assay modified to provide increased sensitivity, he showed elevations above the values of a normal control group but below the putative cut off value for the assay in most patients receiving Adriamycin. Subsequently, both experimental and clinical literature have suggested that elevations are common after Adriamycin therapy and predictive of subsequent cardiac dysfunction (67,97,98). At present, many of the commercially available assays now have comparable sensitivity and newer generations may be even more sensitive (AHJ, Dec 2002, Apple, Wu, Jaffe).

The ideal time for sampling is unclear. In the Cardinale study (67), samples were obtained at 12, 24, 36, and 72 hours. The distribution of elevations was roughly equal at all time points. They indicate that multiple sampling was important for detecting those who subsequently developed a greater degree of LV dysfunction. In our study, we will sample these markers within 1, 6, 12, 24, 36, and 72 hours of completion of the infusion of either the chemotherapy and/or trastuzumab, depending on the treatment the patient is receiving. It is clear that with the more sensitive modern assays and that far more subtle elevations will now likely be detectable. The literature is mixed concerning the most appropriate analyte for use. Cardiac troponin T and cardiac troponin I usually provide consistent answers and it is now clear that even in patients with renal failure, these assays provide diagnostic and prognostic information (Apple, Dec Cir and Defillippo JAMA, July 2003). There is only one assay for cTnT, the Roche assay, and it possesses adequate sensitivity for this evaluation. There are two assays for cTnI that have

adequate sensitivity for this purpose, one from Dade and one from Beckman. It would be optimal to measure cTnT with the Roche assay and cTnI with either the Dade or Beckman assays.

Tumor necrosis factor (TNF) is a serum factor that causes necrosis of tumors and cachexia. It plays a role in the pathophysiology of inflammatory disorders like rheumatoid arthritis and Crohn's disease. The normal heart does not express TNF, however the failing heart is known to produce TNF-α (99).

TNF-α is one of the initial cytokines released in response to inflammation. It modulates its effect by two circulating binding proteins (TNF-receptor I and TNF-receptor II) that are expressed in many cells with different biologic roles. Soluble forms of these two receptors have been identified as the extracellular domain fragments (sTNF-RI and sTNF-RII). TNF also has been shown to stimulate the inflammatory and coagulant complex known as soluble CD40 ligand (Hesscheen ENJM). In patients with CHF, both circulating TNF-α and its soluble receptors are increased. TNF-α exerts a negative inotropic effect directly as well as indirectly through production of nitric oxide (100). Increased TNF levels are also known to correlate with echocardiographic parameters and other blood markers (101). Its increased level in heart failure is well known. Cytokine levels usually decrease with medical treatment for heart failure (102-104). There is currently a multi-center clinical trial testing the role of anti-TNF in patients with symptomatic heart failure. This novel approach may provide proof of principle that targeted intervention may have therapeutic benefit (105), but the data so far have not corroborated that this approach will be as useful as predicted.

1.9b23 Rationale for measuring cytokines such as interleukin-1 beta (IL-1β), and inerleukin-6 (IL-6)

Patients who develop heart failure often have elevated levels of pro-inflammatory cytokines. The mechanism of their increase and source of their production is a subject of intense investigation (106). It is generally accepted, however, that secretion of certain cytokines produces a negative inotropic effect and induces apoptosis of cardiac myocytes (107) via binding to CD40 ligand.

In some studies of patients with known CHF, IL-6, but not TNF-α, reflected hemodynamic derangement (48). Other studies found both IL-6 and TNF-α to correlate with worsening CHF (109-113). Others determined that only TNF-α and IL-1β, but not IL-6, are elevated in heart failure (108).

IL-1, initially called "endogenous pyrogen," is known to be a mediator of inflammation. In the heart, its level increases in cases of transplant rejection and CHF. In cell culture, IL-1 is known to induce cardiac myocyte hypertrophy and have an anti-proliferative effect on fibroblasts (114). In animal models, IL-1β caused myocyte hypertrophy and increased ANP, BNP and β-myosin heavy chain (108-110). In patients with terminal heart failure, IL-1β protein and mRNA were found to be localized to infiltrating macrophages in interstitial regions between myocytes, in myocytes themselves, and in arterial endothelial cells (100).

IL-6 can be elevated in cases of acute myocardial infarction (AMI) and CHF (115-117). The degree of elevation in the myocardium and in the plasma tends to be higher in end-stage heart failure (114-117). Some investigators find higher levels of IL-6 in dilated cardiomyopathy than in ischemic cardiomyopathy (118.

Elevated levels of IL-6 may indicate worsening hemodynamic parameters in dilated cardiomyopathy. In fact, it has been reported that IL-6 is an independent predictor of mortality risk in patients with CHF (119-120).

1.9b3 Rationale for collecting patient characteristics

To better define which patients are at risk for trastuzumab-associated cardiomyopathy, it is important to ascertain patient characteristics known to affect cardiac function so their presence can be taken into account in the analysis. Cardiac output is a function of the product of heart rate and blood pressure. Variability in heart rate has been studied as a significant factor that provides clues of cardiotoxicity (131,111). In addition, the inotropic integrity of the myocardium is affected by the patient's age, cardiovascular status, and medications. Therefore, patient characteristics including resting heart rate, blood pressure, age, body surface area (BSA), current or prior history of specific non-cardiac diagnoses, smoking history, hemoglobin, and current medications for hypertension will be collected. Furthermore, there is the suggestion that drug-induced cardiotoxicity may be more apt to occur in patients with prior cardiac abnormalities such as minor elevations of troponin. Thus, a baseline sample and functional evaluation be undertaken (CXR is best way to detect subtle CHF prior to use of BNP).

Add 16

1.9b4 In April of 2005, there were sufficient events (recurrences, second primary cancers, and deaths) on NSABP B-31 and NCCTG N9831 to trigger the first joint interim analysis assessing the impact of the addition of trastuzumab to paclitaxel following AC chemotherapy in women with operable HER2+ breast cancer. DFS was found to be significantly increased for those who were randomized to trastuzumab relative to those who were not. The test statistic value crossed the pre-specified early-reporting boundary (p=0.001) and as such the B-31 DSMB and the N9831 DMC were independently informed of the interim analysis findings. Both safety monitoring committees recommended that the findings be released. The N9831 DMC further recommended data from Arm B – the sequential schedule of paclitaxel and trastuzumab after AC chemotherapy - be released.

Add 16

The findings of this interim analysis were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in May 2005. The joint analysis team reported that there was a 52% decrease in the hazard of recurrence, second primary cancer, or death for patients randomized to paclitaxel with trastuzumab relative to paclitaxel alone (HR=0.48, 95%CI: 0.39 to 0.60, $p= 2x10^{-12}$). Absolute difference in DFS was estimated to be 12% at 3 years (95%CI: 8 to 15%) and 18% (95%CI: 13 to 24%) at 4 years. There was also a 33% reduction in the hazard of death for patients randomized to paclitaxel with trastuzumab relative to paclitaxel alone (p=0.015). There was increased incidence of class III/IV CHF and cardiac death in patients who received trastuzumab in combination with paclitaxel (3-4%).

The results of an early unplanned comparison of DFS among the treatment arms in N9831, originally requested by the NCCTG DMC, were also presented at the 2005 ASCO meeting. Less than 25% of the events necessary for the final planned analysis had occurred at the time of this analysis. The N9831 study team reported that (1) there was an estimated 13% decrease in the hazard of recurrence, second primaries and death for women randomized to paclitaxel followed by trastuzumab relative to those women randomized to paclitaxel alone (p=0.2936); (2) a 36% decrease in the hazard of recurrence, second primaries and death for women randomized to trastuzumab in combination with paclitaxel relative to those women randomized to paclitaxel followed by trastuzumab (p=0.0114); and (3) the rate of cardiac events (CHF and cardiac death) in the trastuzumab containing arms did not exceed that of the non-trastuzumab containing arm by more that 4%. More follow up is needed to determine whether these early trends continue.

The results of a planned interim analysis from another multicenter phase III clinical trial assessing the impact of the addition of trastuzumab after the completion of at least 4 cycles of adjuvant chemotherapy +/- radiation therapy in women with HER2 positive breast cancer, namely the HERA trial, were such that its IDMC recommended release of the data. Their findings were also presented at the 2005 ASCO meeting. They found a significant increase in DFS, 46% decrease in the hazard of recurrence, second primaries and death for women randomized to trastuzumab relative to those women randomized to observation (HR=0.54, 95%CI:0.43-0.67, p<0.001). The rate of cardiac events (CHF and cardiac death) was 0.5% in the trastuzumab containing arm and 0% in the non-trastuzumab containing arm.

The preponderance of evidence that the addition of trastuzumab to adjuvant chemotherapy significantly prolongs DFS led the N9831 study team to recommend the following modifications to the N9831 trial design (see Table 1.9b5).

Add 18

Add 16,18

1.9b5 Changes to N9831 Study Design Based on Joint Analysis Results

Study Arm	Current Patient Status	Action
Arm A	Receiving AC	Follow Arm C schedule for treatment and cardiac monitoring (see Section 7.17)
Arm A	Completed AC treatment, receiving paclitaxel, and has had a satisfactory post-AC MUGA/Echo according to initiation of trastuzumab guidelines (Section 7.17, footnote 5)	Trastuzumab can be added to the next dose of paclitaxel. Continue trastuzumab until 52 weeks from the start of the trastuzumab The cardiac monitoring should be done at 3, 6, 9, and 18 months from start of trastuzumab.
Arm A	Completed AC treatment, receiving paclitaxel, and MUGA/Echo evaluation DID NOT fall within the initiation of trastuzumab guidelines (Section 7.17, footnote 5), therefore the patient cannot start trastuzumab.	Trastuzumab MAY NOT be initiated. Continue to follow Arm A schedule for treatment and cardiac monitoring schedule as stated in the protocol (Section 7.15).
Arm A	Completed both AC and paclitaxel, is no greater than 6 months from completion of paclitaxel (completed chemotherapy on or after October 25, 2004) and has had a satisfactory MUGA/Echo within the last month according to initiation of trastuzumab guidelines (Section 7.17). *Note: If the post-AC MUGA/Echo was done greater than 1 month ago, schedule another MUGA/Echo and determine whether trastuzumab may be initiated based upon this MUGA/Echo.*	Trastuzumab can be initiated. Continue treatment until 52 weeks from the start of the trastuzumab. The cardiac monitoring should be done at 3, 6, 9, and 18 months from start of trastuzumab.
Arm A	Completed both AC and paclitaxel and is greater than 6 months from completion of paclitaxel (completed chemotherapy prior to October 25, 2004).	Continue to follow Arm A schedule for follow-up evaluations.
Arm B:	Receiving AC	Follow Arm C schedule for treatment and cardiac monitoring as stated in the protocol (Section 7.17).
Arm B:	Completed AC, receiving paclitaxel, and has had a satisfactory post-AC MUGA/Echo according to initiation of trastuzumab guidelines (Section 7.17, footnote 5).	Trastuzumab should be started with the next dose of paclitaxel. Do not wait to finish the paclitaxel. Trastuzumab should be given for 52 weeks from its start. The cardiac monitoring should be done at 3, 6, 9, and 18 months from start of trastuzumab.
Arm B:	Completed AC, receiving paclitaxel, and has NOT had a satisfactory post-AC MUGA/Echo according to initiation of trastuzumab guidelines (Section 7.17, footnote 5).	Trastuzumab may not be initiated. Continue to follow Arm B evaluation and cardiac monitoring schedule as stated in the protocol (Section 7.16).
Arm B:	Completed both AC and paclitaxel	Continue to follow Arm B schedule for treatment and cardiac monitoring as stated in the protocol (Section 7.16).
Arm C:	At any treatment point	Continue to follow Arm C schedule as stated in the protocol.

Add 18

1.9c Rationale for adding 6 year follow-up cardiac testing

The use of trastuzumab after an anthracycline has been linked with increased risk of cardiac events. The medical community has assumed that the risk of cardiac events decreases after trastuzumab is stopped, and that LVEF returns to baseline within a couple years. Because we have a unique opportunity to make an evaluation of whether a change in risk actually occurs, Genentech has agreed to fund an additional LVEF resting MUGA or echocardiogram for patients who are now greater than 6 years from their date of registration to this study.

2.0 Goals

Add 16

In April 2005, the joint interim analysis of NSABP B-31 and NCCTG N9831 found that the addition of trastuzumab to paclitaxel following AC chemotherapy significantly prolongs DFS and increases the rate of cardiac events less than 4%. Thus, one of the primary aims of N9831 has been achieved.

Add 17,18

The next stage of this trial will examine whether there are significant differences in DFS, OS, or cardiac event rates between (1) Arm A and Arm B and (2) Arm B and Arm C. The following patients will be considered evaluable for the comparisons involving Arm A and Arm B:

- Eligible patients randomized to Arm A or Arm B prior to April 25, 2004 will contribute data from the time of their registration to the date of last follow-up or death;

  Note: Patients randomized to Arm A prior to April 25, 2004, will have completed paclitaxel prior to October 25, 2004. On April 25, 2005, when the announcement of the joint analysis results was made, these patients will have completed their chemotherapy more than 6 months ago and as such are not eligible to receive trastuzumab on study.

- Eligible patients randomized to Arm A or Arm B between April 26, 2004 and April 25, 2005, will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first;

  Note: Patients randomized to Arm A between April 26, 2004 and April 25, 2005, would have been receiving chemotherapy or within 6 months of completing chemotherapy when the announcement of the joint analysis results was made on April 25, 2005. As of April 25, 2005, these patients were eligible to receive trastuzumab for a maximum of 52 weeks concurrently with paclitaxel then trastuzumab alone, immediately following paclitaxel, or within 6 months of completing paclitaxel.

  Note: Patients randomized to Arm B prior to January 24, 2005, would have completed paclitaxel prior to April 25, 2005 when the announcement of the joint analysis results was made and as such they were not eligible to switch to or start trastuzumab concurrently with paclitaxel. Although the treatment schedule of patients randomized to Arm B between April 26, 2004 and January 25, 2005 was not affected by the announcement of the joint analysis findings, to keep the follow-up period consistent for the Arm A versus Arm B comparison, patients randomized to Arm B between April 26, 2004 and April 25, 2005, will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first.

Add 17

The following patients will be considered evaluable for the comparisons involving Arm B and Arm C:

- Eligible patients randomized to Arm B or Arm C from May 25, 2000 to January 23, 2002, or from September 2, 2002 to January 24, 2005, will contribute data from the time of their registration to the date of last follow-up or death;

  Note: Patients randomized to Arm B prior to January 24, 2005, would have completed paclitaxel prior to April 25, 2005 when the announcement of the joint analysis results was made and as such they were not eligible to switch to or start trastuzumab concurrently with paclitaxel.

- Eligible patients randomized to Arm B or Arm C between January 24, 2005 and April 25, 2005, will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first;

  Add 17

  Note: Patients randomized to Arm B after January 24, 2005, would not have completed paclitaxel prior to April 25, 2005, when the announcement of the joint analysis results was made and as such they are eligible to switch to or start trastuzumab concurrently with paclitaxel.

  Add 17

  Note: To keep the follow-up period consistent for the Arm B versus Arm C comparison, patients randomized to Arm C between January 24, 2005 and April 25, 2005, will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first.

2.1 Treatment

2.11 Primary

Add 16

2.111a (Stage I – Joint Analysis) To compare the combination of AC followed by weekly paclitaxel with the combination of AC followed by the combination of weekly paclitaxel and trastuzumab in terms of DFS.

Add 16

2.111b (Stage I-Joint Analysis) To compare the combination of AC followed by weekly paclitaxel with the combination of AC followed by the combination of weekly paclitaxel and trastuzumab in terms of the rate of cardiac events

Add 16

2.112 (Stage II) To compare the combination AC followed by weekly paclitaxel with the sequential schedule of the combination of AC, weekly paclitaxel, and trastuzumab in terms of disease-free survival (DFS).

Add 16

2.113 (Stage II) To compare the sequential schedule of the combination of AC, weekly paclitaxel, and trastuzumab with the combination of AC followed by the combination of weekly paclitaxel and trastuzumab in terms of DFS.

Add 16

2.114 (Stage II) To compare the combination AC followed by weekly paclitaxel with the sequential schedule of the combination of AC, weekly paclitaxel, and trastuzumab in terms of the rate of cardiac events

2.12 Secondary

2.121 To compare the combination of AC followed by weekly paclitaxel with the sequential schedule of the combination of AC, weekly paclitaxel, and trastuzumab in terms of overall survival (OS).

2.122 To compare the combination AC followed by weekly paclitaxel with the combination of AC followed by the combination of weekly paclitaxel and trastuzumab in terms of OS.

2.123 To compare the sequential schedule of the combination AC, weekly paclitaxel, and trastuzumab with the combination of AC followed by the combination of weekly paclitaxel and trastuzumab in terms of OS.

2.2 Translational

2.21 To determine whether higher levels of shed ECD (extracellular domain) or autoantibodies to HER-2 and HER-1 measured in the serum prior to treatment are prognostic for DFS and survival.

Add 7, 15

2.22 To determine the concordance of central review of HER-2 overexpression as measured by the HercepTest® (DAKO) and Vysis FISH.

Add 13

2.23 For each treatment arm, levels of brain natriuretic peptide (BNP), troponin-T (TnT), troponin-I (cTnI), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), CD40 ligand, and troponin levels will be compared and contrasted.

Add 16

2.24 To determine whether genetic markers are prognostic for cardiac adverse events associated with treatment.

3.0 Patient Eligibility

Add 7

3.1 Required characteristics at time of registration

Add 10

3.11 Required tumor parameters for **node positive** disease: **NOTE:** This study will continue to use the AJCC 5th edition for TNM classification and staging (see Appendix VII).

3.112 Operable, histologically confirmed adenocarcinoma of the female breast and positive lymph nodes.

Add 2

- Node positivity may be determined by either an axillary node dissection or a positive sentinel node finding by H&E.

Add 10

NOTE: Positive nodes refers to H&E visible nodal metastases. IHC positive only cells in lymph nodes will not be considered positive nodes.

- One or more positive lymph nodes whose tumors are T_{1-3}, pN_{1-2}, M_0 are eligible
- cN2 disease is not eligible
- pN2 disease is eligible

Add 7

- One positive lymph node by sentinel node biopsy or at least 6 axillary nodes must be examined on axillary node dissection with at least one positive lymph node
- Metaplastic carcinoma is eligible

3.113 ER/PgR determination.

Add 6,7

3.114 HER-2 positive (pre-entry requirement for registration).
- FISH must show gene amplification **OR**
- IHC assay must show a strong positive (3+) staining score.
  NOTE: DCIS components should not be counted in the determination of degree of IHC staining or FISH amplification.

Add 10

3.12 Required tumor parameters for **high-risk node-negative** disease. **NOTE:** This study will continue to use the AJCC 5th edition for TNM classification and staging (see Appendix VII)

3.121 Operable, histologically confirmed adenocarcinoma of the female breast and negative lymph nodes.

Add 10

- Node status may be determined by either axillary node dissection or sentinel node biopsy with H&E staining. To be considered node negative, either of the following must be true: 1) negative sentinel node biopsy or 2) no positive lymph nodes found among at least 6 axillary nodes examined on axillary node dissection.
- **NOTE:** IHC positive only cells in lymph nodes will not be considered positive nodes.
- Tumors >2.0 cm (irrespective of hormonal receptor status) or > 1.0 cm if ER-negative and PR-negative disease.

Add 10 3.122 ER/PgR determination.

Add 10 3.123 HER-2 positive (pre-entry requirement for registration).
- FISH must show gene amplification **OR**
- IHC assay must show a strong positive (3+) staining score.
  NOTE: DCIS components should not be counted in the determination of degree of IHC staining or FISH amplification.

3.13 Prior treatment

3.131 ≤84 days from mastectomy or ≤84 days from axillary dissection or sentinel node detection if the patient's most extensive breast surgery was a breast sparing procedure. (This timing is per a decision by the Breast Intergroup.)

3.132 Surgical resection margins.

All tumor should be removed by either a modified radical mastectomy or a segmental mastectomy with axillary node dissection (see Section 3.112).

Add 6
- Mastectomy: There will be no evidence of gross or microscopic tumor (invasive or DCIS) at the surgical resection margins noted in the final surgery or pathology reports. Patients with close margins are eligible.
- Segmental mastectomy (lumpectomy): Margins must be clear of invasive cancer and DCIS
- Axillary dissection or sentinel node dissection: There will be no gross residual adenopathy

3.133 TAM therapy

Add 7
- May have received up to four weeks of TAM therapy, or any other hormonal agent, for this malignancy.

Add 7
- May have received TAM or raloxifene for purposes of chemoprevention (e.g., Breast Cancer Prevention Trial) or for other indications (including previous breast cancer if LCIS) but must be discontinued before registration on this study.

Add 13
- May never have received TAM, raloxifene, or any other hormonal agent.

3.14 ≥18 years of age with any menopausal status.

3.15 Adequate bone marrow function.
- ANC ≥1500/mm^3
- PLT ≥100,000/mm^3

3.16 Adequate hepatic function
- Total bilirubin ≤1.5 x UNL
- AST ≤2.0 x UNL

Add 11

3.17 Left ventricular ejection fraction (LVEF) within institutional normal range. If LVEF is > 75%, the investigator should consider performing a second review of the MUGA/echocardiogram or performing a repeat MUGA/echocardiogram prior to registration. Such re-reviews or repeat MUGA/echocardiogram are **not permitted** after registration.

Add 7

3.18 Willingness to discontinue sex hormonal therapy, e.g., birth control pills, ovarian hormonal replacement therapy, etc., prior to registration and while on study.

Add 7

3.19a Willingness to discontinue any hormonal agent such as raloxifene (Evista) prior to registration and while on study.

3.19b Non-breast malignancies that have not recurred within the last 5 years and are deemed to be at low risk for recurrence.

Add 8

EXCEPTIONS: These non-breast malignancies are eligible even if diagnosed ≤5 years prior to registration:

Add 7

- Squamous or basal cell carcinoma of the skin that has been effectively treated
- Carcinoma in situ of the cervix that has been treated by surgery only
- Lobular carcinoma in situ (LCIS) of the ipsilateral or contralateral breast treated by surgery and/or tamoxifen only

Add 3,10

3.19c Patients undergoing breast conservation therapy (i.e., lumpectomy and axillary dissection) must have plans to receive radiation therapy to the breast +/- regional lymphatics following completion of the chemotherapy. For patients treated with mastectomy, the use of radiation therapy is required for 4 or more positive lymph nodes and must be started after completion of chemotherapy. The use of radiation therapy is at the discretion of the investigator for 0-3 positive lymph nodes but, if used, must be started after the completion of chemotherapy.

Add 7

3.19d Prior to registration, the physician must designate if it is planned for the patient to receive radiation therapy (for adjuvant radiation therapy post-mastectomy or, less commonly, post-conservative therapy but not primary breast radiation as part of breast conserving treatment) (RT guidelines in Appendix II).

3.19e Willing and able to sign an informed consent.

Add 7,8,10,12

3.2 Required characteristics at time of randomization

Gene amplified by FISH or strong positivity (3+) by HercepTest® on central review. Note: The patient registers based on community HER-2 testing using FISH or IHC, AC chemotherapy is initiated. The tumor block or slides must be received ≤ 2 weeks from time of registration to the NCCTG Operations Office for central HER-2 testing.

Add 7

3.3 Contraindications at time of registration

3. 31 Any of the following because of the teratogenic potential of these chemotherapy drugs:

- Pregnant women
- Nursing women
- Women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (condoms, diaphragm, intrauterine device [IUD], surgical sterilization, or abstinence, etc.) Hormonal birth control methods are not permitted.

3.32 Locally advanced tumors (classification T4) at diagnosis including tumors fixed to chest wall, peau d'orange, skin ulcerations/nodules, or clinical inflammatory changes (diffuse brawny cutaneous induration with an erysipeloid edge).

Add 10

3.33 Prior history of breast cancer, except LCIS.

Add 5,12

3.34 Bilateral invasive carcinoma, either metachronous or synchronous (EXCEPTION: Patients diagnosed with unilateral invasive carcinoma and metachronous or synchronous DCIS of the contralateral breast treated with mastectomy are eligible).

3.35 Prior chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.

3.36 Active, unresolved infection.

3.37 Active cardiac disease

- Any prior myocardial infarction
- History of documented congestive heart failure (CHF)
- Current use of digitalis or beta-blockers for CHF

Add 4,5

- Any prior history of arrhythmia or cardiac valvular disease requiring medications or clinically significant
- Current use of medications for treatment of arrhythmias or angina pectoris
- Current uncontrolled hypertension (diastolic >100 mmHg or systolic >200 mmHg)
- Clinically significant pericardial effusion

3.38 Prior anthracycline or taxane therapy for any malignancy.

3.39a Sensitivity to benzyl alcohol.

Add 7

3.39b Neurology/Neuropathy-Sensory ≥grade 2 per the NCI's Common Toxicity Criteria Version 2.0. EXCEPTION: Any chronic neurologic disorder will be looked at on a case-by-case basis by the study chair.

4.0 Test Schedules

Add 16

4.1 Test Schedule

Tests and procedures	≤21 days prior to registration	Q 3 months for 1 year, q 6 months for years 2-5	Within 3 days prior to day 1 of each AC cycle (q 21 days)	Twice per week during AC	During paclitaxel	Every 6 weeks during trastuzumab Rx	Observation q 3 months for 1 year, q 6 months for years 2-5, then yearly for a maximum of 15 years or until PROG
History and exam, wt, PS[13]	X		X		X[14]	X	X
Pelvic exam[1]	X						
Height	X						
Hematology WBC ANC HgB PLT	X[6]		X	X[10]	X[8]	X	X
Chemistry creatinine total bilirubin AST	X[6]				X[14]		X
Bone scan	X[2]						X[2]
Chest x-ray	X[3]						
Add 13, Blood collection for cardiac markers	X[20]			X[20]	X[20]	X[20]	
Add 13, Blood samples for translational research studies[R]	X[4]	X[11]					
Add 16 Blood samples for DNA collection[21,R]		X[21]					
Tumor block/serum submission at time of first breast cancer recurrence[19]							
EKG	X[3]						
Mammogram or breast ultrasound	X[5]						annually
Add 18 MUGA or echocardiogram[R,9,12]	X[15,18]						X[22]
Pregnancy test	X[16]						

Add 16,18

4.2 Cardiac Monitoring Schedule – LVEF MUGA or Echocardiogram[R,9,12,22]

Post Registration Schedule	**For Arm A patients who are not eligible to receive trastuzumab or chose not to receive trastuzumab**	**For Arm A patients who chose to receive trastuzumab**	**For Arm B patients who chose to receive trastuzumab in combination with paclitaxel**	**Arm B where trastuzumab is given sequentially and Arm C**
1	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose
2	6 months from registration	1 month prior to the start of trastuzumab	1 month prior to the start of trastuzumab	3 months after the start of trastuzumab
Add 17 3	9 months from registration	3 months after the start of trastuzumab	3 months after the start of trastuzumab	6 months after the start of trastuzumab
4	18 months from registration	6 months after the start of trastuzumab	6 months after the start of trastuzumab	3 months after last dose of trastuzumab
5		9 months after the start of trastuzumab	9 months after the start of trastuzumab	
6		15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	
Add 18 Update 2 7[22]	≥6 years post-registration	≥6 years post-registration	≥6 years post-registration	≥6 years post-registration

FOOTNOTES FOUND ON NEXT PAGE

1. ≤12 months - required only for women who have a uterus.
2. If clinically indicated.
3. ≤90 days prior to registration. If chest CT scan at time of diagnosis, a chest x-ray is not needed.

Add 5,7

4. See Section 14.1. Draw prior to start of AC.
5. Mammograms obtained as part of the initial diagnosis, biopsy, and surgery will suffice (do not need to be repeated).
6. Arms A, B, and C: ≤90 days prior to registration.

Add 7,8

7. Repeat MUGAs may be necessary, see Section 8.5. If the patient goes off study having begun post-AC treatment but prior to its completion, all remaining MUGA/echocardiogram should be done per the cardiac test schedule.
8. Weekly within three days prior to retreatment.

Add 4,7

9. An echocardiogram (2-D) to measure ejection fraction (LVEF) only is adequate for this study. Use same method for each evaluation at the same radiology facility where the baseline was done whenever possible.
10. At MD discretion.

Add 4,10

11. **NOTE: This requirement has been completed.** NCCTG patients only for a total of 105 patients. See Section 14.16. Once patient enters the observation phase, bloods can be drawn to coincide with observation timing.

Add 7,13

12. **Rapid submission of MUGA/echocardiogram reports and reporting form(s) are *required.*** Fax directly to N9831 QCS, NCCTG Operations Office (507/538-0962) all MUGA/echocardiogram reports ≤14 days. Fax directly to N9831 QCS, NCCTG Operations Office (507/538-0962) reporting form(s) ≤14 days after learning of a cardiac event. (See Section 10.0 for additional adverse event reporting requirements.)

Add 4,7,13

13. Path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, and NCI Cooperative Group Adjuvant Breast Cancer HER2 Reporting Form must be faxed to N9831 QCS, NCCTG Operations Office, 507/538-0962 ≤14 days from registration for surgical quality control review.
14. Monthly.

Add 5

15. ≤30 days.
16. For women of childbearing potential only. Must be done within 7 days prior to registration.

Add 7,15

17. If patient is unable to start or continue trastuzumab, MUGA/echocardiogram still needs to be done at 6, 9, and 18 months from registration.

Add 11

18. If LVEF is >75%, the investigator should consider performing a second review of the MUGA/echocardiogram or performing a repeat MUGA/echocardiogram prior to registration. Such re-reviews or repeat MUGA/echocardiograms are **not permitted** after registration.

Add 11

19. See Section 14.0 for baseline serum submission and 17.0 for HER-2 tissue overexpression confirmation. See Section 17.0 for baseline tissue submission. Also see Section 14.17 and 17.3 for submission of materials at time of first breast cancer recurrence (Section 11.0).

Add 13

20. See Section 14.3 for complete guidelines.

Add 16

21. Blood collection for genetic testing should be done once per patient at next patient visit after this addendum is approved by the local IRB, but not later than 7 years after registration (see Section 14.5).

Add 18,19 Update 2

22. Follow-up LVEF MUGA or echocardiogram should be done one time for **all** patients still in observation ≥6 years post-registration to assess potential late cardiac toxicities. This exam should use the same method as the post-AC exam for this patient. Data from a clinical LVEF evaluation may be reported for patients in event monitoring.

    NOTE: If patient is more than 6 years post-registration when Addendum 18 is approved by the local IRB, an LVEF MUGA or echocardiogram should be done at the time of the next clinical evaluation after Addendum 18 is approved by the local IRB, but no later than December 31, 2009.

R Research funded (see Section 14.0 [kits provided] and 19.0).

5.0 Stratification Factors:

Add 10

5.1 Nodal status: Node Positive (axillary nodal dissection with 1-3+nodes) vs. Node Positive (axillary nodal dissection with 4-9+nodes) vs. Node Positive (axillary nodal dissection with 10+ nodes) vs. Node Positive (positive sentinel node *no or negative* axillary nodal dissection performed) vs. Node Negative (negative sentinel node with *no* axillary nodal*)* vs. Node Negative (axillary node dissection with no positive nodes).

Add 11

5.2 Receptor status: ER positive or PR positive vs. other.

6.0 Registration/Randomization Procedures

6.1 Registration procedures

6.11 NCCTG institutions

6.111 To register a patient, fax (507/284-0885) a completed eligibility checklist to the Randomization Center between 8 a.m. and 4:30 p.m. Central Time Monday through Friday.

Add 10

6.112 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

Add 3,5,7,13

6.113 Path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form, and MUGA/echocardiogram reports **must** be faxed directly to Vicky Cafourek, NCCTG Operations Office, 507/538-0962 **≤14 days** after registration.

Add 7,13

6.114 Upon the completion of the patient's HER-2 status, the NCCTG registering institution will be contacted by fax to the person and fax number provided on the Intergroup Registration Form to either relay the patient's treatment assignment or indicate the patient goes to event-monitoring phase. If questions concerning HER-2 status, the institution should contact Vicky Cafourek 507-284-5369.

Add 11

6.12 ECOG institutions

Add 10

6.121 Submitting Regulatory Documents

Before an ECOG institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form
2. Copy of IRB Informed Consent Document
   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. A) CTSU IRB Certification Form **or** B) HHS 310 Form **or** C) IRB Approval Letter

NOTE: The above submissions must include the following details:
- Indicate all sites approved for the protocol under an assurance number
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version date
- Type of review (full board vs. expedited)
- Date of review
- Signature of IRB official

Add 11

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed: http://www.ctsu.org/rss2_page.asp
If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or e-mail CTSUContact@westat.com**. Monday through Friday, 9:00 a.m.-6:00 p.m.**

Patient must not start protocol treatment prior to registration and must begin ≤ 7 days after registration.

Add 11

Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG webpage by using the Web-based Patient Registration Program (http://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this program. The following information will be requested: Protocol Number, Investigator Identification (including institution and/or affiliate name and investigator's name); Patient

Add 11

Identification (including patient's initials, chart number, social security number, and demographics [sex, birth date, race, nine-digit zip code, and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. After completing the checklist on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 a.m. and 4:30 p.m. Eastern Time. ECOG members should not call the NCCTG directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

Add 1,3,5,7,13

6.122 A fully completed eligibility checklist, path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form, and MUGA/echocardiogram report **must** be faxed directly to Vicky Cafourek, NCCTG Operations Office, 507/538-0962 **≤14 days** after registration.

Add 7,13

6.123 Upon the completion of central review of the patient's HER-2 status, the ECOG registering institution will be contacted by fax to the person and fax number provided on the Intergroup Registration Form to either relay the patient's treatment assignment or indicate the patient goes to event-monitoring phase. If questions concerning HER-2 status, the institution should contact Vicky Cafourek 507-284-5369.

6.13 CALGB institutions

Confirm all eligibility criteria as listed in Section 3.0. Registration will be accepted through institutions with direct registration privileges. Complete the NCCTG Eligibility Checklist and call the CALGB Registrar (919-286-4704, Monday - Friday, 9:00 AM - 4:30 PM, Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient's Social Security #, or hospital ID #
Patient's Name, I.D.#
Date of Signed Informed Consent
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (Sec. 3.0) (yes, no)
List of prior CALGB protocols
Date of most recent Institutional Review Board approval (<1 year)

Add 7

The CALGB Registrar will then contact the NCCTG Randomization Center to register the patient.

Add 3,5,7,13

A fully completed eligibility checklist, path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form, and MUGA/echocardiogram report **must** be faxed directly to Vicky Cafourek, NCCTG Operations Office, 507/538-0962 **≤14 days** after registration.

Add 7,13

Upon the completion of central review of the patient's HER-2 status, the CALGB registering institution will be contacted by fax to the person and fax number provided on the Intergroup Registration Form to either relay the patient's treatment assignment or indicate the patient goes to event-monitoring phase. If questions concerning HER-2 status, the institution should contact Vicky Cafourek 507-284-5369.

6.14 SWOG institutions

6.141 SWOG Group Member and Affiliates: SWOG Group Member and Affiliate investigators will call the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 a.m. and 1:30 p.m. (PT) Monday through Friday, excluding holidays. The Statistical Center will confirm that the patient is eligible and will request the date informed consent was obtained and the date of IRB approval for the treating facility for each entry. The Statistical Center will then contact the NCCTG Randomization Center to register the patient after which the Statistical Center will contact the institution to confirm registration.

Add 7

Add 1,2,3,5,7,13

A fully completed eligibility checklist, path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form, and MUGA/echocardiogram report **must** be faxed directly to Vicky Cafourek, NCCTG Operations Office, 507/538-0962 **≤14 days** after registration.

Add 7,13

Upon the completion of central review of the patient's HER-2 status, the SWOG registering institution will be contacted by fax to the person and fax number provided on the Intergroup Registration Form to either relay the patient's treatment assignment or indicate the patient goes to event monitoring. If questions concerning HER-2 status, the institution should contact Vicky Cafourek 507-284-5369.

6.142 SWOG CCOP Institutions: SWOG CCOP institutions will call the Southwest Oncology Group CCOP Office at 206/652-CCOP (206/652-2267), 7:00 a.m. to 1:30 p.m. (PT) Monday through Friday, excluding holidays. The CCOP Office will confirm that the patient is eligible and will request the date informed consent was obtained and the date of IRB approval for the treating facility for each entry. The CCOP Office will then contact the NCCTG Randomization Center to register the patient after which the CCOP Office will contact the institution to confirm registration.

