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

Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer

Schneider, et al

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SELECTION OF PATIENTS

NOTE: Questions regarding eligibility should be directed to the ECOG Study Chair at (718) 904-2555, the Study Chair Liaison at (718) 904-2321 or the ECOG Coordinating Center at (617) 632-3610.

NOTE: Patients who have tumors that are known to overexpress HER2/neu are encouraged to enroll on trial N9831 rather than this trial. N9831 will examine the role of Herceptin as a component of adjuvant therapy.

3.1 Patients with operable histologically confirmed adenocarcinoma of the female breast with histologically involved lymph nodes (T1, 2, or 3; N1 or 2; M0; AJCC Stage IIA, IIB, IIIA) and high risk axillary node-negative disease (T2N0, stage IIA; T3N0, stage IIB).

NOTE: For node-negative patients, the primary tumor must measure at least 2.1 cm in maximum diameter in order to be eligible. For the purposes of eligibility and stratification, lymph nodes will be characterized as positive or negative for metastases on the basis of conventional H&E staining; lymph nodes that are negative by H&E staining and positive by immunohistochemistry will be considered negative for metastases.

3.11 Patients who have at least one axillary lymph node positive for metastasis (by conventional H&E staining) should have at least six axillary lymph nodes removed at axillary dissection. An exception to this rule will be for patients with a positive sentinel lymph node biopsy enrolled on American College of Surgery Trial Z0011; patients enrolled on Z0011 who have been randomized to receive no axillary dissection (the experimental arm) will be eligible for participation in this study.

3.12 Patients who have had less than 6 lymph nodes removed are eligible if the lymph node(s) were obtained by a sentinel node biopsy procedure and the node(s) were negative for metastasis by conventional H&E staining. Additional axillary nodes may also be obtained as long as these nodes were also found negative for metastases by conventional H&E staining.

3.13 Patients enrolled on national sentinel node studies (American College of Surgery Trial Z0010, Z0011, and NSABP B-32) are eligible as long as they meet the criteria outlined in Sections 3.11 and 3.12.

3.2 Patients must have adequate hematologic, hepatic and renal function as assessed within 8 weeks prior to randomization, including a:

3.21 Neutrophil count of > 1,500/mm^3 and platelet count of > 100,000/mm^3.

3.22 Normal serum creatinine (< 1.5 mg/dL).

3.23 Normal total bilirubin (< 1.5 mg/dL) and SGOT (AST) < 2 x the upper limits of normal.

3.3 No prior history of myocardial infarction, congestive heart failure, or significant ischemic or valvular heart disease.

3.4 Pregnant or breast-feeding women must not participate since clinical evidence suggests these treatments may be associated with potential toxicity to the child. Women of childbearing potential must use an accepted and effective barrier form method of contraception.

3.5 Patients must be > 18 years.

3.6 Patients must be disease-free of prior invasive malignancies for > 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.

3.7 Patients must not have had a hypersensitivity reaction to: 1) paclitaxel (Taxol) or other drugs formulated in Cremophor EL (polyoxethylated castor oil), or 2) docetaxel (Taxotere) or other drugs formulated in polysorbate.

3.8 Prior Treatment

3.81 Within 84 days from the final surgical procedure required to adequately treat the primary tumor(s). Patients with bilateral synchronous disease are eligible so long asat least one primary tumor meets the criteria in Section 3.1.

3.82 All tumors should be removed by either a modified radical mastectomy or local excision plus an axillary lymph node dissection (i.e., breast conservation therapy) before randomization. A sentinel lymph node biopsy is also acceptable so long as criteria 3.11 and 3.12 are met. There must be adequate (at least 1 mm, i.e. > 1 mm) tumor-free margins of resection (for invasive and ductal carcinoma *in-situ*) in order for the patients to be eligible. Patients with lobular carcinoma *in-situ* involving the resection margins are eligible.

