SWOG S0221: A phase III trial comparing chemotherapy schedules in high-risk early breast cancer.

Budd, et al

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SWOG

PHASE III TRIAL OF CONTINUOUS SCHEDULE AC + G Vs. Q 2 WEEK SCHEDULE AC, FOLLOWED BY PACLITAXEL GIVEN EITHER EVERY 2 WEEKS OR WEEKLY FOR 12 WEEKS AS POST-OPERATIVE ADJUVANT THERAPY IN NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE BREAST CANCER

PARTICIPANTS: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU. **Patients enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (see Appendix 19.4)**

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Cyclophosphamide (Cytoxan®) (NSC-26271)
Doxorubicin (Adriamycin®) (NSC-123127)
Filgrastim (r-metHuG-CSF) (NSC-614629)
Paclitaxel (Taxol®) (NSC-673089)
Pegfilgrastim (Neulasta®)
Trimethoprim Sulfa (Bactrim®)

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(Version Date 01/5/12)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

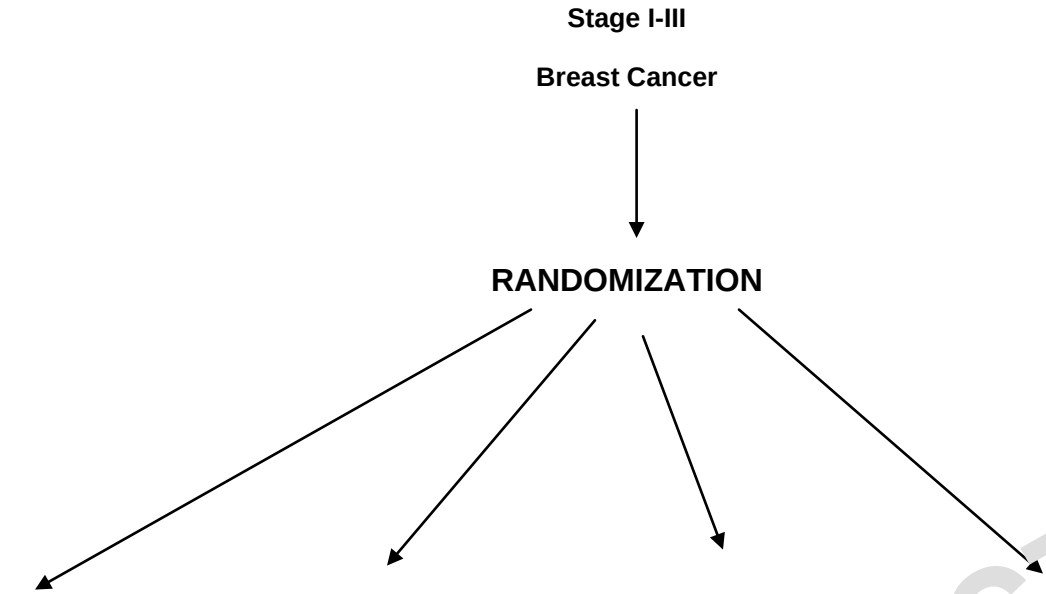
Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all associated forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Members' side of the website located at https://www.ctsu.org.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888/823-5923 Fax: 215/569-0206	CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 9:00 am – 5:30 pm EST, Monday – Friday (excluding holidays) [Registrations received after 5:30 pm EST will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 am – 5:30 pm EST.]	Southwest Oncology Group Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For treatment- or toxicity-related questions contact the Study PI of the Coordinating Group.		
For eligibility questions contact the Southwest Oncology Group Data Operations Center by phone or email: Phone: 206/652-2267; Email: breastquestion@crab.org		
For questions unrelated to patient eligibility, treatment or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 1-888/823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org		

CTSU logistical information is found in Appendix 9.4.