Add 7

Add 1,3,5,7,13

A fully completed eligibility checklist, path report, NCI Cooperative Group Adjuvant Breast Cancer Pathology Reporting Form, NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form, and MUGA/echocardiogram report **must** be faxed directly to Vicky Cafourek, NCCTG Operations Office, 507/538-0962 **≤14 days** after registration.

Add 7,13

Upon the completion of central review of the patient's HER-2 status, the SWOG registering institution will be contacted by fax to the person and fax number provided on the Intergroup Registration Form to either relay the patient's treatment assignment or indicate the patient goes to event monitoring. If questions concerning HER-2 status, the institution should contact Vicky Cafourek 507-284-5369.

6.143 Southwest Oncology Group institutions will follow their normal procedures for documentation of IRB approval.

Add 14 6.15 NCIC CTG institutions

Before an NCIC CTG institution may enter patients, protocol specific regulatory documents must be submitted to the NCIC CTG.

All investigators must have completed NIH mandated ethics education training with respect to human subjects protection. Evidence of completion of this education must be on file at the NCIC CTG prior to approving any investigator on the Participant's List for this study. For investigators who have not already completed this education, a recommended route for doing so is to complete an on-line training program available at http://cme.nci.nih.gov. The program can be completed in approximately an hour and a half and will issue a completion certificate, a copy of which must be forwarded the NCIC CTG to evidence completion.

This study is being conducted under a Clinical Trial Application (CTA) in Canada. Accordingly, the protocol must be conducted in compliance with Division 5 of the Canadian Food and Drug Regulations and ICH-Good Clinical Practice Guidelines. Please note that the Division 5 Canadian Food and Drug Regulations pertaining to the conduct of clinical trials were amended and came into force on September 1, 2001; the conduct of this protocol must comply with these regulations.

This study is affiliated with the US National Cancer Institute (NCI U.S.). Therefore the conduct of the study must comply with U.S. regulations regarding the Protection of Human Subjects (Title 45, Part 46, U.S. Code of Federal Regulations). In addition to the Research Ethics Board (REB) composition, function and review requirements as specified in these regulations, your centre must have a current assurance as issued by the Office of Human Research Protections (OHRP) in the U.S. Currently, centres may meet this requirement by having either a Cooperative Project Assurance (CPA) or a Federal Wide Assurance (FWA) as issued by the OHRP. Please contact our office if you require further information regarding applicable U.S. regulations or an assurance.

Further information regarding these regulatory and ethics requirements may be accessed on the NCIC CTG private website at the following address: http://www.ctg.queensu.ca/private/ethics/default.html. Applicable guidelines/regulations are found under the "Links to Related Websites" under the "Ethics, Regulatory and Consents" section. A username and password are required to access this website. Please contact our Operations Office if you require assistance in this regard.

The following documentation must be on file at the NCIC CTG central office prior to randomization:

1. Written documentation of full board Research Ethics Board (REB) approval of the protocol and sample consent form. The REB of an institution must approve the consent form document that will be used at that centre. Please note that if the approval letter or form from the REB does not clearly indicate that a 'full board' review was done, then either a revised letter/form or the minutes of the REB meeting evidencing a full board review was done must be submitted.

   If an REB refuses to approve this protocol (or an amendment/revision to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal.

2. Documentation of completed human subjects' protection education for each investigator on the Participant's List, if not already on file with the NCIC CTG

3. A completed Health Canada 'Research Ethics Board Attestation' form.

   A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

   - The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;
   - The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice,; and
   - The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

   This documentation must be received by the NCIC CTG central office before the centre can be locally activated.

4. Written documentation confirming the applicable investigator brochure (and safety updates if applicable) was forwarded to the REB. The IB will be included in the Central Activation package.

5. Completed "Confirmation of Initial Ethical Approval' form confirming the protocol was approved by a properly constituted REB and that only REB members independent of the investigator(s) conducting the study participated in deliberations or voting concerning the approval of the study.

6. Copy of the REB approved consent form on institutional letterhead.

   A sample consent form is provided. It may be modified to meet local requirements as long as the necessary elements are retained. It is advised that if you do modify the consent form, you should submit a copy to NCIC CTG for review prior to submission to your local REB. The consent form must contain statements giving permission for medical/study reports concerning the patient to be sent to the NCIC CTG and other sponsoring and monitoring agencies, and for representatives of the NCIC CTG and these agencies to inspect medical/study reports on-site.

   Since this study is conducted under a CTA all ICH-GCP elements as listed in section 4.8.10 of the ICH-Good Clinical Practice Guideline must be included in the consent form. If your centre does modify the sample consent please ensure no ICH-GCP elements are eliminated in the modification process.

   As this is an NCI US affiliated study, the content of the consent form must meet the requirements of the OHRP. If your centre does modify the sample consent, it is recommended that you use the checklist (this document is also available under the "Generic Activation Forms" link provided above or directly at: http://www.ctg.queensu.ca/trials/generic_forms_public/generic_consent_form_checklist.pdf to ensure that no OHRP elements are eliminated in the modification process. Please note that it is important that descriptions of risks and alternative therapy are not reduced.

7. Current laboratory accreditation and normal values.

8. Completed NCIC CTG Participant's List.

9. Curriculum vitae (CV) for the principal investigator and all co-investigators must be on file with our office.

   The CV on file must have been updated within the past 2 years. If an investigator wishes to participate and an up-to-date CV is not on file with us, please submit one with the Participants List.

10. Completed Health Canada 'Qualified Investigator Undertaking' form for the principal investigator only.

11. Current NCI US Investigator Number for all Investigators (Principal and Additional Investigators. These numbers are assigned by the NCI US Pharmaceutical Management Branch (PMB) and expire annually. If an investigator does not have a number or their number has expired, a current number is obtained by completing and signing the following:
    - FDA 1572 form
    - Supplemental Investigator Data Form with signature (original or copy accepted)
    - Financial Disclosure Form with original signature

12. Documentation of a current Co-operative Project Assurance (CPA) or Federal Wide Assurance (FWA) number if not already on file with the NCIC CTG.

Continuing Review

Documented annual re-approval of the study is required as long as the trial is open to patient accrual or patients are receiving protocol treatment or undergoing protocol mandated interventions. Annual re-approval must be full board until accrual is complete and all patients have completed protocol treatments and/or protocol mandated interventions.

Amendments/Revisions

All amendments or revisions to the protocol must undergo review by local REBs. Amendments/revisions will be circulated to all participating sites once received from NCCTG, the lead group for this study, with clear instructions regarding REB review. If full board approval of an amendment or revision is required it will be specified.

Retention of Patient Records and Study Files

NCIC CTG will notify all Canadian investigators/institutions when trial related records no longer need to be retained, after consultation with NCCTG. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Registration/Randomization Procedures:

Patients must begin treatment within 7 days after registration. Registrations for all NCIC CTG centres will be done through the NCIC CTG Central Office. Registrations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist and the registration form must be completed prior to registration. Registration may be done by telephone (613-533-6430) or by fax (613-533-2941). As soon as eligibility is ascertained, NCCTG will be contacted by the NCIC CTG to confirm registration. The NCIC CTG will then relay the confirmation of registration information to the centre in writing.

NCIC CTG Contacts
Study Chair:

Dr. Karen Gelmon
Division of Medical Oncology
BCCA - Vancouver Cancer Centre
600 West 10th Avenue
Vancouver, BC Canada V5Z 4E6
Phone: 604-877-6000
Fax: 604-877-0585
E-mail: kgelmon@bccancer.bc.ca

Central Office Contacts:

Ms. Jyoti Kotecha
Intergroup Study Coordinator
NCIC Clinical Trials Group
10 Stuart Street, Queen's University
Kingston, ON Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2941
E-mail: jkotecha@ctg.queensu.ca

Ms. Suzan Moase
Intergroup Research Associate
NCIC Clinical Trials Group
10 Stuart Street, Queen's University
Kingston, ON Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2941
E-mail: *smoase@ctg.queensu.ca*

Dr. Lois Shepherd
Physician Coordinator
NCIC Clinical Trials Group
10 Stuart Street, Queen's University
Kingston, ON Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2941
E-mail: lshepherd@ctg.queensu.ca

Add 7,14

6.16 **All Groups**

Add 14

6.161 Patient eligibility and the existence of a signed consent form will be checked by NCCTG Randomization Center personnel before a patient will be registered into this study.

Add 4,10
Add 10
Add 10
Add 10

- Patient has/has not given permission to have their blood samples stored and used for future research to learn about, prevent, treat, or cure cancer.
- Patient has/has not given permission to have their blood samples stored and used in future research for other medical questions (for example, causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).
- Patient has/has not given permission to have their tissue sample stored and used for future research to learn about, prevent, treat, or cure cancer.
- Patient has/has not given permission to have their tissue samples stored and used in future research for other medical questions (for example, causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).
- Patient has agreed that someone may contact them in the future to ask them to take part in more research.
- Patient has been given the question and answer sheet called "What is tissue banking?"

Add 4,11,12,14

6.162 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG, CALGB, ECOG, NCIC CTG, or SWOG member physician (see Sections 7.141, 7.151, 7.161, 7.171).

Add 14

6.163 Treatment cannot begin prior to registration and must begin ≤7 days after registration.

Add 8,14

6.164 Pretreatment tests must be completed within the guidelines specified on the test schedule.

Add 12,14

6.165 All required baseline symptoms must be graded and documented in patient records.

Add 10,13,14

6.166 NCCTG Randomization Center will automatically register patients separately to the optional translational research components of this study. The following will be recorded:

Add 16

- Patient has/has not given permission to give a blood sample for research testing (Section 14.1).
- Patient has/has not given permission to give a blood sample at the time of recurrence (Section 14.2).
- Patient has/has not given permission to give a blood sample for cardiac markers (Section 14.3).
- Patient has/has not given permission to give a tissue sample at the time of recurrence (Section 17.3).
- Patient has/has not given permission to give a one-time blood sample for genetic testing (Section 14.5).

Add 14

6.167 Study drug availability checked.

6.2 Randomization procedures:

Add 7,8,12

At time of registration, the values of the stratification factors (Section 5.0) will be recorded. The patient will be randomly assigned to one of the following treatment arms. This randomization will be communicated to the registering institution during administration of AC once confirmation of HER-2 amplification by FISH or strong HER-2 positivity by immunohistochemistry is found on central laboratory testing:

Arm A: Paclitaxel →observation
Arm B: Paclitaxel →trastuzumab →observation
Arm C: Paclitaxel + trastuzumab →trastuzumab →observation

7.0 Protocol Treatment

7.1 Treatment schedule - Use actual weight or estimated dry weight if fluid retention. Treatment may be given as inpatient or outpatient at discretion of treating M.D.

7.11 TAM therapy

Add 2,8,12

Premenopausal women: 20 mg daily for 5 years, to be initiated in premenopausal women with ER positive or PR positive tumors at the time of initiation of radiation therapy or within 5 weeks of the completion of weekly paclitaxel treatment for patients not receiving radiation therapy.

For patients who have received either TAM or raloxifene as chemoprevention before enrolling on this study, the use of TAM following weekly paclitaxel treatment will be at the physician's discretion (as per Breast Intergroup decision 5/00).

Add 8,12,13

Postmenopausal women: Patients with ER positive or PR positive tumors may receive any of the following at the investigator's discretion: 1) AI (anastrozole 1mg daily, letrozole 2.5 mg daily, or exemestane 25 mg daily) for 5 years, 2) TAM (20 mg daily) for 5 years, 3) TAM for 5 years followed by an aromatase inhibitor for 5 years in view of the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) trial MA.17 data, or 4) sequential TAM/AI for a minimum of 5 years.

Add 12,13

The specific hormonal agent, with start and end dates, must be documented in the case report forms.

Add 7

7.12 Radiation therapy (when indicated) will commence within 5 weeks of the completion of weekly paclitaxel treatment (see Appendix II for guidelines).

Add 10

Due to concerns about cardiac toxicity associated with adriamycin and trastuzumab, internal mammary chain (IMC) RT must not be administered. If a patient receives IMC RT, the patient will be declared a protocol violation.

7.13 Trastuzumab (Herceptin®) administration and dosage

7.131 Trastuzumab will be administered in an outpatient setting for patients on Arms B and C. Patients will receive a 4 mg/kg IV loading dose on Day 1 followed by 2 mg/kg IV dose weekly.

7.132 The initial dose of trastuzumab will be administered over 90 minutes.

If this first dose is well tolerated, subsequent infusion times may be shortened to 30 minutes. If the initial or a subsequent dose is not well tolerated (e.g., the patient experiences fever, chills, or rigors), subsequent infusion times may be shortened only after a dose is well tolerated.

Add 7,13

7.14 **AC treatment prior to randomization** - *MUGA scan/echocardiogram 3 weeks after last dose of AC must be done and the results faxed to N9831 QCS, NCCTG Operations Office, (507-538-0962) ≤14 days after the scan on 3 Week Post-AC MUGA/Echocardiogram Report Form*

Agent	Time	Dose	Route	Rx Days	ReRx
ADR	N/A	60 mg/m^2	IV push thru running IV of NS	Day 1 weeks 1,4,7,10	Q 3 weeks x 4
CTX	N/A	600 mg/m^2	IV infusion in 250 mL NS over 20-30 minutes		

Add 7,8,11

7.141 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's local physician. In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the local physician. The local physician will be required to supervise the administration of commercial drugs as stipulated in the protocol and provide written documentation that the drugs were administered. For this protocol, the patient must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 14

7.15 **ARM A –** All AC-related toxicity should be resolved prior to starting TAXOL. All 12 doses of TAXOL will be given unless directed to discontinue in TAXOL dose modification Section 8.4. The doses of BEN and DXM may be adjusted after the first dose, based on tolerability.

Add 7,8

Agent	Time	Dose	Route	Rx Days	ReRx
DXM	≤60 min pre-TAXOL	10 mg	IV	Day 1 q week starting week 13	Q week x12
BEN	30-60 minutes pre-TAXOL	50 mg	IV		
CIMET*		300 mg			
NOTE: 3-week post AC MUGA/ECHO must be done before starting TAXOL					
TAXOL	N/A	80 mg/m^2	IV infusion in 250 mL of D_5W or NS over 1 hour**		

Add 10

NOTE: Epinephrine + diphenhydramine will be immediately available during the infusion, if needed.
DXM = dexamethasone BEN = Benadryl CIMET = cimetidine

*Ranitidine (50 mg IV) or famotidine (20 mg IV) may be substituted for CIMET.

**In-line filtration with hydrophilic 0.22 micron filter is required. Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and administered with non-PVC-containing administration sets, such as those that are polyethylene-lined, i.e., nitroglycerin.

Add 4,7,10,11

7.151 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's local physician. In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the local physician. The local physician will provide and supervise the administration of the commercial drug (TAXOL) as stipulated in the protocol and provide written documentation that the drug was administered. For this protocol, the patient must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 14

7.15a For Arm A patients who completed paclitaxel chemotherapy on or after October 25, 2004 who chose to receive trastuzumab and those LVEF levels within one month of starting trastuzumab met the criteria for starting trastuzumab

Agent	Dose	Route	Rx Days	ReRx
HERCEP to begin concurrent with XRT, if XRT is needed.				
HERCEP[1]	First dose - 4 mg/kg	IV over 90 minutes[3]	Day 1 q week starting week 25	Weekly x 52[2]
	Subsequent doses - 2 mg/kg	IV over 30 minutes[3]		

1. See Section 8.5 for instructions should toxicity occur during administration.
2. The duration from start to stop of HERCEP will be 52 weeks. If more than 3 consecutive weekly doses (or a total of 6 weekly doses) (except when those missed doses are associated with a Hold and Repeat per Section 8.56411) have been omitted, the patient is required to go to observation.
3. Initiation of HERCEP
   NOT PERMITTED if a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia while receiving AC.

   PERMITTED IN AN ASYMPTOMATIC PATIENT if a) the LVEF increased or stayed the same or b) the LVEF decreased by ≤15 percentage points but is still at or above the radiology facility's lower limit of normal (LLN).

   PROHIBITED IN AN ASYMPTOMATIC PATIENT IF a) the LVEF decreased ≤15 percentage points and is below the radiology facility's LLN or b) the LVEF decreased by 16 percentage points or more (regardless of the radiology facility's LLN).

Summary of post-AC LVEF requirements for administration of HERCEP in ***asymptomatic*** patients

Absolute change in LVEF between registration and at most one month prior to start of trastuzumab	**Decision regarding initiation of HERCEP treatment**
Increase or no change	Initiate HERCEP
Decrease of ≤15 percentage points but at or above the radiology facility's LLN	Initiate HERCEP
Decrease of ≤15 percentage points and below the radiology facility's LLN	HERCEP is prohibited
Decrease of 16 or more percentage points (regardless of the radiology facility's LLN	HERCEP is prohibited

7.15a1 Treatment by Local Medical Doctor (LMD)

7.15a11 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's LMD.

7.15a12 HERCEP: The **registering (responsible) investigator must** contact the Pharmaceutical Management Branch (PMB), CTEP, to make arrangements for the investigational agent (HERCEP) to be shipped directly to the LMD (**see Section 15.44 for details**).

7.15a13 Patients must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

7.15b For Arm A patients who have not completed paclitaxel chemotherapy and decide to receive trastuzumab in combination with paclitaxel

If during the 12 weeks of TAXOL and HERCEP a dose of TAXOL and HERCEP are missed, only the TAXOL dose is made up, the HERCEP dose is omitted. The doses of BEN and DXM may be adjusted after the first dose, based on tolerability.

Agent	Time	Dose	Route	Rx Days	ReRx
DXM	≤60 min pre-TAXOL	10 mg	IV		
BEN	30-60 minutes pre-TAXOL	50 mg	IV		
CIMET[1]		300 mg			
TAXOL	N/A	80 mg/m^2	IV infusion in 250 mL of D_5W or NS over 1 hour[2]	Day 1 q week starting week 13	Q week x 12
HERCEP alone is to begin after last TAXOL/HERCEP treatment and concurrent with XRT, if XRT is given.					
HERCEP[5]	N/A	1st dose – 4 mg/kg	IV over 90 minutes[3]	Day 1 q week starting with any TAXOL dose	Q week x 52[4]
		Subsequent doses - 2 mg/kg	IV over 30 minutes[3]		

Add 17

Add 17

NOTE: Epinephrine + diphenhydramine will be immediately available during the infusion, if needed.

DXM = dexamethasone BEN = Benadryl CIMET = cimetidine

1. Ranitidine (50 mg IV) or famotidine (20 mg IV) may be substituted for CIMET.
2. In-line filtration with hydrophilic 0.22 micron filter is required. Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and administered with non-PVC-containing administration sets, such as those that are polyethylene-lined, i.e., nitroglycerin.
3. See Section 8.5 for instructions should toxicity occur during administration. Follow instructions for Arm B dose adjustments.
4. The duration from start to stop of HERCEP will be 52 weeks. If more than 3 consecutive weekly doses (or a total of 6 weekly doses) (except when those missed doses are associated with a Hold and Repeat per Section 8.56411), the patient is required to go to observation.
5. Initiation of HERCEP
   -NOT PERMITTED if a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia while receiving AC.
   -PERMITTED IN AN ASYMPTOMATIC PATIENT if a) the LVEF increased or stayed the same or b) the LVEF decreased by ≤15 percentage points but is still at or above the radiology facility's lower limit of normal (LLN).
   -PROHIBITED IN AN ASYMPTOMATIC PATIENT IF a) the LVEF decreased ≤15 percentage points and is below the radiology facility's LLN or b) the LVEF decreased by 16 percentage points or more (regardless of the radiology facility's LLN).

Summary of post-AC LVEF requirements for administration of HERCEP in ***asymptomatic*** patients

Absolute change in LVEF at registration and at most one month prior to start of trastuzumab	**Decision regarding initiation of HERCEP treatment**
Increase or no change	Initiate HERCEP
Decrease of ≤15 percentage points but at or above the radiology facility's LLN	Initiate HERCEP
Decrease of ≤15 percentage points and below the radiology facility's LLN	HERCEP is prohibited
Decrease of 16 or more percentage points (regardless of the radiology facility's LLN	HERCEP is prohibited

7.15b1 Treatment by Local Medical Doctor (LMD)

7.15b11 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's LMD.

7.15b12 HERCEP: The **registering investigator <u>must</u>** contact the Pharmaceutical Management Branch (PMB), CTEP, to make arrangements for the investigational agent (HERCEP) to be shipped directly to the LMD (**see Section 15.44 for details**).

7.15b13 TAXOL: The LMD will provide and supervise the administration of the commercial drug (TAXOL) as stipulated in the protocol and written documentation that the drug was administered.

7.15b14 Patients must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 7,8

7.16 **ARM B –** All AC-related toxicity should be resolved prior to starting TAXOL. All 12 doses of TAXOL must be given before initiating HERCEP unless directed to discontinue in TAXOL dose modification (Section 8.4). The doses of BEN and DXM may be adjusted after the first dose, based on tolerability.

Agent	Time	Dose	Route	Rx Days	ReRx
DXM	≤60 min pre-TAXOL	10 mg	IV	Day 1 q week starting week 13	Q week x 12
BEN	30-60 minutes pre-TAXOL	50 mg	IV		
CIMET[1]		300 mg			
NOTE: 3-week post AC MUGA/ECHO must be done before starting TAXOL					
TAXOL	N/A	80 mg/m^2	IV infusion in 250 mL of D_5W or NS over 1 hour[2]		
HERCEP to begin after last TAXOL treatment and concurrent with XRT, if XRT is needed.					
HERCEP[5]	N/A	First dose - 4 mg/kg	IV over 90 minutes[3]	Day 1 q week starting week 25	Weekly x 52[4]
		Subsequent doses - 2 mg/kg	IV over 30 minutes[3]		

Add 10

NOTE: Epinephrine + diphenhydramine will be immediately available during the infusion, if needed.

DXM = dexamethasone BEN = Benadryl CIMET = cimetidine

1. Ranitidine (50 mg IV) or famotidine (20 mg IV) may be substituted for CIMET.

2. In-line filtration with hydrophilic 0.22 micron filter is required. Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and administered with non-PVC-containing administration sets, such as those that are polyethylene-lined, i.e., nitroglycerin.

Add 16

3. See Section 8.5 for instructions should toxicity occur during administration.

Add 6,7,8,16

4. The duration from start to stop of HERCEP will be 52 weeks. If more than 3 consecutive weekly doses (or a total of 6 weekly doses) (except when those missed doses are associated with a Hold and Repeat per Section 8.56411) have been omitted, the patient is required to go to observation.

5. Initiation of HERCEP

NOT PERMITTED if a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia while receiving AC.

PERMITTED IN AN ASYMPTOMATIC PATIENT if a) the LVEF increased or stayed the same or b) the LVEF decreased by ≤15 percentage points but is still at or above the radiology facility's lower limit of normal (LLN).

Add 8

PROHIBITED IN AN ASYMPTOMATIC PATIENT IF a) the LVEF decreased ≤15 percentage points and is below the radiology facility's LLN or b) the LVEF decreased by 16 percentage points or more (regardless of the radiology facility's LLN).

Add 8 Summary of post-AC LVEF requirements for administration of HERCEP in ***asymptomatic*** patients

Absolute change in LVEF between baseline and 3 weeks after last AC cycle	**Decision regarding initiation of HERCEP treatment**
Increase or no change	Initiate HERCEP
Decrease of ≤15 percentage points but at or above the radiology facility's LLN	Initiate HERCEP
Decrease of ≤15 percentage points and below the radiology facility's LLN	HERCEP is prohibited
Decrease of 16 or more percentage points (regardless of the radiology facility's LLN	HERCEP is prohibited

Add 4,7,10 7.161 Treatment by Local Medical Doctor (LMD)

Add 4,7,10 7.1611 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's LMD.

Add 10 7.1612 HERCEP: The **registering (responsible) investigator <u>must</u>** contact the Pharmaceutical Management Branch (PMB) , CTEP, to make arrangements for the investigational agent (HERCEP) to be shipped directly to the LMD (**see Section 15.44 for details**). NOTE: Patients who were allowed to be treated by their LMD may continue with arrangements made prior to Addendum 10. In this case, patients must be counseled about storage and stability of the investigational agent.

Add 10 7.1613 TAXOL: The LMD will provide and supervise the administration of the commercial drug (TAXOL) as stipulated in the protocol and written documentation that the drug was administered.

Add 10,11,14 7.1614 Patients must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 16

7.16a For Arm B patients who have not completed paclitaxel chemotherapy and decide to receive trastuzumab in combination with paclitaxel

If during the 12 weeks of TAXOL and HERCEP a dose of TAXOL and HERCEP are missed, only the TAXOL dose is made up, the HERCEP dose is omitted. The doses of BEN and DXM may be adjusted after the first dose, based on tolerability.

Agent	Time	Dose	Route	Rx Days	ReRx
DXM	≤60 min pre-TAXOL	10 mg	IV		
BEN	30-60 minutes pre-TAXOL	50 mg	IV		
CIMET[1]		300 mg			
TAXOL	N/A	80 mg/m^2	IV infusion in 250 mL of D_5W or NS over 1 hour[2]	Day 1 q week starting week 13	Q week x 12
HERCEP alone is to begin after last TAXOL/HERCEP treatment and concurrent with XRT, if XRT is given.					
HERCEP[5]	N/A	1st dose – 4 mg/kg	IV over 90 minutes[3]	Day 1 q week starting with any TAXOL dose	Q week x 52[4]
		Subsequent doses - 2 mg/kg	IV over 30 minutes[3]		

Add 17

Add 17

NOTE: Epinephrine + diphenhydramine will be immediately available during the infusion, if needed.

DXM = dexamethasone BEN = Benadryl CIMET = cimetidine

1. Ranitidine (50 mg IV) or famotidine (20 mg IV) may be substituted for CIMET.
2. In-line filtration with hydrophilic 0.22 micron filter is required. Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and administered with non-PVC-containing administration sets, such as those that are polyethylene-lined, i.e., nitroglycerin.
3. See Sections 8.4 & 8.5 for instructions should toxicity occur during administration. Follow instructions for Arm C dose adjustments.
4. The duration from start to stop of HERCEP will be 52 weeks. If more than 3 consecutive weekly doses (or a total of 6 weekly doses) (except when those missed doses are associated with a Hold and Repeat per Section 8.56411), the patient is required to go to observation.
5. Initiation of HERCEP
   NOT PERMITTED if a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia while receiving AC.

   PERMITTED IN AN ASYMPTOMATIC PATIENT if a) the LVEF increased or stayed the same or b) the LVEF decreased by ≤15 percentage points but is still at or above the radiology facility's lower limit of normal (LLN).

   PROHIBITED IN AN ASYMPTOMATIC PATIENT IF a) the LVEF decreased ≤15 percentage points and is below the radiology facility's LLN or b) the LVEF decreased by 16 percentage points or more (regardless of the radiology facility's LLN).

Summary of post-AC LVEF requirements for administration of HERCEP in ***asymptomatic*** patients

Absolute change in LVEF between registration and at most one month prior to start of trastuzumab	**Decision regarding initiation of HERCEP treatment**
Increase or no change	Initiate HERCEP
Decrease of ≤15 percentage points but at or above the radiology facility's LLN	Initiate HERCEP
Decrease of ≤15 percentage points and below the radiology facility's LLN	HERCEP is prohibited
Decrease of 16 or more percentage points (regardless of the radiology facility's LLN	HERCEP is prohibited

7.16a1 Treatment by Local Medical Doctor (LMD)

7.16a11 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's LMD.

7.16a12 HERCEP: The **registering investigator must** contact the Pharmaceutical Management Branch (PMB), CTEP, to make arrangements for the investigational agent (HERCEP) to be shipped directly to the LMD (**see Section 15.44 for details**).

NOTE: Patients who were allowed to be treated by their LMD may continue with arrangements made prior to Addendum 10. In this case, patients must be counseled about storage and stability of the investigational agent.

7.16a13 TAXOL: The LMD will provide and supervise the administration of the commercial drug (TAXOL) as stipulated in the protocol and written documentation that the drug was administered.

7.16a14 Patients must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 7,8,9

7.17 **ARM C –** All AC-related toxicity should be resolved prior to starting TAXOL. All 12 doses of TAXOL must be given before initiating HERCEP alone unless directed to discontinue in TAXOL dose modification Section 8.4. However, if during the 12 weeks of TAXOL and HERCEP a dose of TAXOL and HERCEP are missed, only the TAXOL dose is made up, the HERCEP dose is omitted. The doses of BEN and DXM may be adjusted after the first dose, based on tolerability.

Agent	Time	Dose	Route	Rx Days	ReRx
DXM	≤60 min pre-TAXOL	10 mg	IV		
BEN	30-60 minutes	50 mg	IV		
CIMET[1]	pre-TAXOL	300 mg			
NOTE: 3-week post AC MUGA/ECHO must be done before starting TAXOL/HERCEP.					
TAXOL	N/A	80 mg/m^2	IV infusion in 250 mL of D_5W or NS over 1 hour[2]	Day 1 q week starting week 13	Q week x 12
HERCEP[5]	N/A	1st dose – 4 mg/kg	IV over 90 minutes[3]		
		Subsequent doses - 2 mg/kg	IV over 30 minutes[3]		
HERCEP alone to begin after last TAXOL/HERCEP treatment and concurrent with XRT, if XRT is needed					
HERCEP ALONE	N/A	2 mg/kg	IV over 30 minutes[3]	Day 1 q week starting week 25	Q week x 40[4]

Add 10

Add ,8,10

NOTE: Epinephrine + diphenhydramine will be immediately available during the infusion, if needed.

DXM = dexamethasone BEN = Benadryl CIMET = cimetidine

1. Ranitidine (50 mg IV) or famotidine (20 mg IV) may be substituted for CIMET.

2. In-line filtration with hydrophilic 0.22 micron filter is required. Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and administered with non-PVC-containing administration sets, such as those that are polyethylene-lined, i.e., nitroglycerin.

Add 10,16

3. See Sections 8.4 & 8.5 for instructions should toxicity occur during administration.

Add 6,7,8

4. The duration from start to stop of HERCEP will be 52 weeks. If more than 3 consecutive weekly doses (or a total of 6 weekly doses) (except when those missed doses are associated with a Hold and Repeat per Section 8.56413), the patient is required to go to observation.

5. Initiation of HERCEP

NOT PERMITTED if a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia while receiving AC.

PERMITTED IN AN ASYMPTOMATIC PATIENT if a) the LVEF increased or stayed the same or b) the LVEF decreased by ≤15 percentage points but is still at or above the radiology facility's lower limit of normal (LLN).

Add 8

PROHIBITED IN AN ASYMPTOMATIC PATIENT IF a) the LVEF decreased ≤15 percentage points and is below the radiology facility's LLN or b) the LVEF decreased by 16 percentage points or more (regardless of the radiology facility's LLN).

- ----------

Add 8 Summary of post-AC LVEF requirements for administration of HERCEP in ***asymptomatic*** patients

Absolute change in LVEF between baseline and 3 weeks after last AC cycle	**Decision regarding initiation of HERCEP treatment**
Increase or no change	Initiate HERCEP
Decrease of ≤15 percentage points but at or above the radiology facility's LLN	Initiate HERCEP
Decrease of ≤15 percentage points and below the radiology facility's LLN	HERCEP is prohibited
Decrease of 16 or more percentage points (regardless of the radiology facility's LLN	HERCEP is prohibited

Add 4,7 7.171 Treatment by Local Medical Doctor (LMD)

Add 4,7,10 7.1711 When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be administered by the patient's LMD.

Add 10 7.1712 HERCEP: The **registering investigator <u>must</u>** contact the Pharmaceutical Management Branch (PMB), CTEP, to make arrangements for the investigational agent (HERCEP) to be shipped directly to the LMD (**see Section 15.44 for details**).

NOTE: Patients who were allowed to be treated by their LMD may continue with arrangements made prior to Addendum 10. In this case, patients must be counseled about storage and stability of the investigational agent.

Add 10 7.1713 TAXOL: The LMD will provide and supervise the administration of the commercial drug (TAXOL) as stipulated in the protocol and written documentation that the drug was administered.

Add 10,11,14 7.1714 Patients must return to the registering NCCTG, ECOG, CALGB, NCIC CTG, or SWOG institution for evaluation at least every 12 weeks.

Add 10 **8.0 Dosage Modification Based on Adverse Events**

Add 10 8.1 **ALERT**: ADR reporting may be required for some adverse events. See Section 10.

Add 10 8.2 Adverse events will be graded using the NCI Common Toxicity Criteria (CTC) Version 2.0.

8.3 **AC** dose modifications - based on day of retreatment data

8.31 Blood/Bone Marrow

8.311 ANC <1500

Add 7 8.3111 Delay chemotherapy treatment.

8.3112 Check counts weekly until ANC ≥1500.

Add 7 8.3113 Resume at full dose with G-CSF or GM-CSF support. Begin G-CSF or GM-CSF on day 2 and continue until ANC ≥10,000. G-CSF or GM-CSF should be discontinued at least 24 hours prior to the next cycle. Check CBC beginning on day 8 of G- or GM-CSF therapy. All remaining cycles may be given with G-CSF or GM-CSF at MD discretion.

Add 7 8.3114 AC will be delayed if ANC <1500 on day 1 despite G-CSF or GM-CSF during the previous cycle. If the ANC takes >1-3 weeks to recover to ≥1500, reduce the next dose of AC (A: 50 mg/m^2 and C: 500 mg/m^2). If after the 3-week delay the ANC remains <1500, discontinue AC and proceed with TAXOL when ANC ≥1500.

8.312 PLT <75,000

Add 7 8.3121 Delay AC. PLT transfusions and PLT colony stimulating-factor may be given at the discretion of the investigator.

8.3122 Check counts weekly until PLT ≥75,000.

Add 7 8.3123 If PLT was ≥25,000 but recovers to ≥75,000 within 3 weeks, resume AC at full dose.

Add 7 8.3124 If PLT was <25,000 but recovers to 75,000 within 3 weeks, reduce both agents by 25% on next cycle.

Add 7 8.3125 If after 3-week delay PLT <75,000, discontinue AC and proceed with TAXOL when PLT ≥75,000.

8.32 Cardiovascular

8.321 Monitor for CHF (i.e., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, etc.).

8.322 PACs or PVCs without cardiac dysfunction, e.g., acute dysrhythmias that can occur during and shortly after Adriamycin infusion, are NOT an indication to permanently stop Adriamycin.

Add 7,8

8.323 Discontinue AC when symptoms of heart failure are present and a diagnosis of CHF is confirmed. TAXOL may be initiated at the discretion of the investigator. HERCEP will not be permitted in these instances.

Add 11,12

8.3231 Follow-up at 3, 6, and 12 months from time of CHF diagnosis: hemoglobin, serum troponin I, document medications being taken for CHF, and MUGA/echocardiogram – optional 12-month stress MUGA or stress echocardiogram.

Add 7,8

8.324 Discontinue AC if myocardial infarction while on treatment. TAXOL may be initiated at the discretion of the investigator. HERCEP will not be permitted in these instances.

8.33 Gastrointestinal

8.331 Nausea/vomiting

Add 7

8.3311 Delay AC. Prophylactic antiemetics may be given at the discretion of the investigator. The specific regimen must be recorded in the patient's medical record.

Add 7

8.33111 If ≤grade 1 within 3 weeks, give full AC dose.

Add 7

8.33112 If after a 3-week delay grade remains >1, discontinue AC and proceed with TAXOL when ≤grade 1.

8.332 Diarrhea, stomatitis/pharyngitis

Add 7

8.3321 Grade 2

Add 7

8.33211 Delay AC.

Add 7

8.332111 If ≤grade 1 within 3 weeks, give full AC dose.

Add 7

8.332112 If after a 3-week delay grade remains >1, discontinue AC and proceed with TAXOL when ≤grade 1.

Add 7 8.3322 Grade 3 or 4

Add 7 8.33221 Delay AC.

Add 7 8.332211 If after a 3-week delay grade ≤ 1, the remaining cycles of AC must be given with the following dose reductions:

8.3322111 After first episode, decrease dose to A: 50 mg/m^2 and C: 500 mg/m^2.

8.3322112 If occurs at reduced doses, decrease dose to A: 40 mg/m^2 and C: 400 mg/m^2.

Add 7 8.3322113 If occurs again, discontinue AC.