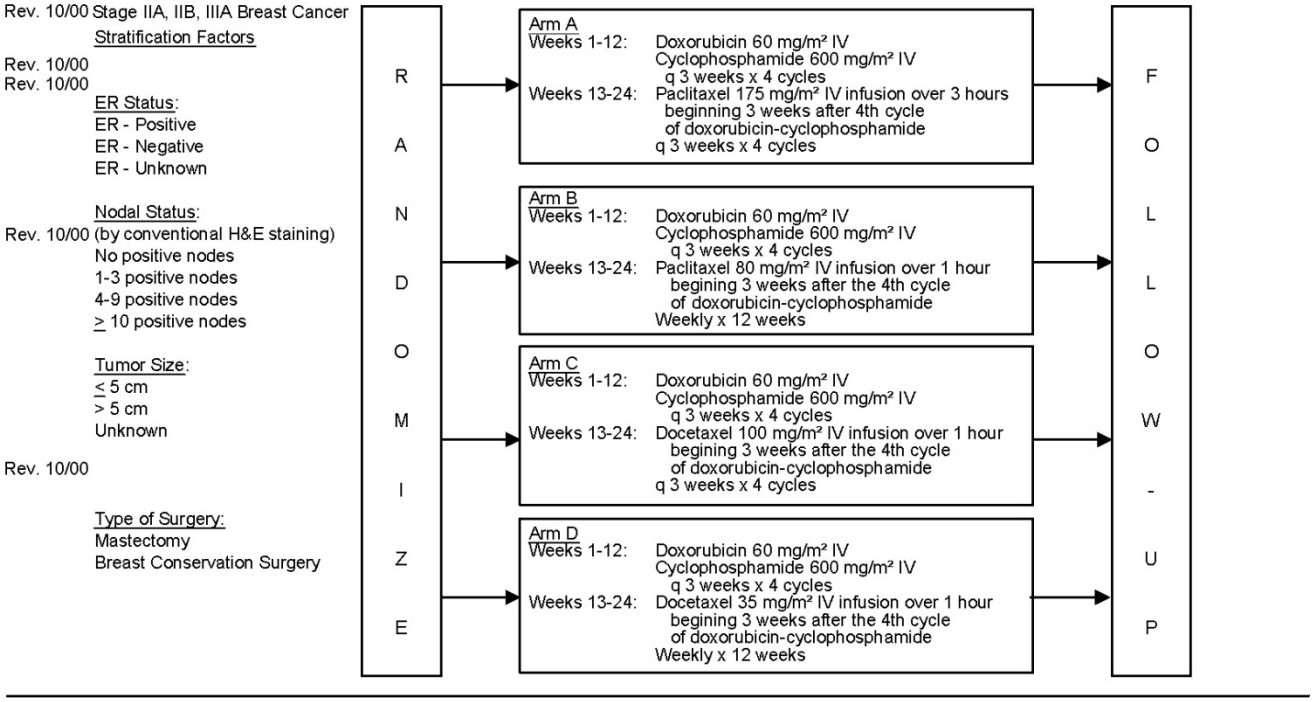
3.83 No prior chemotherapy for this malignancy.

3.84 No prior radiation therapy for this malignancy. Patients who received radiation to the breast for DCIS are eligible. Radiation therapy for DCIS must have been completed
> 2 weeks prior to study entry.

NOTE: Patients who have had segmental mastectomy will be treated with radiotherapy according to standard procedure after completion of all chemotherapy. Patients who have had a modified radical mastectomy may also receive regional radiotherapy after completion of all chemotherapy at the discretion of the treating physician.

3.85 Tamoxifen: Patients may have received up to four weeks of tamoxifen therapy for this malignancy and still be eligible for study entry. Patients who received tamoxifen or another selective estrogen receptor modulator (SERM) for prevention or for other indications (e.g., osteoporosis) are eligible. Tamoxifen therapy or other SERMs should be discontinued before the patient is enrolled on this study.

SCHEMA



NOTE: Doses based on actual body weight.
NOTE: Please see Section 5.11 for premedications prior to paclitaxel and docetaxel.

Rev. 10/00
NOTE: Patients who have tumors that are known to overexpress HER2/neu are encouraged to enroll on trial N9831 rather than this trial. N9831 will examine the role of Herceptin as a component of adjuvant therapy.

Rev. 10/00 **NOTE:** For the purposes of eligibility and stratification lymph nodes that are negative by conventional H&E staining and positive by immunohistochemistry will be considered node-negative. See Section 5.12 for criteria for use of colony stimulating factors, 5.13 for use of tamoxifen and other hormonal therapy, 5.14 for radiation therapy, and 5.3 for chemotherapy dose modification.

Rev. 10/00
Rev. 10/00
Rev. 10/00

TREATMENT PLAN

5.0 TREATMENT PLAN

NOTE: All questions regarding treatment or dose modifications should be directed to the ECOG Study Chair.