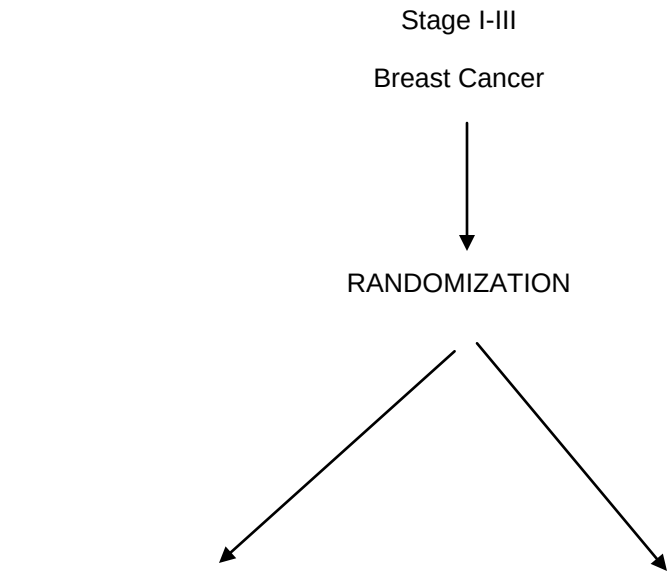
ORIGINAL SCHEMA (closed to accrual 11/10/10)



A = doxorubicin; C = cyclophosphamide; G = G-CSF; T = paclitaxel
PEG-G = pegfilgrastim

NOTE: Women with HER-2 positive tumors may have trastuzumab (Herceptin®) added to their treatment.

AMENDED SCHEMA



A = doxorubicin; C = cyclophosphamide; T = paclitaxel; PEG-G = pegfilgrastim

NOTE: Women with HER-2 positive tumors may have trastuzumab (Herceptin®) added to their treatment.

1.0 OBJECTIVES

1.1 To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with the combination of doxorubicin and cyclophosphamide given every 2 weeks with pegfilgrastim support with that of patients treated with weekly doxorubicin and daily oral cyclophosphamide with filgrastim support, with both treatments to be followed by paclitaxel given according to one of two schedules.

1.2 To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with either 12 weeks of weekly paclitaxel or paclitaxel given every 2 weeks with pegfilgrastim support for 6 cycles following treatment with one of the two randomized doxorubicin/cyclophosphamide regimens discussed above.

1.3 To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with either 12 weeks of weekly paclitaxel or paclitaxel given every 2 weeks with pegfilgrastim support for 6 cycles following treatment with four two-week cycles of doxorubicin and cyclophosphamide with pegfilgrastim support and then overall adjusting for the three regimens of doxorubicin and cyclophosphamide administration.

1.4 To compare the overall survival produced by the treatment arms.

1.5 To compare the toxicity of the treatment arms.

1.6 To examine the association of putative prognostic markers with outcome and the interaction of these markers with treatment.

2.0 BACKGROUND

Although post-operative adjuvant chemotherapy reduces the risk of relapse and death for women with operable breast cancer, the optimal means of administering currently available agents have not been clearly determined. While the investigation of novel agents is a research strategy that should be pursued, meaningful advances in therapy may also come from studies of alternative dose-schedules of agents of known utility. Such studies can be designed empirically on the basis of clinical observations, as an investigation of dose, dose-intensity, or dose density, or to test hypotheses related to the mechanisms of action of the chemotherapeutic agents involved. In the current study, we describe an investigation whose rationale is based upon all of these justifications. Patients with node positive or high-risk node negative disease will be randomly assigned to one of four regimens: 1) doxorubicin/cyclophosphamide (AC2) given every 2 weeks with pegfilgrastim support, followed by paclitaxel, also given every 2 weeks with pegfilgrastim support (T2), 2) an alternative dose-schedule of doxorubicin/cyclophosphamide, with cyclophosphamide given orally on a daily basis and doxorubicin given weekly with filgrastim support (continuous AC+G), followed by T2, 3) AC2 followed by the paclitaxel administered weekly (T1), or 4) the continuous AC+G regimen followed by T1.