Add 7 8.332212 If after a 3-week delay grade remains >1, discontinue AC and proceed with TAXOL when ≤grade 1.

8.34 Hepatic - bilirubin, AST

8.341 ≥grade 2

Add 7 8.3411 Delay AC and determine cause.

Add 7 8.3412 If not due to metastatic disease and returns to ≤grade 2 within 3 weeks, AC should be resumed at full dose.

Add 7 8.3413 If after 3-week delay grade remains > 1, contact study chair.

Add 7 8.35 Febrile Neutropenia

8.351 Fever (≥38°C [101.3°F]) in the presence of neutropenia (ANC <1000)

8.3511 First episode: All remaining cycles will be given at full dose with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

8.3512 Second episode: All remaining cycles will be given at full dose with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

8.3513 Third episode: Remaining cycle will be dose reduced to A: 50 mg/m^2 and C: 500 mg/m^2 given with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 3 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

Add 7

8.36 Infection With/Without Neutropenia

8.361 Grade 3

8.3611 First episode: All remaining cycles at full dose with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

8.3612 Second episode: All remaining cycles will be given at A: 50 mg/m^2 and C: 500 mg/m^2 with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

8.3613 Third episode: Remaining cycle will be given at A: 40 mg/m^2 and C: 400 mg/m^2 with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next cycle(s) and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next cycle(s).

8.362 Grade 4

Add 7

8.3621 Investigator may discontinue AC.

8.3622 If treatment is to continue, follow dose reduction guidelines for grade 3.

Add 10 8.4 **TAXOL** dose modifications - Since AC and TAXOL are substantially different in toxicity and mechanisms of action, any adverse event that occurs during AC administration and resolves prior to TAXOL administration dose not require dose reduction or delay in TAXOL treatment. A patient who discontinues AC treatment due to adverse event can still proceed with TAXOL according to the protocol if AC adverse event has resolved within 3 weeks. The first TAXOL dose must occur following the post-AC MUGA scan/echocardiogram and after any AC-related adverse event has resolved. **NOTE: If AC-related adverse event has not resolved within 3 weeks, TAXOL must be omitted (Arm B & C patients – see Section 8.55).**

Add 7

8.41 Blood/Bone Marrow – based on levels on the day of scheduled treatment

Add 3 8.411 ANC <1000

8.4111 Delay TAXOL. Arm C patients continue HERCEP.

Add 5,7,8 8.4112 Check counts weekly until ANC ≥1000. Begin G-CSF or GM-CSF on day 2 and continue until ANC ≥10,000. G-CSF or GM-CSF should be discontinued at least 24 hours prior to the next dose. Check CBC beginning on day 4 or 5 of G-CSF or GM-CSF therapy.

Add 3,5,7,8 8.4113 If ANC recovers to ≥800 within 3 weeks, all remaining doses may be given with G-CSF or GM-CSF at investigator discretion. If ANC takes ≤1 week to recover to >1000, give full TAXOL dose at the next dose. If the ANC takes 1-3 weeks to recover, give TAXOL at 70 mg/m^2. If after the 3-week delay the ANC is <1000 but is ≥800, give TAXOL at 60 mg/m^2. If after the 3-week delay ANC remains <800, the patient must discontinue TAXOL.

Add 7,8 8.4114 Delay TAXOL if ANC <1000 on day 1 despite G-CSF or GM-CSF given during the previous dose.

AND/OR

8.412 PLT <75,000

Add 7 8.4121 Delay TAXOL. Arm C patients continue HERCEP. PLT transfusions and PLT colony stimulating-factor may be given at the discretion of the investigator.

8.4122 Check counts weekly until PLT ≥75,000.

Add 7 8.4123 If PLT was ≥25,000 but recovers to ≥75,000 within 3 weeks, resume TAXOL at full dose.

Add 7,8 8.4124 If PLT was <25,000 but recovers to ≥75,000 within 3 weeks, continue TAXOL at 70 mg/m^2 at the next dose.

Add 7 8.4125 If after 3-week delay PLT remains <75,000, discontinue TAXOL but continue HERCEP.

8.42 Cardiovascular

8.421 No dose modifications for cardiotoxicity.

8.422 Asymptomatic decrease in LVEF

Add 7,16

8.4221 A decline in LVEF is not expected with TAXOL. However, MUGA scans/echocardiograms must be done for Arms A, B, and C at 6, 9, and 18 months from registration and must be repeated based on Sections 8.4222 and 8.56411. It is important that these MUGA scan/echocardiogram schedules be followed since they serve as the basis for comparison of asymptomatic LVEF drop in Arms B and C. Section 8.4222 presents guidelines to be followed for repeat MUGA scans/echocardiograms for Arm A. For guidelines on performing MUGA scans/echocardiograms on Arms B and C, please see Section 8.56411.

Add 16

8.4222 Guidelines for performing repeat MUGA scan/echocardiogram for Arm A patients not receiving HERCEP who have an ***asymptomatic*** decrease in LVEF from baseline.

Asymptomatic decrease in LVEF percentage points from baseline			
Relationship of LVEF to the radiology facility's LLN	**Decrease of <10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥16 percentage points**
Within radiology facility's normal limits			Repeat MUGA/echocardiogram after 4 weeks
1 to 5 percentage points below the radiology facility's LLN	Repeat MUGA/echocardiogram after 4 weeks	Repeat MUGA/echocardiogram after 4 weeks	Repeat MUGA/echocardiogram after 4 weeks
≥6 percentage points below the radiology facility's LLN	Repeat MUGA/echocardiogram after 4 weeks	Repeat MUGA/echocardiogram after 4 weeks	Repeat MUGA/echocardiogram after 4 weeks

Add 7

Additional MUGA scans/echocardiograms following a repeat MUGA/echocardiogram and prior to the next scheduled MUGA scan/echocardiogram may be performed at the discretion of the investigator.

Add 7

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

8.423 Symptomatic decrease in LVEF

Add 11

8.4231 If symptomatic congestive heart failure (CHF) occurs at a time when the patient is still taking TAXOL, resumption of TAXOL is at the discretion of the investigator. The investigator must confirm a diagnosis of CHF either with a MUGA scan/echocardiogram or echocardiogram. A chest x-ray is also required. All reports must be faxed with the appropriate MUGA/echocardiogram reporting form to the NCCTG Operations Office within 14 days of the MUGA scan/echocardiogram. Any diagnosis of CHF (regardless of when it occurs) must be reported using the congestive heart failure reporting form.

Add 11,12

8.4232 Follow-up at 3, 6, and 12 months from time of CHF diagnosis: hemoglobin, serum troponin I, document medications being taken for CHF, and MUGA/echocardiogram – optional 12-month stress MUGA or stress echocardiogram.

8.424 Arrhythmia

8.4241 Asymptomatic, not requiring treatment

8.42411 Interrupt or slow infusion.

Add 8

8.42412 Subsequent infusion for that dose and future doses should be done under continuous cardiac monitoring.

8.4242 Symptomatic, not requiring treatment

8.42421 Hold and conduct cardiac evaluation.

8.42422 Resume at discretion of the investigator.

Add 7

8.4243 Symptomatic, requiring treatment or life-threatening

8.42431 Discontinue TAXOL.

Add 12

8.425 Myocardial infarction

Discontinue treatment.

8.43 Gastrointestinal

8.431 Nausea/vomiting

Add 7

8.4311 Delay TAXOL. Arm C patients continue HERCEP. Prophylactic antiemetics should be used at the discretion of the investigator. The specific regimen must be recorded in the patient's medical record.

Add 7

8.4312 If grade returns to ≤1, continue TAXOL. If after a 3-week delay grade >1, discontinue TAXOL.

8.432 Diarrhea, stomatitis/pharyngitis

Add 7

8.4321 Grade 2

Add 7

8.43211 Delay TAXOL. Arm C patients continue HERCEP.

Add 7

8.43212 If grade returns to ≤1, continue TAXOL. If after a 3-week delay grade >1, discontinue TAXOL.

8.4322 Grade 3

Add 7

8.43221 Delay TAXOL. Arm C patients continue HERCEP.

Add 7

8.43222 If grade returns to ≤1within 3 weeks, continue TAXOL at 70 mg/m^2. If grade 3 occurs at 70 mg/m^2, decrease TAXOL dose to 60 mg/m^2. If grade 3 occurs again at 60 mg/m^2, discontinue TAXOL.

Add 7

8.43223 If after a 3-week delay grade >1, discontinue TAXOL.

8.4323 Grade 4

Add 7

8.43231 Discontinue TAXOL. Arm C patients continue HERCEP.

8.44 Hepatic

Add 7

8.441 Because the plasma clearance of TAXOL is reduced in patients with hepatic impairment, careful evaluation of liver enzymes is necessary *before* the administration of *each cycle* of TAXOL.

8.442 A rising bilirubin or AST >grade 2 should be evaluated. If the rise is not due to metastatic liver disease, the following guidelines should be followed to ensure patient safety:

8.4421 Bilirubin

8.44211 Grade 1

8.442111 No dose modifications or delays.

Add 7

8.44212 Grade 2, 3, or 4

Add 7

8.442121 Delay TAXOL. Arm C patients continue HERCEP.

Add 7

8.442122 If grade returns to ≤1 within 3 weeks, continue TAXOL at 70 mg/m^2. If grade >1 toxicity occurs at 70 mg/m^2, decrease TAXOL dose to 60 mg/m^2. If grade >1 toxicity occurs again at 60 mg/m^2, discontinue TAXOL.

Add 7

8.442123 If after the 3-week delay the toxicity has not decreased to ≤grade 1, discontinue TAXOL.

8.4422 AST

8.44221 Grade 1

8.442211 No dose modifications or delays.

Add 7 8.44222 Grade 2, 3, or 4

Add 7 8.442221 Delay TAXOL. Arm C patients continue HERCEP.

Add 7 8.442222 If grade returns to ≤ 1 within 3 weeks, continue TAXOL at 70 mg/m^2. If grade >1 toxicity occurs at 70 mg/m^2, decrease TAXOL dose to 60 mg/m^2. If grade >1 toxicity occurs again at 60 mg/m^2, discontinue TAXOL.

Add 7 8.442223 If after the 3-week delay the toxicity has not decreased to <grade 1, discontinue TAXOL.

Add 7 8.45 Febrile Neutropenia

8.451 Fever (≥38°C [101.3°F]) in the presence of neutropenia (ANC <1000)

Add 8 8.4511 First episode: All remaining doses will be given at full dose with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next dose.

Add 8 8.4512 Second episode: Remaining doses will be reduced to T: 70 mg/m^2 given with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next dose.

Add 8 8.4513 Three episodes: Remaining doses will be reduced to T: 60 mg/m^2 given with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next doses.

8.4514 More than three episodes: Contact study PI.

Add 7

8.46 Infection With/Without Neutropenia

8.461 Grade 3

Add 8

8.4611 First episode: All remaining doses at full dose with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next dose.

Add 8

8.4612 Second episode: All remaining doses will be given at T: 70 mg/m^2 with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next dose.

Add 8

8.4613 Three episodes: Remaining doses will be given at T: 60 mg/m^2 with G-CSF or GM-CSF and ciprofloxacin hydrochloride (500 mg po bid) or antibiotic of choice. G-CSF or GM-CSF will be given beginning on day 2 of the next dose and continued until ANC ≥10,000. Ciprofloxacin hydrochloride or antibiotic will be given for at least 7 days starting on day 5 of the next dose.

8.4614 More than three episodes: Contact study PI.

8.462 Grade 4

Add 7

8.4621 Investigator may discontinue TAXOL.

8.4622 If treatment is to continue, follow dose reduction guidelines for grade 3.

8.47 Neurology - neuropathy motor and sensory

Add 7

8.471 Grade 2 or 3

Add 7

8.4711 Delay TAXOL. Arm C patients continue HERCEP.

Add 7

8.4712 If grade returns to ≤1 within 3 weeks, continue TAXOL at 70 mg/m^2. If grade >1 toxicity occurs at 70 mg/m^2, decrease TAXOL dose to 60 mg/m^2. If grade >1 toxicity occurs again at 60 mg/m^2, discontinue TAXOL.

Add 7

8.4713 If after the 3-week delay the toxicity has not decreased to ≤grade 1, discontinue TAXOL.

8.472 Grade 4

Add 7

8.4721 Discontinue TAXOL. Arm C patients continue with HERCEP.

8.48 Pain - Arthralgia and myalgia

Add 7

8.481 Grade 2

Add 7

8.4811 Delay TAXOL. Arm C patients continue HERCEP. 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.

Add 7

8.4812 If grade returns to ≤1 within 3 weeks, continue TAXOL.

Add 7

8.4813 If after the 3-week delay toxicity has not decreased to ≤grade 1, discontinue TAXOL.

8.482 Grade 3 or 4

Add 7

8.4821 Delay TAXOL. Arm C patients continue HERCEP. Administer prophylactic steroids as described for grade 1 or 2.

Add 7

8.4822 If grade returns to ≤1 within 3 weeks, continue TAXOL at 70 mg/m^2. If grade >1 toxicity occurs at 70 mg/m^2, decrease TAXOL dose to 60 mg/m^2 and continue prophylactic steroids. If grade >1 toxicity occurs again at 60 mg/m^2, discontinue TAXOL.

Add 7

8.4823 If after the 3-week delay the toxicity has not decreased to ≤grade 1, discontinue TAXOL.

8.49a Allergy/Immunology

8.49a1 No dose modifications.

8.49a2 Grade 3 or 4

Add 7

8.49a21 Require immediate and permanent discontinuation of TAXOL with aggressive symptom management.

Add 5,7,8

8.5 **HERCEP** dose modifications - See Appendix IV The start of HERCEP cannot be delayed more than 3-4 weeks.

8.51 No cardioprotective drugs are permitted. The mechanism that underlies the cardiotoxicity observed with HERCEP is unknown. In addition, there are no data about the use of cardioprotective agents such as dexrazoxane (Zinecard®).

8.52 ***No dose modifications***.

Add 7,16

8.53 Must be discontinued if more than 3 consecutive weeks (or a total of 6 weeks) (except when those missed doses are associated with a Hold and Repeat per Section 8.56411) have been missed.

8.54 Infusion-associated symptoms

8.541 During the first infusion, a symptom complex of fever and/or chills may occur. These are usually mild-to-moderate and may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These symptoms occur infrequently during subsequent infusions. Treat fever and chills as stated in Sections 8.57 and 8.58. Management of other symptoms is at the physician's discretion.

8.55 HERCEP when TAXOL is delayed or discontinued

Add 7

8.551 If TAXOL is delayed or discontinued for any reason *other than cardiotoxicity or severe hypersensitivity reactions that occurred when both TAXOL and HERCEP were administered,* HERCEP may continue.

8.56 Considerations regarding cardiac dysfunction and HERCEP administration.

8.561 Initiation of HERCEP will depend on review of the post-AC MUGA scan/echocardiogram results.

Add 5

8.562 If HERCEP is initiated, a decision about whether to continue or discontinue must occur after the completion of all chemotherapy and while the patient is on HERCEP alone (see Appendix IV). Two goals must be considered in evaluating the benefits and risks of continuing HERCEP after chemotherapy is completed: 1) the protection of patients from serious myocardial adverse event and 2) the ability to assess the potential benefit of continuing HERCEP in patients with node-positive, HER2-positive breast cancer.

Add 10

8.563 In the sections that follow, definitions of a cardiac adverse event to be used when making treatment decisions are outlined. The descriptions of left ventricular dysfunction are similar, but not exactly the same, as the definition of a cardiac adverse event as defined by the CTC. Institutions will be required to report a cardiac adverse event on the Adverse Event Form according to the CTC guidelines. However, treatment should follow the directions outlined in the protocol.

Add 7

8.564 The baseline MUGA scan/echocardiogram is the LVEF measured at registration prior to receiving AC therapy. Individual patients should have their MUGA scans/echocardiograms performed at the same radiology facility to eliminate variability between facilities.

8.5641 Asymptomatic decrease in LVEF

8.56411 Decision to continue or stop is based on:
measured ejection fraction as it relates to the radiology facility's LLN **and** change in ejection fraction from baseline. Guidelines for performing MUGA scan/echocardiogram and management of HERCEP patients who have an ***asymptomatic*** decrease in LVEF from baseline are in the table below:

Add 5,10

Asymptomatic decrease in LVEF percentage points from baseline			
Relationship of LVEF to the radiology facility's LLN	**Decrease of <10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥16 percentage points**
Within normal limits	Continue	Continue	Hold and repeat MUGA/echocardiogram after 4 weeks
1 to 5 percentage points below the LLN	Continue and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks
≥6 percentage points below the LLN	Continue and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks[2]	Hold and repeat MUGA/echocardiogram after 4 weeks[2]

Add 8

Add 7

Add 5 NOTE 1: See Appendix IV for examples of treatment decisions for asymptomatic patients with decreased LVEF.

NOTE 2: If HERCEP is held or discontinued during therapy with TAXOL, TAXOL may be continued at the discretion of the investigator.

Add 5 NOTE 3: If HERCEP is not started or discontinued during therapy, MUGA scan/echocardiogram still needs to be done at 6, 9, and 18 months.

NOTE 4: Rules for interpreting and applying "repeat" MUGA scan/echocardiogram results

- HERCEP must be permanently discontinued when two consecutive "hold" categories occur.
- HERCEP must be permanently discontinued when three intermittent "hold" categories occur. (At the discretion of the investigator, HERCEP may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.)

- If LVEF is maintained at a "continue and repeat MUGA/echocardiogram" or improves from a "hold" to a "continue and repeat MUGA/echocardiogram" category, additional MUGA scans/echocardiogram prior to the next scheduled MUGA scan/echocardiogram will be at the discretion of the investigator.

8.565 Symptomatic decrease in LVEF

8.5651 Grade 3 CHF

8.56511 Monitor for signs and symptoms of CHF (i.e., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.).

8.56512 If patient develops these signs and symptoms, hold treatment.

8.56513 If CHF occurs while on TAXOL plus HERCEP, resumption of TAXOL is at the discretion of the investigator.

8.56514 Confirm diagnosis of CHF either with a MUGA scan/echocardiogram. A chest x-ray is also required. Once CHF diagnosis is confirmed, HERCEP must be permanently discontinued and all reports must be faxed with the Congestive Heart Failure Report Form to the NCCTG Operations Office within 14 days of the MUGA scan/echocardiogram.

Add 11

Add 11,12

8.56515 Follow-up at 3, 6, and 12 months from time of CHF diagnosis: hemoglobin, serum troponin I, document medications being taken for CHF, and MUGA/echocardiogram – optional 12-month stress MUGA or stress echocardiogram.

8.5652 Grade 4 (severe refractory CHF or requiring intubation)

8.56521 Discontinue treatment and submit Congestive Heart Failure Report Form.

Add 11,12

8.56522 Follow-up at 3, 6, and 12 months from time of CHF diagnosis: hemoglobin, serum troponin I, document medications being taken for CHF, and MUGA/echocardiogram – optional 12-month stress MUGA or stress echocardiogram will be done as follow-up for CHF diagnosis.

8.566 Ischemia

8.5661 Grade 1

8.56611 Continue treatment with frequent monitoring.

8.5662 Grade 2

8.56621 Hold treatment and conduct cardiac evaluation.

8.56622 Based on this evaluation, treatment may be continued at the discretion of the investigator.

8.5663 Grade 3 or 4

Add 7

8.56631 Discontinue treatment.

8.567 Arrhythmia

8.5671 Grade 1

8.56711 Continue treatment with careful monitoring OR hold treatment (and TAXOL if patient is receiving TAXOL) and conduct cardiac evaluation.

8.56712 Based on cardiac evaluation, treatment with HERCEP and TAXOL or HERCEP alone may continue or discontinue at the discretion of the investigator.

8.56713 If HERCEP is discontinued, TAXOL may also be discontinued at the discretion of the investigator.

8.5672 Grade 2

8.56721 Hold treatment (and TAXOL if patient is receiving TAXOL) and conduct cardiac evaluation.

8.56722 Based on cardiac evaluation, treatment with HERCEP and TAXOL or HERCEP alone may continue or discontinue at the discretion of the investigator.

8.56722 If HERCEP is discontinued, TAXOL may also be discontinued at the discretion of the investigator.

Add 7

8.5673 Grade 3 or 4

8.56731 Discontinue HERCEP.

8.56732 TAXOL is not permitted.

Add 12

8.568 Myocardial infarction

Discontinue treatment.

8.57 Fever

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

8.5711 Stop infusion and give antipyretics. Once temperature is <38°C, resume infusion at a slower rate.

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

Add 7

8.5721 Stop infusion immediately and give antipyretics.

8.5722 Monitor patient for minimum of 1 hour.

8.5723 If temperature drops to <38°C within 3 hours, resume infusion at a slower rate.

8.5724 If fever does not resolve within 3 hours, inpatient monitoring is strongly recommended.

Add 7 8.57241 If temperature drops to <38°C within 3 days, re-challenge at a slower rate.

Add 7 8.57242 If temperature remains >38°C after 3 days, abandon this administration and subsequent administration is at discretion of investigator.

8.58 Chills

8.581 Treat with actaminophen and/or diphenhydramine hydrochloride. Meperidine may be given at the investigator's discretion.

8.59a Gastrointestinal

8.59a1 Diarrhea

Add 7 8.59a11 Any grade

Antidiarrheal medication may be given at investigator's discretion.

8.59b Allergy/Immunology

8.59b1 Allergic reaction/hypersensitivity (including drug fever)

8.59b11 Any grade

Add 7

Add 7 8.59b111 Stop the infusion and give diphenhydramine hydrochloride.

Add 7,8 8.59b112 If toxicity resolves within 3 hours, treatment in next dose is allowed at a slower rate and under close observation.

Add 7.8 8.59b113 If toxicity does not resolve in 3 hours, overnight observation is recommended and treatment in next dose under close observation is at discretion of investigator.

Add 15 8.59c Pulmonary

Any (e.g., Adult Respiratory Distress Syndrome [ARDS], pneumonitis/pulmonary infiltrates, etc)

Delay trastuzumab until cause is known. If pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to trastuzumab cannot be excluded), trastuzumab must be permanently discontinued.

Add 8

8.6 **TAM or aromatase inhibitors** dose modifications

8.61 ***No dose modifications.***

8.62 Temporary discontinuation will be instituted in case of the following:

8.621 Blood/Bone Marrow

8.6211 Significant toxicity (leukopenia, granulocytopenia, thrombocytopenia)

Add 8

8.62111 Occurring at any time subsequent to the completion of the last dose of all chemotherapy, testing should be repeated to ensure accuracy.

8.62112 If values confirmed, discontinue for at least 4 weeks.

8.62113 Carefully evaluate for other potential causes, including metastatic disease.

8.62114 Repeat test at monthly intervals or more frequently depending on the severity of the abnormality noted.

8.62115 When return to acceptable level, therapy may resume.

8.62116 Follow-up testing will be done 1 month after resuming therapy, or sooner if indicated, to ensure that no further toxicity occurs.

8.62117 If toxicity returns, permanently discontinue therapy.

8.622 Hepatic toxicity

8.6221 ≥grade 2 elevation of AST

Add 8

8.62211 Occurring at any time subsequent to the completion of the last dose of all chemotherapy, the test should be repeated to ensure accuracy.

8.62212 If value confirmed, discontinue for at least 4 weeks.

8.62213 Carefully evaluate for other potential causes, including metastatic disease.

8.62214 Repeat test at monthly intervals or more frequently depending on the severity of the abnormality noted.

8.62215 When returns to ≤grade 1, therapy may resume.

8.62216 Follow-up testing will be done 1 month after resuming therapy, or sooner if indicated, to ensure that no further toxicity occurs.

8.6222 Grade 3 or 4

Add 8

8.62221 When unequivocally related to anti-estrogen therapy, decision to retreat after toxicity returns to ≤grade 1 must be done only after careful deliberation.

8.62222 If toxicity returns, permanently discontinue therapy.

8.623 Other

8.6231 Deep venous thrombosis, pulmonary embolism, etc.

8.6232 May be discontinued permanently only after discussing with study chair.

8.624 Hot flashes

8.6241 Vitamin E, clonidine, venlafaxine hydrochloride, fluoxetine, or phenobarbital/ergotamine tartrate/belladonna (Bellergal-S®) is permitted.

8.6242 Other non-hormonal therapies may be used at investigator's discretion.

8.6243 Megestrol acetate may be used for no greater than 2 months; it use must be documented on the patient's medical record.

8.6244 Other hormonal therapies are not permitted.

8.625 Vaginal discharge

8.6251 Patients should report unusual discharge so infection can be ruled out.

8.6252 In absence of pathogens, no treatment is indicated.

8.626 Menstrual irregularities, postmenopausal bleeding, and/or pelvic pain or pressure

8.6261 If postmenopausal bleeding, require immediate clinical examination and testing for women with a uterus.

9.0 Ancillary Treatment

9.1 It is anticipated that nausea and vomiting may be a significant side effect of the treatment regimen. Therefore, the following combination regimen may be used: Dexamethasone, 10-20 mg IV, plus a 5-HT_3 receptor antagonist prior to AC chemotherapy. Prochlorperazine or another antiemetic at the physician's discretion may be used before weekly paclitaxel treatment.

9.2 All supportive care measures for optimal medical care will be given during the period of study.

9.3 No cardioprotective drugs are permitted.

10.0 Adverse Event Reporting and Monitoring

Add 7,13 10.1 The appropriate MUGA/echocardiogram reporting form must be faxed to N9831 QCS at 507/538-0962 ≤14 days whenever one or more of the following circumstances applies to a patient in either treatment group.

Add 7 10.11 Congestive heart failure – Complete Congestive Heart Failure Report Form

10.12 Probable (sudden deaths without documented etiology) and definite cardiac deaths (due to CHF, myocardial infarct [MI], or documented primary arrhythmia) – Complete Cardiac Death Report Form

10.13 MUGA/echocardiograms

10.131 3-week post-AC
Complete 3-Week Post-AC MUGA/echocardiogram Report Form

Add 7 ~~10.132 Arm A~~
~~6 months, 9 months, 18 months after registration – Complete MUGA/Echocardiogram Report Form~~

Add 7 ~~10.133 Arms B & C~~
~~6 months and 9 months after registration, and 3 month after last delivered dose of HERCEP – Complete MUGA/Echocardiogram Report Form~~

Add 16 10.132 Complete MUGA/Echocardiogram Report Form as indicated in the table below.

Post Registration Schedule	**For Arm A patients who are not eligible to receive trastuzumab or chose not to receive trastuzumab**	**For Arm A patients who chose receive trastuzumab**	**For Arm B patients who chose receive trastuzumab in combination with paclitaxel**	**Arm B where trastuzumab is given sequentially and Arm C**
1	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose
2	6 months from registration	1 month prior to the start of trastuzumab	1 month prior to the start of trastuzumab	3 months after the start of trastuzumab
Add 17 3	9 months from registration	3 months after the start of trastuzumab	3 months after the start of trastuzumab	6 months after the start of trastuzumab
4	18 months from registration	6 months after the start of trastuzumab	6 months after the start of trastuzumab	3 months after last dose of trastuzumab
5		9 months after the start of trastuzumab	9 months after the start of trastuzumab	
6		15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	

10.14 Repeat MUGA/echocardiograms – Complete Repeat MUGA/Echocardiogram Report Form

10.2 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for adverse event monitoring and reporting. The CTC version 2.0 can be accessed from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

Add 4

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTC. Next, determine whether the event is expected or unexpected (see Section 10.22) and if the adverse event is related to the medical treatment or procedure (see Section 10.23). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). **Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).**

Add 10

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB) **according to local IRB's policies and procedures**.

10.22 Expected vs. Unexpected Events

Agent(s) under a CTEP IND:

- Expected AEs for expedited reporting purposes are listed on the CTEP Agent Specific Adverse Event List (ASAEL), a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). To access the CAEPR for an agent under a CTEP IND, contact the AdEERS MD Help Desk at adeersmd@tech-res.com.
- Unexpected AEs are those not listed in the ASAEL.

Other agents:

- The determination of whether an AE is expected is based on available sources including the package insert, the Investigator's Brochure, or the protocol (including the model consent form).
- Unexpected AEs are those not listed on the available sources, including the package insert, the Investigator's Brochure, or the protocol (including the model consent form).

Add 17

10.23 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.24 Additional instructions for trials that include both investigational agent(s) (those under an IND) and a commercial agent(s):

- When an investigational agent (an agent under an IND) is used in combination with a commercial agent(s) on the same treatment arm, the combination is considered investigational. Expedited reporting will follow the requirements for investigational agents. However, if the event occurs prior to the participant having received any investigational agent, expedited reporting may follow the requirements for commercial agents.
- When a study includes an investigational agent(s) and a commercial agent(s) on separate treatment arms:
  - If the event is specifically associated with the treatment arm that includes an investigational agent(s), expedited reporting follows the requirements for investigational agents.
  - If the event is associated with a treatment arm containing only commercial agent(s), expedited reporting follows the requirements for commercial agents.

10.25 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

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND 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 7 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.

Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."

March 2005

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 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days 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.

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

- In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (available on the CTEP Home Page at http://ctep.cancer.gov). Refer to CTEP, NCI Guidelines: Adverse Event Reporting Requirements for back-up submission instructions. When internet connectivity is interrupted, a 24-hour notification is made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification that is called in, must be entered into electronic AdEERS by the original submitter of the report at the site.
- Refer to Section 10.22 of this protocol for additional expedited reporting requirements.

10.26 Expedited Reporting Requirements for Commercial Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE[1]
Submit a full expedited report via AdEERS within 7 working days[2]	X	X

1. Any increased incidence of a known AE (as reported in the package insert or the literature), including adverse events resulting from a drug overdose.
2. In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (accessible from the CTEP Home Page at http://ctep.cancer.gov). Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for back-up submission instructions.

10.28 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Any Cardiac Toxicity >Grade 1	Submit NCI Cooperative Group Adjuvant Breast Cancer Rapid Cardiac Toxicity Notification Form to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. Note: If AdEERS report was submitted for the event, this form does not need to be submitted
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment. Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.

10.281 NOTE: The Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form is not being used for this study

10.3 ECOG institutions

Add 8,11

All ECOG investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the NCCTG reporting guidelines in Section 10.0. Both 24-hour and written/electronic adverse event reports should be made directly to the NCCTG according to the instructions in that section.

Add 10

Add 10

Reporting of AML/MDS

	NCI/CTEP Secondary AML/MDS Report Form[1]
AML/MDS	X

[1] To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and NCCTG accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

ECOG Telephone Number: (617) 632-3610
ECOG FAX Number: (617) 632-2990
ECOG Mailing Address:
ECOG Coordinating Center
FSTRF
ATTN: Adverse Event
900 Commonwealth Avenue
Boston, MA 02215

Add 7,10

NCI Fax Number: (301) 230-0159
NCI Mailing Address:
Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

NCCTG Fax Number: (507) 538-0962
NCCTG Mailing Address:
200 First Street SW
Rochester, MN 55905

10.4 CALGB institutions:

Add 4

All CALGB investigators are responsible for reporting of adverse drug reactions according to the NCI guidelines. CALGB participants should employ definitions of adverse events as provided by NCCTG's reporting guidelines in Sections 10.21 and 10.22. Adverse reactions, both written and telephone reports, **should be made directly to NCCTG** according to the instructions in those sections.

10.5 SWOG institutions:

Add 7

In addition to following the adverse event reporting guidelines required by NCCTG in Section 10.2 above, Southwest Oncology Group investigators must contact the Southwest Oncology Group SAE Program within 24 hours of the event at 210-677-8808. Copies of supporting data (pre-study forms, treatment and toxicity forms from pre-study through the event, and documentation of IRB notification) must be submitted within 10 working days to:

SAE Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217

Add 14,16

10.6 Serious Adverse Event (SAE) Reporting for NCIC CTG institutions

a. Investigator Reporting Responsibilities to NCIC CTG:

All NCIC CTG investigators are responsible for reporting adverse events according to the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 2.0. A copy of the CTCAE version 2.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 2.0

NCIC CTG participants should employ the definitions of adverse events provided by the NCCTG guidelines in section 10.0 of this protocol. Both 24-hour and written/electronic adverse event reports should be made directly to the NCCTG according to the instruction in Section 10.0.

Information regarding the use of AdEERS can be found at:
http://ctep.cancer.gov/reporting/adeers.html.

b. NCIC CTG Reporting Responsibilities:

The NCIC CTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e., events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

Add 17

c. Investigator Responsibility for Reporting Serious Adverse Events to Local Research Ethics Boards:

Investigators will be notified directly by NCCTG of all SAEs from this trial. NCIC CTG will not be involved in distributing these reports to NCIC CTG investigators. Investigators must notify their local Research Ethics Boards (REBs) of all reports received and documentation from the REB acknowledging receipt of these reportable adverse events must be kept on file in the centre along with the SAE report.

In addition, all expedited adverse events occurring within a centre should be reported to local REBs.

Add 4,14 10.7 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Toxicity Criteria (CTC) Version 2.0 grading unless otherwise stated:

Add 10

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)		X
Cardiovascular	Cardiac left ventricular function	X	X
Add 1 Constitutional symptoms	Fatigue (lethargy, malaise, asthenia)	X	X
Dermatology/Skin	Nail changes	X	X
Gastrointestinal	# stools per day	X	
	Diarrhea		X
	Nausea		X
	Stomatitis/pharyngitis (oral/pharyngeal mucositis)		X
	Vomiting		X
Infection/Febrile Neutropenia	Febrile neutropenia		X
	Infection		X
Neurology	Neuropathy - motor	X	X
	Neuropathy - sensory	X	X
Pain	Arthralgia (joint pain)	X	X
	Myalgia (muscle pain)	X	X
Add 4,7 Hepatic	Bilirubin	X	X

Add 16 10.71 The NCCTG Routine AE Data Submission Policy does not apply, as this study does not collect AE attribution. Submit Grade 2 or greater AEs to the NCCTG Research Base via the Nadir/AE Log when AEs experienced by the patient are not specified in Section 10.3.

Add 16 10.72 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation - Definition and Documentation of Breast Cancer Recurrence and Second Primary Cancers

At the time of reevaluation, patients will be classified in the following manner:

- No evidence of disease (NED).

- Breast cancer recurrence (REC). Local/regional breast cancer recurrence is defined as the development of tumor (except LCIS) in the ipsilateral breast (after lumpectomy); in the soft tissue/chest wall and/or skin of the ipsilateral chest wall; or tumor in the ipsilateral internal mammary, infraclavicular, or axillary nodes or soft tissue of ipsilateral axilla. Suspected tumor recurrence in the ipsilateral breast, chest wall structures or lower (level I ± II) axillary nodal areas must be confirmed by biopsy or cytology. Histologic or cytologic confirmation of tumor is recommended for internal mammary or infraclavicular/high axillary nodal recurrence. A distant recurrence is defined as development of tumor in areas other than the local/regional area that is documented by a positive cytology aspirate, biopsy, or imaging studies.

Add 3

- New primary (NEWP): A new primary is defined as the development of contralateral breast cancer or a second cancer other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix or LCIS of the breast that is histologically confirmed.

Further treatment after the documentation of a breast cancer recurrence or second primary cancer is left to the discretion of the treating physician.

12.0 Descriptive Factors

12.1 Menopausal status:

Premenopausal: <6 months since last menstrual period and no prior bilateral oophorectomy and not on estrogen replacement vs.

Postmenopausal: Prior bilateral oophorectomy OR >12 months since last menstrual period with no prior hysterectomy vs.

Other 1: Above categories not applicable for women age <50 vs.

Other 2: Above categories not applicable for women age ≥50.

12.2 Surgery/radiation therapy: Lumpectomy + breast irradiation vs. lumpectomy + breast irradiation + regional irradiation vs. mastectomy without irradiation vs. mastectomy with irradiation.

13.0 Treatment/ Follow-up Decision at Evaluation of Patient

Add 7

13.1 All patients who start AC must submit tumor specimens (as outline in Section 17.0) for central review of HER-2.

13.2 Patients who have not recurred or developed a second primary may continue treatment according to the schema unless excessive toxicity occurs.

Add 7,10

13.3 Patients who recur or develop a second primary cancer other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast as defined in Section 11.0 will be removed from the treatment phase and will go to yearly event monitoring.