5.1 Administration Schedule
Doses based on actual body weight.

5.11 Chemotherapy
5.111 Arm A

NOTE: See Section 5.3 for criteria for administering therapy (5.311 and 5.312), dose modification (5.313 and 5.32-5.37), and use of colony stimulating factors (5.12 and 5.3121). Please note that the neutrophil threshold for administering weekly taxane therapy (at least 1000/mm3) is lower than it is for administering doxorubicin/cyclophosphamide and every three week taxane therapy (at least 1500/mm3). Weeks 1-12: Doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV). Repeat every 3 weeks x 4 cycles Weeks 13-24: Paclitaxel 175 mg/m² IV infusion over 3 hours. Repeat every 3 weeks x 4 cycles. Begin paclitaxel 3 weeks after the 4th cycle of doxorubicin-cyclophosphamide. Premedication prior to paclitaxel: Patients

should receive intravenous dexamethasone 20 mg, diphenhydramine 50 mg, and an H2 blocker approximately 30 minutes prior to the paclitaxel infusion (37-40).

5.12 Arm B

NOTE: See Section 5.3 for criteria for administering therapy (5.311 and 5.312), dose modification (5.313 and 5.32-5.37), and use of colony stimulating factors (5.12 and 5.3121). Please note that the neutrophil threshold for administering weekly taxane therapy (at least 1000/mm3) is lower than it is for administering doxorubicin/cyclophosphamide and every three week taxane therapy (at least 1500/mm3).Weeks 1-12: Doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV). Repeat every 3 weeks x 4 cycles. Weeks 13-24: Paclitaxel 80 mg/m² IV infusion over 1 hour. Repeat every week x 12 weeks. Begin paclitaxel 3 weeks after the 4th cycle of doxorubicin-cyclophosphamide. Premedication for paclitaxel: Patients should receive intravenous dexamethasone 10 mg, diphenhydramine 50 mg, and an H2 blocker approximately 30 minutes prior to the paclitaxel infusion (37-40).

5.113 Arm C

NOTE: See Section 5.3 for criteria for administering therapy (5.311 and 5.312), dose modification (5.313 and 5.32-5.37), and use of colony stimulating factors (5.12 and 5.3121). Please note that the neutrophil threshold for administering weekly taxane therapy (at least 1000/mm3) is lower than it is for administering doxorubicin/cyclophosphamide and every three week taxane therapy (at least 1500/mm3). Weeks 1-12: Doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV). Repeat every 3 weeks x 4 cycles. Weeks 13-24: Docetaxel 100 mg/m² IV infusion over 1 hour. Repeat every 3 weeks x 4 cycles. Begin docetaxel 3 weeks after the 4th cycle of doxorubicin-cyclophosphamide. Premedication for docetaxel: Patients should receive oral dexamethasone 8 mg BID x 3 days beginning one day prior to the docetaxel infusion.

5.114 Arm D

NOTE: See Section 5.3 for criteria for administering therapy (5.311 and 5.312), dose modification (5.313 and 5.32-5.37), and use of colony stimulating factors (5.12 and 5.3121). Please note that the neutrophil threshold for administering weekly taxane therapy (at least 1000/mm3) is lower than it is for administering doxorubicin/cyclophosphamide and every three week taxane therapy (at least 1500/mm3). Weeks 1-12: Doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV). Repeat every 3 weeks x 4 cycles. Weeks 13-24: Docetaxel 35 mg/m² IV infusion over 1 hour. Repeat every week x 12 weeks. Begin docetaxel 3 weeks after the 4th cycle of doxorubicin-cyclophosphamide.

Premedication for docetaxel: All patients should receive dexamethasone 8 mg PO bid the day before the 1st and 2nd weekly dose of docetaxel. If there is no hypersensivitiy reaction after the 1st and 2nd treatments, this may be discontinued in subsequent cycles. All patients should also receive intravenous dexamethasone 10 mg approximately 30 minutes prior to every docetaxel infusion. If a hypersensitivity reaction occurs at the 3rd or greater cycle (after the pretreatment oral dexamethasone is discontinued), the physician has the option of resuming this pretreatment regimen (8 mg PO bid given the day prior to each treatment) rather than using the dexamethasone premedication regimen outlined in Sections 5.321 and 5.322.

5.12 Colony Stimulating Factors (e.g., G-CSF, GM-CSF or Erythropoietin)

Patients who have an episode of febrile neutropenia or who have persistent neutropenia that prevents treatment on schedule may receive CSFs (e.g., G-CSF, GM-CSF or erythropoietin) at the discretion of

the treating physician using guidelines recommended by ASCO (41). CSFs may be used after doxorubicin cyclophosphamide or after paclitaxel or docetaxel. CSFs are usually not necessary with weekly taxane therapy. Erythropoietin may be used at the discretion of the treating physician in order to treat or prevent anemia.