Rationale for the Control Arm: AC given every 2 weeks (AC2) followed by paclitaxel given every 2 weeks (T2)

The combination of doxorubicin and cyclophosphamide has been a commonly used and well-studied regimen in the adjuvant therapy of breast cancer. This regimen has been demonstrated to be equivalent to "classic" CMF, and has been the subject of several clinical trials seeking to optimize the dose and schedule of the AC regimen. The original doses of doxorubicin (60 mg/m^2/cycle) and cyclophosphamide (600 mg/m^2/cycle) appear optimal, with dose escalation of neither doxorubicin nor cyclophosphamide resulting in an improved therapeutic outcome. *(1 - 3)* The addition of 4 cycles of chemotherapy with paclitaxel (175 mg/m^2/course), administered every 3 weeks has resulted in an improved relapse-free and overall survival, though, curiously, an unplanned retrospective analysis has indicated that, at present, this benefit is exerted primarily in the hormone receptor negative subset. *(1, 4)* O4
n the basis of these data, paclitaxel has been approved by the US Food and Drug Administration for the adjuvant therapy of breast cancer, and the combination of AC followed by paclitaxel is one of several "standard" regimens commonly employed in the United States.

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The optimal scheduling of the component drugs of the AC followed by paclitaxel regimen was investigated in a recently analyzed intergroup adjuvant breast cancer study, CALGB 9741. In this trial, patients with node-positive breast cancer were randomly assigned to treatment with one of 4 different schedules of 4 doses each of doxorubicin 60 mg/m^2, paclitaxel 175 mg/m^2, and cyclophosphamide 600 mg/m^2. Patients received either: 1) sequential therapy with doxorubicin, followed by paclitaxel, followed by cyclophosphamide, with each drug given every 3 weeks, 2) sequential therapy with doxorubicin, followed by paclitaxel, followed by cyclophosphamide, but with each drug given every 2 weeks with filgrastim support, 3) concurrent doxorubicin and cyclophosphamide followed by paclitaxel, with drug courses administered every 3 weeks, or 4) concurrent doxorubicin and cyclophosphamide followed by paclitaxel, with drug courses administered every 2 weeks with filgrastim support. The study employed a 2 x 2 factorial design, with the factors being 1) sequential drug administration vs. concurrent AC followed by paclitaxel, and 2) 21 vs 14 day treatment intervals. A total of 2005 patients were entered on this trial between September 15, 1997 and March 31, 1999. As of April 29, 2002, the median follow-up was 3.0 years. A total of 182 (9%) deaths and 315 (16%) failures had been recorded. This study showed no difference in death rate between the concurrent and sequential administration of doxorubicin and cyclophosphamide (p=0.67). However, drug administration every 2 weeks produced a significant survival advantage over drug administration every 3 weeks (p=0.013), with 75 and 107 deaths being reported in the respective groups. A multivariate Cox proportional hazards model for overall survival showed a risk ratio of 1.45 (p=0.014) favoring the q 2 week schedule, a result that persisted after adjusting for standard baseline covariates (risk ratio 1.4[illegible] p=0.013). These findings were also found in analysis of disease-free survival, where the sequence of drug administration made no difference in outcome (p=0.63), but the q 2 week schedule was superior to drug administration every 3 weeks (p=0.007). A multivariate Cox proportional hazards model for disease-free survival showed a risk ratio of 1.36 (p=0.0[illegible]2) favoring the q 2 week schedule, with similar results being seen after adjusting for standard baseline covariates (risk ratio 1.35, p=0.01). Based upon these results, treatment with doxorubicin/cyclophosphamide administered every 2 weeks with growth factor support, followed by paclitaxel administered every 2 weeks with growth factor support, has been selected as the control arm for this trial. The other arms of this randomized trial will investigate additional modifications to the doses and schedules of doxorubicin, cyclophosphamide, and paclitaxel in an effort to optimize the administration of these agents and to investigate biologic hypotheses.