13.4 Patients who require a treatment delay of >3 weeks will go to observation, except during the trastuzumab alone phase where there is the potential need for omission of trastuzumab due to factors such as illness and/or vacation. If more than 3 consecutive weekly doses or a total of 6 weekly doses have been omitted (except when those missed doses are associated with a Hold and Repeat per Section 8.56411), the patient is required to go to observation. *The protocol-specified schedule for obtaining MUGA scans/echocardiograms should be followed if the patient goes to observation.*

Add 7,10

13.5 If patient refuses to continue on study prior to or at completion of AC (regardless of central testing results), the patient will go to yearly event monitoring.

Add 7,10

13.6 If a patient refuses to continue on study, having started their post AC treatment, the patient will go to yearly event monitoring. The cardiac test schedule should be followed.

Add 7

13.7 If a patient has registered onto the study and then refuses to participate and did not receive any AC, the patient will be declared a cancellation by the NCCTG Operations Office. Only on study material needs to be submitted.

Add 8,10,12

13.8 If a patient has registered onto the study and is found to be ineligible or cancel per central path review, all data up to the time of ineligibility/cancellation, and yearly event monitoring and type of adjuvant therapy following declaration of ineligibility or cancellation must be completed. If the patient started post AC treatment, the cardiac schedule should be followed.

14.0 Pharmacologic Studies

14.1 Evaluation of soluble HER-1 (sHER-1) and HER-2 (sHER-2) receptors

14.11 The prognostic significance of sHER-2 serum values in the outcome of breast cancer patients is controversial with some studies documenting that high levels of sHER-2 are an indicator of worse outcome for patients receiving paclitaxel or doxorubicin treatment (11). The relationship of sHER-2 proteins with other members of the HER family, in terms of tumor growth and response to chemotherapy, also deserves

special attention. Recent work in the laboratory of Dr. Nita Maihle has resulted in the identification and characterization of two novel transcripts encoding sHER-1 isoforms (19). Further studies to evaluate the potential relationship of tissue or serum sHER-1 and sHER-2 levels are warranted in view of the potential significance for future patient care.

14.12 Research in Dr. Maihle's laboratory has resulted in the development of an Acridinium-Linked ImmunoSorbent Assay (ALISA) to detect sHER-1 proteins in body fluids (20). A study using this ALISA on a set of serum samples from patients with advanced epithelial ovarian cancer (Stage III/IV) yielded the following results (21). Serum sHER-1 levels in patients with stage III or IV epithelial ovarian cancer are significantly lower prior to ($P < 0.0001$) and shortly after ($P < 0.0001$) cytoreductive staging laparotomy than in healthy women of similar ages. It is noteworthy that the range of preoperative serum sHER-1 levels in the advanced stage ovarian cancer patients barely overlapped with the range of serum sHER-1 levels in the healthy women. Moreover, serum sHER-1 levels increased to levels seen in healthy women for many of the ovarian cancer patients who were surgically debulked of tumor and who provided a second serum sample during the course of combination chemotherapy. These date suggest that serum sHER-1 isoforms are not synthesized by epithelial ovarian tumors themselves, but rather, that these tumors affect serum sHER-1 levels. Altered and/or changing serum sHER-1 levels may, therefore, provide important diagnostic and/or prognostic information useful for the management of patients with epithelial ovarian cancer. Given these exciting findings and the common involvement of HER family members in the growth of both human breast and ovarian carcinomas, we are eager to explore the clinical utility of both sHER-1 and sHER-2 levels in breast cancer patients.

14.13 Functionally, sHER-1 molecules have been shown to bind epidermal growth factor (31-34) (Lee and Maihle, unpublished data), to inhibit the tyrosine kinase activity of the HER-1 receptor (35), and to have growth inhibitory effects *in vitro* (36-38) and *in vivo* (39-40). These observations suggest that sHER-1 molecules may suppress cellular growth in normal tissues in a dominant negative manner, and that decreased circulating and interstitial sHER-1 levels may promote cellular proliferation in hyperplastic and malignant tissues. Moreover, tumors overexpressing full-length HER receptors may further lower circulating and pericellular sHER-1 levels by the process of ligand dependent endocytosis.

14.14 We plan to address two clinically relevant questions concerning the usefulness of serum sHER-1 and sHER-2 levels as biomarkers of breast cancer. First, are pretreatment serum sHER-1 and sHER-2 levels and/or ratios useful prognostic indicators? Second, are changing serum sHER-1 and sHER-2 levels and/or ratios useful indicators of disease recurrence during adjuvant chemotherapy? We specifically predict that successful chemotherapy may be associated with higher serum sHER-1 levels and lower sHER-2 levels, because serum sHER-2 appears to be a proteolytic product of HER-2 expressing tumors (41-42) whereas sHER-1 does not appear to be a tumor product (21).

Add 14

14.15 Baseline blood samples (ECOG, CALGB, NCCTG, SWOG, NCIC CTG)

14.151 Samples should be drawn in conjunction with the required hematology groups, preferably between 7 a.m. and 8 a.m.

14.152 Enough blood will be drawn to generate approximately 10 mL of serum.

Add 19

14.153 Blood samples will be processed into serum by participating institutions. Serum samples will be transferred to individual collection tubes and frozen to -20°C within 4 hours. All serum samples will be sent to Biospecimen Accessioning and Processing (BAP) on dry ice within 24 hours. BAP Recieving will deliver the serum samples to the NCCTG Biospecimen Resource laboratory, directed by Dr. Wilma Lingle (Mayo Clinic Rochester, Stabile 13-10A-Brenda Booth, NCCTG Biospecimen Coordinator), within 2 hours of receipt; the samples will be transferred to -70°C storage immediately. These stringent steps are absolutely essential to ensure that serum protein degradation does not occur. The sample will be banked in the NCCTG Biospecimen Resource laboratory for future studies.

Add 3,10,11

14.16 Three-month and 6-month draws (NCCTG only)

14.161 Samples should be drawn in conjunction with the required hematology groups, preferably between 7 a.m. and 8 a.m.

14.162 Blood samples will be drawn at 3-month intervals for the first year and at 6-month intervals for years 2 through 5 for 35 patients per treatment arm for a total of 105 patients (**accrual has been met**). Enough blood will be drawn to generate approximately 10 ml of serum.

Add 8

Add 19

14.163 Blood samples will be processed into serum by NCCTG participants. Serum samples will be transferred to individual collection tubes and frozen to -20°C within 4 hours. All serum samples will be sent to BAP on dry ice within 24 hours. BAP will deliver the serum samples to the NCCTG Biospecimen Resource laboratory, directed by Dr. W. Lingle (Mayo Clinic Rochester, Stabile 13-10A-Brenda Booth, NCCTG Biospecimen Coordinator), within 2 hours of receipt; the samples will be transferred to -70°C storage immediately. These stringent steps are absolutely essential to ensure that serum protein degradation does not occur. The sample will be banked in the NCCTG Biospecimen Resource laboratory for future studies.

Add 3,10,11

Add 11,13

14.2 At time of first breast cancer recurrence

14.21 Serum must be collected at the time of first breast cancer recurrence (see Section 11.0). This sample will be banked for future research purposes. In the future, we plan to evaluate proteins such as soluble HER2 receptor, which could be important to understand the biology of breast cancer. Additionally, other serum markers which correlate with tumor relapse and patient outcome will be evaluated, based on state of the art scientific knowledge. For now, the samples will be stored until a formal protocol is developed.

14.22 Enough blood will be drawn to generate approximately 10 mL of serum.

Add 13

14.3 Blood collection schedule for cardiac markers (55 patients per arm [total 165] who have been enrolled since activation of Addendum 13 and have provided consent)

14.31 Blood is to be collected to have optional serum and plasma markers ***at the following time points.***

14.311 ***All patients enrolled in the translational cardiac biomarker component***

(1) First blood draw is to be taken after registration, but before chemotherapy, at the same time as the N9831 blood collection; and if possible, on the same day as the start of AC (before the infusion of chemotherapy).

(2) Second blood draw is to be taken within 1 hour of completion of the 1st or 2nd dose of AC infusion.

(3) Third blood draw is to be taken within 1 hour of completion of the 1st or 2nd dose of their post AC treatment (either paclitaxel alone or paclitaxel plus trastuzumab).

Note: Some patients randomized to Arm C may not be able to receive trastuzumab due to post AC decrease in LVEF. A blood draw should still be done at this time.

Add 16

(4) Fourth blood draw for patients on *any* arm who are not prohibited from receiving trastuzumab due to decreases in LVEF and choose to receive trastuzumab.

This blood draw is to be taken within 1 hour of completion of the 1st or 2nd dose of trastuzumab.

Please contact N9831 QCS if questions arise.

If a patient participating in this portion of the study develops congestive heart failure (CHF) at any time while participating in N9831, a one-time blood draw will be requested in order to study the same serum and plasma markers as noted in Section 14.32.

14.32 Serum and plasma cardiac markers to be evaluated are:

14.321 Serum parameters

- Troponin-T (TnT)
- Troponin-I (TnI)
- Tumor necrosis factor- alpha (TNF-α)
- Interleukin-1 beta (IL-1β)
- Interleukin-6 (IL-6)
- CRP
- CD40 ligand

14.321 Plasma parameter

- Brain natriuretic peptide (BNP)

Add 13 14.4 Supplies

Add 19 14.41 Kits will be supplied through BAP. Participating institutions may obtain kits by faxing the BAP Supply Order Form (found in the Forms Packet) to 507/538-1403. **Allow at least two weeks to receive the kits. BAP will <u>not</u> be able to forward kits to you by express mail.**

14.42 **<u>ALL</u>** sections of the form/specimen collection labels <u>must</u> be completed.

14.43 All samples should be sent **Monday-Thursday ONLY** to address indicated on the provided Fed Ex mailing label.

Add 19 14.43 **<u>NOTE:</u>** Because we are now being charged by BAP for all outgoing kits, a **small**, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry.

.

Add 19 14.44 BAP will receive the samples and send to the appropriate laboratories.

Add 16 14.5 Blood Collection for Genetic Testing

14.51 A one time collection of a blood sample for DNA evaluation will be done for each patient enrolled in this study. DNA samples from a patient group of this size will be invaluable in cancer research and evaluation of future cancer treatments.

Add 19 14.511 The consent form accompanying this addendum also provides for this collection (see Appendix VIII), which will use blood collection kits provided by BAP.

14.512 For this sample, one 10ml EDTA tube will be collected Monday – Thursday and shipped refrigerated by overnight express.

Add 19 14.513 Each kit will contain instructions for kit use and for shipping the kit back to BAP via Federal Express.

14.514 Please do not obtain consent until there are kits available at your site. Once consent is received, kits may be administered.

Add 19 14.52 Kits will be provided through BAP.

Add 19 14.521 Participating institutions may obtain kits by faxing the BAP Kit Request Form (in the Forms Packet) to BAP as instructed on the form.

14.522 Allow at least two weeks to receive the kits. Kits will only be shipped via regular mail.

14.6 Return of Research Results

Because the results generated by the testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the results will not be disclosed to the patients or their physicians.

If, at any time, results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Doxorubicin (ADR) (Commercial)

15.11 Preparation and storage: Intact vials are stable when protected from light at room temperature. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. Note the manufacturer's expiration date for the commercial solutions. Add 5, 10, 25, 50, or 75 mL of preservative-free normal saline to the 10, 20, 50, 100, or 150 mL vial to produce a solution containing 2 mg/mL.

Add 10

15.12 Known potential adverse events: Myelosuppression can be dose-limiting. Alopecia is usually complete. Nausea and vomiting may be severe. Other GI toxicities, anaphylactic reaction, red discoloration of urine, and facial flushing may occur. Cardiovascular effects are more common with cumulative doses above 550 mg/m^2. Tissue necrosis can occur if the drug is leaked outside the vein.

15.13 Nursing guidelines:

15.131 ADR is a vesicant. Check IV patency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.

15.132 Beware of ADR flare that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction.

15.133 Monitor CBC. Observe for signs of infection, bleeding, and anemia.

15.134 Advise patient of red discoloration of urine for 24 hours after drug administration.

15.135 Assess for stomatitis and treat accordingly (may try vitamin E oil dabbed directly onto sore areas). Stomatitis generally occurs 7-10 days after drug administration, begins with a burning sensation, and advances to ulceration.

15.136 Advise patient of probable and complete alopecia 2-4 weeks after initial injection. Regrowth begins 2-3 months after treatment.

15.137 Administer antiemetics as necessary. Refer to Section 9.2.

15.138 Monitor for signs and symptoms of cardiomyopathy (dyspnea, steady weight gain, nonproductive cough, heart rate changes). Assess heart and lung sounds. Monitor vital signs, i.e. resting pulse. Calculate total cumulative dose with each administration.

15.139a Advise patient of probable facial flushing for several hours after drug administration.

15.139b Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.

15.139c Doxorubicin may potentiate toxicity of cyclophosphamide and exacerbate cyclophosphamide-induced hemorrhagic ceptitis.

15.14 Drug procurement: Commercially available.

15.2 Cyclophosphamide (CTX) (Commercial)

15.21 Preparation and storage: Tablets and injectable powder are stored at room temperature. The temperature is not to exceed 90°F. Reconstituted parenteral solutions are stable for 24 hours at room temperature or six days if refrigerated. Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 mL of sterile water, respectively, resulting in a solution of 20 mg/mL. Shake vials vigorously and warm slightly in lukewarm water to facilitate the dissolving of crystals. The lyophilized form is more easily solubilized.

Add 10

15.22 Known potential adverse events: Myelosuppression, hemorrhagic cystitis, alopecia, nausea, and vomiting are all common, SIADH is dose–related (more common with single doses >2 gm/m^2), cardiac (if dose level ≥2 gm/m^2). Liver dysfunction, headaches, dizziness, interstitial pulmonary fibrosis, cardiac necrosis may occur. Secondary leukemia, myelodysplastic syndrome and anaplylaxis are rare.

15.23 Nursing guidelines

15.231 Leukopenia nadir occurs 8-14 days after administration and recovery is usually 18-25 days. Monitor CBC.

15.232 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.

15.233 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria.

15.234 Advise patient in possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

15.235 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.

15.236 Report and record any complaint of lightheadedness, facial “heat sensation,” diaphoresis during administration.

15.237 Advise female patients of possible menstrual changes or a menorrhea.

Add 10

15.238 Advise patient of probable and complete alopecia 2-4 weeks after initial injection. Regrowth begins 2-3 months after treatment.

15.239 Corticosteroids, phenothiazine, imipramine, and allopurinol may inhibit Cytoxan metabolism and modify its effect. They may also increase bone marrow suppression.

15.24 Drug procurement: Commercially available in 25 and 50 mg tablets. Also available for injection in 100 mg, 200 mg, 500 mg, 1 gm and 2 gm vials.

15.3 Paclitaxel (TAXOL) (Commercial)

15.31 Preparation and storage: Supplied as a concentrated sterile solution, 6 mg/ml in 5 ml (30 mg) vials and 17 ml (100 mg) vials in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to use. Unopened vials of paclitaxel are stable until the date indicated on the package when stored between 2°-25°C (36°-77°F) in the original package. The intact vials are not adversely affected by freezing. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of the drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable up to 27 hours at ambient temperature (25°C) and room lighting conditions.

Paclitaxel will be prepared by diluting the total dose in 250 ml of 5% Dextrose or Normal Saline. Paclitaxel must be prepared in glass, polyolefin, or polypropylene containers and non-PVC (polyethylene-lined) tubing due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter or pore size not >0.22 microns into the IV fluid pathway distal to the infusion pump. Frequent changing of filters (e.g., every twelve hours) may be necessary because of clogging during the infusion. Solution exhibiting excessive particulate matter formation should not be used.

Add 10

15.32 Known potential adverse events: Myelosuppression; nausea and vomiting; stomatitis; mucositis, pharyngitis; typhlitis; ischemic colitis; neutropenic colitis; arrhythmia; heart block; ventricular tachycardia; myocardial infarction; bradycardia; atrial arrhythmia; hypotension; hypertension (possibly related to concomitant medication - dexamethasone); sensory (taste); peripheral neuropathy; seizures; mood changes; hepatic encephalopathy; encephalopathy; erythema, induration, tenderness, and rarely, ulceration, radiation recall, and rash associated with infiltration; acute anaphylactoid and urticarial reactions; flushing, rash and pruritus; hepatic failure; hepatic necrosis; alopecia; fatigue; arthralgia; myalgia; light-headedness; myopathy; visual abnormalities (blurred vision and a sensation of flashing lights); pneumonitis.

15.33 Nursing guidelines

15.331 Premedicate with dexamethasone, diphenhydramine, and cimetidine, ranitidine, or famotidine as per protocol.

15.332 Assess the patient frequently for the first 30 minutes. Paclitaxel hypersensitivity reactions usually occur early in the infusion. Have anaphylaxis tray available.

15.333 Instruct the patient about the importance of taking their premedications at home.

15.334 If a reaction occurs, stop the infusion. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per MD's order.

15.335 Most cardiac disturbances occur during the later hours of the infusion, are self-limiting, and abate quickly after discontinuing the infusion.

15.336 Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. salt, 1 tsp. baking soda, and 1 qt. boiled water). May also try vitamin E oil dabbed directly onto sore areas 4-6 times daily.

15.337 Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

15.338 Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy.

15.34 Drug procurement: Commercially available.

15.4 Trastuzumab (HERCEP) (Investigational) (NSC #688097, IND #6667)
(See Appendix III for Cooperative Research and Development Agreement (CRADA) requirements):

15.41 Preparation and storage: Vials of trastuzumab are shipped at room temperature by next day air and must be placed in a refrigerator 2-8°C (36-46°F) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. DO NOT FREEZE. Trastuzumab may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions. A 19-guage or larger needle should be used during drug admixture to avoid sheer-induced stress. The vials will bear an expiration date. Participating sites will be notified by any dating extensions, when lots have expired, and how to handle disposition of the agent.

Trastuzumab, manufactured by Genentech Inc., is supplied as a freeze-dried preparation at a nominal content of 440 mg per vial for parenteral administration. Investigatonal supplies labeled as 400 mg actually contain 440 mg. These supplies will be used until exhausted, at which time new lots labeled with the actual content of 440 mg will be utilized. Commercially distributed trastuzumab is labeled as 440 mg. The study drug is formulated in histidine, trehalose, and polysorbate 20. Each 440 mg vial of trastuzumab is supplied with Bacteriostatic Water for Injection (BWFI), USP (containing 1.1% benzyl alcohol). Reconstitute each vial as follows using aseptic technique: 1) Using a sterile syringe, slowly inject 20 mL of BWFI into the vial directing the stream into the lyophilized cake. The vacuum in the vial will automatically draw the water from the syringe into the vial; 2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE. The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted formulation (440 mg vial) is designed for multiple uses. Unused drug may be stored for 28 days at 2°C-8°C (36°F-46°F). Reconstituted trastuzumab should be clear to slightly opalescent and colorless to pale yellow.

Add 10

15.42 Known potential adverse events:

<u>Incidence more frequent (>5%)</u>

Infusion-associated symptoms: Chills and/or fever, occasionally accompanied by rigors, occurred in approximately 40% of patients during the first infusion of Herceptin®. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, and diphenhydramine (with or without reduction in the rate of Herceptin® infusion). Meperidine for rigors is effective. Other signs and/or symptoms may include nausea, vomiting, pain, headache, dizziness, dyspnea, rash. The symptoms occurred less frequently with subsequent infusions. Rarely, infusion reactions have resulted in death.

Herceptin® administration can result in the development of Ventricular Dysfunction and CHF. Left ventricular function should be evaluated in all patients prior to and during treatment with Herceptin®. Discontinuation of Herceptin® treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction appears to increase in patients who receive Herceptin® in combination with anthracycline and cyclophosphamide (28% versus 7% when used as a single agent).

The incidence of generalized pain, abdominal pain, back pain appears to be more frequent in patients receiving Herceptin® in combination with chemotherapy. Occasionally pain at tumor sites has been reported.

The following have also been reported in > than 5% of patients: diarrhea (25%), myalgia, peripheral edema, and weakness.

Incidence less frequent (1-5%)

Allergic/hypersensitivity reactions that have been reported include rash, pruritis, urticaria, anaphylaxis (rarely resulting in death) or anaphylactoid signs and symptoms (erythematous rash on the chest and neck, dyspnea, bronchospasm, angioedema, ARDS, hypotension, wheezing, pleural effusions, pulmonary infiltrates, non-cardiogenic pulmonary edema, and pulmonary insufficiency and hypoxia requiring supplemental oxygen or ventilatory support).

Incidence rare (<1%)

Abnormal liver function tests, hepatitis, bone pain, tumor-site pain, pancytopenia, hypotension, anorexia, febrile neutropenia, worsening of pre-existing peripheral neuropathy; paresthesias, and thromboembolic disease.

Pulmonary events that have been reported include pleural effusions, pulmonary infiltrates, non-cardiogenic pulmonary edema, and pulmonary insufficiency and hypoxia requiring supplemental oxygen or ventilatory support including adult respiratory distress syndrome and death have occurred. Most patients with fatal events had significant pre-existing pulmonary compromise secondary to intrinsic lung disease and/or malignant pulmonary involvement. Because it appears that patients with significant pre-existing pulmonary compromise may be at greater risk, these patients should be treated with extreme caution. Patients experiencing any of the severe infusion-associated symptoms should have the trastuzumab infusion discontinued and appropriate medical therapy administered. Patients should be closely monitored until complete resolution of their symptoms. In addition, patients should be informed of the possibility of delayed severe reactions.

Add 11 Although definitive attribution cannot be confirmed, recent safety reports have documented several cases of myocardial ischemia or infarction.

15.43 Nursing guidelines:

15.431 The most common adverse events related to trastuzumab are fever (>38°C), chills, and occasional rigors, most often infusion-related after the initial dose. Treat with acetaminophen as necessary. Meperidine may be needed for rigors. Instruct patient and family to report any fever >101°F. Patients with underlying pulmonary pathology should be closely monitored.

15.432 Transient, localized tumor-site pain may be experienced within 8 hours of infusion. Advise patient that acetaminophen is helpful.

15.433 Provide symptomatic management of the possible mild-to-moderate nausea/vomiting/diarrhea.

15.434 Assess heart and lung sounds. Monitor vital signs (resting pulse, BP). Be alert to early signs to cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales. Trastuzumab may potentiate heart failure in combination with doxorubicin.

15.435 Advise patient of possible fatigue, loss of strength, and weakness. Have patient pace activities with frequent rest periods.

15.44 Drug procurement: Trastuzumab is manufactured by Genentech Inc. and distributed by the DCTD. Trastuzumab may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (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). Completed Clinical Drug Requests (form NIH-986) should be submitted to the Pharmaceutical Management Branch by fax (301/480-4612) or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, RM. 707, Bethesda, MD 20892.

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 DCTD, using the NCI Drug Accountability Record Form. (See the NCI Investigators Handbook for Procedures for Drug Accountability and Storage.)

Add 7,10

LMD Treatment - When it has been determined that a patient is tolerating therapy without excessive toxicity at a stable dose level, investigational supply trastuzumab may be administered by the patient's local physician. The following steps must be followed: 1) The NCCTG Operations Office must be informed (contact N9831 QCS). 2) For the patient to remain on study as a Group registered patient, the registering investigator must remain as the responsible investigator. 3) LMD must accept responsibility for the patient's treatment in accordance with the protocol and must notify the registering investigator of any adverse events and submit to NCCTG. 4) LMD must be an active registered NCI investigator or must register with NCI. 5) The registering investigator's IRB should be informed that an LMD will be treating one of his/her patients. 6) LMD must have IRB approval or be covered under the investigator's IRB. 7) LMD must maintain drug accountability records. **Once the registering investigator feels that the above-noted points have been addressed, he/she should notify PMB in writing (fax 301-402-4870)** that these elements have been addressed and provide the name, address and telephone number of the LMD using the "Request for Drug Shipment to Local Physician" form (see Forms Packet) along with a completed Clinical Drug Request. This form **must be completed by the registering investigator. All requests for PMB/CTEP to ship CTEP-supplied agent to an LMD must be made by the registering investigator ONLY.**

15.5 Tamoxifen (Nolvadex®, Tamoxifen citrate, TAM) (Commercial)

15.51 Preparation and storage: Tamoxifen is available in 10 mg or 20 mg tablets and is stored at room temperature in dark containers.

Add 10

15.52 Known potential adverse events: Thrombocytopenia, leukopenia, anemia, rash, erythema, hair thinning and/or partial hair loss, nausea, vomiting, anorexia, diarrhea or constipation, increased risk of endometrial cancer, vaginal bleeding or discharge, menstrual changes, pruritus vulvae, vaginal dryness, ovarian cysts, uterine polyps, hyperplasia, endometriosis, increased liver enzymes, fatty liver, cholestasis, hepatitis, hepatic necrosis, liver cancer, depression, dizziness, lightheadedness, headache, confusion, syncope, hot flashes, thrombophlebitis, thromboembolism, pulmonary embolism, fluid retention, edema, retinopathy, corneal opacity, hypercalcemia, birth defects, impotence**,** cataracts.

15.53 Nursing guidelines:

15.531 Carefully monitor patient for initial tumor flare reaction. Instruct patient in tumor flare signs and symptoms and to report any pertinent changes to health care team.

15.532 Instruct patient and family to recognize symptoms of hypercalcemia and to report them to health care team.

15.533 Advise female patients of possible increased fertility with tamoxifen. Hormonal contraceptives are contraindicated. Discuss acceptable alternative forms of birth control with patients.

15.534 Treat nausea and vomiting as necessary.

15.535 Instruct patient to avoid skipping a dose. If a dose is missed, instruct patient to not take the dose later or to double up on a dose.

15.536 Discuss possibility of hot flashes. Estrogen is contraindicated. Instruct patient in comfort measures.

15.537 Encourage moderate exercise; i.e., walking, to counter possible weight gain.

15.54 Drug procurement: Commercially available.

Add 10

15.6 Anastrozole commercial supply (Arimidex®)

15.61 Formulation and Storage: Anastrozole is commercially available from AstraZeneca as 1 mg tablets. Store at 15 C to 30 C (59 F to 86 F).

15.62 Category and Mechanism of Action: Anastrozole is a potent and selective nonsteroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect o formation of adrenal corticosteroids or aldosterone. In postmenopausal women, the principal source of circulating estrogen is conversion of adrenally generated androstenedione to estrone b aromatase in peripheral tissues.

15.63 Administration: Oral. Anastrozole is well absorbed and not affected by food.

15.64 Dose: 1 mg PO once daily without regard to meals.

15.65 Known potential adverse events:

Common (greater than 5%):
- Cardiovascular: Flushing, peripheral edema, chest pain
- Central nervous system: Headache, dizziness, depression
- Dermatologic: Rash
- Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, anorexia, dry mouth
- Genitourinary: Pelvic pain
- Neuromuscular & skeletal: Increase bone and tumor pain, muscle weakness, paresthesia
- Respiratory: Dyspnea, cough, pharyngitis

Less Common (2% to 5%):
- Cardiovascular: Hypertension and thrombophlebitis
- Central nervous system: Somnolence, confusion, insomnia, anxiety, nervousness, fever, malaise, accidental injury
- Dermatologic: Hair thinning and pruritus
- Endocrine & metabolic: Breast pain
- Gastrointestinal: Weight loss
- Genitourinary: Urinary tract infection
- Hematologic: Anemia, leukopenia
- Neuromuscular & skeletal: Myalgia, arthralgia, pathological fracture, neck pain
- Respiratory: Sinusitis, bronchitis, rhinitis
- Miscellaneous: Flu-like syndrome, infection

15.66 Nursing guidelines

15.661 May take with food if needed for nausea. Instruct patient to report unrelieved nausea or vomiting.

15.662 Manage hot flashes with non-hormonal interventions (ie: venlafaxine XR 75 mg daily).

15.663 Assess for changes in bowel patterns. Manage diarrhea with non-prescription drugs. Instruct patient to report unrelieved diarrhea.

15.67 Drug procurement: Commercially available.

Add 10 15.7 Exemestane commercial supply (Aromasin®)

15.71 Formulation and storage: Exemestane is commercially available from Pharmacia as 25 mg tablets. Store at 15 C to 30 C (59 F to 86 F).

15.72 Category and mechanism of action: Exemestane is an irreversible, steroidal aromatase inactivator. It prevents conversion of androgens to estrogens by tying up the enzyme aromatase. In breast cancers where growth is estrogen-dependent, this medicine will lower circulating estrogens.

15.73 Administration: Oral. Exemestane is well absorbed.

15.74 Dose: 25 mg PO once daily after a meal.

15.75 Known potential adverse events:

Common (greater than 10%):
Central nervous system: Fatigue, pain, depression, insomnia, and anxiety
Endocrine & metabolic: Hot flashes
Gastrointestinal: Nausea

Less Common (1% to 10%):
Cardiovascular: Edema, hypertension, and chest pain
Central nervous system: Dizziness, headache, fever, hypoesthesia, and confusion
Dermatologic: Rash, itching, alopecia
Gastrointestinal: Vomiting, abdominal pain, anorexia, constipation, diarrhea, increased appetite, and dyspepsia
Genitourinary: Urinary tract infection
Neuromuscular & skeletal: Weakness, paresthesia, pathological fracture, and arthralgia
Respiratory: Dyspnea, cough, bronchitis, sinusitis, pharyngitis, and rhinitis
Miscellaneous: Flu-like syndrome, diaphoresis, lymphedema, and infection

Rare (less than 1% and limited to important or life-threatening):
GGT increased, transaminases increased.

15.76 Nursing guidelines:

15.761 Advise patients to take after a meal.

15.762 Manage hot flashes with non-hormonal interventions (ie, venlafaxine XR 75 mg daily).

15.763 Instruct patient to report uncontrolled nausea, insomnia.

15.764 Assess for changes in bowel patterns and manage diarrhea or constipation. Instruct patient to report unrelieved diarrhea or constipation.

15.76 Drug procurement: Commercially available.

15.8 Letrozole commercial supply (Femara®)

Add 10

15.81 Formulation and storage: Letrozole is commercially available from Novartis as 2.5 mg tablets. Store at 15 C to 30 C (59 F to 86 F).

15.82 Category and mechanism of action: Letrozole is a nonsteroidal, competitive inhibitor of the aromatase enzyme system which binds to the heme group of aromatase, a cytochrome P450 enzyme which catalyzes conversion of androgens to estrogens. This leads to inhibition of the enzyme and a significant reduction in plasma estrogen levels. Letrozole does not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens. Patients treated with letrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

Add 10

15.83 Administration: Oral. Letrozole is well absorbed and not affected by food.

15.84 Dose: 2.5 mg PO once daily without regard to meals.

15.85 Known potential adverse events:

Common (greater than 10%):
- Cardiovascular: Hot flushes
- Central nervous system: Headache, fatigue
- Gastrointestinal: Nausea
- Neuromuscular & skeletal: Musculoskeletal pain, bone pain, back pain, and arthralgia.
- Respiratory: Dyspnea, cough.

Less Common (2% to 10%):
- Cardiovascular: Chest pain, peripheral edema, and hypertension
- Central nervous system: Pain, insomnia, dizziness, somnolence, depression, anxiety, vertigo
- Dermatologic: Rash, alopecia, and pruritus
- Endocrine & metabolic: Breast pain, hypercholesterolemia
- Gastrointestinal: Vomiting, constipation, diarrhea, abdominal pain, anorexia, dyspepsia, weight loss, weight gain.
- Neuromuscular & skeletal: Weakness

Rare (less than 2% and limited to important or life threatening):
Angina, cardiac ischemia, coronary artery disease, hemiparesis, hemorrhagic stroke, myocardial infarction, portal vein thrombosis, pulmonary embolism, thrombocytopenia, thrombotic stroke, transient ischemic attack, venous thrombosis.

Add 10

15.86 Nursing guidelines

15.861 Manage hot flashes with non-hormonal interventions (ie: venlafaxine XR 75 mg daily).

15.862 Manage pain (arthralgias). Instruct patient to report unrelieved pain.

15.863 May take with food if needed for nausea. Instruct patient to report unrelieved nausea or vomiting.

15.864 Assess for changes in bowel patterns. Manage diarrhea or constipation with non-prescription drugs. Tell patients to report unrelieved diarrhea or constipation.

Add 10

15.87 Drug procurement: Commercially available.

16.0 Statistical Considerations and Methodology

16.1 Study design

This study will use a dynamic allocation procedure to allocate an equal number of patients to one of the three treatment regimens (26). This procedure will balance the marginal distributions of the stratification factors between these three treatment regimens. The stratification factors that will be used are lymph node status, and receptor status.

Add 10

16.2 Definition and documentation of efficacy endpoints

The primary endpoint is the duration of disease-free survival (DFS). DFS is the time from registration to first adverse event, where an adverse event is defined as any local, regional, or distant recurrence of breast cancer; the development of a contralateral breast cancer or second primary other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast; or death from any cause without the documentation of one of these adverse events. Overall survival (OS) is defined to be time from registration to death due to any cause.

16.3 Accrual

Add 11

16.31 Original assumptions

The total number of eligible patients to be accrued is 3,000 (1,000 for each of the three treatment regiments). The accrual rate anticipated on C9741 is 135 patients per month. Assuming that 30-35% of women with node positive breast cancer have scores of 3+ for HER-2 expression by IHC, the institution's participating in C9741 will accrue 41-47 women with 3+ HER-2 expression. With additional institutions committed to participating in this trial, we estimate the accrual rate for this trial will be approximately 56 eligible patients per month. Thus, the accrual period will be approximately 4.5 years.

Add 7,10

Add 11,15

16.32 Revisions due to temporary closure of Arm C and changes to eligibility criteria:

The temporary closure of Arm C and changes to the eligibility criteria allowing the enrollment of high-risk node-negative patients necessitates modifications to the study design. The total number of patients to be accrued is 3,300 eligible patients (1,150 patients will be randomized to Arms A and B and 1,000 patients to Arm C). Based on our prior accrual experience on this trial, we anticipate that 55 eligible patients per month will be enrolled following the initiation of Addendum 10. Thus, the total accrual will be up to 3,700 patients and will take approximately 5.75 years.

16.4 Sample size determination for the primary endpoint of disease-free survival

Three pairwise comparisons will be performed. To maintain an overall alpha level of 0.05, the comparison of the treatment regimen of AC followed by paclitaxel with the treatment regimen of AC followed by paclitaxel and then trastuzumab will be performed at an alpha level of 0.01; the comparison of the treatment regimen of AC followed by paclitaxel with the treatment regimen of AC followed by the combination of paclitaxel and trastuzumab will be performed at an alpha level of 0.01; and the comparison of the treatment regimen of the AC followed by paclitaxel then trastuzumab with the treatment regimen of AC followed by the combination of paclitaxel and trastuzumab will be performed at an alpha level of 0.03.

The first two pairwise comparisons will address (a) whether women who receive AC followed by paclitaxel then by trastuzumab have a significantly different DFS than women who receive AC followed by paclitaxel and (b) whether women who receive AC followed by the combination of paclitaxel and trastuzumab have a significantly different DFS than women who receive AC followed by paclitaxel. It is anticipated for both pairwise comparisons the median DFS will be 6 years on the poorer treatment arm. For each pairwise comparison, it is also

assumed that the following holds true: 1) approximately 56 eligible patients per month over 4.5 years, 2) the follow-up period after accrual terminates will be 2 years, 3) the distributions of DFS times for each treatment regimen follow an exponential distribution, and 4) the hazard rates are proportional, then a sample size of 1000 eligible patients per treatment arm will yield a 88% power to detect a 25% decrease in the hazard rate using a two-sided alpha=0.01 logrank test. This is equivalent to a 33% increase in the median DFS from 6 years to 8 years. The expected number of relapses is 685.

The third pairwise comparison will address whether women who receive AC followed by paclitaxel then trastuzumab have a significantly different DFS than women who receive AC followed by the combination of weekly paclitaxel and trastuzumab. It is anticipated that the median DFS on the poorer treatment arm is 7 years. Assuming 1) an accrual rate of 56 eligible patients per month over 4.5 years, 2) the follow-up period after accrual is terminated will be 2 years, 3) the distributions of DFS times for each treatment regimen follow an exponential distribution, and 4) the hazard rates are proportional, a sample size of 1000 eligible patients per treatment arm will yield an 83% power to detect a 22% decrease in the hazard rate using a two-side alpha=0.03 logrank test. This is equivalent to a 29% increase in the median DFS from 7 years to 9 years. The expected number of relapses is 614.