5.13 Tamoxifen and Other Hormonal Therapy

Tamoxifen is recommended (20 mg PO daily for 5 years) for patients whose primary tumor was estrogen and/or progesterone receptor positive. It is recommended that tamoxifen therapy begin within 4 weeks of the last dose of chemotherapy.
Tamoxifen may be withheld at the discretion of the treating physician if there is a contraindication to tamoxifen therapy. Other forms of hormonal therapy may be substituted for tamoxifen if there is a contraindication to tamoxifen therapy (e.g., surgical/medical oophorectomy for premenopausal women, aromatase inhibitors for postmenopausal women). Megesterol acetate may be used for the symptomatic management of hot flashes if clinically indicated at the discretion of the treating physician if non-hormonal therapies (e.g., venlafaxine) are either not effective or contraindicated.

During the past several years, several studies demonstrated a role for use of aromatase inhibitors (A.I.s) in postmenopausal women with ER and/or PR-positive breast cancer, including anastrazole (Arimidex), letrozole (Femara), and exemestane (Aromasin). The Arimidex, Tamoxifen, Alone or in Combination Study (ATAC) demonstrated that anastrazole significantly reduced the risk of recurrence compared with tamoxifen after a median followup of 33 months (hazard ratio 0.83; 95%confidence intervals 0.70 to 0.96, p=0.013). (42) Similar results were reported in an updated analysis with longer followup. (43) Goss and colleagues compared letrozole with a placebo in patients completing five years of adjuvant tamoxifen therapy; this study demonstrated letrozole significantly reduced the risk of recurrence (hazard ratio 0.57; 95% confidence intervals 0.43 to 0.75, p=0.00008). (45) Coombes and colleagues randomized patients who had completed 2-3 years of adjuvant tamoxifen to either continued tamoxifen or exemestane, and demonstrated that changing to exemestane significantly reduced the risk of recurrence (hazard ratio 0.68; 95%confidence intervals 0.56 to 0.82, p<0.0001). (44) It is important to note that all of these trials included only postmenopausal women, since A.I.s are effective only inthis setting.

The American Society of Clinical Oncology (ASCO) Technology Assessment Working Group has published several position papers concerning the use of A.I.S.The first paper published in May 2002 concluded the following: "*The panel was influenced by the compelling, extensive, and long term data available on tamoxifen. Overall, the panel considers the results of the ATAC trial and the extensive supporting data to be very promising but insufficient to change the standard practice at this time. A 5-year course of adjuvant tamoxifen remains the standard therapy for women with hormone receptor positive breast cancer….*" (46). An updated evaluation published in July, 2003 came to the same conclusion. (47). Another update published in 2004 concluded: "*Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3 years or 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized*." (48)Given the increasing evidence that A.I.s. may play an important role as a component of adjuvant therapy for postmenopausal women with breast cancer, the following guidelines are suggested for patients enrolled on E1199 who are

currently taking tamoxifen: (1) postmenopausal women who are currently taking tamoxifen may be changed to an aromatase inhibitor prior to completing five years of tamoxifen, (2)postmenopausal women who have completed a 5-year course of adjuvant tamoxifen are advised to receive an aromatase inhibitor for a period of five years, and (3) for patients who have completed a five year course of adjuvant hormonal therapy including an A.I (either used from the beginning or after an initial course of tamoxifen), it is currently unknown whether continuing an A.I. beyond five years is beneficial; A.I.s may be continued beyond five years at the discretion of the treating physician.

NOTE: For postmenopausal women who have not yet initiated tamoxifen (or within the last 3-6 months initiated tamoxifen), administration of an aromatase inhibitor (e.g., anastrazole ([Arimidex]) rather than tamoxifen is permissible even if there is no contraindication to tamoxifen therapy. Patients who have already initiated tamoxifen should remain on tamoxifen if they agree to do so, as there is no information about the effectiveness of an aromatase inhibitor after previous tamoxifen use in the adjuvant setting.

5.14 Radiotherapy
Patients who have had segmental mastectomy will be treated with radiotherapy according to standard procedure after completion of all chemotherapy. Patients who have had a modified radical mastectomy may also receive radiotherapy after completion of all chemotherapy at the discretion of the treating physician.

DOSE MODIFICATIONS

5.3 Dose Modifications

There will be no dose escalations.
All toxicities should be graded according to the Common Toxicity Criteria (version 2.0).
Patients who receive a dose reduction of doxorubicin-cyclophosphamide will receive the full dose of the taxane for the first taxane dose.

NOTE: See Section 5.3 for criteria for administering therapy (5.311 and 5.312), dose modification (5.313 and 5.32-5.37), and use of colony stimulating factors (5.12 and 5.3121). Please note that the neutrophil threshold for administering weekly taxane therapy (at least 1000/mm3) is lower than it is for administering doxorubicin/cyclophosphamide and every three week taxane therapy (at least 1500/mm3).