Rationale for the AC+G regimen

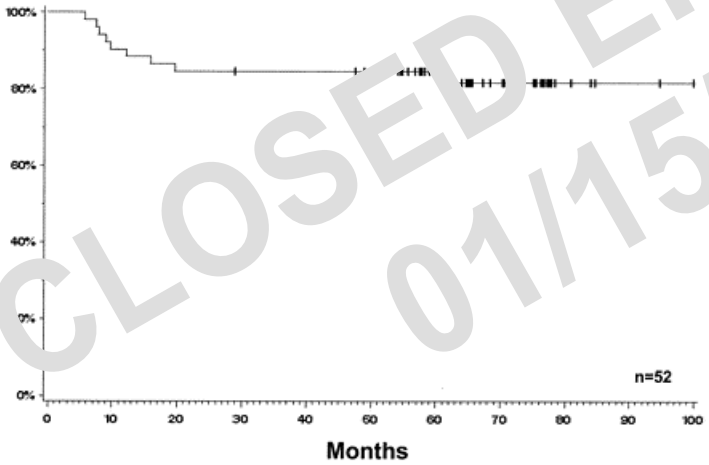
When given to patients with advanced breast cancer, "Classical" CMF with cyclophosphamide administered orally and methotrexate and 5-fluorouracil given intravenously on Days 1 and 8 of a 28 day cycle, produces an objective response rate and survival experience superior to that produced by intravenous CMF with all three drugs given intravenously every 21 days. *(5)* Other, less direct, evidence indicates that regimens incorporating daily oral cyclophosphamide are superior to regimens utilizing intermittent intravenous cyclophosphamide. In a multinational European adjuvant chemotherapy study, the anthracycline-containing regimen 5-fluorouracil/epirubicin/cyclophosphamide (FEC) was superior to 5-fluorouracil/methotrexate/cyclophosphamide (IV CMF) when all drugs were given intravenously in both regimens, but a similar IV FEC regimen was not superior to "classical" CMF utilizing oral cyclophosphamide. Similarly, when cyclophosphamide is given orally with 5-fluorouracil and either doxorubicin or epirubicin (CAF or CEF) and compared with an oral CMF regimen, the anthracycline-containing regimen has been found to be superior. However, the National Surgical Adjuvant Breast and Bowel Project has repeatedly compared four cycles of treatment with the combination of doxorubicin and intravenous cyclophosphamide (AC) with 6 cycles of treatment with "classical" (oral) CMF and found the two regimens to be of equal efficacy. While one explanation for these observations is that the reason that the AC regimen is not superior to oral CMF is because the AC regimen is of inadequate duration, this argument is countered by the observation that 8 cycles of high dose epirubicin/cyclophosphamide appears to be equivalent to 6 months of therapy with oral CMF. One might conclude from this, then, that the reason that CAF is superior to CMF while AC is equivalent must be related to either the inclusion of 5-fluorouracil in the CAF regimen or to the use of daily oral cyclophosphamide in the CAF and CEF regimens, allowing the advantage of the anthracycline to be made manifest. Overall, anthracycline-

containing regimens have been shown to be superior to CMF-type regimens when the route of administration of cyclophosphamide is the same in both regimens. When an anthracycline-containing regimen which utilizes intravenous cyclophosphamide is compared to a CMF regimen utilizing oral cyclophosphamide, however, the anthracycline and non-anthracycline regimens have produced generally similar results. These observations imply that the advantage related to the use of daily oral cyclophosphamide as opposed to intermittent intravenous administration of the drug is equivalent in magnitude to the advantage of an anthracycline given at an optimal dose over methotrexate. These findings suggest specifically that daily oral cyclophosphamide is superior to intermittently administered intravenous cyclophosphamide, and generally that dose and schedule are important considerations in the administration of cytotoxic therapy.