Add 10

16.41 Impact of temporary closing of Arm C

During the period Arm C was closed to accrual, approximately 300 patients were enrolled onto this trial – 150 patients on Arm A and 150 on Arm B. Modifications to the study design and allocation scheme were undertaken to reduce the impact of potential differences between the study participants enrolled prior to the temporary closure of Arm C, during the temporary closure of Arm C, and after the re-opening of accrual to Arm C.

16.411 Dynamic allocation scheme

The dynamic allocation procedure described in Section 16.1 was utilized to randomize approximately 275 patients to each of the three treatment arms prior to the closure of Arm C such that the marginal distributions of the stratification factors were balanced between these 3 treatment arms.

The allocation scheme was started anew on the day Arm C was closed to accrual. During the period Arm C was closed to accrual, 150 patients had been randomized to each of the two open treatment arms, Arm A and Arm B. These patients were randomized so that the marginal distributions of the stratification factors were balanced between the two treatment arms during this time period.

When accrual to Arm C was re-opened, the allocation procedure was again started anew. This will result in the marginal distributions of the stratification factors being balanced between all three treatment arms from point accrual to Arm C was re-opened to the end of the accrual period.

16.412 Patient evaluable for a particular pairwise comparison

Pairwise treatment comparisons will be made utilizing only those patients randomized to the trial when both treatment arms were simultaneously open to accrual. That is, the comparison of treatment efficacy between Arm A's regimen and Arm C's regimen will utilize only those patients randomized to Arm A and Arm C when both treatment arms were simultaneously open to accrual – approximately 1000 patients per treatment arm. The comparison of treatment efficacy between Arm A's regimen and Arm B's regimen will utilize all eligible patients randomized to these treatment arms – approximately 1150 patients per treatment arm.

Add 10

16.42 Impact of expanding the eligibility criteria to include high-risk node-negative patients

The study design was also modified to accommodate the inclusion of patients with high-risk node-negative breast cancer. An estimate of the median DFS rate among women who met the study criteria for high-risk node-negative disease was derived from the findings of Allred et al (48) and Andrulis et al (49) to be approximately 11.2 years. Recall, Allred et al estimated the 4-year DFS rate to be 78% among women with high-risk node-negative breast cancer where high-risk was defined as ER-negative or (ER-positive and > 3 cm) tumors. Andrulis et al estimated the 4-year DFS rate to be 78% among women with node-negative HER-2 gene amplified breast cancer.

It is anticipated that approximately 60 high-risk node-negative patients will be enrolled per treatment arm. Thus, the median survival in the treatment group with the poorest DFS is estimated to be 6.3 years. Under these additional assumptions, study design was revised as follows:

Add 10

16.421 Comparing Arm A (AC→T) to Arm C (T+H→H): Power calculations were performed assuming a 5.75-year accrual period that is comprised of three segments and a 1.75 year follow-up period after the close of accrual. The first segment of the accrual period is the actual accrual experience before the closure of Arm C. The second segment is a 7-month period where none of the patients accrued to this study are evaluable for this analysis. The third segment is the accrual experience following the reopening of enrollment to Arm C. It is assumed that the accrual rate during the third segment will be 55 patients per month.

A sample size of 1000 patients per treatment arm accrued and followed in this manner will yield a power of 86% to detect a 25% decrease in the DFS hazard rate using a two-sided alpha=0.01 log rank test. This is equivalent to a 33% increase in the median DFS from 6.3 to 8.4 years. The expected number of relapses is 663.

Add 10

16.422 Comparing Arm B (AC→T→H) to Arm C (AC→T+H→H): Power calculations were performed assuming a 5.75-year accrual period that is comprised of three segments and a 1.5 year follow-up after the close of accrual. The first segment of the accrual period is the actual accrual experience before the closure of Arm C. The second segment is a 7-month period where none of the patients accrued to this study are evaluable for this analysis. The third segment is the accrual experience following the reopening of enrollment to Arm C. It is assumed that accrual rate during the third segment will be 55 patients per month. A sample size of 1000 patients per treatment arm accrued and followed in this manner will yield a power of 81% to detect a 22% decrease in the DFS hazard rate using a two-sided alpha=0.03 log rank test. This is equivalent to a 29% increase in the median DFS fro 7.3 to 9.4 years. The expected number of relapses is 590.

Add 10

16.423 Comparing Arm A (AC→T) to Arm B (AC→T→H): If the accrual rate for the remainder of the 5.75-year accrual period is 55 patients per month and the follow-up period after the closure of accrual is 1.75 years, a sample size of 1150 patients per treatment arm will yield a power of 92% to detect a 25% decrease in the DFS hazard rate using a two-sided alpha=0.01 log rank test. This is equivalent to a 33% increase in the median DFS from 6.3 to 8.4 years. The expected number of relapses is 789.

Add 10,16,17

16.43 Impact of the release of trial efficacy findings following the joint interim analysis

16.431 Comparison Arm A (AC→T) to Arm C (T+H→H):

Add 17

This study goal was accomplished through the joint analysis. Further exploration of this question will be limited to

- Eligible patients randomized to Arm A or Arm C from May 25, 2000 to January 23, 2002, or from September 2, 2002 to April 25, 2004, when both treatment arms were open to accrual, will contribute data from the time of their registration to the date of last follow-up or death;
- Eligible patients randomized to Arm A and Arm C between April 26, 2004 and April 25, 2005 will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first.

Add 17

Limiting the analysis cohort in this manner will ensure that the Arm A versus Arm C comparison does not include any of the patients from Arm A who were eligible to receive trastuzumab as well as ensure that the patients who are included in this analysis were randomized to treatment during the same study period and have the same potential follow-up window.

Add 17

During the 3.3 year study period from May 25, 2000 to January 23, 2002, and from September 2, 2002 to April 24, 2004, 1231 eligible patients (Arm A – 614 and Arm C – 617) were entered on study. An additional 325 eligible patients (Arm A – 312 and Arm C – 319) were entered on study from April 24, 2004 to April 25, 2005.

Add 17

As the patients enrolled from April 24, 2004 to April 25, 2005, will provide follow-up data anywhere from 1 to 365 days, these patients will not be taken into account in the sample size determination – realizing the resulting sample size will yield a slightly higher power than stated.

Assuming the median PFS time is 6.3 years on the poorer treatment arm (original assumption), the minimum DFS hazard ratio that can be detected with a power of at least 85% by a two-sided alpha=0.01 log rank test was determined for a number of different follow-up periods.

Add 17

Follow-up period	Power	Hazard ratio	Expected number of events
1.5 years	86%	1.54	298
2.0 years	86%	1.49	344
2.5 years	86%	1.45	390

Add 17

16.432 Comparing Arm B (AC→T→H) to Arm C (AC→T+H→H):

Add 17

To assess whether DFS or OS differ with respect to whether 52 weeks of trastuzumab is begun concurrently with paclitaxel or following paclitaxel:

- Eligible patients randomized to Arm B or Arm C from May 25, 2000 to January 23, 2002, or from September 2, 2002 to January 24, 2005, will contribute data from the time of their registration to the date of last follow-up or death; and
- Eligible patients randomized to Arm B or Arm C between January 24, 2005 and April 25, 2005, will contribute data from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first.

Add 17

During the 4.0 year study period from May 25, 2000 to January 23, 2002 and from September 2, 2002 to January 24, 2005, 1725 eligible patients (Arm B – 867 and Arm C – 858) were entered on study. An additional 154 eligible patients (Arm B – 76 and Arm C – 75) were entered on study from January 25, 2005 to April 25, 2005.

Add 17

As the patients enrolled from January 25, 2005 to April 25, 2005, will provide follow-up data anywhere from 1 to 90 days, these patients will not be taken into account in the sample size determination – realizing the resulting sample size will yield a slightly higher power than stated.

Add 17

Assuming the median DFS time is 7.3 years on the poorer treatment arm (original assumption) and the follow-up period is 4 years, a two-sided alpha=0.03 log rank test will have a power of 81% to detect a 22% decrease in the DFS hazard rate. This is equivalent to a 28% increase in the median DFS fro 7.3 to 9.3 years. The expected number of relapses is 647.

(Note that by increasing the length of the original follow-up period from 1.5 to 4 years we are able to accomplish the original trial goal.)

Add 17

The minimum DFS hazard ratio that can be detected with a power of at least 84% by a two-sided alpha=0.03 log rank test for other follow-up periods lengths is tables below.

Add 17

Follow-up period	Power	Hazard ratio	Expected number of events
2.0 years	86%	1.37	435
3.0 years	88%	1.33	545
4.0 years	84%	1.28	647

Add 17

16.433 Comparing Arm A (AC→T) to Arm B (AC→T→H):

Add 17

To assess the addition of trastuzumab following AC→T prolongs DFS or OS,

- Eligible patients randomized to Arm A or Arm B prior to April 25, 2004, will contribute data from the time of their registration to the date of last follow-up or death; and
- Eligible patients randomized to Arm A or Arm B between April 26, 2004 and April 25, 2005, will contribute date from the time of their registration to the date of last follow-up or April 25, 2005, whichever comes first.

Add 17

During the 3.9 year study period from May 25, 2000 to April 24, 2004, 1528 eligible patients (Arm A – 763 and Arm B – 765) were entered on study. An additional 154 eligible patients (arm A – 312 and Arm B – 321) were entered on study from April 25, 2004 to April 25, 2005.

Add 17

As the patients enrolled from April 25, 2004 to April 25, 2005, will provide follow-up data anywhere from 1 to 365 days, these patients will not be taken into account in the sample size determination – realizing the resulting sample size will yield a slightly higher power than stated

Add 17

Assuming the median DFS time is 6.3 years on the poorer treatment arm (original assumption) and the follow-up period is 4 years, a two-sided alpha=0.01 log rank test will have a power of 86% to detect a 25% decrease in the DFS hazard rate. This is equivalent to a 33% increase in the median DFS fro 6.3 to 8.4 years. The expected number of events is 647.

Add 17

(Note that by increasing the length of the original follow-up period from 1.75 to 4 years we were able to accomplish the original trial goal.)

Add 17

The minimum DFS hazard ratio that can be detected with a power of at least 84% by a two-sided alpha=0.01 log rank test for other follow-up periods lengths is tables below.

Add 17

Follow-up period	Power	Hazard ratio	Expected number of events
2.0 years	88%	1.43	442
3.0 years	87%	1.37	552
4.0 years	86%	1.33	647

Add 17

Study Course

<table>
<tr><th></th><th>May 25, 2000 to January 23, 2002</th><th>January 24, 2002 to September 1, 2002</th><th>September 2, 2002 to April 25, 2004 **</th><th>April 25, 2004 to January 24, 2005**</th><th>January 25, 2005 to April 25, 2005**</th></tr>
<tr><td>Arm A</td><td>Open to enrollment</td><td>Open to enrollment</td><td>Open to enrollment – patients may not receive trastuzumab as they would have completed paclitaxel more than 6 months prior to April 25, 2005</td><td colspan="2">Open to enrollment – patients may receive trastuzumab for a maximum of 52 weeks either concurrently with paclitaxel then trastuzumab alone or immediately following paclitaxel or at most 6 months after the completion of paclitaxel</td></tr>
<tr><td>Arm B</td><td>Open to enrollment</td><td>Open to enrollment</td><td colspan="2">Open to enrollment – patients received trastuzumab following completion of paclitaxel as they would have completed chemotherapy prior to the April 25, 2005 release of joint analysis results</td><td>Open to enrollment – patients may receive trastuzumab for a maximum of 52 weeks either concurrently with paclitaxel then trastuzumab alone or immediately following paclitaxel as they would have been either receiving AC or paclitaxel at the time of the April 25, 2005 release of joint analysis results</td></tr>
<tr><td>Arm C</td><td>Open to enrollment</td><td>Closed to enrollment*</td><td colspan="3">Open to enrollment – patients received trastuzumab for a maximum of 52 weeks concurrently with paclitaxel then followed by trastuzumab alone</td></tr>
</table>

*per addendum #8 based on cardiac safety concerns

**per treatment guidelines following the announcement on April 25, 2004 of the results of the comparison of AC →T to AC →T + H →H from N9831 and B-31.

16.434 Impact on interim analysis plan – At the time of the planned joint interim analysis, an unplanned analysis of the efficacy data from N9831 was performed. These results, together with the findings of the joint interim analysis, were used in determining treatment options for patients enrolled on Arms A and B of N9831. As such, for each pair-wise treatment comparison, the alpha level for its final analysis will be reduced by the portion of alpha considered spent using O'Brien-Fleming type alpha spending function if a planned interim analysis was performed at that percentage of total events.

For each pair-wise treatment comparison, the first interim analyses originally planned to occur when approximately 50%of the expected number of events for that particular comparison had been document will be dropped . The remaining two interim analysis of each pair-wise treatment comparison will remain. As the interim analysis plan depends on events, not time, it is to remain as previously described.

16.5 Analysis plan for efficacy endpoints

16.51 Efficacy endpoints

Add 7,15 A patient enrolled after the implementation of Addendum 7 is considered to be eligible for the definitive analysis if she fulfills all the requirements of registration and on central review has a tumor that strongly overexpresses HER-2 (3+ by HercepTest®) or is HER-2 gene amplified by FISH.

Add 15 A patient enrolled before the implementation of Addendum 7 is considered to be eligible for the definitive analysis if she fulfilled all the requirements of registration at the time of her enrollment regardless of whether her tumor was later centrally reviewed for Her2 overexpression or HER-2 gene amplification.

Definitive analysis will be based on the intention-to-treat principle with all eligible patients belonging to the treatment arm to which they were randomized. The distribution of DFS times and OS times for each treatment group will be estimated using the Kaplan-Meier method (29). For each of the three pairwise comparisons of the treatment regimens, a stratified logrank test (27) and Cox partial likelihood score test (28) will be used to assess whether the distribution of DFS times or the distribution of OS times differ with respect to treatment regimen having adjusted for the number of positive lymph nodes and receptor status. For DFS and OS, Cox modeling with the Cox partial likelihood score test (28) will be used to examine the strength of association between these time to event distributions and such additional potential prognostic factors as menopausal status, surgery/radiation therapy, FISH amplification, IHC results, level of sHER1 expression and level of sHER2 expression.

Summary statistics for patient and tumor characteristics, eligibility rates, length of follow-up, and treatment acceptance rates will be calculated by assigned treatment arm.

16.52 Adverse events

For each type of toxicity reported, the proportion of patients on each treatment arm experiencing a severe level of that toxicity will be determined overall and by phase of the regimen (AC, weekly paclitaxel +/- trastuzumab, observation +/- trastuzumab). For each agent, the total dose delivered as a percentage of the starting dose will be determined. For each treatment regimen, the summary measures for toxicity will also include the proportion of patients hospitalized with febrile neutropenia during chemotherapy.

16.53 Efficacy interim monitoring

Careful monitoring of this trial will occur every 6 months to coincide with the NCCTG meetings. Special attention will be given to toxicity, patient survival, and DFS. Formal comparisons of DFS will be made when approximately 50%, 67%, 75% and all of the expected number of events have occurred for that comparison. The Lan-DeMets method for computing discrete sequential two-sided boundaries with an alpha spending function yielding O'Brien-Fleming type boundaries (43) will be used to account for sequential testing and to maintain the overall preset type I error rate. For the pairwise comparisons with overall type I error rate of 0.01, the alpha levels for the interim analyses and final analysis are 0.00014, 0.00107, 0.00117, and 0.00762, respectively. For the pairwise comparison with an overall type I error rate of 0.03, the alpha levels for the interim analyses and the final analysis are 0.00116, 0.00476, 0.00402, and 0.02005, respectively.

The distribution of DFS times from one treatment group will be compared with that of another of each for the interim analyses. The results of these three pairwise comparisons together with the data on patient accrual, toxicity, and survival times will form the basis of a recommendation to the NCCTG Data Monitoring Committee (DMC). The following table lists the possible results of each pairwise comparison and the possible recommendation to the NCCTG DMC if patient accrual is on target, excessive toxicity is not encountered, and the number of early deaths is not unexpectedly high.

INTERIM ANALYSIS COMPARISONS			RECOMMENDATIONS
AC → P vs. AC → P + T → T	AC →P vs. AC → P → T	AC → P+T → T vs. AC → P →T	
NS	NS	NS	Continue trial
AC → P better	NS	AC → P → T better or NS	Close AC → P+T → T
NS	NS	AC → P → T better	Close AC → P+T → T
NS	AC → P better	AC → P+T → T better or NS	Close AC → P → T
NS	NS	AC → P+T → T better	Close AC → P → T
AC → P+T → T better or NS	AC → P → T better	NS	Close AC → P
AC → P+T → T better	NS	NS	Close AC → P
AC → P better	AC → P better	AC → P+T+T better or AC → P →T better or NS	Stop trial
AC → P+T → T better	AC → P → T better	AC → P → T better or AC → P+T → T better	Stop trial
AC → P+T → T better	AC → P better or NS	AC → P+T → T better	Stop trial
AC → P better or NS	AC → P → T better	AC → P → T better	Stop trial

Add 7

16.54 The PFS and OS of those patients who, on central review, were found to have tumors that do not strongly overexpress HER-2 and are not HER-2 gene amplified will be estimated by the Kaplan-Meier method (29).

16.6 Cardiac safety monitoring plan and data analysis - This plan was originally developed to closely monitor the development of adverse cardiovascular events and to provide a formal mechanism by which to prematurely terminate accrual if excessive cardiac toxicity was observed. The study chair will periodically review the data from the first 1000 MUGA/echocardiogram reports with the study cardiologists.

16.61 Patients are considered evaluable for cardiotoxicity analysis if they have (1) completed the AC phase of their treatment regimen; (2) their post AC cardiac evaluation indicates they are eligible to begin treatment with trastuzumab, that is, they exhibit no significant symptoms related to LV dysfunction, cardiac ischemia, or arrhythmia while receiving AC, they have not had a ≥16% point decrease in resting LVEF from pretreatment LVEF levels, and they have not had a decrease in LVEF from pretreatment LVEF levels of ≤15%, which places their LVEF level beneath their institutional lower limit of normal; and (3) they have begun their post-AC therapy.

16.62 Cardiovascular events to be included in cardiac toxicity analysis

The cardiovascular events to be included in the cardiac safety analysis include cardiac left ventricular function events and definite or probable cardiac deaths which occur at any time after post-AC treatment is begun (cycle 5 day 1) but prior to documentation of a breast cancer recurrence, contralateral breast cancer, or second primary cancer.

A cardiac left ventricular function event is defined as the occurrence of symptomatic CHF with any objective findings (e.g., rales, S3, elevated jugular venous pressure) confirmed by MUGA scan/echocardiogram or ECG and chest x-ray.

Definite cardiac deaths are deaths due to CHF, myocardial infarct (MI), or documented primary arrhythmia.

Probable cardiac deaths are sudden deaths without documented etiology.

16.63 Interim analysis of cardiac toxicity data

Formal interim analyses are planned after the first 100, 300, and 500 patients evaluable for cardiotoxicity on each treatment arm either 1) have been followed for at least 6 months after the start of their post-AC treatment (day 1 of cycle 5) and have had their protocol-required MUGA/echocardiogram at 6 months post-AC treatment or 2) have terminated post-AC prior to 6 months post-AC treatment due to disease recurrence, development of a second primary, excessive toxicity, or refusal. With an accrual rate of 56 patients per month, these interim analyses should occur approximately 12, 22, and 33 months after the protocol opens.

The timing of each interim analysis is based on patient accrual. At the time of a particular interim analysis, some patients may have been followed only 6 months after the start of their post AC treatment while other patients may have been followed a few years after the start of their post AC treatment. All cardiovascular events described in Section 16.62 documented prior to a particular interim analysis will be used in that particular interim analysis and all subsequent interim analyses. Once completed, an interim analysis will not be repeated.

The level of cardiotoxicity on a treatment arm containing trastuzumab will be considered unacceptable if the percentage of patients with cardiotoxicity on that treatment arm containing trastuzumab is greater than 4 percentage points above the percentage of patients with cardiotoxicity on the AC then paclitaxel arm. Thus at each interim analyses, two pairwise comparisons will be made. For a given treatment arm containing trastuzumab, the null hypothesis that the difference between the percentage of patients with cardiotoxicity on that particular treatment arm containing trastuzumab and the percentage of patients with cardiotoxicity on the AC then paclitaxel arm is less than or equal to 4% will be tested against the alternative hypothesis that the percentage of patients with cardiotoxicity on that particular treatment arm containing trastuzumab and the percentage of patients with cardiotoxicity on the AC then paclitaxel arm is greater than 4%. If the null hypothesis is rejected, then accrual to that particular treatment arm containing trastuzumab will be suspended pending the outcome of a meeting of the NCCTG External Monitoring Committee examining this finding. If the null hypothesis is not rejected, accrual to that particular treatment arm containing trastuzumab will continue.

A lag of approximately 9 months is expected between the accrual of the 300th, 900th, and 1500th patient and their completion of 6 months treatment beyond AC therapy and their second post-AC MUGA/echocardiogram. This results in several additional patients being accrued onto this study beyond the 300th, 900th, and 1500th patient awaiting the findings of the interim analyses of the cardiotoxicity data. In order to ensure that the cardiac interim monitoring is not lagging substantially behind patient accrual, accrual will be temporarily suspended after the 2000th patient is enrolled if the second cardiac interim analysis has not been performed. Based on the simulation results presented in the table in Section 16.63, the probability of stopping accrual to a particular treatment arm containing trastuzumab after the third cardiotoxicity interim analysis not having stopped accrual to that arm after the second cardiotoxicity interim analysis is quite low if the true difference in the proportion of women experiencing toxicity is 0.04 or less.

Let

X_{aj} be the number of women with a documented cardiotoxicity after the start of post-AC treatment with paclitaxel alone at the time of the jth interim analysis.

X_{bj} be the number of women with a documented cardiotoxicity after the start of post-AC treatment with paclitaxel then trastuzumab at the time of the jth interim analysis.

X_{cj} be the number of women with a documented cardiotoxicity after the start of post-AC treatment with paclitaxel plus trastuzumab at the time of the jth interim analysis.

P_a be the true probability that a woman treated with AC then paclitaxel will experience an adverse cardiac event after the start of post-AC treatment.

P_b be the true probability that a woman treated with AC then paclitaxel then trastuzumab will experience an adverse cardiac event after the start of post-AC treatment.

P_c be the true probability that a woman treated with AC then paclitaxel with trastuzumab will experience an adverse cardiac event after the start of post-AC treatment.

n_j is the number of evaluable patients on each arm at the time of the jth interim analysis.

The test statistic which will be used at each interim analysis

To test H_0: $P_b - P_a \leq 0.04$ against H_a: $P_b - P_a > 0.04$ is given by

$$Z = \frac{X_{bj} - X_{aj} - 0.04}{(S_{ab})^{1/2}} \qquad j=1,2,3$$

where S_{ab} is the estimated variance of $X_{bj} - X_{aj} - 0.04$ under the null hypothesis

$$S_{ab} = \frac{\hat{P}_a (1 - \hat{P}_a) + \hat{P}_b (1 - \hat{P}_b)}{n_j}$$

and $\hat{P}_a$ is the value of P_a which maximizes the log likelihood function

$$\log n_j! - \log x_a! - \log (n_j - x_a)! + \log n_j! - \log x_b! - \log (n_j - x_b)! + + X_a \log P_a + (n_j - X_a) \log (1 - P_a) + X_b \log P_b + (n_j - X_b) \log (1 - P_b)$$

under the constraint that $\hat{P}_b - \hat{P}_a = 0.04$

A corresponding test statistic will be constructed for testing H_o: $P_c - P_a \leq 0.04$ against H_a: $P_c - P_a > 0.04$. Each test will be performed at a nomial 0.05 alpha level,

The table in Section 16.63 presents the estimated probability that accrual to a particular arm containing trastuzumab will be terminated using this cardiac toxicity interim analysis plan. Each entry in the table is based on 40,000 simulated replications of the interim analysis plan assuming the true probability that a woman treated with AC then paclitaxel will experience an adverse cardiac event after the start of post-AC treatment, P_a, is 0.01. This value of P_a was chosen because the proportion of patients assigned to the AC-Taxol arm on the NSABP B-28 trial who had cardiac events such as those described in Section 16.62 was 0.004 (as of 11/2/99), and with the higher level of surveillance in this trial, we anticipate a slightly higher incidence of reported cardiac events. For example, if $P_a = 0.01$ and the true difference in the proportion of patients experiencing cardiac toxicity $P_b - P_a$ is 0.04 then the probability of stopping accrual to the AC then paclitaxel followed by trastuzumab arm after the first 100 patients are accrued to that arm is 0.124, after the first 300 patient is 0.126, and after the first 500 patients is 0.096. Thus, the probability of terminating accrual to that treatment arm is 0.347.

16.63: Probability that accrual to a particular treatment arm containing trastuzumab will be terminated because of excessive cardiac toxicity using the proposed interim analysis plan.

Increase in cardiac event rate on arm containing trastuzumab	After 100 patients per arm*	After 300 patients per arm*	After 500 patients per arm*	Probability that accrual will be terminated*	Conditional probability of stopping after 3rd interim analysis not having stopped after 2nd interim analysis
0%	0.000	.000	0.000	0.000	0.000
1%	0.000	.000	0.000	0.000	0.000
2%	0.004	.000	0.000	0.004	0.000
3%	0.020	0.005	0.002	0.026	0.002
4%	0.059	0.038	0.024	0.121	0.026
5%	0.124	0.126	0.096	0.347	0.129
6%	0.224	0.243	0.164	0.631	0.307
7%	0.338	0.342	0.167	0.847	0.522
8%	0.460	0.374	0.117	0.951	0.705
9%	0.578	0.345	0.065	0.988	0.844
10%	0.674	0.295	0.028	0.998	0.922

*P_a is assumed to be 0.01 based on the results of NSABP B-28 trial.

16.64 Analysis of cardiac toxicity data to be performed at the time of definitive efficacy endpoint analysis

For each treatment arm, an estimate of the true incidence rate of cardiovascular events (as described in Section 16.62) will be obtained by determining the number of women who have had a documented cardiovascular event and dividing by the total number of months each woman was at risk for a cardiovascular event. A woman is considered to be at risk for a cardiovascular event from the start of her post AC treatment until the documentation of breast cancer recurrence, contralateral breast cancer, second primary cancer or death, whichever occurs first. The incidence rate observed in one treatment arm will be compared to that from another treatment arm by obtaining an estimate of the true incidence rate ratio and constructing its corresponding 95% confidence interval.

Within each treatment arm, an estimate of both the true incidence rate of cardiovascular events among those who started right chest wall radiation and the true incidence rate of cardiovascular events among those who started left chest wall radiation will be obtained. The incidence rate for cardiovascular events among those who started right chest wall radiation will be compared to that among those who started left chest wall radiation by obtaining an estimate of the true incidence rate ratio and constructing its corresponding 95% confidence interval.

Add 16

16.7 Cardiovascular adverse events among those who had a satisfactory post-AC cardiac evaluation and began their post-AC treatment.

16.71 Analysis cohort:

16.711 Definition of patient cohort to be included in the comparison of cardiac rates between Arm A and Arm B.

Eligible patients randomized to Arm A or Arm B who had a satisfactory post-AC cardiac evaluation and completed paclitaxel prior to October 25, 2004. (This will ensure that this comparison does not include any of the patients from Arm A who were offered trastuzumab or any of the patients from Arm B who were eligible to receive some or all of their trastuzumab concurrently with paclitaxel as well as ensure that the patients who are included in this analysis were randomized to treatment during the same study period.)

16.712 Definition of patient cohort to be included in the comparison of cardiac rates between Arm A and Arm C.

Eligible patients randomized to Arm A or Arm C when both treatment arms were open to accrual and who had a satisfactory post-AC cardiac evaluation and completed paclitaxel prior to October 25, 2004. (This will ensure that this comparison does not include any of the patients from Arm A who were offered trastuzumab as well as ensure that the patients who are included in this analysis were randomized to treatment during the same study period.)

16.713 Definition of patient cohort to be included in the comparison of cardiac rates between Arm B and Arm C.

Eligible patients randomized to Arm B or Arm C when both treatment arms were open to accrual and who had a satisfactory post-AC cardiac evaluation and completed paclitaxel prior to April 25, 2005. (This will ensure that this comparison does not include any of the patients from Arm B who were eligible to receive some or all of their trastuzumab concurrently with paclitaxel as well as ensure that the patients who are included in this analysis were randomized to treatment during the same study period.)

16.72 Analysis plan for each pair-wise comparison

For each treatment arm, the incidence rate for a cardiac event will be estimated by the number of cardiac events divided by person-years of follow-up and its corresponding 95% CI will be constructed using the properties of the Poisson distribution.

Poisson regression will be used to examine whether age at study entry, history of hypertension medication use, post-AC LVEF levels, decrease in post-AC LVEF levels from pre-treatment levels, or treatment arm is significantly associated with the development of CHF or cardiac death after completion of AC chemotherapy.

Add 16

16.8 Factors associated with prohibition of trastuzumab administration

16.81 Analysis cohort:

All eligible patients enrolled onto this trial prior to January 1, 2005. (This restriction will ensure that the patients who are included in this analysis completed post-AC cardiac evaluation prior to the release of the joint interim analysis findings.)

16.82 Analysis plan:

Add 16,17

The proportion of eligible patients who met the criteria for prohibition of trastuzumab administration will be estimated by the number of eligible patients who were met the criteria for prohibition of trastuzumab administration divided by the total number of eligible patients who completed AC chemotherapy and had a post-AC cardiac evaluation. Its corresponding 95% CI will be constructed using the properties of the binomial distribution.

Logistic regression will be used to examine whether age at study entry, history of hypertension medication use or pre-treatment LVEF levels associated with meeting the criteria for prohibition of trastuzumab administration.

16.9a sHER-1 and sHER-2 levels

16.9a1 Cox's models will be used to assess the association between time to event distributions and baseline levels of sHER-1 and sHER-2 expression.

16.9a2 Thirty-five patients from each treatment arm will have their sHER-1 and sHER-2 levels determined at predetermined time points throughout the study in order to assess whether the trajectory of these levels differs among those who recur within 2 years of study entry and those who do not.

Add 15

16.9b HER-2 expression ascertained by central pathology

Tissue specimens will be submitted to the NCCTG Operations Office for centralized determination of HER-2 overexpression using the HercepTest®, immunohistochemistry (IHC), and fluorescence in situ by hybridization (FISH). The proportion of women found not to have a 3+ level of HER-2 overexpression by both the HercepTest® and IHC will be determined and its corresponding 95% confidence interval constructed.

Agreement between the results of HercepTest® and that of IHC will be assessed using weighted Kappa statistics. The proportion of patients with 3+ level of HER-2 overexpression found by both the HercepTest® and IHC will be obtained and its corresponding 95% confidence interval constructed (positive agreement). Similarly, the proportion of patients with 0, 1+, or 2+ levels of HER-2 overexpression found by both the HercepTest® and IHC will be obtained and its corresponding 95% confidence interval constructed (negative agreement). These analyses will be performed among all patients and then separately for those found to be amplified by FISH and those found not to be amplified by FISH.

Add 13

16.9c Effect of AC, Paclitaxel, and Trastuzumab on Cardiac Serum Markers

The statistical analyses will be primarily descriptive. Because a fairly large number of possible relationships will be considered, it is understood that even those relationships that are found to be statistically significant (e.g. associated with p-values <0.05) are subject to subsequent confirmation, based on data that are independent from those generated by this companion study.

16.9c1 Characteristics of patients enrolled on sub-study from each treatment arm

For each treatment arm, descriptive statistics will be used to summarize patient characteristics at study entry, breast disease features, non-study treatment elements, and cardiac features. The factors to be summarized include age, performance status, medication for hypertension, hemoglobin, administration of adjuvant radiotherapy, serum and plasma cardiac marker levels, and LVEF level.

16.9c2 Bio-markers to be evaluated:

16.9c21 Definition of serum abnormalities:

Troponin-T (TnT) >0.01 mcg/ml
Troponin-I (TnI) >0.03 mcg/ml
Tumor necrosis factor- alpha (TNF-α) ND >4.71 pg/mL
Interleukin-1 beta (IL-1β) >0.54 pg/mL
Interleukin-6 (IL-6) >10 pg/mL
CRP >3

16.9c22 Definition of plasma abnormalities:

Brain natriuretic peptide (BNP) > 100
NT-proBNP > 300
CD 40 ligand >1.5 ng/ml

16.9c3 Analysis of pre-treatment bio-marker data

Pre-treatment bio-marker data will be examined overall and by assigned treatment arm.

For each of the bio-markers, point and interval estimates of the proportion of patients whose pre-treatment level falls outside of the normal range will be constructed using the properties of the binomial distribution.

The strength of the association between the bio-markers, pre-treatment LVEF level, systolic and diastolic blood pressure levels, and resting heart rate will be explored using pair wise Spearman rank correlation coefficients.

16.9c4 Analysis of post-treatment AC bio-marker data

Biomarker levels ascertained immediately after the 1st or 2nd dose of AC will be examined in terms of percent change from baseline levels as well as its presence within the normal range. For each bio-marker, a Wilcoxon signed rank test will be used to assess whether the percent change in the bio-marker level differs significantly from zero among all patients. The McNemar test will be used to assess whether the proportion of patients who had a bio-marker level in the NR prior to treatment that fell outside the NR following AC is the same as the proportion of patients who had a bio-marker level outside the NR prior to treatment that fell within the NR following AC.

16.9c5 Analysis of all bio-marker data

For each patient, each of the cardiac parameters will be plotted against time. The percentage change from baseline in each of these parameters will also be plotted against time. These plots will be visually assessed for trends within treatment groups as well as for similarities and differences between treatment groups.

For each patient, the maximum bio-marker level and the time point where the biomarker is at its maximum will be ascertained as well as the time point when the bio-marker level first falls outside the normal range. For each treatment arm and each time point, the median and range of the distribution of the bio-marker level will be obtained. At each time point, the proportion of patients with a bio-marker level falling outside the normal range will be determined as well as the proportion of patients whose bio-marker level falls outside the normal range for the first time.

For each bio-marker, repeated measures modeling will be used to assess whether levels are increasing with time in a given treatment arm. Also, for each individual, a regression line will be fit to their (transformed, if necessary) bio-marker data. A Wilcoxon rank sum test will be used to assess whether these slopes differ with respect to assigned treatment.

It is recognized that patients will not necessarily remain on N9831 for at least 18 months due to refusal, toxicity, progression, co-morbid conditions, and death.

16.9c6 Sample size

For each biomarker, a regression line will be fit to each individual's data. The slope of each individual's fitted regression equation will be used to summarize the behavior of the marker for that individual. A Wilcoxon rank sum test will then be used to assess whether these slopes differ with respect to assigned treatment. With a sample size of 55 patients per treatment arm, a two-sided alpha=0.05 Wilcoxon rank sum test will have approximately 90% to detect at least a 0.60 standard deviation difference between the median slopes of two treatment groups.

16.9c7 Timing of analyses

Final analysis of parent N9831 trial will take place after all evaluable subjects have been followed for at least 18 months. The status of this study will be reviewed at least every 6 months to coincide with the semi-annual group meeting of the NCCTG. The information will also be shared with the NCCTG Data Monitoring Committees at least once every 6 months as per cooperative group policy.

Add 15

16.9d Statistical analysis for the joint analysis of the impact of trastuzumab on DFS and OS among patients enrolled on NCCTG N9831 and NSABP B-31 (Arms A and C of N9831 only)

16.9d1 Overview

A joint analysis of the efficacy data from NCCTG N9831 and NSABP B-31 will be performed to assess whether there is an increase in benefit with AC followed by paclitaxel and trastuzumab then trastuzumab alone relative to AC followed by docetaxel. Data from patients randomized to Arm B of N9831 (AC→T→H) and patients randomized to Arm A of N9831 when Arm C was temporarily closed to accrual will not be included in this analysis.

16.9d2 Primary and Secondary Endpoints

Disease-free survival (DFS) will be considered to be the primary endpoint of this joint analysis. DFS events include local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy; regional recurrence; distant recurrence; contralateral breast cancer; other second primary cancer (excluding 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.
A secondary endpoint of this joint analysis is overall survival where survival time is defined as the time from registration to death due to any cause.