If treatment is held > 3 weeks for toxicity, the protocol treatment will be discontinued.

NOTE: When reducing doses according to Section 5.3, use the dose from the previous cycle to calculate the appropriate reduced dose.

5.31 Criteria for Administering Therapy

5.311 For doxorubicin/cyclophosphamide, paclitaxel, or docetaxel given every 3 weeks:
Repeat every 3 weeks if ANC > 1500/mm^3, platelets > 100,000/mm^3 and patient has satisfactorily recovered from non-hematologic toxicity. If ANC < 1500/mm^3, delay treatment until ANC > 1500/mm^3 and resume at 100% dose. Colony stimulating factors (CSFs) may be used at the discretion of the treating physician according to ASCO guidelines (see Section 5.12). If the platelet count is < 100,000/mm^3, delay treatment until > 100,000/mm^3 and permanently reduce subsequent doses of the same therapy by 25%.

5.312 For weekly paclitaxel or docetaxel:
Repeat every week if ANC > 1000/mm^3, platelets >100,000/mm^3 and patient has satisfactorily recovered from non-hematologic toxicity. If ANC <1000/mm^3, delay treatment until ANC > 1000/mm^3 and resume at 100% dose. CSFs may be used at the discretion of the treating physician according to ASCO guidelines (see Section 5.12).If the platelet count is <

100,000/mm³, delay treatment until > 100,000/mm³ and permanently reduce subsequent doses of the same therapy by 25%. Patients with fatigue may continue therapy on a weekly basis if grade 0, 1, or 2. Patients with grade 3 or 4 fatigue should have treatment withheld until recovery to grade 0, 1, or 2 (see Section 5.37) and reduce subsequent doses by 25%. Weekly taxane therapy should be administered weekly for 12 consecutive weeks and for a maximum of 12 doses. For patients who require omission or delay of a dose for medical reasons, (e.g., toxicity) or non-medical reasons (e.g., holiday, vacation), it is suggested that all 12 doses be completed within 105 days (15 weeks) from the initiation of weekly taxane therapy.

5.313 Dose Modifications for Toxicity
Any patient experiencing any of the following will have chemotherapy reduced by 25% subsequent doses of the same regimen.

5.3131 Grade 3 or 4 febrile neutropenia (fever > 38.5°C, ANC < 1,000/mm³) between courses.

NOTE: Patients who have uncomplicated febrile neutropenia unassociated with grade 3 - 4 infection may continue full dose chemotherapy in conjunction with colony stimulating factors (see Section 5.12) at the discretion of the treating physician.

5.3132 Bleeding episode with a platelet nadir < 40,000/mm³.

5.3133 Platelet nadir < 20,000/mm³ with or without a bleeding episode.

5.3134 Failure to recover the platelet count to > 100,000/mm³ on the planned day of therapy.

5.3135 Grade 3 or 4 diarrhea.

5.3136 Grade 3 or 4 mucositis. On the Toxicity Form, please categorize mucositis as indicated in the CTC, version 2.0, as colitis, esophagitis, gastritis, or stomatitis/pharyngitis, etc.

5.3137 Grade 2 neuropathy (for paclitaxel or docetaxel) (See Section 5.35 for criteria for management of peripheral neuropathy). On the Toxicity Form, please categorize neuropathy as indicated in the CTC, version 2.0, as neuropathy-motor, neuropathy-sensory, or neuropathy-cranial.

5.3138 Other grade 3 or 4 non-hematologic toxicity that in the judgement of the treating physician is poorly tolerated by the patient and requires a dose reduction. If on a subsequent course, these toxicities recur, chemotherapy will be reduced by another 25% (i.e., reduce by 25% from the dose used in the previous cycle).

5.32 Anaphylaxis/ Hypersensitivity

5.321 Mild symptoms (Grade 1) (e.g., mild flushing, rash, pruritis): Complete taxane infusion. Supervise at bedside. No treatment required. For patients with mild symptoms during the first cycle of paclitaxel or docetaxel, subsequent cycles may (at the discretion of the treating physician) be given with oral dexamethasone premedication (20 mg PO 12 and 6 hours prior to the infusion) in addition to intravenous dexamethasone 10-20 mg, diphenhydramine 50 mg and an H2 blocker minutes prior to the infusion.