Based upon these observations and pilot studies performed at the University of Washington, the Southwest Oncology Group has performed a Phase II trial of weekly doxorubicin (24 mg/m^2/week) and daily oral cyclophosphamide (60 mg/m^2/day) with concurrent G-CSF support in patients with locally advanced breast cancer. *(6)* A median delivered dose-intensity of doxorubicin of 21.5 mg/m^2/week in 122 patients evaluable for toxicity was associated with no instance of febrile neutropenia, Grade 4 myelosuppression in 16 patients and Grade 3 myelosuppression in 43 patients. In this study, 21/89 patients who had undergone surgical resection had pathologic complete responses of their primary tumor (24%) and 20% of patients had both pathologic complete responses of their primary tumor and nodal negativity. An additional 20 patients had microscopic evidence of residual disease, but no gross disease (macroscopic CR), for an overall pathologic + macroscopic complete response rate of 46%. Based upon the acceptable toxicity and promising activity of this dose-schedule of doxorubicin and cyclophosphamide, the Southwest Oncology Group is performing a randomized Phase III trial comparing the pathologic response rate of the continuous AC+G regimen to conventional intravenous AC in patients with locally advanced breast cancer.

Furthermore, Livingston and colleagues have studied this regimen with and without weekly 5-FU in the adjuvant therapy of patients with high-risk operable breast cancer and have reported an 86% 5-year event-free survival in 52 node-positive patients *(7)*. In this experience, there were 3 patients (6%) admitted with febrile neutropenia, with 2 of the 3 being among the 30 patients who received FAC+G and one being among the 22 patients who received the AC+G regimen. Grade 4 neutropenia was observed in 2/22 (9%) patients treated with AC+G and in 3/30 (10%) patients treated with FAC+G; a single case of Grade 3 thrombocytopenia was noted, that in a patient receiving FAC+G, with no cases of Grade 4 thrombocytopenia being observed. In the total University of Washington and Southwest Oncology Group experience, consisting of 185 and 122 patients, respectively, there has been one case of acute leukemia observed, accounting for the single treatment-related death currently associated with the (F)AC+G regimen. This case occurred 5 months following the completion of treatment and manifested the 11q23 translocation associated with anthracycline-related acute leukemia and myeloproliferative disorders. While there are valid concerns regarding the possibility of leukemogenesis with the administration of an anthracycline and the concurrent use of G-CSF and an alkylating agent, available information does not indicate that the risk of myeloid malignancy is any greater than that observed with other doxorubicin- or epirubicin-based regimens. Thus, information exists to suggest that regimens containing daily oral cyclophosphamide are superior to regimens utilizing intravenous cyclophosphamide and that the administration of doxorubicin on

Figure 1: Disease Free Survival After continuous AC+G chemotherapy for high-risk breast cancer[7]



a weekly schedule and the use of G-CSF appears to allow the dose-intensity of doxorubicin to be maintained with acceptable toxicity and promising efficacy.

One way to examine these observations is to consider the "dose density" of the AC+G regimen relative to other anthracycline-containing chemotherapy combinations. 5-FU was initially included in the AC+G regimen, but was dropped in order to minimize hand-foot syndrome. Table 1 compares the dose delivery of the (F)AC+G regimen with other FAC combinations, based upon the original work with the (F)AC+G regimen performed at the University of Washington.

Table 1: Delivered Dose Intensity of Adjuvant Breast Cancer Chemotherapy Regimens Containing 5-Fluorouracil, Doxorubicin and Cyclophosphamide

	MDAH FAC *(13,14)*	ECOG CAF *(12)*	Continuous FAC *(11)* (RDI*)	Continuous FAC + G-CSF*(15)* (RDI*)
5-fluorouracil	267	175	242 (0.91/1.38)	270 (1.01/1.54)
Doxorubicin	13.3	10.5	13.2 (0.99/1.26)	19.8 (1.49/1.89)
Cyclophosphamide	133	245	250 (1.88/1.02)	414 (3.11/1.69)
Adjusted cyclophosphamide**	133	221	225 (1.69/1.02)	373 (2.80/1.69)
RDI, *** regimen	1.00	1.09	1.26	1.87
RDI, ***regimen, adjusted	1.00	1.04	1.20	1.77

*RDI = Relative dose intensity, continuous weekly FAC or continuous weekly FAC + G-CSF vs. other. This is the delivered dose intensity of each agent of our regimens (with and without G-CSF) divided by that from the reported reference regimens (MDAH FAC, ECOG CAF).