This joint analysis will be carried out unless one of the trials terminates early due to the results of the interim cardiac safety analysis or the planned efficacy interim analyses.

The analysis plan for the combined trial data will be based on one-sided tests at the 0.025 level of significance. The definitive joint analysis of DFS will take place after 710 events have been reported (aggregated over both trials) and the joint analysis of OS will take place after the report of the 710th death. It is anticipated that the DFS analysis will be reported approximately 24 months before the data are mature enough to perform the definitive analysis of OS.

16.9d3 Evaluability

16.9d31 Primary Analysis of DFS and OS will be based on the intent-to-treat principle, i.e., all patients will be analyzed according to their randomly assigned treatment assignments. All randomized patients will be included except those NCCTG patients accrued after the institution of centralized HER2 testing, who were to be found to be negative by central review. Also, NCCTG patients enrolled from 2/1/2002 to 9/3/2002 will be excluded from control Arm A, since accrual to Arm C was suspended during that time.

16.9d32 A secondary analysis of DFS and OS will be restricted to the eligible patients who meet all of the following conditions:

- All patients enrolled on B-31 who received at least one dose of AC.
- All patients enrolled on N9831 prior to 2/1/2002 who were randomized to either Arm A or Arm C and received at least one dose of AC.
- All patients enrolled on N9831 after 9/3/2002 who were randomized to either Arm A or Arm C and received at least one dose of AC.
- patient must be alive and disease-free a the time of their post-AC cardiac evaluation.
- patient must have had a satisfactory post-AC cardiac evaluation allowing initiation of trastuzumab.
- patient must not have been found not to have HER-2-positive disease (protein overexpression by IHC or gene amplification by FISH) by the central/reference laboratory review (by the central laboratory used by the individual trial.
- patient must have begun post-AC therapy.

In these secondary analyses, time to event will be measured from the date of the post-AC cardiac evaluation. 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 primary analyses are reported.

16.9d4 Statistical Analysis Plan

A stratified log-rank test will be used to assess whether DFS or OS differs with respect to the addition of trastuzumab to a chemotherapy regimen including AC and paclitaxel. The strata to be used reflect differences in the conduct of these two clinical trials, the temporary closure of Arm C on the N9831 trial, and modifications in the administration schedule of paclitaxel on the B-31 trial. Specifically, the strata are trial (N9831 vs. B-31), paclitaxel schedule (q3 weeks vs. weekly), pathologic nodal status (0, 1-3, 4-9, 10+ positive nodes) and hormone receptor status (ER and PR negative, ER and/or PR positive).

A site-of-first-event table will be constructed, breaking down first events into the following categories: local recurrence, regional recurrence, distant recurrence, contralateral breast cancer, other second primary cancer, or death prior to cancer recurrence.

The DFS and OS distribution will be estimated using the Kaplan-Meier method. Ninety-five percent confidence intervals will be reported for relative risks, for DFS and OS at the 5-year point, and for absolute benefit as defined by differences in DFS and OS.

For both DFS and OS, Cox modeling will be performed to explore whether findings are confounded by any imbalances in patient or tumor characteristics such as ECOG performance status, tumor size, tumor grade, age at registration, type of surgical treatment, and inclusion of radiotherapy.

16.9d5 Power considerations

We wished to power the analysis to be able to detect a 25% decrease in event rate (for DFS) or rate of mortality (for OS). We also wished to attenuate this target efficacy to account for the following factors.

(1) To date, approximately 9% of patients have failed to begin treatment with trastuzumab (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 trastuzumab).

(2) Not all patients truly overexpress or amplify HER-2. Following early centralized assessments of the reproducibility of HER-2 determinations in both N9831 and B-31, requirements for HER-2 testing to establish eligibility were tightened in both trials. In N9831, central laboratory testing is now required to establish eligibility. In B-31, IHC tests must now be completed only at approved laboratories. These amendments appear to have significantly improved assay reproducibility. We will assume that 95% of the patients who receive trastuzumab truly have HER-2 positive disease.

Given this set of conditions,

- approximately 9% randomized to a regimen containing trastuzumab will never receive trastuzumab and thus receive no benefit from trastuzumab.

- approximately 0.95 x 0.91 x 100% of the patients randomized to a regimen containing trastuzumab will receive trastuzumab and truly have HER-2 positive tumors and thus potentially benefit from trastuzumab.

- approximately 0.05 x 0.91 x 100% of the patients randomized to a regimen containing trastuzumab will receive trastuzumab and truly have HER-2 negative tumors and thus receive no benefit from trastuzumab.

A 25% reduction in risk is attenuated to (0.91)*(0.95)*25%=21.6%. To achieve at least 90% power at a 0.025 significance level to reject the null hypothesis that the addition of trastuzumab to AC then paclitaxel in the adjuvant setting is not efficacious in favor of the alternative that the addition of trastuzumab yields at least a 25% reduction in the risk (attenuated to 21.6%) of an event, the final analysis will begin when the 710^{th} event has been reported.

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 OS, we assume a mortality rate of 0.047 per year, corresponding to a 5-year survival rate of 79%. 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 710^{th} event is predicted to occur around 12/31/2005. Allowing 6 months for events to be reported and the database locked, we predict that the DFS analysis should occur around 6/30/2006. Similarly, the 710^{th} death is predicted to occur around 12/31/2007. Allowing 6 months for deaths to be reported and the database locked, we predict that the OS analysis will occur around 6/30/2008.

16.9d6 Interim analysis

Semi-annual reports of the progress of the individual trials will be reported to their respective Data Monitoring Committees.

16.9d6.1 Timing

Following the report of the 355th event in both trials combined, the first interim analysis will be conducted. Subsequent interim analyses will coincide with the semi-annual NSABP DMC meetings.

Both the NSABP DMC and the NCCTG DMC will be given a report of the findings of these interim analyses. Decisions regarding reporting combined data early will be jointly made by the NSABP and the NCCTG Data Monitoring Committees.

16.9d6.2 Interim analysis that takes place while enrollment in either trial is ongoing.

If the hypothesis of equivalence is rejected (in favor of the hypothesis that trastuzumab increases DFS) at the nominal one-sided 0.0005 level, the NSABP and NCCTG study teams will jointly consider recommending to their respective Data Monitoring Committees that the findings of the joint analysis be reported.

If N9831 is still open to accrual, the NCCTG study team will also consider recommending that Arm A of N9831 be closed to further accrual and the trastuzumab containing treatment arms continue accrual in an attempt to address whether efficacy differs with respect to administration schedule of trastuzumab.

16.9d6.3 Analysis Plan

At each interim analysis, consideration will be given to stopping the trials early if the hypothesis of equivalence is rejected (in favor of the hypothesis that trastuzumab *increases* DFS) at the nominal one-sided 0.0005 level. If N9831 is still open to accrual, the NCCTG study team will also consider recommending that Arm A of N9831 be closed to further accrual and the trastuzumab containing treatment arms continue accrual in an attempt to address whether efficacy differs with respect to administration schedule of trastuzumab.

Consideration will be given to stopping the trial for futility if the event rate among patients randomized to a trastuzumab-containing regimen exceeds that among patients randomized to a non-trastuzumab-containing regimen. If N9831 is still open to accrual, the NCCTG study team will also consider recommending that Arm C of N9831 be closed to further accrual and Arms A and B continue to accrue in an attempt to examine the relative clinical benefit of the addition of trastuzumab following AC → T chemotherapy.

At the final analysis, the nominal level of the test will be determined by alpha-spending so that the overall type I error rate is .025 (one-sided).

Add 13,15

16.9e Inclusion of women and minorities

This study will be available to all eligible patients, regardless of race or ethnic origin.

Within the United States, lower breast cancer incidence rates have been reported for Blacks, Asians, American Indians, and Hispanics in comparison to non-Hispanic whites (22-25). Yet, Blacks tend to have lower breast cancer survival rates. Several factors are thought to explain this difference. Among them are younger age at diagnosis, delay between onset of symptoms and diagnosis/treatment, higher stage, lower hormone receptor levels, lower socioeconomic levels, and cultural beliefs and attitudes.

There is no information currently available regarding differential effects of these regimens in subsets of patients defined by race or ethnicity. Race was examined as a prognostic factor in the CALGB trial 8541, which assessed three dose levels of CAF in women with node positive breast cancer. After adjusting for CAF dose, extent of nodal involvement, tumor size, receptor status, and age, race was not found to be of prognostic significance (24,25).

An analysis of toxicity patterns and outcome will be carried out in the subsets defined by race and comparisons will be made across racial groups. However, these analyses will have very little statistical power due to small sample sizes expected in each racial subgroups.

If accrual to this study is similar to that of CALGB 9344, we expect about 16% of patients will be classified as minorities by race. Expected sizes of racial by gender subsets are shown in the following table:

	RACIAL/ETHNIC CLASSIFICATION*						
GENDER	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	--	37	370	148	3108	37	3700
Male	--	--	--	--	--	--	--
Total	0	37 (1%)	370(10%)	148(4%)	3108(84%)	37(1%)	3700

Add 10

*Racial and Ethnic Categories:

American Indian or Alaskan Native: A person having origins in any of the original peoples of North American 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.

Add 15

16.9f Data Monitoring Committee (DMC)

In accordance with the NCI's current DMC policy, an external DMC will meet every 6 months in conjunction with the NCCTG semi-annual group meetings to review the progress of this protocol and be kept aware of efficacy and toxicity issues. They will have telephone conferences in the interim, if the need arises. The leadership of this NCCTG adjuvant trastuzumab trial and the leadership of NSABP's adjuvant trastuzumab trial B-31 have agreed to share all relevant cardiotoxicity data with their respective DMCs.

Add 16

16.9g Release of germline DNA data

There are currently no specific germline DNA testing results being generated in this study. Anticipated tests do not currently have significant clinical relevance to the patient or their family members. Therefore, any results generated will not be shared with the patient or physician. To minimize the risk of inadvertent release of such information, when such data are available, these results will be stored in a password protected database separate from the clinical record. The only link between the germline DNA results and clinical record will be via a computer generated id.

Add 17

17.0 Pathology Considerations – The procedures that follow are being done to confirm overexpression but patient eligibility will not be dependent on the findings as results will not be reported until the time of analysis.

Add 2

Because of concerns over false-positive assays, the initial 100 samples will be centrally reviewed by the DAKO HercepTest™ by Dr. Patrick Roche, Director of Immunohistochemistry Laboratory at Mayo Clinic Rochester. These results will not be communicated back to the referring institution nor will they affect eligibility. If a discrepancy (review does not show HER-2 overexpression) occurs in more than 20 of the initial 100 samples, then consideration of performing all the assays centrally will be entertained. The first 100 samples for review will be assayed as they are received and results reported to the data monitor as soon as possible.

Add 7

As of Addendum 7: 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 HER-2 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/pAbl cocktail and CB11 monoclonal. However, due to new information published by Mass et al. (ASCO 2001, abstract #85) that showed that tumors determined to be HER-2 positive by FISH had a better response to trastuzumab than FISH negative tumors, the central assays were changed to HercepTest™ and FISH. There was also an initial provision that if more than 20 of the first 100 samples tested by the central laboratory were found to be neither 3+ by HercepTest® or HE-2 gene amplified by FISH, the possibility of central HER-2 testing for eligibility determination would be considered. Results of this assessment on the first 119 samples received revealed poor agreement with the IHC staining performed by community laboratories and central laboratory; 25% would have been determined to be ineligible if assayed centrally using both the HercepTest™ and FISH. When HercepTest™ and FISH were performed by a central laboratory, there was a 96% concordance rate with the central assays (personal communication, Edith A. Perez, M.D., Sept 2001). See Appendix VI for the quality control results.

Add 15

17.1 HER-2 overexpression by HercepTest® (DAKO)

Add 10

17.11 Dr. Daniel Visscher, Mayo Clinic Rochester will be performing this immunohistochemistry.

17.12 Immunoperoxidase staining for HER-2 will be performed on paraffin-embedded tissue sections. Tissue sections are cut at 4μ and mounted on Superfrost-plus charged slides. Staining with the FDA-approved HercepTest® (Dako Corporation, Carpenteria, CA) will be performed on a Dako Autostainer according to the manufacturer's recommendations. Epitope retrieval will be performed with the citrate solution supplied in the HercepTest® kit in a water bath. After immunostaining, sections are lightly counterstained with hematoxylin, dehydrated, and coverslipped with Permount. All immunostained sections will be evaluated and scored on 0 – 3+ scale according to the criteria established for interpretation of the FDA-approved HercepTest®. These criteria are outlined below:

Interpretation of HER2 Staining

Staining Intensity Score	Staining Pattern	HER2 Overexpression Assessment
0	No staining is present or partial membrane staining is present in <10% of malignant cells.	Negative
1+	Weak/barely perceptible membrane staining is present in >10% of malignant cells, but the cells are only stained in part of their membrane.	Negative
2+	Weak to moderate complete membrane staining is present in >10% of malignant cells.	Weak Positive
3+	Moderate to strong complete membrane staining in present in >10% of malignant cells.	Strong Positive

17.13 Tissue microarray

Add 11

17.131 One of the most important ways to improve the outcome of women with breast cancer is to conduct scientifically sound correlative studies of molecular markers in tumor specimens and correlate them with clinical outcome. Although this has been tried in the past by evaluating single characteristics, molecular techniques have improved to the point where we can analyze more than 20,000 markers at a time, generate clusters of molecular expression and then perform correlative studies. This approach is possible through the preparation and use of tissue microarrays. Specimens from patients on this study are already being evaluated centrally for HER-2 testing. However, we have not been preparing the necessary microarrays that will then allow for the necessary future correlative analysis. We propose to prospectively prepare microarrays at the same time we conduct the central HER-2 testing (this is already being done in the other 3 worldwide studies evaluating trastuzumab in the adjuvant setting). Testing of these microarrays will not be done until a formal proposal is developed and approved by the NCCTG, Breast Intergroup, and NCI. Preparing these specimens will minimize future mailing requests for blocks, minimize time and personnel expenses, and most importantly, expedite future analysis that will have a direct beneficial effect on patients.

Add 11

17.132 Tissue microarrays will be constructed from formalin-fixed, paraffin-embedded primary breast cancer tissue from patients enrolled in N9831. Dr. Visscher will read the HercepTest slides and "dot" with a permanent marker six tumor areas that are most intensely stained. Individual donor blocks are overlaid with the corresponding HercepTest slide, and the areas for tissue microarray sampling are marked. Using instrumentation developed at Mayo Clinic, three cylindrical cores of 0.6 mm diameter are removed from each donor paraffin block and transferred to a recipient paraffin block at defined array positions. Recipient paraffin blocks are previously constructed and modeled to contain appropriate diameter holes in a grid pattern that is maximally 12 holes wide by 18 holes in length for a total of 216 tissue cores per block. This construction design permits multiple blocks with identical array patterns to be constructed simultaneously. For orientation purposes, 29 cores from liver are included in one row of 18 cores and one column of 12 rows (with one shared core at the intersection). The remaining cores are assigned to 60 primary tumor blocks with three cores/block. The remaining three cores from each tumor block will be included in a duplicate array. Approximately 200 sections can be cut from a single tissue microarray.

Add 11

17.2 HER-2 amplification by FISH

17.21 Robert Jenkins, M.D., Ph.D. and his staff, Mayo Clinic Rochester, will be performing the FISH.

17.22 The method of FISH is described in Jenkins et al (30). Briefly, tissue sections will be deparaffinized, dehydrated, incubated in 2 X SSC at 75°C for 15 min, digested in pepsin solution [4 mg/mL in 0.9% NaCl (pH 1.5)] for 15 min at 37°C, rinsed in 2 X SSC at room temperature for 5 min, and air-dried. Dual-probe hybridization using directly labeled fluorescent DNA probes (VYSIS, Downers Grove, IL) for the centromere region of chromosome 17 (CEP17) for HER-2/neu will be performed on a 5-μm section using a Spectrum Green-labeled CEP17 probe together with a Spectrum Orange-labeled probe for HER-2/neu. The probe mixture will be hybridized to an area of the slide containing invasive or *in situ* carcinoma as determined by the study pathologist and on adjacent H&E stained section. Probes and target DNA were denatured simultaneously in an 80°C oven for 5 min, and the slide will be incubated at 37°C overnight. Posthybridization washes will be performed using 1.5 M urea/0.1 X SSC at 45°C for 30 min and 2 X SSC at room temperature for 2 min. Nuclei will be counterstained with 4,6-diamindino-2-phenylindole and antifade compound *p*-phenylenediamine.

17.23 The number of FISH signals will be counted in 300 non-overlapping interphase nuclei from the lesions of interest (invasive adenocarcinoma) with a Zeiss Axioplan microscope equipped with a triple-pass filter (I02-104-1010; VYSIS). Nuclei from stromal elements will not be enumerated. The number of HER-2/neu signals and CEP17 signals will be counted for each nucleus, and an overall mean HER-2/CEP17 ratio will be calculated for each lesion. Lesions with ratios >2.0 will be defined as having HER2/neu amplification.

Add 13

17.3 Follow-up block at time of first breast cancer recurrence

Submission of a tissue block is requested at the time of first breast cancer recurrence (see Section 11.0) if a biopsy is done. This sample will be banked for future research purposes. We plan to evaluate markers that correlate with tumor relapse and patient outcome, based on state of the art scientific knowledge.

Submit along with the pathology report to:

Add 17

NCCTG Operations Office
ATTN: Christy Maszk
NW Clinic
200 First Street, SW
Rochester, MN 55905

Add 2,3,7,8,11,14

17.4 All participating institutions (CALGB, ECOG, NCCTG, SWOG, NCIC CTG)

Add 10,11,13

17.41 Within 14 days of registration, submit the paraffin block or 15 unstained sections at 4 microns on Superfrost Plus slides (Fisher Scientific Catalog #22-034-979) and an H & E stained slide along with a copy of the surgical pathology report and the NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form:

Add 17

NCCTG Operations Office
ATTN: Christy Maszk
NW Clinic
200 First Street, SW
Rochester, MN 55905

17.42 Block or slides should be placed in individual plastic bags and each bag labeled with the cooperative group membership name, study patient number, patient's initials, protocol number, surgical accession number, and source (e.g., primary, nodal).

Add 10
Update 2

17.43 All material will be forwarded to Dr. Wilma Lingle, Mayo Clinic Rochester for processing. All material will be forwarded from the following cooperative group pathology offices to NCCTG.

17.431 ECOG institutions

ECOG Pathology Coordinating Center
Robert H. Lurie Comprehensive Cancer Center of Northwestern
University Medical School
Olson Pavilion – Room 8501
710 North Fairbanks Court
Chicago, IL 60611
Phone: (312) 503-3384
FAX: (312) 503-3385

17.432 CALGB institutions

Add 11

CALGB PCO
The Ohio State University
M364 Starling-Loving Hall
320 West 10th Avenue
Columbus, OH 43210-1239
Telephone: 614-293-7073
Fax: 614-292-5618

Add 17

17.433 SWOG institutions

SWOG Solid Tumor Tissue Bank
The University of Cincinnati
Department of Pathology and Laboratory Medicine
231 Albert Sabin Way
Cincinnati, OH 45267-0529

ATTN: Chris Hackett 1251 MSB
Phone: 513-558-4675
e-mail: hacketcb@UCMAIL.UC.EDU

Or

ATTN: Gayle Gatto 1208 MSB
Phone: 513-558-1848
e-mail: gattoga@uc.edu
Fax: 513-558-2289

Add 14

17.434 NCIC CTG institutions

NCIC CTG institutions

Please see section 17.4 of the protocol for instructions regarding the collection of pathology specimens. Pathology material along with a copy of the surgical pathology report and the NCI Cooperative Group Adjuvant Breast Cancer HER-2 Reporting Form will be forwarded to:

Add 17

NCCTG Operations Office
ATTN: Christy Maszk
NW Clinic
200 First Street, SW
Rochester, MN 55905

Update 2

17.44 Patients who participate in this study will be asked to consent to banking these specimens for future research. For those patients who consent to specimen banking, the samples left over from the central pathology testing will be kept by the NCCTG.

For those patients who do not consent to specimen banking, the samples collected will be returned to their originating institution at the institution's request.

18.0 Records and Data Collection Procedures

18.1 Patient identification labels will be produced for each patient entry. The labels are produced for use on the data forms and will be mailed to the cooperative group offices twice weekly for routing to the randomizing locations. Additional labels may be obtained by directly calling the NCCTG Randomization Center (507) 284-4130.

18.2 Each cooperative group will be responsible for insuring that all materials contain the patient's initials, NCCTG registration number, and NCCTG protocol number. Patient's name must be removed.

Add 7,13,16,18

18.3 Cardiac reporting – Fax all reports and forms ≤14 days to N9831 QCS at 507/538-0962.

Forms due ≤14 days of event	**For Arm A patients who are not eligible to receive trastuzumab or chose not to receive trastuzumab**	**For Arm A patients who chose receive trastuzumab**	**For Arm B patients who chose receive trastuzumab in combination with paclitaxel**	**Arm B where trastuzumab is given sequentially and Arm C**
3-Week Post-AC MUGA/Echocardiogram Report Form	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose	3 weeks after last AC dose
MUGA/Echocardiogram Report Form	6 months from registration	1 month prior to the start of trastuzumab	1 month prior to the start of trastuzumab	3 months after the start of trastuzumab
MUGA/Echocardiogram Report Form	9 months from registration	3 months after the start of trastuzumab	3 months after the start of trastuzumab	6 months after the start of trastuzumab
MUGA/Echocardiogram Report Form	18 months from registration	6 months after the start of trastuzumab	6 months after the start of trastuzumab	3 months after last dose of trastuzumab
MUGA/Echocardiogram Report Form		9 months after the start of trastuzumab	9 months after the start of trastuzumab	
MUGA/Echocardiogram Report Form		15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	15 months after the start of trastuzumab (or 3 months after last dose of trastuzumab)	
Congestive Heart Failure Report Form	Suspicion of Congestive Heart Failure	Suspicion of Congestive Heart Failure	Suspicion of Congestive Heart Failure	Suspicion of Congestive Heart Failure
Cardiac Death Report Form	Death due to cardiac or unknown causes	Death due to cardiac or unknown causes	Death due to cardiac or unknown causes	Death due to cardiac or unknown causes
Longterm Cardiac Follow-up Form	≥6 years post-randomization	≥6 years post-randomization	≥6 years post-randomization	≥6 years post-randomization

Add 17

Add 18

18.4 Data reporting – The following materials are required and are to be submitted by fax or mail directly to the NCCTG Operations Office, ATTN N9831 QCS, (see Section 18.8) according to the following schedule.

Forms	Active-Monitoring Phase (Compliance with Test Schedule)								Observation or Off Treatment Prior to PROG	Event-Monitoring Phase (Completion of Active-Monitoring Phase)	At each occurrence
	Initial Material			Follow-up Material							
	≤14 days after registration	≤14 days from registration	≤9 months from registration	At each evaluation	At end of treatment	At end of all adjuvant hormonal therapy	At time of first breast cancer recurrence		Q 3 months for 1 year q 6 months for years 2-5 then yearly for a maximum of 15 years or until PROG	Yearly for a maximum of 15 years	New primary
Pathology Material (See Section 17.0 re each respective group)		X					X (see Section 17.3)				
Blood Draw Schedule (ECOG, CALGB, SWOG)	X[3]						X (see Section 14.17)				
Blood Draw Schedule (NCCTG)	X[3]			X[2,3]			X (see Section 14.17)				
Update 1 Baseline Blood Specimen Submission for Cardiac Markers Form	X[4]										
Update 1 Active Monitoring Blood Specimen Submission for Cardiac Markers Form				X[4]							
Add 17 Active Monitoring Blood Specimen Submission for Genetic Testing Form[5]				X[5]	X[5]	X[5]			X[5]	X[5]	
Add 17 NCI Cooperative Group Adjuvant Breast Cancer Tissue Specimen Submission for Collection of Baseline Tissue Form				X[6]	X[6]	X[6]			X[6]	X[6]	
NCI Cooperative Group Adjuvant Breast Cancer Tissue Specimen Submission for 1st Breast Cancer Recurrence Form											
NCI Cooperative Group Adjuvant Breast Cancer On-Study Form	X										
Eligibility checklist, path report, MUGA/echocardiogram reports	X[3]										
NCI Cooperative Group Adjuvant Breast Cancer Treatment Summary – All Patients				X							
NCI Cooperative Group Adjuvant Breast Cancer Radiotherapy Report Form[1]					X (at end of RT)						
NCI Cooperative Group Adjuvant Breast Cancer Follow-up Form					X (end of chemo/ HERCEP)				X	X	X
NCI Cooperative Group Adjuvant Breast Cancer Hormonal Therapy Form			X								
NCI Cooperative Group Adjuvant Breast Cancer Termination of Hormonal Therapy Form						X					
Add 16 Post Joint Analysis Arm A/B Start of Herceptin Treatment Form					X (at end of chemo)						
Add 18 Longterm Cardiac Follow-up Form									**X**[7]		

1. For patients who do not receive any scheduled radiation therapy, submit a radiation therapy reporting form with the reason radiation was not given.
Update 1 2. At 3-month intervals for the first year and at 6-month intervals for Years 2 through 5 for 35 patients per treatment arm for a total of 105 patients.
3. Faxed to N9831 QCS at 507-538-0962.
4. For submission time points, refer to Section 14.311. Fax directly to the Operations Office at ≤24 hours of specimen collection for all patients.
Add 17 5. One blood specimen per patient to be submitted at any time during active treatment, observation or event monitoring.
Add 17 6. Tissue specimens collected one time per patient, to be submitted at any time during active treatment, observation or event monitoring, if not previously submitted.
Add 18 Update 2 Update 3 7. Longterm cardiac follow-up should be done one time for **all** patients still in observation after patient reaches 6 years post-registration. Patients >6 years post-registration as of 26Sep2008, should have exam at next clinical visit after Addendum 18 is approved by the local IRB, but no later than December 31, 2009. Data from a clinical LVEF evaluation (if done) may be reported for patients in event monitoring.

Add 8

18.5 Any materials deemed incomplete by the NCCTG Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate institution responsible for the patient.

18.6 Overdue lists: A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate cooperative group will be responsible for contacting the patients' institutions in order to obtain the overdue material.

Add 8

18.7 Correction forms: If a correction is made by NCCTG, a correction form will be sent to the appropriate institution to make the correction on the institution's form. In cases of disagreement with a given correction, a query letter may be written.

Add 8,13,14,17

18.8 <u>All participating institutions (CALGB, ECOG, NCCTG, SWOG, NCIC CTG)</u>:

Materials should be submitted at the required intervals directly to:

NCCTG Operations Office
ATTN: N9831 QCS
Northwest Clinic Room 3-24
200 First Street SW
Rochester, MN 55905

<u>NCIC CTG institutions:</u>

Add 19

[This section has been removed at the request of NCIC CTG since no patients were enrolled through NCIC CTG.]

Update 3

NCIC CTG Sample Consent Form
[This section has been removed at the request of NCIC CTG since no Canadian centers participated through NCIC CTG.]

On Site Monitoring/Auditing
NCIC CTG on-site auditing will be conducted at active participating centres at least once every three years during the course of the study. The auditors will require access to REB files and patient medical records to verify appropriate ethical review the data submitted on CRFs.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care.

Add 7

19.2 Tests to be research funded: IHC and FISH assays done centrally at Mayo Clinic Rochester to confirm overexpression as well as sHER-2 and sHER-1 assays (Section 14.0) are funded by Genentech Inc.

19.3 Other budget concerns:

Add 4,7,8,13

19.31 Funding will be provided for **ejection fraction only** MUGA scans/echocardiograms at 3-week post-AC, 6, 9, and 18 months and 1 repeat. The baseline MUGA scans/echocardiograms will be the responsibility of the patient or third-party payers. The budgeted costs associated with these are $475 for the MUGA and $170 for the echocardiogram, which are in line with Medicare charges.

Up to $10 will be provided for handling costs associated with the blood draws (see Forms Packet for reimbursement request).

Add 12,13

Funding will also be provided for the congestive heart failure evaluation (hemoglobin [$50 maximum], serum troponin I [$50 maximum], MUGA [$450 maximum]/echocardiogram [$170 maximum], optional 12-month stress MUGA

Add 18

or stress echocardiogram [full reimbursement after NCCTG invoices Genentech]).

Add 18

19.32 Submit reimbursement requests (see Forms Packet for ***current*** reimbursement request form) to:

N9831 Reimbursement
NCCTG Operations Office
200 First Street SW PL-4
Rochester, MN 55905

19.33 Trastuzumab will be provided free of charge by the NCI.

Add 18

19.34 Funding will also be provided for the post 6-year **ejection fraction only** resting MUGA scans or echocardiograms (must match post-AC assessment). Maximum payments are: $1000 (one thousand US dollars) for one **ejection-fraction only** resting MUGA per patient OR $700 (seven hundred US dollars) for **ejection-fraction only** resting echocardiogram per patient.

Sites will also be paid $50 (fifty US dollars) per patient for the submission of the completed Longterm Cardiac Follow-up Form. Sites may request reimbursement after NCCTG receives the accurately completed form.

A separate Longterm Cardiac Follow-up Reimbursement Form will be provided with Amendment 18.

20.0 References

1. Bland KI, Menck HR, Scott-Conner C, et al: The national cancer data base 10-year survey of breast carcinoma treatment at hospitals in the United States. Cancer 83:1262-1273, 1998.

2. Perez EA: Paclitaxel in Breast Cancer. The Oncologist 3:373-389, 1998.

3. Henderson IC, Berry D, Demetri G, et al: Improved disease free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (pts) with node-positive breast cancer (BC). Proc Am Soc Clin Oncol 17:101a, 1998.

4. Nabholtz JM, Gelmon K, Bontebal M, et al: Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858-1867, 1996.

5. Winer E, Berry D, Dugan D, et al: Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer - results from CALGB 9342. Proc Am Soc Clin Oncol 17:101a, 1998.

6. Winer E: Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer - results from CALGB 9342. Oral presentation, American Society of Clinical Oncology Annual Meeting, Los Angeles, CA, 1998.

7. Seidman AD, Hudis CA, Albanel J, et al: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:3353-3361, 1998.

8. Perez EA, Irwin DH, Patel R, et al.: A large phase II trial of paclitaxel administered as a weekly one-hour infusion in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 18:126a(abstr 480), 1999.

9. Perez EA: Personal communication, June 1999.

10. E1199 study, 1999.

11. Perez EA: Her-2 as a prognostic, predictive, and therapeutic modality in breast cancer. Cancer Control 6(3):233-240, 1999.

12. Baselga J, Tripathy D, Mendelsohn J, et al: Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 14:737-744, 1996.

13. Cobleigh MA, Vogel CL, Tripathy NJ, et al: Efficacy and safety of Herceptin (humanized anti-HER-2 antibody) as a single agent in 222 women with HER-2 overexpression who relapsed following chemotherapy for metastatic breast cancer. Proc Am Soc Clin Oncol 17:97a (abstr 376), 1998.

14. Slamon D, Leyland-Jones B, Shak S, et al: Addition of Herceptin (humanized anti-HER-2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2/MCB) markedly increases anticancer activity: a randomized multinational controlled phase III trial. Proc Am Soc Clin Oncol 17:98a (abstr 377), 1998.

15. Pegram M: Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p 185-Her2/neu monoclonal antibody plus cisplatin in patients with Her2/neu overexpressing metastatic breast cancer refractory to chemotherapy treatment. J Clin Oncol 16:2659-2671, 1998.

16. Vogel CL, Cobleigh MA, Tripathy D. et al.: Efficacy and safety of Herceptin (trastuzumab, humanized anti-Her2 antibody) as a single agent in first-line treatment of Her2 overexpression in metastatib breast cancer (Her2 +/MBC). Breast Cancer Res Treat 50:232 (abstract), 1998.

17. Seidman AD: Personal communication, November 1998.

18. Fornier M, Seidman AD, Esteva FJ, et al.: Weekly (w) Herceptin (H) + 1 hour Taxol (T): phase II study of Her2 overexpressing (H2+) and nonoverexpressing (H2-) metastatic breast cancer (MBC). Proc Am Soc lin Oncol 18:126a, 1999 (Abstract #482)

19. Reiter JL and Maihle NJ: A 1.8 kb alternative transcript from the human epidermal growth factor receptor gene encodes a truncated form of the receptor. Nucleic Acids Res., 24:4050-4056, 1996.

20. Baron, A. T., J. M. Lafky, et al.: A sandwich type acridinium-linked immunosorbent assay (ALISA) detects soluble ErbB1 (sErbB1) in normal human sera. J. Immunol. Methods 219: 23-43, 1998.

21. Baron, A. T., J. M. Lafky, et al.: Serum sErbB1 and EGF levels as tumor biomarkers in women with stage III or IV epithelial ovarian cancer. Cancer Epidemiology Biomarkers & Prevention 8: 129-137, 1999.

22. NCI: Cancer among blacks and other minorities: Statistical profiles. NIH Publication No. 86-2785, Rockville, MD, NCI. 1986.

23. Savitz DA: Changes in spanish surname cancer rates relative to other whites, Denver area, 1969-71 to 1979-81. Am J of Public Health. 76:1210-15, 1986.

24. Le Marchand L: Ethnic variation in breast cancer survival: A review. Breast Cancer Research and Treatment. 18 Suppl 1:S119-26, 1991.

25. Lannin DR, Mathews HF, Mitchell J, Swanson MS, Swanson FH, and Edvards MS: Influence of socioeconomic and cultural factors on racial differences in late stage presentation of breast cancer.JAMA:279(22):1801-1807, 1998.

26. Pocock SL and Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115, 1975.

27. Peto R and Peto J: Asymptotically efficient rank invariant procedures (with discussion). J. R. Statist. Soc. Series A, 135:185-207, 1972.

28. Cox DR: Regression models and life-tables (with discussion). J. R. Statist. Soc., Series B, 34:187-220, 1972.

29. Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. JSAS 53:457-481, 1967.

30. Jenkins RB, Qian J, Lieber MM, Bostwick DG: Detection of c-myc oncogene amplification and chromosomal anomalies in metastatic prostatic carcinoma by fluorescence *in situ* hybridization (FISH). Cancer Res 57:524-531, 1997.

31. Greenfield C, Hiles I, et al.: Epidermal growth factor binding induces a conformational change in the external domain of its receptor. EMBO J. 8: 4115-4123, 1989.

32. Hurwitz DR, Emanuel SL, et al.: EGF induces increased ligand binding affinity and dimerization of soluble epidermal growth factor (EGF) receptor extracellular domain. J. Biol. Chem. 266: 22035-22043, 1991.

33. Lax I., Fischer R, et al.: Noncontiguous regions in the extracellular domain of EGF receptor define ligand-binding specificity. Cell Regulation 2: 337-345, 1991.

34. Cadena DL and Gill GN: Expression and purification of the epidermal growth factor receptor extracellular domain utilizing a polycistronic expression system. Protein Expr. Purif. 4: 177-186, 1993.

35. Basu A, Raghunath M, et al.: Inhibition of tyrosine kinase activity of the epidermal growth factor (EGF) receptor by a truncated receptor form that binds to EGF: role for interreceptor interaction in kinase regulation. Mol. Cell. Biol. 9: 671-677, 1989.

36. Weber W, Gill GN, et al.: Production of an epidermal growth factor receptor-related protein. Science 224: 294-297, 1984.

37. Petch LA, Harris J, et al.: A truncated, secreted form of the epidermal growth factor receptor is encoded by an alternatively spliced transcript in normal rat tissue. Mol. Cell. Biol. 10: 2973-2982, 1990.

38. Flickinger TW, Maihle NJ, et al.: An alternatively processed mRNA from the avian c-*erbB* gene encodes a soluble, truncated form of the receptor that can block ligand-dependent transformation. Mol. Cell. Biol. 12: 883-893, 1992.

39. Nieto-Sampedro M: Astrocyte mitogen inhibitor related to epidermal growth factor receptor. Science 240: 1784-1786, 1988.

40. Nieto-Sampedro M and Broderick JT: A soluble brain molecule related to epidermal growth factor receptor is a mitogen inhibitor for astrocytes. J. Neurosci. Res. 22: 28-35, 1989.

41. Lin YJ and Clinton GM: A soluble protein related to the HER-2 proto-oncogene product is released from human breast carcinoma cells. Oncogene 6: 639-643, 1991.