5.322 Moderate symptoms (Grade 2) (e.g., moderate rash, flushing, mild dyspnea, chest discomfort): Stop taxane infusion. Give intravenous diphenhydramine 20-25 mg and intravenous dexamethasone 10 mg. Resume taxane infusion after recovery of symptoms at a low rate, 10 ml/hour for 15 minutes, the 25 ml/hr for 15 minutes, then if no further

symptoms, at full dose rate until infusion is complete. If moderate or severe symptoms recur after rechallenge, stop taxane infusion, discontinue protocol treatment, and report as an adverse event. For patients with moderate symptoms during the first cycle of paclitaxel or docetaxel, subsequent cycles should be given with oral dexamethasone premedication (20 mg PO 12 and 6 hours prior to the infusion) in addition to intravenous dexamethasone 10-20 mg, diphenhydramine 50 mg and an H2 blocker 30 minutes prior to the infusion.

5.323 Severe life-threatening symptoms (Grade 3) (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria): Stop taxane infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. The protocol treatment will be discontinued and the episode will be reported as an adverse event.

5.33 Cardiovascular

5.331 Symptomatic EKG-documented arrhythmia: Stop chemotherapy. Manage arrhythmia according to standard practice.

5.332 Clinical congestive heart failure: Grade 3 or 4 cardiac left ventricular function by CTC criteria. Discontinue doxorubicin and cyclophosphamide (if the patient is still receiving doxorubicin/cyclophosphamide therapy). May continue and complete taxane therapy after symptoms of CHF resolve with medical therapy.

5.34 Fluid Retention

Fluid retention is a recognized complication of docetaxel that may be ameliorated by diuretics. Although the diuretic used is at the discretion of the treating physician, it is advised that patients who require therapy receive furosemide or an alternative loop diuretic with appropriate potassium supplementation as needed.

5.341 Asymptomatic peripheral edema or pleural effusion: Initiate diuretic therapy and continue docetaxel.

5.342 Symptomatic peripheral edema: Initiate diuretic therapy or increase intensity of diuretics if the patient is already receiving diuretics. Continue docetaxel.

5.343 Symptomatic pleural effusion: Discontinue protocol treatment.

NOTE: Patients with pleural effusions do not require thoracentesis unless the treating physician feels that the effusion is attributable to progressive disease.

5.35 Peripheral Neuropathy

NOTE: Up to 2 dose reductions in taxane therapy are permitted for peripheral neuropathy. For patients who require further dose reduction for neuropathy, protocol treatment should be discontinued.

5.351 Grade 3 or 4: Hold therapy. If the neuropathy improves to < grade 2, resume taxane with a 25% dose reduction. If grade 3/4 toxicity persists > 3 weeks, protocol treatment will be discontinued.

5.352 Grade 2: Reduce taxane dose by 25%.

5.353 Grade 1: Continue taxane at full dose.

5.36 Cystitis

5.361 Cyclophosphamide-related gross or microscopic hematuria is correlated with the concentration of metabolized drug in the bladder. It is uncommon with the dose used in this trial. Adequately hydrate patients to ensure frequent voiding. At the discretion of the treating physician, patients may be treated with mesna if cyclophosphamide causes gross hematuria or symptomatic cystitis or protocol treatment may be discontinued. Discontinue cyclophosphamide permanently and discontinue protocol treatment if hemorrhagic cystitis recurs.

5.37 Other Toxicities

5.371 Excessive lacrimation: Excessive tearing of the eyes may occur with weekly docetaxel, usually begins after the sixth week of therapy, and resolves after discontinuation of therapy. For patients with grade 2 or 3 toxicity, may reduce the taxane dose by 25%.

5.372 Nail changes: Ridging and softening of the nails, and separation of the nail from the nail bed may occur with weekly docetaxel. It usually resolves within several months after discontinuation of therapy. For patients with grade 2 toxicity, may reduce the taxane dose by 25%.

5.373 Fatigue: Fatigue may occur with any chemotherapy regimen, but may bemore common with weekly taxane therapy. For patients with grade 3 fatigue (decrease in ECOG performance status by > 2 levels, or loss of ability to perform some activities) or grade 4 fatigue (bedridden or disabled), should hold therapy and follow the guidelines indicated below:

5.3731 Fatigue resolves to grade 0, 1 or 2 within 3 weeks: Resume taxane therapy with 25% dose reduction, complete 12 doses of therapy.

5.3732 Fatigue does not resolve to grade 0, 1 or 2 after 3 weeks: Discontinue therapy.

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EARLY CESSATION OF THERAPY
5.5 Duration of Therapy
Patients will receive protocol therapy unless an adverse reaction occurs as listed above:

5.51 Disease Recurrence: If a patient recurs locally or distantly, protocol treatment should be terminated. Contralateral breast cancer is not considered disease recurrence.