**Bioavailability based on 90% absorption of oral cyclophosphamide.

***RDI, average of each of the three drugs divided by MDAH FAC as reference regimen, as per the method of Hryniuk, who did not adjust for the oral bioavailability of cyclophosphamide. Presented, American Society of Clinical Oncology, May 1995, Dallas, Texas.

The AC+G regimen, based upon the above comparison, maximizes the dose density of the component drugs within the framework of manageable toxicity. These regimens differ not only in dose density, however. The continuous administration of cyclophosphamide and weekly schedule of doxorubicin may optimize not only the cytotoxic effects of the regimen, but may invoke putative anti-angiogenic effects as well.

Preclinical studies indicate that repeated moderate-dose exposure may optimize the anti-angiogenic effects of cytotoxic agents, a concept that has been termed "metronomic" chemotherapy. *(8 - 11)* When cyclophosphamide was administered on a weekly basis it was found to be able to induce complete remissions in animal models of L1210 leukemia and Lewis lung carcinoma, and was 3-fold more active than cyclophosphamide administered according to a conventional, high-dose intermittent schedule in cyclophosphamide-resistant Lewis lung carcinoma and EMT-6 breast cancer cell lines. *(8)* Furthermore, additional pre-clinical studies have indicated that a "metronomic" schedule is particularly appropriate when chemotherapy is to be given in conjunction with an anti-angiogenic agent. *(8, 9)* This observation provides further rationale to develop a "metronomic" chemotherapy schedule for clinical use, in order to establish a chemotherapeutic regimen to which anti-angiogenic agents could be added with maximal effect. Based upon the demonstrated tolerability of the continuous AC+G regimen when given in the setting of a cooperative group study, its promising activity in the treatment of locally advanced and high-risk operable disease, and a pre-clinical model suggesting that this schedule should be superior to conventional dose-schedules, we propose to compare continuous AC with the new standard of AC administered every 2 weeks in a Phase III trial to be performed in patients with high-risk node-negative and node-positive breast cancer.

Rationale for the Further Investigation of Weekly Paclitaxel

The optimal dose and schedule of paclitaxel remains under investigation. Adequate cytotoxic concentrations of paclitaxel (≥ 0.01 mmol/L) are achieved and maintained for at least 26 hours following weekly administration of paclitaxel at 100 mg/m^2. *(12, 13)* Neurotoxicity prevents escalation of paclitaxel beyond this dose when the agent is administered weekly, and the median dose of patients treated with an intended dose of 100 mg/m^2 was 91 mg/m^2/week in the Phase I evaluation of this schedule. *(12)* A weekly dose of 80 mg/m^2 has been found to be tolerable in a broad experience, including in recently completed adjuvant chemotherapy trial, **E1199**.

While the results of Phase III comparisons of weekly vs. every 3 week paclitaxel administration are awaited in the metastatic disease and adjuvant settings, data are available in the pre-operative therapy of breast cancer. Investigators at MD Anderson Cancer Center have reported the results of pre-operative therapy of operable breast cancer with alternative dose-schedules of paclitaxel administered prior to definitive surgery. *(14)* In this trial, patients were randomized to receive paclitaxel administered weekly or every 3 weeks as preoperative therapy for operable breast cancer. Among the patients randomized to receive weekly paclitaxel, node-negative patients received paclitaxel 80 mg/m^2/week for 12 weeks while node-positive patients received paclitaxel 150 mg/m^2/week for 3 weeks, followed by a one week break for 4 cycles. All patients randomized to "standard" paclitaxel received paclitaxel 225 mg/m^2 every 3 weeks for 4 cycles. After completion of paclitaxel therapy, all patients received additional chemotherapy with 4 cycles of 5FU, Adriamycin, and cyclophosphamide, followed by local therapy. The high dose weekly paclitaxel regimen proved too neurotoxic to recommend for further development, but the weekly dose of 80 mg/m^2/week was well-tolerated. Overall, the pathologic complete response (pCR) rate of 28.8% for patients receiving one of the weekly regimens was superior to the pathologic complete response rate of 13.6% for patients receiving paclitaxel every 3 weeks ($p < 0.01$). For the node positive patients, the pCR rate was 38% for patients randomized to the weekly regimen and 13.7% for patients randomized to receive paclitaxel every 3 weeks. For the node-negative patients, the pCR was 29.4% for patients randomized to receive weekly paclitaxel as compared to 13.4% for patients randomized to receive the taxane every 3 weeks.