42. Zabrecky JR., Lam T, et al.: The extracellular domain of p185/*neu* is released from the surface of human breast carcinoma cells, SK-BR-3. J. Biol. Chem. 266: 1716-1720, 1991.

43. Lan KKG and DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70(3):659-63, 1983.

Add 10 44. Green MC, Buzdar A, Smith T et al: Weekly (wkly) paclitaxel (P) followed by GAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC-final results. Proc Am Soc Clin Oncol 2000 (abstract #135). Accessed from http://www.asco.org.

Add 10 45. Konecny G, Thomssen M, Pegram H et al: HER-2/neu gene amplification and response to paclitaxel in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 2001 (abstract #88). Accessed from http://www.asco.org.

Add 10 46. ECOG E1199: Phase III atudy of doxorubicin-cyclophosphamide therapy followed by paclitaxel or docetaxel given weekly or every 3 weeks in patients with axillary node-positive or high risk node-negative breast cancer. Accessed from http://www.ecog.org.

Add 10 47. CALGB C40101: Phase III randomized trial of adjuvant cyclophosphamide and doxorubicin versus paclitaxel in women with high-risk node negative breast cancer. Accessed from http://www.calgb.org.

Add 10 48. Allred DC, Clark GM, Tandon AK, et al: HER-2/neu in node negative breast cancer: prognostic significance of overexpression influenced by the presence of in situ carcinoma. Classic Papers and Current Comments 5(4):900-907, 2001.

Add 10 49. Andrulis I, Bull M, Blackstein D, et al: Neu/erbB-2 amplification identifies a poor prognosis group of women with node negative breast cancer. J Clin Oncol 16:1340-1349.

Add 10 50. Goldhirsch A, Glick J, Gelber R, et al: Meeting highlight: International consensus panel on the treatment of primary breast cancer. J Clin Oncol 19:3817-3827.

Add 10 51. Gusterson BA, Gelber RD, Goldhirsch A, et al: Prognostic important of c-erbB-2 expression in breast cancer. Classic Papers and Current Comments 5(5):908-916, 2001.

Add 10 52. Press M, Bernstein L, Thomas P, et al: HER-2/neu gene amplification characterized by florescence in situ hybridization: Poor prognosis in node negative breast carcinomas. J Clin Oncol 15:2894-2904, 1997.

Add 10 53. BCIRG 006: A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, carboplatin, and trastuzumab (TCH) in the adjuvant treatment of node positive and high risk node negative patients with operable breast cancer containing the HER2 alteration. Personal communication, Alessandro Rive, M.D., 2002.

Add 10 54. Breast International Trial Group, HERA: A randomized three-arm multi-centre comparison of one year and two years of Herceptin® versus no Herceptin® in women with HER2 positive primary breast cancer who have completed adjuvant chemotherapy. Personal communication, 2002.

Add 11 55. Petricoin EF, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, Steinberg SM, Mills GB, Simone C, Fishman DA, Liotta LA. Use of proteomic patterns in serum to identify ovarian cancer. Lancer 359:572-577, 2002.

Add 11 56. Petricoin EF, Paweletz CP, Liotta LA. Clinical applications of proteomics: Proteomic pattern diagnostics. J Mammary Gland Biology & Neoplasia 7:433-440, 2002.

Add 11 57. Ma X-J, Salinga R, Tuggle JT, et al: Gene expression profiles of human breast progression. PNAS 100:5974-5979.

Add 12 58. Coombes RC, Hall E, Gibson LJ, et al: A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. NEJM 350(11):1081-1092, 2004.

Add 12 59. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. NEJM 349(19):1-10, 2003.

60. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 91:710-717, 1979.

61. Dresdale A, Bonow RO, Wesley R, et al. Prospective evaluation of doxorubicin-induced cardiomyopathy resulting from postsurgical adjuvant treatment of patients with soft tissue sarcomas. *Cancer* 52:51-60, 1983.

62. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, Ingle JN, Rodeheffer RJ, Gersh BJ, Jaffe AS. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol 22:3700-4.

63. Swain SM, Whaley FS, Gerber MC, et al. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. *J Clin Oncol* 15:1333-1340, 1997.

64. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235:177-182, 1987.

65. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244:707-712, 1989.

66. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001.

67. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinelli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2000;36(2):517-22.

68. Mair J, Friedl W, Thomas S, et al. Natriuretic peptides in assessment of left-ventricular dysfunction. *Scand J Clin Lab Invest Suppl* 230:132-142, 1999.

69. Fruhwald FM, Fahrleitner A, Watzinger N, et al. Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy. *Eur Heart J* 20:1415-1423, 1999.

70. Chen HH & Burnett JC. Natriuretic peptides in the pathophysiology of congestive heart failure. *Curr Cardiol Rep* 2:198-205, 2000.

71. Pemberton CJ, Yandle TG, Rademaker MT, et al. Amino-terminal proBNP in ovine plasma: evidence for enhanced secretion in response to cardiac overload. *Am J Physiol* 275:H1200-2008, 1998.

72. Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 87:1402-1412, 1991

73. Valli N, Gobinet A, Bordenave L, et al. Review of 10 years of the clinical use of brain natriuretic peptide in cardiology. *J Lab Clin Med* 134:437-444, 1999.

74. Chien K, Zhao Y, Crone S. ErbB2 Myocyte survival pathways are essential in the prevention of dilated cardiomyopathy. *Herceptin Investigator's Meeting*, 2000.

75. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 90:195-203, 1994.1994

76. Clerico A, Lervasi G, Del Chicca M, et al. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. *J Endocrinol Invest* 21:170-179, 1998.

77. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351:9-13, 1998.

78. Yu CM, Sanderson JE, Shum IO, et al. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J* 17:1694-1702, 1996.

79. Yu CM & Sanderson JE. Plasma brain natriuretic peptide—an independent predictor of cardiovascular mortality in acute heart failure. *Eur J Heart Fail* 1:59-65, 1999.

80. Suzuki T, Yamaoki K, Nakajima O, et al. Screening for cardiac dysfunction in asymptomatic patients by measuring B-type natriuretic peptide levels. *Jpn Heart J* 41:205-214, 2000.

81. Tsutamoto T, Wada A, Maeda K, et al. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. *Eur Heart J* 20:1799-1807, 1999.

82. Waku S, Iida N, Ishihara T. Significance of brain natriuretic peptide measurement as a diagnostic indicator of cardiac function. *Methods Inf Med* 39:249-253, 2000.

83. Yoshitomi Y, Nishikimi T, Kojima S, et al. Plasma natriuretic peptides as indicators of left ventricular remodeling after myocardial infarction. *Int J Cardio* 64:153-160, 1998.

84. Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. *Heart* 81:114-1120, 1999.

85. Friedl W, Mair J, Thomas S, et al. Natriuretic peptides and cyclic guanosine 3',5'-monophosphate in asymptomatic and symptomatic left ventricular dysfunction. *Heart* 76:129-136, 1996.

86. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amironovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent care setting. J Am Coll Cardiol 2001;37(2) 379-85.

87. Maisel AS, Koon J, Krishnaswamy P, Kazanegra R, Clopton P, Gardetto N, Morrisey R, Garcia A, Chiu A, De Maria A. Utility of B-natriuretic peptide as a rapid, point-od-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001;141(3):367-74.

88. Jaffe AS. CONCISE REVIEW: Troponins in Cardiovascular Diagnosis and Assessment of Prognosis. Harrison's Online Textbook of Internal Medicine. E Braunwald section editor. McGraw Hill, 1999.

89. Missov E and Mair J. A novel biochemical approach to congestive heart failure: cardiac troponin T. *Am Heart J* 138:95-99, 1999.

90. Del Carlo CH & O'Connor CM. Cardiac troponins in congestive heart failure. *Am Heart J* 138:646-653, 1999.

91. Ravkilde J, Nissen H, Horder M, et al. Independent prognostic value of serum creatine kinase isoensyme MB mass, cardiac troponin T and myosin light chain levels in suspected acute myocardial infarction. Analysis of 28 months of follow-up in 196 patients. *J Am Coll Cardiol* 25:574-581, 1995.

92. Setsuta K, Seino Y, Takahashi N, et al. Clinical significance of elevated levels of cardiac troponin T in patients with chronic heart failure. *Am J Cardiol* 84:608-611, 1999.

93. Ottani F, Galvani M, Nicolini FA, Ferrinin D, Pozzati A, Di Pasquale G, Jaffe AS. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Hear J 2000;140(6):917-27.

94. Lopez-Jimenez F, Goldman L, Sacks DB, et al. Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. *J Am Coll Cardiol* 29:1241-1245, 1997.

95. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. Circulation 1997; 96(9):2953-8.

96. Jaffe AS. Elevations in cardiac troponin measurements: False false-positives. Cardiovascular Toxicology 2001; 1(2): 87-92.

97. Ooi DS, Zimmerman D, Graham J, Wells GA. Cardiac troponin T predicts long-term outcomes in hemodialysis patients. Clin Chem 2001;47(3):412-7.

98. Missov E, Calzolari C, Davy JM, Leclercq F, Rossi M, Pau B. Cardiac troponin I in patients with hematologic malignancies. Coron Artery Dis 1997;8(8-9):537-41.

99. Feldman AM, Combes A, Wagner D, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol* 35:537-544, 2000.

100. Ceconi C, Curello S, Bachetti T, et al. Tumor necrosis factor in congestive heart failure: a mechanism of disease for the new millennium? *Prog Cardiovasc Dis* 41:25-30, 1998.

101. Nozaki N, Yamaguchi S, Shirakabe M, et al. Soluble tumor necrosis factor receptors are elevated in relation to severity of congestive heart failure. *Jpn Circ J* 61:657-664, 1997.

102. Liu L & Zhao SP. The changes of circulating tumor necrosis factor levels in patients with congestive heart failure influenced by therapy. *Int J Cardiol* 69:77-82, 1999.

103. Tsutamoto T, Wada A, Maeda K, et al. Angiotensin II type 1 receptor antagonist decreases plasma levels of tumor necrosis factor alpha, interleukin-6 and soluble adhesion molecules in patients with chronic heart failure. *J Am Coll Cardiol* 35:714-721, 2000.

104. Gullestad L, Aukrust P, Ueland T, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. *J Am Coll Cardiol* 34:2061-2067, 1999.

105. Torre-Amione G, Vooletich MT, Farmer JA. Role of tumor necrosis factor-alpha in the progression of heart failure: therapeutic implications. *Drugs* 59:745-751, 2000.

106. Petretta M, Condorelli GL, Spinelli L, et al. Circulating levels of cytokine and their site of production in patients with mild to severe chronic heart failure. *Am Heart J* 140:E28, 2000.

107. Pulkki KJ. Cytokines and cardiomyocyte death. *Ann Med* 29:339-343, 1997.

108. Prabhu SD, Chandrasekar B, Murray DR, et al. Beta-adrenergic blockade in developing heart failure: effects on myocardial inflammatory cytokines, nitric oxide, and remodeling.

109. Thaik CM, Calderone A, Takahashi N, et al. Interleukin-1 beta modulates the growth and phenotype of neonatal rat cardiac myocytes. *J Clin Invest* 96:1093-1099, 1995.

110. Harada E, Nakagawa O, Yoshimura M, et al. Effect of interleukin-1 beta on cardiac hypertrophy and production of natriuretic peptides in rat cardiocyte culture. *J Mol Cell Cardiol* 31:1997-2006, 1999.

111. Francis SE, Holden H, Holt CM, et al. Interleukin-1 in myocardium and coronary arteries of patients with dilated cardiomyopathy. *J Mol Cell Cardiol* 30:215-223, 1998.

112. Pannitteri G, Marino B, Campa PP, et al. Interleukins 6 and 8 as mediators of acute phase response in acute myocardial infarction. *Am J Cardiol* 89:622-625, 1997.

113. Gabriel AS, Ahnve S, Wretlind B, et al. IL-6 and IL-1 receptor antagonist in stable angine pectoris and relation of IL-6 to clinical findings in acute myocardial infarction. *J Inter Med* 248:61-66, 2000.

114. Kubota T, Miyagishima M, Alvarez RJ, et al. Expression of proinflammatory cytokines in the failing human heart: comparison of recent-onset and end-stage congestive heart failure. *J Heart Lung Transplant* 19:819-824, 2000.

115. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 31:391-398, 1998.

116. Deng MC, Erren M, Lutgen A, et al. Interleukin-6 correlates with hemodynamic impairment during dobutamine administration in chronic heart failure. *Int J Cardiol* 57:129-134, 1996.

117. Roig E, Orus J, Pare C, et al. Serum interleukin-6 in congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 82:688-690, 1998.

118. Plenz G, Song ZF, Reichenberg S, et al. Left-ventricular expression of interleukin-6 messenger-RNA higher in idiopathic dilated than in ischemic cardiomyopathy. *Thorac Cardiovasc Surg* 46:213-216, 1998.

119. Orus J, Roig E, Perez-Villa F, et al. Prognostic value of serum cytokines in patients with congestive heart failure. *J Heart Lung Transplant* 19:419-425, 2000.

120. Maeda K, Tsutamoto T, Wada A, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. *J Am Coll Cardiol* 36:1587-1593, 2000.

121. Ottani F, Galvani M, Nicolini FA, Ferrini D, Pozzati A, DiPasquale G, Jaffe A. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. [Journal Article. Meta-Analysis] American Heart Journal 140(6):917-27, 2000 Dec.

122. Galvani M, Ottani F, Ferrini D, Ladenson JH, Destro A, Baccos D, Rusticali F, Jaffe AS. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. [Journal Article] Circulation 95(8):2053-9, 1997 April 15.

123. James S, Armstrong P, Califf R, Simoons ML, Venge P, Wallentin L, Lindahl B. Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: prospective verification in the GUSTO-IV trial. [see comment]. [Clinical Trial. Journal Article. Multicenter study. Randomized Controlled Trial. Validation Studies] American Journal of Medicine 115(3):178-84, 2003 Aug 15.

124. Morrow DA, Cannon CP, Rifai N. Frey MJ, Vicari R, Lakkis N, Robertson DH, Hille DA, DeLucca PT, DiBattiste PM, Demopoulos LA, Weintraub WS, Braunwald E. TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. [See comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] JAMA 286(19):2405-12, 2001 Nov 21.

125. Morrow DA, Antman EM, Tanasijevic M, Rifai N, de Lemos JA, McCabe CH, Cannon CP, Braunwald E. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. [Journal Article. Multicenter Study] Journal of the American College of Cardiology. 36(6):1812-7, 2000 Nov 15.

126. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST and B-type natriuretic peptide. [Journal Article] Circulation 105(15):1760-3, 2002 Apr 16.

127. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. [see comment]. [Clinical Trial. Controlled Clinical Trial. Journal Article] Circulation 107(22):2786-92, 2003 Jun 10.

128. Morrow DA, de Lemos JA, Sabatine MS, Murphy SA, Demopoulos LA, DiBattiste PM, McCabe CH, Gibson CM, Cannon CP, Braunwald E. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. [see comment] [erratum appears in J Am Coll Cardiol. 2003 May 21;41(10):1852]. [Journal Article] Journal of the American College of Cardiology 41(8):1264-72, 2003 Apr 16.

129. James SK, Armstrong P, Barnathan E, Califf R, Lindahl B, Siegbahn A, Simoons ML, Topol EJ, Venge P, Wallentin L, GUSTO-IV-ACS Investigators. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. [see comment]. [Journal Article] Journal of the American College of Cardiology, 41(6):916-24, 2003 Mar 19.

130. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. [see comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] New England Journal of Medicine. 343(16):1139-47, 2000 Oct 19.

131. Meinardi MT, van der Graaf WT, van Veldhuisen DJ, et al. Detection of anthracycline-induced cardiotoxicity. *Cancer Treat Rev* 25:237-247, 1999.

Appendix I

Add 17 ***NOTE: This consent form is no longer in use as of Addendum 16***

TITLE: N9831, Phase III Trial of Doxorubicin and Cyclophosphamide (AC) Followed by Weekly Paclitaxel With or Without Trastuzumab as Adjuvant Treatment for Women With HER-2 Over-expressing or Amplified Node Positive or High-Risk Node Negative Breast Cancer (an Intergroup Study)

Add 10

PARTICIPANTS:

This is an important form. Please read it carefully. It tells you what you need to know about this study. If you agree to take part in this research study, you need to sign the form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why Is This Study Being Done?

This study is being done to:

- see if the addition of Herceptin® to standard chemotherapy drugs (Adriamycin®, Cytoxan®, and Taxol®) is beneficial for women with node positive and high risk node negative breast cancer whose tumors have an excess amount of the HER-2 gene. Herceptin® is an antibody that attacks cancer cells and may be able to control tumor growth. Herceptin® alone has been taken in research studies by many patients with breast cancer for periods of over 12 months and was well tolerated.

Add 13

- better understand how chemotherapy and trastuzumab (also known as Herceptin®) affect heart function by collecting blood samples at different time points.

How Many People Will Take Part In The Study?

Add 10,15 Up to 3,700 patients are expected to take part in this clinical trial.

What Will Happen In The Study?

Add 7 You will have a full medical history and physical examination taken along with blood tests, chest x-ray, an electrocardiogram (a test that records the electrical activity of your heart), a MUGA or echocardiogram (a test that learns the function of your heart), a mammogram, and other tests that the doctor might feel are needed to fully learn about your disease and see if you can be on this study. One of the items we will look at is the HER-2 score of your breast cancer obtained by your local community pathologist. This score is obtained by looking at certain cells in your tissue and how they are affected when they are stained. If your score is in the acceptable range, which means that your breast cancer tissue has increased amounts of HER-2, you will be registered to get Adriamycin® and Cytoxan® (AC) by vein over about 30 minutes one day every three weeks for a total of four treatments. However, we have found in previous cases that these scores differ from laboratory to laboratory. Therefore, your tissue will also be sent to different laboratories at Mayo Clinic Rochester for confirmation of the score. If the score is not confirmed, you will not be able to continue taking part in this study and the rest of your treatment will be according to your doctor's further discussions with you. It has been recognized that patients who do not have a high HER-2 score do not respond to Herceptin® treatment and we would not want to expose you to any undue side effects. This will occur in about 25% of the patients who go on this study. You and your doctor will be informed of this before completing the AC chemotherapy part of your treatment.

After all treatment with AC is done (about week 12) and you are allowed to continue treatment, within this study, you will be put in one of the study groups by chance. It is like flipping a coin. Which group you are put in is done by a computer. You and the doctor cannot choose what group you will be in.

Arm A - You will get Taxol® by vein over 1 hour one day every week for a total of 12 treatments. You will NOT get Herceptin®. Total length of treatment will be about six months.

Day 1 of Weeks 13-24	Taxol®

Arm B - You will get Taxol® by vein over 1 hour one day every week for a total of 12 treatments. After all treatment with Taxol® is done (about week 24), you will get Herceptin® by vein one day every week for one year. The first dose of Herceptin® will be given over about 90 minutes. You will be watched for 1 hour after the first dose of Herceptin®. If you do well this first dose, other doses will be given over about 30 minutes. Total length of treatment will be about 18 months.

Add 7,8

Add 7

Day 1 of Weeks 13-24	Taxol®
Day 1 of Weeks 25-77	Herceptin®

Add 8,9

Arm C - You will get Taxol®, by vein over 1 hour plus Herceptin® by vein one day every week, for a total of 12 treatments. After all treatment with Taxol® plus Herceptin® is done (about week 24), you will get Herceptin® alone one day every week for ten months. The first dose of Herceptin® will be given over about 90 minutes. You will be watched for 1 hour after the first dose of Herceptin®. If you do well this first dose, other doses will be given over about 30 minutes. Total length of treatment will be about one year.

Add 4,7,8

Add 7

Day 1 of Weeks 13-24	Taxol® and Herceptin®
Day 1 of Weeks 25-65	Herceptin®

Regardless of which treatment arm you are on, at the end of all chemotherapy (Adriamycin®, Cytoxan®, Taxol®) you may also get tamoxifen, a hormonal therapy, for five years if your tumor is estrogen or progesterone receptor positive. If you are postmenopausal and your tumor is estrogen or progesterone receptor positive, you could get an anti-estrogen drug called an aromatase inhibitor (which could be either anastrozole, letrozole, or exemestane as per discussions between you and your doctor) for five years instead of tamoxifen. If you are postmenopausal and are already taking TAM, you will continue to take it for five years and then be able to take an aromatase inhibitor for an additional five years. Both tamoxifen and aromatase inhibitors are given by mouth each day; they have been proven helpful in lessening the risk of the return of breast cancer. Your doctor will talk this over with you. It is a part of standard care and not a part of the research question being asked in this study.

Add 8,12

If your surgery was a lumpectomy (removal of the tumor and surrounding tissue but not the entire breast), you will also get radiation therapy after your chemotherapy has ended. Radiation therapy may also be given for some patients who have had a mastectomy (removal of the entire breast and underlying tissue). Your doctor will talk this over with you.

Optional Biology Studies

Add 10,11

This study also has research laboratory tests that will use a small sample of blood (about 2 tablespoons) collected by drawing some blood from a vein. The blood will be taken just before treatment starts. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your doctor, and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Add 11,12

You can take part in the treatment part of this study without taking part in giving the extra blood for research purposes.

Please read the following statements and mark your choice:

1. I agree to give blood samples, before I start treatment, to laboratories associated with NCCTG for research testing.

   ☐ Yes ☐ No Please initial here:_____ Date:_____

Add 12,13

If your disease comes back, you will be asked to have a blood sample taken, and if you have a biopsy done, a part of your biopsy tissue will be sent to NCCTG laboratories for banking purposes for future research of breast cancer. The investigators plan to evaluate various blood and tissue markers that will help them to better understand how your cancer responds to treatment based on state of the art scientific knowledge at that time.

You can take part in the treatment part of this study without taking part in giving the extra blood and extra tissue at the time your disease comes back for research purposes.

Please read the following statements and mark your choice:

1. I agree to give my blood and tissue (if a biopsy is done) samples at the time of my first breast cancer recurrence to laboratories associated with NCCTG for future research testing.

   ☐ Yes ☐ No Please initial here:_____ Date:_____

Optional Cardiac Marker Studies

The investigators also want to better understand how chemotherapy and Herceptin® affects heart function by collecting blood samples at different time points. The blood will be tested for heart markers, substances in the blood that may give clues that heart damage has happened. We do not know if these markers will show heart damage or if they will be able to tell who is at risk for heart damage. The results of these research blood tests will not be told to you or your study doctor. They will not be used to change any of your treatments given in N9831. The blood taken will not be used for genetic research. You will not have to pay for any of these tests.

Add 13,14 All patients enrolled on this study as of December 24, 2004 may have a blood sample (2 tablespoons) before starting treatment and within one hour after the 1) first or second dose of AC, 2) the first or second dose of paclitaxel (Arm A and B of N9831), 3) the first or second dose of paclitaxel plus Herceptin® (Arm C of N9831, and 4) the first or second dose of Herceptin® given alone (Arm B and C of N9831).

Please read the following statements and mark your choice:

Add 13,14 1. I agree to give a blood sample before starting treatment and within one hour after the 1) first or second dose of AC, 2) the first or second dose of paclitaxel (Arm A and B of N9831), 3) the first or second dose of paclitaxel plus Herceptin® (Arm C of N9831, and 4) the first or second dose of Herceptin® given alone (Arm B and C of N9831).

☐ Yes ☐ No Please initial here:_____ Date:_____

How Long Will I Be In The Study?

You will be followed on the study for about 15 years.

What Are The Risks Of The Study?

The treatment of breast cancer uses powerful drugs that have side effects, some very serious, but rarely fatal. You may need to be admitted to the hospital for treatment of the side effects. Every effort will be taken to lessen side effects, but there is no way to tell which side effects may happen or how bad they may be. Unless otherwise stated, the side effects are reversible.

Bone marrow suppression (all drugs): The drugs used to kill cancer cells also kill some normal body cells, especially those that grow fast (blood cells, hair, cells that line the mouth, stomach, and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells), and causing blood to clot (platelets). A lowering in the number of these blood cells can lead to an increased risk of bleeding, infection, and tiredness. Should these happen, they can be treated with transfusions and antibiotics.

Hair loss (all drugs): Hair will fall out about three weeks after the first dose of chemotherapy but will grow back when chemotherapy has stopped. Hair color may change slightly and hair is sometimes curlier.

Nausea and vomiting, loss of appetite (all drugs): If needed, medication will be prescribed.

Fever (all drugs): May happen in the absence of infection. More commonly, a fever is a sign of infection in patients getting chemotherapy. If you have a fever, chills, rigors (severe shaking), or any other signs or symptoms of an infection, it is very important that you call your doctor at once.

Sensitivity to sunlight (Adriamycin®): Take care in sunbathing or going out in the sun because your skin will be more sensitive and may burn more easily than normal. Use a sun screen lotion with a SPF of at least 15.

Liver irritation (Taxol®): Liver inflammation is temporary, usually mild, and does not lead to any long-term damage. Liver failure and destruction of liver cells are less common but are more serious side effects.

Mouth and throat sores, diarrhea (Adriamycin®, Taxol®): Temporary irritation to the mouth and the lining of the bowel may lead to mouth ulcers (similar to canker sores) and to watery diarrhea.

Darkening of the nail beds (Adriamycin®, Taxol®): Temporary darkening of the nail beds is possible but not harmful.

Neurologic abnormalities (Taxol®, Herceptin®): Temporary unsteadiness when walking, lightheadedness, dizziness, headache, tingling of the fingers and toes, muscle weakness, loss of reflexes, sensation of flashing lights and blurred vision may happen. More serious side effects are rare but have happened with higher doses: cranial nerve paralysis, seizures, and death.

Watery or sore eyes (Adriamycin®): The eyes may itch, water, and become sensitive to bright light.

Changes in menstrual cycle (Cytoxan®): Your periods may temporarily be irregular and may stop permanently. In some, but not all cases, patients will be unable to become pregnant.

Heart (Adriamycin®, Taxol®, Herceptin®): A small number of patients given Adriamycin® over a period of months (at cumulative doses usually higher than those used in this treatment plan) have had shortness of breath and swollen ankles because of heart muscle weakness. There is a possibility that giving Herceptin® with Adriamycin® may increase the risks of heart failure. Because of this, your heart function will be carefully followed during this study. Report any of these symptoms to your doctor. Irregular heartbeat sometimes happens during or following Taxol® infusion. Slowing of the heart rate, which is usually not noticed by the patient, is the most common. There may be fluid accumulation around the heart. Rarely, serious and life-threatening abnormal heart rhythms and heart attacks have happened. Should this happen, Taxol® and/or Herceptin® will be stopped and appropriate treatment will be given.

Add 11,12

Add 13,14 **Lung (Taxol®, Herceptin®):** Infiltrates (inflammation) with potential difficulty breathing. This is a rare, but potentially serious side effect.

Discolored urine (pink or red) (Adriamycin®): This may happen up to 48 hours after the drug is given. This is ***not*** due to blood and is not harmful.

Kidney damage (Cytoxan®): Very unlikely but the risk is lower by drinking plenty of fluids.

Bladder irritation (Cytoxan®): May rarely cause burning on urination or bloody urine. This can be lessened by drinking plenty of fluids. Drink whatever you like during the day of the injection and for two more days. Empty your bladder often. If unable to drink fluids or pass urine or if urine is bloody, call your doctor. Other measures may be taken to lessen the risks of bladder irritation if any sign of this happens in a patient.

Mild allergy (Cytoxan®): Nose stuffiness, sinus congestion, sneezing, watery eyes, and running nose may happen during or immediately after injection of the drug.

Severe allergic reaction (Taxol®, Herceptin®): A fast heart rate, wheezing, low blood pressure, sweating, itching and a face rash may happen within a few minutes of treatment. These reactions have sometimes been avoided by medications given before treatment and can usually be controlled with steroids or adrenaline if they happen. This reaction is rarely severe or fatal the first time. If you become allergic, your doctor will talk about the possible risks versus benefits of continuing treatment. You will be watched closely while treatment is given and medication for controlling an allergic reaction will be immediately available. Death due to hypersensitivity
Add 1 reaction has happened. Severe reactions may be more common in patients who already have breathing problems or lung disease. Although medications will be available to lessen reactions, they may not prevent them. If you develop any chest discomfort during or after a treatment with
Add 4,11 Herceptin®, you should contact your doctor immediately or go to the nearest emergency care facility.

The Herceptin® will contain benzyl alcohol, a preservative that has been known to cause toxicity in newborns. This drug should not be given to anyone with a known sensitivity to benzyl alcohol.

Skin ulcer (Adriamycin®, Herceptin®): This drug can be irritating to the tissue if it leaks out of the vein. Tell the person giving the drug if you feel any burning, stinging, or pain while the drug is being given. If the area of injection becomes red and swollen after the injection, notify your doctor at once. In the unlikely event of a severe reaction, deep tissue damage may result, and a skin graft may be needed.

Flu-like symptoms (Taxol®): Headache, muscle aches, joint pain, low back pain, tiredness, drowsiness, and weakness may happen.

Tamoxifen: Tamoxifen may cause changes in the lining of the uterus (endometrium). In addition, in a few patients tamoxifen has been associated with an increased risk of uterine cancer. Of course, if you have had a total hysterectomy, there is no risk of getting uterine cancer.

Tamoxifen side effects that frequently happen are hot flushes; a feeling of being sick to the stomach; throwing up; menstrual irregularities including vaginal discharge, bleeding, and dryness. An infrequent side effect is abnormal occurrence of blood clots. Women taking tamoxifen may be at a slightly higher risk for getting cataracts (a clouding of the lens inside the eye). As women age, they are more likely to get cataracts whether or not they take tamoxifen. Cataracts may lead to poor vision. Tamoxifen can raise sensitivity to blood thinners such as coumadin.

Add 10 **Anastrozole:** Common side effects (happens in greater than 5% of patients): Hot flushes, fluid retention (swelling in legs, puffiness around the eyes, generalized), pain (in chest, bone, and pelvic areas, in legs and joints, and at the tumor site); headache, dizziness, depression, rash, feeling sick to the stomach, throwing up, loose stools, abdominal pain, loss of appetite, dry mouth, muscle weakness, tingling of the arms and leg, shortness of breath, cough, inflammation of the throat area. Less common side effects
(happens in 2-5% of the patients): High blood pressure, inflammation of the veins, problems sleeping, confusion, anxiety, fever, nervousness, feeling out of sorts, hair thinning, rash, breast pain, weight loss, infections (upper and lower respiratory tract and urinary tract), loss of energy, lowered blood counts that can lead to infection and bleeding and bruising, muscle and joint pain, neck pain, inflammation of the nose and throat areas, flu-like symptoms, infection, possible fracture.

Add 10 **Letrozole:** Common side effects (happens in more than 10% of patients): Hot flushes, headache, tiredness, feeling sick to the stomach, pain (in chest, rib, and back areas, in legs and joints, muscles, and at the tumor site), shortness of breath, cough. Less common side effects (happens in 2-9% of patients): Chest pain, fluid retention (swelling in legs, puffiness around the eyes, generalized), high blood pressure, problems sleeping, dizziness, depression and anxiety, rash, loss of hair, breast pain, throwing up, trouble passing stool, loose stools, abdominal pain, loss of appetite, weight loss or weight gain, increase in cholesterol levels, stomach discomfort after eating. Rare side effects (happens in less than 2% of patients): Blood clots, heart problems (heart attack, coronary artery disease, etc.).

Add 10 **Exemestane:** Common side effects (happens in more than 9% of patients): Hot flashes; fatigue; pain (in chest, rib, and back areas, in legs and joints, and at the tumor site); problems sleeping; depression or anxiety; difficulty with breathing; feeling sick to the stomach; decreased number of a type of blood cell called lymphocytes, which could increase your chance of infection. Less common side effects (happens in about 3 to 9% of patients): Dizziness, sweating, fluid retention (swelling in legs, puffiness around the eyes, generalized), high blood pressure, burning or prickling sensations, skin rash, itching, flu-like symptoms, fever, coughing, infections (upper and lower respiratory tract and urinary tract), weakness, weight gain, throwing up, loose stools, abdominal pain, loss of appetite, increased appetite, constipation, intestinal or stomach discomfort, headache, hair loss, confusion, numbness or loss of feeling, especially in hands and feet. Rare but serious side effects may include changes in blood test results that indicate problems with liver and/or kidney function.

Add 15

Add 11 Exemestane causes breaks in the genetic material (DNA) of human cells grown in the laboratory. Studies to test whether exemestane causes cancer in rats and mice have not been completed yet, but it is known that drugs that cause breaks in DNA sometimes cause cancer in people

Radiation therapy: During radiation therapy, you may get some or all of the following side effects: Redness and irritation of the skin in the area being treated. After ending radiation therapy, you may get none, some, or all of the following side effects: Tanning and dryness of the skin in the treatment area, swelling of the arm, and chest or breast discomfort. Less common side effects may be lung or heart injury, broken rib(s), reduced arm motion, or the start of another cancer. Herceptin® when used with radiation may make the radiation-induced side effects to be worse and may cause side effects related to the heart.

This study may be harmful to an unborn or breast-fed child. Effective nonhormonal contraceptive methods (condoms, diaphragm, intrauterine device [IUD], surgical sterilization, abstinence) must be used by you or your sexual partner while involved in this study and for at least two months after the study's discontinuation. Women who can still become pregnant must have a pregnancy test before taking part in this study. The pregnancy test requires a urine test or a blood test be drawn from a vein within 7 days prior to the study. If the pregnancy test is positive, you will not be able to take part in the study. You will be told the results of the pregnancy test prior to initiation of this study.

Are There Benefits To Taking Part In This Study?

No benefit can be guaranteed by taking part in this study, and the chance of benefit from this study cannot be accurately predicted.

Will Any Biological Sample(s) Be Stored and Used In The Future?

Add 3 You have had a biopsy (or surgery) to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to make decisions about your care. We would like to keep some of the tissue and blood that is left over for future research. This tissue and blood will be stored and may be used in research to learn more about cancer and other diseases. The samples may be stored for a long time, even after your death. You have a say in how your stored samples are used in future research. You can still take part in the treatment study without giving your samples. Some of the future studies may

Add 8 or may not be testing the genes that you inherited from your parents (also known as genetic testing). Reports about the research done with your tissue and/or blood will not be given to you or your doctor because the research will not have an effect on your care.

Your samples will be stored safely and will be given a code (rather than your name) when it is used in research. This code will allow your samples to be used without anyone knowing that it is your sample.

Add 4,5,8 Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may lead to the development of new products in the future.

Add 7 Please read each sentence below and think about your choice. After reading each sentence, circle the answer that is right for you. If you have any questions, talk to your doctor or nurse.

Add 10 1. I permit my blood sample to be stored and used for future research to learn about, prevent, treat, or cure cancer.

Please mark one box:
☐ Yes ☐ No Please initial here:_____ Date:_____

Add 10 2. I permit my blood sample to be stored and used in future research for other medical questions (for example, causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).

Please mark one box:
☐ Yes ☐ No Please initial here:_____ Date:_____

Add 10

3. I permit my tissue sample to be stored and used for future research to learn about, prevent, treat, or cure cancer.

Please mark one box:
☐ Yes ☐ No Please initial here:_____ Date:_____

Add 10

4. I permit my tissue sample to be stored and used in future research for other medical questions (for example, causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).

Please mark one box:
☐ Yes ☐ No Please initial here:_____ Date:_____

5. I agree that someone may contact me in the future to ask me to take part in more research.

Please mark one box:
☐ *Yes* ☐ *No* Please initial here:_____ Date:_____

6. I have been given the question and answer sheet called "What is tissue banking?"

Please mark one box:
☐ **Yes** ☐ **No** Please initial here:_____ Date:_____

What Other Choices Do I Have if I Don't Take Part In This Study?

Other choices are different forms of chemotherapy, other experimental treatments, radiation therapy, or you have the option of choosing no treatment. You should talk to your doctor about each of these choices before you decide if you will take part in this study.

What Are The Costs of Tests and Procedures?

You and/or your health plan will need to pay for all tests and procedures that are part of this study because they are needed for your regular medical care. The drugs Adriamycin®, Cytoxan®, Taxol®, and tamoxifen are commercially available. Herceptin® will be provided free of charge.