5.52 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to Section 11.0.

5.53 Patient withdraws consent.

5.54 All patients, including those who discontinue protocol therapy, are followed until death.

MEASUREMENT OF EFFECT

6.0 MEASUREMENT OF EFFECT

NOTE: Recurrence must be documented by biopsy and/or evidence of disease on radiologic studies. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence and estrogen and progesterone receptor data should be obtained.

6.1 Local, Regional Recurrence
The development of a local or regional recurrence of breast cancer.

6.2 Distant Recurrence
The development of a distant recurrence of breast cancer.

6.3 Disease-Free Survival
Date of randomization to the date of first treatment failure (recurrence or death before recurrence).

6.4 Survival
Date of randomization to date of death.

OBJECTIVES
2.0 OBJECTIVES
In women with axillary node-positive and high risk axillary node-negative breast cancer, the objectives of this trial are:

2.1 To determine whether docetaxel improves disease-free survival and overall survival when compared to paclitaxel following 4 cycles of doxorubicin-cyclophosphamide therapy.

2.2 To determine whether weekly administration of taxanes (paclitaxel or docetaxel) for 12 weeks improves disease-free survival and overall survival when compared with the conventional (every3 weeks) schedule for 4 cycles following 4 cycles of doxorubicin-cyclophosphamide therapy.

2.3 To compare the toxicity of docetaxel given weekly for 12 weeks to that of docetaxel given every 3 weeks for 4 cycles.

2.4 To compare the toxicity of paclitaxel given weekly for 12 weeks to that of paclitaxel given every 3 weeks for 4 cycles.

2.5 To compare the toxicity of paclitaxel given every 3 weeks for 4 cycles to that of docetaxel given every 3 weeks for 4 cycles.

2.6 To compare the toxicity of paclitaxel given weekly for 12 weeks to that of docetaxel given weekly for 12 weeks.

STATISTICICAL CONSIDERATIONS
9.0 STATISTICAL CONSIDERATIONS
In this study, subjects will be randomized to one of four treatment arms as specified in Section 5.0.
All subjects will receive doxorubicin and cyclophosphamide (AC) every 3 weeks for 4 cycles followed by either paclitaxel or docetaxel as follows: in Arm A, subjects will receive paclitaxel every 3 weeks for 4 cycles; in Arm B, subjects will receive paclitaxel weekly for 12 weeks; in Arm C, subjects will receive docetaxel every 3 weeks for 4 cycles; and in Arm D, subjects will receive docetaxel weekly for 12 weeks. The primary endpoint of this study is disease-free survival (DFS), defined to be time from randomization to disease recurrence or death without recurrence. The primary comparisons are the comparison of paclitaxel to docetaxel regardless of schedule, and the comparison of every 1 week to every 3 weeks schedules regardless of taxane used.

It is assumed accrual will average 3938 patients per year for 1.27 years (5000 total), and at least 95.2% of the patients entered will be eligible (at least 4762 total eligible patients). The 5-year DFS on the standard treatment arm, Arm A, is assumed to be 73.3%. This is based on the assumption that 2/3 of the patients accrued will be node positive and 1/3 will be node negative. For the node positive patients, we assumed a 5-year DFS on the standard arm, Arm A, of 70.0% (this is slightly greater than expected for C9741 since this trial will include mostly HER2/Neu negative patients); for the node negative patients, an

80.0% 5-year DFS on the standard arm was assumed. With a total information of 1042 observed failures among eligible patients and with interim monitoring as described below, this design gives 86% power to detect a 17.5% reduction in the failure hazard rate from using docetaxel instead of paclitaxel, or from using an every 1 week schedule instead of an every 3 weeks schedule at an overall two-sided significance level of .05. This reduction in the failure rate corresponds to an improvement in 5-year DFS rates from 73.3% to 77.4% for each comparison.

Interim analyses are planned annually beginning about 2 years after study activation, continuing until full information (1042 events) is reached. The exact number of interim analyses and the information times of these analyses will depend on the actual accrual and failure rates, but the power of the design is not sensitive to variation in these rates. Under the accrual and failure rate assumptions given above, interim analyses would be conducted at roughly 34%, 57% and 79% of the total information. The information for the final analysis should be available about 5 years after activation. However, if more than 1/3 of the patients are node negative, then slightly longer follow-up will be needed to reach full information. The two primary comparisons will be evaluated using a 2-sided logrank test with critical values at each analysis determined from the O'Brien-Fleming use function boundary for an overall 5% type I error rate for each comparison. A correction for multiple comparisons is not used because the two tests are for two distinct hypotheses. That is, a difference between paclitaxel and docetaxel would only be concluded if that test is significant, not if only the schedule comparison is significant.

The test for paclitaxel versus docetaxel will be stratified on schedule, number of positive nodes (0 versus at least 1) and estrogen receptor status (positive versus negative versus unknown), and the est for schedule will be stratified on taxane used, number of positive nodes and estrogen receptor status. To ensure that balance is achieved in the different arms with regards to radiotherapy, the study statistician will follow the numbers of patients treated with post-mastectomy chest wall irradiation in all treatment arms. The DMC will be informed if there is a > 25% relative difference in the proportion of patients treated with post-mastectomy radiotherapy when comparing the arms with the most frequent and the least frequent use of irradiation. The statistician will discuss with the DMC the need to modify the way treatment is assigned to patients or propose an adjustment to the statistical analysis to handle the imbalance.

If one or both of the two primary comparisons is significant, then pairwise comparisons of each of the other arms to the every 3 weeks paclitaxel arm, which has been studied extensively in C9344 and C9741 and could be thought of as the current standard, will be performed. Full information for these comparisons is approximately 1400 total observed failures among eligible patients. This is expected to be reached by 7 years after study activation. Interim analyses for the pairwise comparisons will be performed annually starting at the final analysis for the primary comparisons (only if at least one of the primary comparisons is significant) which should give interim analyses at roughly 5 and 6 years after activation, with full information for these comparisons reached at 7 years. The comparisons of the individual arms to the standard arm, Arm A, with interim monitoring as described above, will have at least 80% power to detect a 22% reduction in the failure hazard rate for any of the experimental arms (Arms B, C and D), using 2-sided nominal 5% level tests, corrected for the multiple comparisons made. This reduction in the failure rate corresponds to an improvement in 5-year DFS rates from 73.3% to 78.5% for each comparison.

Although overall survival is not a primary endpoint, the study will have 81% power to detect an improvement in 5-year overall survival from 81.0% to 84.04% with the accrual of 4762 eligible patients over 1.27 years and 4.7 years of additional follow-up. The 5-year overall survival rate for the control arm, Arm A, is based on the assumption that subjects who are node positive have a 5-yr overall survival rate of 78%, while subjects who are node negative have a 5-yr overall survival rate of 87%. As stated earlier, we are assuming that 2/3 of the subjects accrued in this study will be node positive and the remaining 1/3 will be node negative. This improvement corresponds to a 17.5% decrease in the hazard rate from using docetaxel instead of paclitaxel, or from using the weekly schedule instead of the every 3 weeks schedule. Interim analyses are not planned for this secondary endpoint.

In the presence of mild interaction between drug and treatment schedule, the power of the study remains at reasonable levels. For instance, if we assume a 15% reduction in the failure hazard rate from being in Arm C instead of Arm A and a 22% reduction from being in Arm D instead of Arm B, this design gives 89% power to

detect these differences between the 2 drugs. These reductions correspond to an improvement in 5-year DFS from 73.3% to 76.8% for Arm A to Arm C and an improvement in 5-year DFS from 76.8% to 81.4% for Arm B to Arm D. Assuming the same reductions from using the weekly instead of the every 3 weeks schedule within drug, that is, a 15% reduction in failure rate for employing the weekly schedule instead of the every 3 weeks schedule for paclitaxel and a 22% reduction for using the weekly schedule for docetaxel instead of the every 3 weeks schedule, this study design will also yield 89% power to detect these differences between the 2 schedules. Considering another scenario that assumes a 12% decrease in failure hazard rates from Arm A to Arm C and a 22% reduction from Arm B to Arm D, this design gives 83% power to detect these differences in the 2 drugs. These reductions correspond to an improvement in 5-year DFS from 73.3% to 76.1% for Arm A to Arm C and an improvement in 5-year DFS from 77.4% to 81.9% for Arm B to Arm D. These reductions translate to a decrease in failure hazard rate of 17.5% from the every 3 weeks to the every 1 week schedule for paclitaxel and a reduction of 27% for docetaxel. This design yields 97% power to detect these differences between the 2 schedules. The high power is due to the large reduction in failure hazard rate assumed from using the every 1 week instead of the every 3 weeks schedule within docetaxel. Power for these designs, which assume some interaction between drug and treatment schedule, were obtained using simulations.

Based on previous data from E5188 and S9313, the anticipated accrual in subgroups defined by gender and race is:

	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	26	75	350	299	4100	150	5000
Total	26	75	350	299	4100	150	5000

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.