Add 7,8,12,

You and/or your health plan will need to pay for all costs associated with administration of this treatment. The blood draw for research purposes will be done at the same time as the blood draws needed for your regular medical care. Baseline MUGA scan/echocardiogram will be paid for by you or your health plan as these are clinically indicated tests when receiving AC treatment. The study will reimburse $475 for MUGA scans or $170 for echocardiograms done following AC treatment and at 6, 9, 18 months, and one repeat, if needed. If your institution will charge more than that, you need to check with your health insurer to see if these additional charges will be covered. You or your health plan might also have to pay for other drugs or treatments that are given to help you control side effects.

Add 13,14

If you have congestive heart failure, the follow-up testing will be paid for as follows: hemoglobin ($50 maximum), serum troponin ($50 maximum), MUGA ($475 maximum) or echocardiogram ($l70 maximum). If a stress MUGA or stress echocardiogram is done it will be reimbursed 100%.

Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

What Are My Rights If I Take Part In This Study?

Taking part in this research study is your decision. You do not have to take part in this study, but if you do, you can stop at any time. Whether you take part or don't take part will not affect the medical care you get now or in the future.

The investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. You will be told of important new findings or any changes in the study or procedures that may happen.

Who Can Answer My Questions?

You may talk to Dr. (_____), telephone (_____), at any time about any question you have on this study.

Where Can I Get More Information About Clinical Trials?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Add 9

Visit the NCI Web site: http://www.cancer.gov/

What Happens If I Am Injured Because I Took Part In This Study?

You will not get free medical care or payment for any bad side effects from taking part in this study. Medical services will be given at the usual charge. You can get further information about policies, the conduct of this study, or the rights of research subjects from ( ).

What About Confidentiality?

Data from this study may be published. However, your name and other identifying information will not be sent outside without written permission unless the law allows it. Your medical record will be used by the investigators in this study. ECOG patients: Records of patient progress while on the study will be kept in a confidential file at the Eastern Cooperative Oncology Group, the Cancer and Leukemia Group B, the Southwest Oncology Group, the National Cancer Institute of Canada Clinical Trials Group, and North Central Cancer Treatment Group. Representatives of Genentech, Inc. will be able to look at your medical records to check the entries on the case report forms. Your medical records may also be made available to the North Central Cancer Treatment Group, the National Cancer Institute, and the Food and Drug Administration as provided in federal regulations.

Add 14

I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in this study.

_____ _____
(Date) (Signature of Participant)

_____ _____
(Date) (Signature of Individual Obtaining Consent)

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What Are The Risks Of The Study" or "What Other Choices Do I Have If I Don't Take Part In This study?" should always be tried to be used in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This should be specific for each institution.

Appendix II

RADIATION THERAPY GUIDELINES

BACKGROUND

Postoperative radiation therapy (RT) is an integral component of breast conservation therapy (1), and whole breast RT +/- tumor bed RT boost will be administered to all patients treated with lumpectomy. For patients treated with mastectomy and axillary node dissection for axillary node-positive disease, postoperative chest wall and regional nodal RT may also be of benefit (2,3). However, consensus regarding indications for its use and the technical details of its administration is not currently available (4,5). Thus, the use of regional nodal RT (in patients treated with whole breast RT after lumpectomy) or the use of postmastectomy chest wall and regional nodal RT is at investigator discretion. However, investigators must declare at the time of randomization whether the patient will receive RT (see Sections 3.19c and 3.19d), and if so, they must describe the nature of the RT treatment area (see Section 12.2).

Add 10

Although Overgaard *et al.* (2) and Ragaz *et al.* (3) incorporated internal mammary chain (IMC) RT into the postmastectomy setting, it remains uncertain whether exclusion of the IMC nodes is detrimental to patient outcome (5-7). Due to concerns about cardiac toxicity associated with Adriamycin and Herceptin®, *IMC RT will not be administered within the context of this study*. The following RT guidelines are provided for use in association with this clinical study:

WHOLE BREAST RT

All patients who underwent a breast preserving surgical procedure will receive postoperative RT in accordance with the following:

Time to Treatment: RT will begin within five weeks after Taxol treatment is completed and may be given concurrently with Herceptin® +/- TAM therapy. Although occasionally necessary for medical reasons, delays in initiation of RT beyond the specified interval are discouraged.

Treatment Planning: Treatment planning on a simulator for each field treated with photon RT is recommended. The whole breast and underlying chest wall should be treated through opposed medial and lateral tangential fields. A half-beam block (i.e., beam-splitting), or gantry angulation, technique should be used to achieve coplanarity (i.e., non-divergence) of the deep field margins.

> Patient Position: The patient should be supine, +/- table wedge, with the ipsilateral arm abducted approximately ≥ 90° and supported appropriately.
>
> Field Margins: As clinically determined, these should be 1.5-2.0 cm around palpable or radiologically-evident breast tissue in all four directions (superior, inferior, medial, lateral).

Blocks: Blocking material or multileaf collimation with ≥ 5 HVL attenuation will be utilized in the half beam block technique to comply with field margin and normal tissue dose requirements. In addition, in those patients receiving regional nodal RT, blocking at the superior border of the tangential fields may be necessary to obtain a precise matchline with the nodal field.

Normal Tissues: No more than 3.0 cm (demagnified) of lung will be included within the tangential fields as measured along the transverse plane of the central axis. For left-sided primary tumors, care will be taken to exclude as much of the heart as possible from the tangential fields.

Treatment Equipment: Megavoltage units with peak photon energies of ≤ 6 MV should be used. An occasional (large breasted) patient may be treated with 10 MV if necessary to comply with dose homogeneity requirements. A source-axis distance or source-skin distance of ≥ 100 cm should be used.

Doses: A total cumulative dose of 45.0 Gy-50.4 Gy should be delivered in 25-28 fractions of 1.8 Gy-2.0 Gy; the dose should be prescribed at a point 2/3 the distance from the apex of the breast to the deep margin at midseparation of the beams (for source-to-skin set ups) or at the isocenter (for source-to axis set-ups). Both tangential fields should be treated once per day, 5 days per week, for a total duration of approximately five weeks.

Beam Verification (Port) Films: Beam verification films on the radiation treatment machine should be obtained of each treatment field until satisfactory. Thereafter, beam verification films of each treatment field should be obtained each 5-10 treatments and at the time of any field modification(s).

Dosimetry: A transverse contours at the central axis (or at the central aspect of the field), should be obtained. Employing computerized dosimetry for the above-mentioned contours, the maximum dose inhomogeneity should be +10% (measured by an isodose area >2 cm^2 rather than "hot spots") and -5%. It is expected that compensating blocking and wedge filters or tissue compensating devices would be used to maximize dose homogeneity.

BREAST TUMOR BED RT (BOOST)

The use of an RT boost is optional and the decision to administer a boost may be based on the physician's assessment of the extent of the surgical resection and pathologic measurement of the tumor-free margin. If used, the boost should be initiated upon completion of the whole breast RT. Either electron beam or interstitial implants are acceptable; a cone-down photon beam boost is discouraged.

Electron Boost: Employ a field size and energy to fully encompass the lumpectomy site. For secondary collimation, an insert (template) material with ≤5% transmission will be employed. An additional target dose of 10 Gy-20 Gy (total dose to the primary tumor site of 60 Gy-66 Gy) should be administered in 1.8 Gy-2.2 Gy once daily fractions, 5 days per week. Care will be taken in selecting beam energies so as to minimize dose to the underlying lung +/- heart.

Implant Boost: The implant should be tailored so that a dose of 10 Gy-16 Gy is prescribed (at 40-60 cGy/hr) to the reference isodose, which should be chosen to smoothly encompass the implant volume and minimize any contiguous isodose volume of 150% x the reference dose (or dose rate). Tubes should not be closer to the skin than 1 cm (where they parallel the skin surface), and sources should not be closer to the skin than l cm at tube entry/exit points. Orthogonal films and isodose plans of the implant should be done.

POST-MASTECTOMY CHEST WALL RT

Time to Treatment: RT will begin within five weeks after Taxol treatment is completed and may be given concurrently with Herceptin® +/- TAM therapy. Although occasionally necessary for medical reasons, delays in initiation of RT beyond the specified interval are discouraged.

Treatment Planning: Treatment planning on a simulator is recommended in all patients, and for each field treated with photon RT. The entire chest wall should be treated through opposed medial and lateral tangential photon fields. A half-beam block (i.e., beam-splitting), or gantry angulation, technique should be used to achieve coplanarity (i.e., non-divergence) of the deep margins. For patients in whom the surgical incision and/or drain site(s) extend beyond the tangential photon field margins, an *en face* electron beam field(s) may be used to treat this area(s) in continuity with the photon fields.

Patient Position: The patient should be supine +/- table wedge, with the ipsilateral arm abducted approximately ≥ 90° and supported appropriately .

Field Margins (opposed tangential fields): The field margins may be defined as follows: Superior -at the level of the inferior aspect of the sternoclavicular joint. Inferior - 2 cm inferior to the level of the contralateral inframmamary fold. Medial - the anterior midline. Lateral - the mid-axillary line.

Field Margins (electron beam): The margins will include the surgical incision and/or drain site(s) with a 3 cm geometric margin, and will be treated in continuity with the photon tangential fields.

Blocks: Blocking material or multileaf collimation with ≥ 5 HVL attenuation will be utilized in the half beam block technique to comply with field margin and normal tissue dose requirements; in addition, blocking at the superior border of the photon, tangential fields may be necessary to obtain a precise matchline with the nodal field. For electron beam secondary collimation, an insert (template) material with ≤ 5% transmission will be employed.

Normal Tissues: No more than 3.0 cm (demagnified) of lung will be included within the tangential fields as measured along the transverse plane of the central axis. For left-sided primary tumors, care will be taken to exclude as much of the heart as possible from the tangential fields.

Bolus Material: To assure adequate superficial (skin) dose in the opposed tangential photon fields, bolus may be used, as necessary, to achieve an erythematous skin reaction.

Treatment Equipment Megavoltage units with peak photon energies of ≤ 6 MV may be used to treat the opposed medial and lateral tangential photon fields. For the supplemental electron beam field(s), when used, energies of 6-9 MeV may be selected. A source-axis distance or source-skin distance of ≥ 100 cm is recommended.

Doses: A total cumulative dose of 45.0 Gy-50.4 Gy should be delivered in 25-28 fractions of 1.8 Gy-2.0 Gy; the dose should be prescribed at a point 2/3 the distance from the chest wall skin surface to the deep margin at midseparation of the beams (for source-to-skin set ups) or at the isocenter (for source-to axis set-ups). Both tangential fields should be treated once per day, 5 days per week, for a total duration of approximately five weeks.

Beam Verification (Port) Films: Beam verification films on the RT treatment machine should be obtained of each treatment field until satisfactory. Thereafter, beam verification films of each treatment field should be obtained each 5-10 treatments and at the time of any field modification(s).

Dosimetry: A transverse contour at the central axis (or at central aspect of the field), should be obtained for the purpose of generating composite isodose distributions. Employing computerized dosimetry for the above mentioned contours, the maximum dose inhomogeneity allowed will be +10% (measured by an isodose area > 2 cm^2 rather than "hot spots") and -5%. It is expected that wedge filters or tissue compensating devices will be used to maximize dose homogeneity.

Chest Wall RT Boost: The use of an RT boost (e.g., mastectomy scar) is optional and the decision to administer a boost may be based on the physician's assessment of the extent of the surgical resection and pathologic measurement of the tumor-free margin. If used, the boost should be initiated upon completion of the chest wall RT. An electron beam approach is acceptable; a cone-down photon beam boost is discouraged.

Electron Boost: Employ a field size and energy to fully encompass the site. For secondary collimation, an insert (template) material with ≤5% transmission will be employed. An additional target dose of 10 Gy-20Gy (total dose to the primary tumor site of 60 Gy-66Gy) should be administered in 1.8 Gy-2.2 Gy once daily fractions, 5 days per week. Care will be taken in selecting beam energies so as to minimize dose to the underlying lung +/- heart.

REGIONAL LYMPHATIC RT

RT to the supraclavicular and axillary lymph node regions may be employed at the physician's discretion and should be given concurrent with whole breast or chest wall RT. For patients in whom sentinel node biopsy only was performed, strong consideration to regional lymphatic RT should be given. The intent of this treatment field should be to treat the supraclavicular and axillary lymph nodes proximal to (i.e., beyond) the axillary dissection. However, in patients with extension of carcinoma beyond the confines of the lymph node capsule (i.e., extracapsular extension) and/or ≥ 4 involved axillary lymph nodes, the entire axillary contents may be treated. *No attempt will be made to include the internal mammary lymph nodes within a separate treatment field, within the supraclavicular/axillary nodal fields (i.e., the "hockey stick") or within the breast tangential treatment fields.*

Treatment Planning: Treatment planning on a simulator is required in all patients and for each field treated with photon radiation.

Patient Position: The patient should be supine, +/- table wedge, with the ipsilateral arm abducted approximately >90° and supported appropriately.

Technique: The preferred method of treatment should be through a photon beam field angled into the ipsilateral side at approximately 10°-15° so as to avoid RT of the entire trachea, esophagus, and spinal cord (e.g., for treatment of the right side, the field direction would be left anterior oblique).

Field Margins: The field margins should be defined as follows:

Superior - level of the thyrocrycoid membrane. If necessary, a trapezial ridge "splash" block to avoid fall off over the skin surface may be used.

Inferior - to coincide with the superior border of the medial breast or chest wall tangential field. Commonly, this will be at the level of the inferior aspect of the sternoclavicular joint. A half beam block technique, so as to avoid field divergence, is strongly encouraged.

Medial – approximately 1cm to the contralateral side of the anterior midline. A superior-medial block to shield the spinal cord should, if necessary, be used with oblique treatment techniques and should be used with AP techniques to limit spinal cord cumulative maximum dose to < 45 Gy.

Lateral - the location of this border should be determined by the extent of axillary lymph node involvement and may be defined as follows: a) axillary apical and supraclavicular nodal RT - the lateral field margin should extend approximately 1.5 cm lateral to the surgical clips (when so placed) or to the medial-most aspect of the humeral head; b) full axillary and supraclavicular nodal RT - the lateral field margin should be extended to the level of the mid-humeral head. Blocking should be used to shield the humeral head. It is recommended that full axillary RT be administered in the patient who underwent only a sentinel node biopsy.

Field Margins (posterior axillary boost): In patients with extensive axillary node involvement, a posterior-to-anterior (PA) field may be used with field margins defined as follows:

Superior - coracoid process; blocking bisects clavicle in craniocaudal dimension.

Inferior - to coincide with the inferior margin of the supraclav/axillary field.

Medial - junction of 1st rib and clavicle, medially.

Lateral - to coincide with the lateral margin of the supraclav/axillary field; if necessary, blocking should be used to shield the humeral head.

Treatment Equipment: Megavoltage units with peak photon energies ≤ 6 MV should be used. A source-skin distance of ≥ 100 cm should be used.

Doses: For the supraclavicular/axillary field, a total cumulative dose of 45.0 Gy-50.4 Gy specified at the medial supraclavicular fossa (off axis point) to a depth of 3 cm should be delivered in 25-28 fractions of 1.8-2.0 Gy. This field should be treated once per day, 5 days per week for a total duration of approximately five weeks.

For patients in whom the full axilla is treated, a posterior axillary boost may be used to supplement dose fall-off from the supraclavicular/axillary field. A total cumulative dose of 45.0 Gy-50.4 Gy (that includes the dose contribution from the anterior-oblique supraclavicular/axillary field) specified at midplane should be delivered at central axis of the posterior axillary boost field at a once per day rate of 1.8-2.0 Gy, five days per week, over approximately five weeks. Treatment of this field should be given concurrently with the supraclavicular/axillary field.

Beam Verification (port) Films: Beam verification films on the radiation treatment machine should be obtained of each treatment field until satisfactory. Thereafter, beam verification films of each treatment field should be obtained each 5 treatments and at the time of any modification(s).

REFERENCES

1. Anonymous. NIH Consensus Conference. Treatment of early-stage breast cancer. *JAMA*. 1991; 265:391-395.
2. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82B trial. *NEnglJMed*. 1997; 337:949-955.
3. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *NEnglJMed*. 1997; 337:956-962.
4. Goldhirsch A, Glick JH, Gelber RD, Senn HJ. Meeting Highlights - International Consensus Panel On the Treatment of Primary Breast Cancer. *JNatlCancer Inst*. 1998; 90:1601-1608.
5. Recht A, Bartelink H, Fourquet A, et al. Postmastectomy radiotherapy: questions for the twenty-first century. *JClinOncol*. 1998; 16:2886-9.
6. Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer*. 1983; 51:1941-3.
7. Arriagada R, Le MG, Mouriesse H, et al. Long-term effects of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *RadiotherOncol*. 1988; 11:213-222.

.

Appendix III

NCI/Genentech Inc. Cooperative Research and Development Agreement for Development of Trastuzumab

The agent(s) (hereinafter referred to as "Agent(s)"), trastuzumab, used in this protocol is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Genentech Inc. (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment, Diagnosis and Centers. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.

2. For a clinical protocol where there is an investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). Clinical trial data developed under a CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) 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 Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) 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:

    Regulatory Affairs Branch, CTEP, DCTDC, NCI
    Executive Plaza North, Room 718
    Bethesda, Maryland 20892
    Fax 301/402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

Appendix IV

EVALUATION OF CARDIAC TOXICITY

To evaluate the benefits and risks of continuing trastuzumab 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 trastuzumab in patients with node-positive, HER2-positive breast cancer.

The following guidelines are recommended:

Add 3

Schedule each patient's MUGA scan/echocardiogram at the same radiology facility throughout the study.

Add 10

There are several conditions wherein a repeat MUGA scan/echocardiogram 4 weeks later is required. Please refer to Section 8.4222 for Arm A and Section 8.56411 for Arms B and C.

In some patients, anthracycline-induced myocardial dysfunction may occur months after doxorubicin is discontinued. Therefore, it is important to monitor myocardial function throughout the study in Arm A as well as Arms B and C to determine whether, and to what degree, there may be additional myocardial toxicity associated with trastuzumab in the adjuvant setting.

In the decision to continue or stop trastuzumab in an asymptomatic patient, both the *specific ejection fraction and the change in ejection fraction from baseline* must be considered.

Patients should be monitored for signs and symptoms of congestive heart failure (CHF) (i.e., dyspnea, tachycardia, cough, neck vein distension, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.). Patients who develop these signs and symptoms must permanently discontinue trastuzumab.

Appendix V

As of Addendum 11, this appendix has been deleted.

Appendix VI

HER-2 Quality Control Results

Add 7

Central HER-2 testing was performed using HercepTest™ and FISH on the first 119 samples received by the NCCTG. 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 1. Three quarters of the 119 women were found to have tumor specimens that were either HER-2 gene amplified and HER-2 expressed or HER-2 overexpressed but not HER-2 gene amplified.

Table 1: HER-2 Quality Control Results of First 119 Tissue Samples

Test Used for Eligibility	Central HercepTest™		Central FISH		Negative by Both Central Assays
	0-2+	3+	Not Amplified	Amplified	
HercepTest™ 3+ (n=59)	15(25%)	44 (75%)	22(37%)	37(63%)	15(25%)
Other IHC (n=51)	14(27%)	37(73%)	15(29%)	36(71%)	14(27%)
FISH (n=9	2(22%)	7(78%)	3(33%)	6(67%)	2(22%)

Appendix VII AJCC 5th Edition Cancer Staging Manual – Breast
[no longer needed for patient care/protocol evaluation]

NCI Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

---

version date: 07Jun2006

Add 17 Added as of Addendum 16 – ***Re-consent required for all patients with Addendum 16***

N9831 Phase III Trial of Doxorubicin and Cyclophosphamide (AC) Followed by Weekly Paclitaxel With or Without Trastuzumab as Adjuvant Treatment for Women With HER-2 Over-expressing or Amplified Node Positive or High-Risk Node Negative Breast Cancer

POST-JOINT ANALYSIS CONSENT FORM

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

You are being asked to take part in this research study because you have been enrolled in N9831.

Why is this research study being done?

Recently released results from the N9831 study and two similar studies at other organizations (NSABP B-31 and the HERA trial) suggest that trastuzumab treatment helps to prevent breast cancer from coming back for a longer time. We are now offering trastuzumab (Herceptin®) treatment to all people enrolled on N9831, no matter which study group they were assigned to when
Add 17 they started this study, if their health is good enough and they meet study requirements to do so.

The purpose of this research study is to

- **follow people who were enrolled in N9831 prior to the release of results from a joint analysis with another study (NSABP B-31).**
- **allow people who were enrolled in N9831 in Group A (Arm A) to receive experimental trastuzumab (Herceptin®), if they are eligible.**
- **allow people who were enrolled in N9831 in Group B (Arm B) to receive experimental trastuzumab (Herceptin®) sooner than planned, if they are eligible.**
- **create a sample resource of genetic material of all persons enrolled in this study.**
- **better understand how genetics affects the risk of heart problems while taking the study medications.**

How many people will take part in the research study?

About 3500 people will take part in this study.

What will happen if I take part in this research study?

You have already been enrolled in the N9831 study, and you have already received testing and
Add 17 treatment. You will continue to receive treatment, testing and follow-up on N9831.

If you have not already received trastuzumab (Herceptin®), you will have testing including MUGA scans or echocardiograms (Echos) to make sure that your heart is healthy enough for you to take trastuzumab. If the tests on your heart show you are eligible to take trastuzumab, you will be given the choice to take experimental trastuzumab or not. The trastuzumab used for this study is called "experimental" because it may not be exactly the same as commercial Herceptin®. (For example, it may be made in a different plant or packaged differently.)

In addition, all patients who have entered this study will be asked for an additional blood sample for genetic testing. Giving this blood sample is optional. We are hoping to learn more about whether genetics (traits you inherit from your parents) affect whether a person is more likely to have heart problems during cancer treatment.

The following table shows which patients can receive trastuzumab and when:

Study Group	Where you are	What will happen
A	You are currently receiving AC (chemotherapy).	Follow Group C schedule for treatment and cardiac testing.
A	You have completed AC treatment, and are currently getting paclitaxel, and you have had an acceptable post-AC MUGA/Echo according to study guidelines for trastuzumab	Trastuzumab can be added to the paclitaxel. You may continue trastuzumab until 52 weeks from the start of the trastuzumab. You will have cardiac testing (heart testing with MUGA scans or echocardiograms) done at 3, 6, 9, and 18 months from start of trastuzumab.
A	You have completed AC treatment, you are receiving paclitaxel, and your MUGA/Echo results DID NOT fall within the guidelines for trastuzumab	Trastuzumab MAY NOT be given. You will continue to follow Group A schedule for treatment and cardiac testing.
A	You have completed both AC and paclitaxel, and it is no more than 6 months after you completed paclitaxel (completed chemotherapy on or after October 25, 2004) and you had an acceptable MUGA or Echo within the last month according to trastuzumab guidelines. *Note: If the post-AC MUGA/Echo was done more than 1 month ago, schedule another MUGA/Echo which will decide whether trastuzumab may be started.*	Trastuzumab can be given. You may continue trastuzumab until 52 weeks from the start of the trastuzumab. You will have cardiac testing (heart testing with MUGA scans or echocardiograms) done at 3, 6, 9, and 18 months from start of trastuzumab.
A	You have completed both AC and paclitaxel and it is more than 6 months after completing paclitaxel (completed chemotherapy prior to October 25, 2004).	You will continue to follow Group A schedule for follow-up.
B	You are currently receiving AC (chemotherapy).	You will follow Group C schedule for treatment and cardiac testing.
B	You have completed AC, are currently receiving paclitaxel, and have had an acceptable post-AC MUGA/Echo according to guidelines for trastuzumab.	You may start trastuzumab with the next dose of paclitaxel without waiting to finish the paclitaxel. You may continue trastuzumab for 52 weeks from its start. You will have cardiac testing done at 3, 6, 9, and 18 months from start of trastuzumab.
B	You have completed AC and are now receiving paclitaxel, and you have NOT had an acceptable post-AC MUGA/Echo according to guidelines for trastuzumab.	Trastuzumab MAY NOT be given. You will continue to follow Group B treatment and cardiac testing schedule.
B	You have completed both AC and paclitaxel treatment.	You will continue to follow Group B schedule for treatment and cardiac testing.
C	At any treatment point	Continue to follow Group C schedule.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- **routine blood tests**
- **routine testing to see how your cancer is**

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- **MUGA scans or echocardiograms (Echos)**

If you have not been given experimental trastuzumab before AND the tests and procedures show that you can have trastuzumab:

If you have not started treatment with paclitaxel, you will get paclitaxel (Taxol®), by vein over 1 hour plus trastuzumab (Herceptin®) by vein one day every week, for a total of 12 treatments. After all treatment with paclitaxel plus trastuzumab is done (about week 24), you will get trastuzumab alone one day every week for ten months. The first dose of trastuzumab will be given over about 90 minutes. You will be watched for 1 hour after the first dose of trastuzumab. If you do well this first dose, other doses will be given over about 30 minutes. Total length of treatment will be about one year.

Day 1 of Weeks 13-24	paclitaxel (Taxol®) and trastuzumab (Herceptin®)
Day 1 of Weeks 25-65	trastuzumab (Herceptin®)

If you have already started treatment with paclitaxel OR you have completed paclitaxel therapy less than 6 months ago, you will get trastuzumab alone one day every week for 1 year. The first dose of trastuzumab will be given over about 90 minutes. You will be watched for 1 hour after the first dose of trastuzumab. If you do well this first dose, other doses will be given over about 30 minutes.

When I am finished taking trastuzumab…

Your doctor will continue to watch your health to see if your cancer comes back or you have other problems because of taking trastuzumab.

How long will I be in the research study?

You will be asked to take study medications for about one year. After you are finished taking trastuzumab, the study doctor will ask you to visit the office for follow-up exams for at least five years. You will be followed on this study for about 15 years.

We would also like to keep track of your health for the rest of your life. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your health every year helps us look at the long-term effects of the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be checked by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the trastuzumab. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study. All the risks and side effects listed in the consent form you signed in order to take part in this study are still a possibility. Please review these risks and side effects with your study doctor. We have included the risks of investigational trastuzumab, since some people who would not have gotten this drug before April 25, 2005, may now be able to receive it.

Risks and side effects related to the trastuzumab include those which are:

Likely (more than 20% of people taking trastuzumab have these effects)

- **Body pain including pain at tumor site**
- **Fever**
- **Nausea (feeling sick to your stomach)**
- **Vomiting (throwing up)**
- **Chills**
- **Headache**
- **Diarrhea (loose stools)**
- **Cough**
- **Abdominal pain (pain in belly)**
- **Shortness of breath**
- **Back pain**
- **Rash**
- **Loss of appetite (not feeling hungry, not wanting to eat)**
- **Runny nose and/or sore throat**
- **Dizziness**
- **Anxiety (feeling worried or afraid)**
- **Sleeplessness**
- **Numbness or tingling in hands and/or feet**
- **Low blood counts (can lead to infection or bleeding)**
- **Weakness**
- **Fatigue (feeling tired, run down or short of breath)**
- **Infection**
- **Easy bruising or bleeding**
- **Nosebleeds**

Less likely (20% or less of people taking trastuzumab have these effects)

- **Nervousness (feeling edgy, restless)**
- **Depression (feeling down or blue)**
- **Irregular heartbeat**
- **Allergic reactions**
- **Liver problems (as seen on blood tests)**
- **Trouble breathing**
- **Lung congestion**
- **Fluid in the lungs (may feel short of breath, have pain when breathing)**
- **Poor lung function (may feel short of breath)**
- **Low oxygen level in blood (may feel tired, rundown)**
- **Bone pain**
- **Pneumonitis (swelling of the lungs)**
- **Scarring in the lungs**

Rare but serious (less than 2-3% of people taking trastuzumab have these effects)

- **Congestive heart failure (CHF).**
- **Adult/Acute respiratory distress syndrome (ARDS).**
- **Severe reaction to trastuzumab during or after infusion which may result in death.**

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors know trastuzumab is more useful against cancer compared to the usual treatment, there is no proof of this result for you yet. We do know that the information from this study will help doctors learn more about trastuzumab as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.
Your other choices may include:

- **Getting treatment or care for your cancer without being in a study, including treatment with trastuzumab (Herceptin®)**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **North Central Cancer Treatment Group (NCCTG)**
- **Genentech, the company providing trastuzumab (Herceptin®) for this study**
- **The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people**

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

If, during the study, trastuzumab (Herceptin®) becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* **if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____** *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* **at _____** *[telephone number].*

For questions about your rights while taking part in this study, call the _____ ***[name of center]*** Institutional Review Board (a group of people who review the research to protect your rights) at _____ ***(telephone number).*** ***[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]***

***You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).** *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

*[The following tissue consent has been taken from the NCI Cancer Diagnosis Program's model tissue consent form found at the following url **http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf**]*

About Using Biological Samples for Research

This study also has laboratory tests that will be done to study small samples of blood. You may have given blood samples for this study before, but we are now asking for one more sample for genetic testing. A blood sample will be taken by drawing some blood from a vein in your arm or hand. The blood may be taken once, at any time while you are on this study.

The blood samples will be sent to: laboratories associated with NCCTG where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help researchers better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

You can take part in the treatment portion of this study without taking part in these research tests.

Please read the following statements and mark your choice:

1. I agree to provide a blood sample for genetic testing to laboratories associated with NCCTG for research testing planned as part of this study.

☐ Yes ☐ No Please initial here: _____ Date: _____

We would like to keep some of the blood sample that is left over for future research. If you agree, this sample will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research"
Add 17 http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf to learn more about tissue research.

Your sample may be helpful for research whether you do or do not have cancer. The research that may be done with your samples is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your sample will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the blood sample for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood sample can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your sample. Then any sample that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your sample is used for this kind of research, the results will not be sent to you and will not be put in your health records.

In the future, we may find that the research we have done is important for your health care or your family's healthcare. If that happens, we will work with your doctor to make sure you get the information and tell you and your family how the research may affect your lives.

Your sample will be used only for research and will not be sold. The research done with your sample may help to develop new products in the future.

Benefits

The benefits of research using blood samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My blood sample may be kept for use in research to learn about, prevent, or treat cancer.

   ☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood sample may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   ☐ Yes ☐ No Please initial here: _____ Date: _____

Add 17 The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

Add 17 **How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG, who will contact you.

Add 17 ***Please read the following statements and mark your choice:***

3. My blood sample may be sent by NCCTG to outside researchers.

☐ Yes ☐ No Please initial here: _____ Date: _____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

NCI Informed Consent Template for Cancer Treatment Trials (English Language)

NOTES FOR LOCAL INVESTIGATORS:

- *The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/*
- *A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.*
- *Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035 or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.*
- *Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.*

**These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

---

version date: 17May2010
Added as of Addendum 18 – ***Re-consent required for all patients still in observation phase with Addendum 18***

N9831 Phase III Trial of Doxorubicin and Cyclophosphamide (AC) Followed by Weekly Paclitaxel with or Without Trastuzumab as Adjuvant Treatment for Women With HER-2 Over-expressing or Amplified Node Positive or High-Risk Node Negative Breast Cancer

LONGTERM FOLLOW-UP CARDIAC EVALUATION CONSENT FORM

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

You are being asked to take part in this research study because you have been enrolled in N9831.

Why is this research study being done?

The purpose of this research study is to

- **follow people who were enrolled in N9831 for long-term cardiac risks**

How many people will take part in the research study?

About 3500 people will take part in this study.

What will happen if I take part in this research study?

You have already been enrolled in the N9831 study, and you have already received testing and treatment. You will continue to receive follow-up care on N9831.

<u>During the study</u>

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- **One ejection fraction echocardiogram (Echo) (a painless test that looks at the electrical activity of your heart)**
  For the echocardiogram, you will undress from the waist up and put on a gown. The sonographer will apply a gel to your chest and then rub an instrument over your chest and watch a screen to see how your heart is working.

OR

- **One ejection fraction resting multigated acquisition (MUGA) scan (a test that looks at how your heart is working)**
  For the MUGA scan, a small amount of your blood will be drawn into a syringe from a vein in your arm. While still connected to your arm, a small amount of radioactive material will be mixed with the blood in the same syringe and then re-injected into your vein. The radiographer will watch your heart on a screen to see how it is working.

Please read the following statements and mark your choice:

I agree to have one additional echocardiogram or MUGA scan as part of this study.

☐ Yes ☐ No Please initial here:_____ Date:_____

How long will I be in the research study?

You will be in this cardiac study long enough to have the Echo or MUGA scan. You will be followed on N9831 for about 15 years from the time you enrolled.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away, but in some cases, side effects can be serious, long lasting, or may never go away.

The risks of an LVEF echocardiogram include: Rarely a rash on the skin because of the gel used.

The risks of an LVEF MUGA scan include: pain, bruising or bleeding at the site of the injection. You will be exposed to radiation. The amount of radiation you will receive has a low risk of harmful effects.

You should talk to your study doctor about any side effects that you have while taking part in the study. All the risks and side effects listed in the consent form you signed in order to take part in N9831 may still be a possibility. Please review these risks and side effects with your study doctor.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may not make your health better. We do know that the information from this study will help doctors learn more about trastuzumab as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

This portion of the study is only being done to gather information. You do not have to take part in this portion of N9831.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **North Central Cancer Treatment Group (NCCTG)**
- **Genentech, the company providing trastuzumab (Herceptin®) and funding for this study**
- **The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people**
- **Institutional Review Boards**

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company may need to pay for some or all of the costs of treating your cancer in this study. The study will reimburse up to $1,000 for one ejection-fraction only resting MUGA scan OR up to $700 for one ejection-fraction only resting echocardiogram. If your institution cannot do this specific test or will charge more than this amount, you need to check with your health insurer to see if these additional charges will be covered. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* **if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____** *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* **at _____** *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ ***[name of center]*** Institutional Review Board (a group of people who review the research to protect your rights) at _____ ***(telephone number).*** ***[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]***

***You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).** *[*Only applies to sites using the CIRB.]*

IMPORTANT
SITES PLEASE NOTE: This section of the consent form has been included for sites that did not reconsent for recurrence blood and tissue samples with Addendum 13 or for genetic blood samples with Addendum 16 – please delete this portion if your patients have already been consented for these studies. *[Delete this text box before finalizing consent form.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

[The following tissue consent has been taken from the NCI Cancer Diagnosis Program's model tissue consent form found at the following url ***http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf****]*

About Using Biological Samples for Research

This study also has laboratory tests that will be done to study small samples of blood. You may have given blood samples for this study before, but we are now asking for one more sample for genetic testing. A blood sample will be taken by drawing some blood from a vein in your arm or hand. The blood may be taken once, at any time while you are on this study.

The blood samples will be sent to: laboratories associated with NCCTG where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help researchers better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

You can take part in the treatment portion of this study without taking part in these research tests.

Please read the following statements and mark your choice:

1. I agree to provide a blood sample for genetic testing to laboratories associated with NCCTG for research testing planned as part of this study.

☐ Yes ☐ No Please initial here: _____ Date: _____

If your breast cancer comes back, you will be asked to have a blood sample taken, and if you have a biopsy done, a part of your biopsy tissue will be sent to NCCTG laboratories for banking purposes for future research of breast cancer. The investigators plan to evaluate various blood and tissue markers that will help them to better understand how your cancer responds to treatment based on state of the art of scientific knowledge at that time.

You can take part in the treatment part of this study without taking part in giving the extra blood and extra tissue at the time your disease comes back for research purposes.

Please read the following statements and mark your choice:

1. I agree to give my blood and tissue (if a biopsy is done) samples at the time of my first breast cancer recurrence to laboratories associated with NCCTG for future research testing.

   ☐ Yes ☐ No Please initial here:_____ Date:_____

We would like to keep some of the samples that are left over for future research. If you agree, these samples will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf to learn more about tissue research.

The research that may be done with your samples is not designed specifically to 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 record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your samples. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be sent to you and will not be put in your health records.

In the future, we may find that the research we have done is important for your health care or your family's healthcare. If that happens, we will work with your doctor to make sure you get the information and tell you and your family how the research may affect your lives.

Your 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. If that were to happen, you would not be paid.

Benefits

The benefits of research using samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My samples may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My samples may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

The sample(s) will be stored at the NCCTG Research Base, Mayo Clinic, Rochester, Minnesota. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. If so, NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG, who will contact you.

Please read the following statements and mark your choice:

3. My blood sample may be sent by NCCTG to outside researchers.

☐ Yes ☐ No Please initial here: _____ Date: _____

End of optional section
Delete this text box before finalizing consent form.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.