In the effort to define the optimal dose and schedule for paclitaxel, an important comparison to make is that between the weekly and the every-3-week schedules, both of which appear to be superior to the conventional every-3-week schedule. This comparison will be made in this trial.

Rationale for the Choices of Hematopoietic Support:

Filgrastim will be used as the hematopoietic growth factor to support patients randomized to treatment with weekly AC+G, based upon the safety data from the Seattle pilot studies and the Southwest Oncology Group studies discussed above. Available pharmacokinetic data indicate that it is likely that low concentrations of pegfilgrastim present 7 days following a dose of the agent are likely to be sufficient to stimulate hematopoiesis. *(15, 16)* Because experience with the concurrent administration of doxorubicin, cyclophosphamide, and filgrastim or pegfilgrastim is minimal, the Food and Drug Administration has not allowed pegfilgrastim to be studied with the AC+G regimen in the adjuvant setting. Should data supporting the safety of the incorporation of pegfilgrastim into the AC+G regimen become available during the course of the study, consideration will be made to amending the protocol to allow the use of pegfilgrastim in patients receiving AC+G.

While filgrastim was used as the hematopoietic growth factor in C9741, patients in the current trial randomized to the q 2 week regimens will be supported with pegfilgrastim. This is based upon 1) the greater convenience to the patient and health care system of pegfilgrastim, 2) evidence that hematologic recovery is sufficient two weeks following chemotherapy to allow retreatment, 3) pharmacokinetic data indicating that the serum concentrations of pegfilgrastim present 2 weeks following chemotherapy are insufficient to stimulate hematopoiesis, and 4) existing data from clinical trials which document the safety and efficacy of pegfilgrastim used in support of anthracycline-based chemotherapy combinations administered every 2 weeks. *(15 - 21)*

reported the results of pegfilgrastim administration following 104 courses of q 2 week ABVD chemotherapy in 11 patients with Hodgkin's Disease. No instance of neutropenic fever was observed and the mean absolute neutrophil counts on the days of ABVD therapy for Cycles 1 - 8 were 5.6, 4.9, 7.5, 7.3, 8.2, 6.4, 8.9, and 7.1 x 10^6/L, respectively. *(19)* Moore has presented the results of pegfilgrastim administration following CHOP-R, administered every 2 weeks in a community oncology practice setting. Eight-four cycles were administered to the first 15 patients in the trial, with only 3 cycles having been delayed for myelosuppression. No dose reductions were necessary and 90% of cycles were administered on time. *(20, 21)* Thus, clinical results support the pharmacologic rationale for the use of pegfilgrastim following q 2 week anthracycline-based chemotherapy. Safety data will be continually monitored and reviewed by the study coordinators and the Data Safety Monitoring Committee of the Southwest Oncology Group.

Overall Trial Design

This study will investigate two primary hypotheses:

1. AC+G administered according to a continuous, "metronomic" schedule is superior to AC administered according to an accelerated but more conventional schedule. We predict that patients treated with AC+G will have a longer disease-free and overall survival than patients treated with conventional AC.

2. The administration of paclitaxel on a weekly basis is superior to the administration of this agent every 2 weeks with filgrastim support. We predict that treatment with weekly paclitaxel will produce a longer disease-free and overall survival than that treatment with paclitaxel administered every 2 weeks with filgrastim or supportive when administered following doxorubicin/cyclophosphamide therapy.

This trial will be open to patients eligible for post-operative adjuvant chemotherapy for node-positive or high-risk node negative breast cancer. This patient population is one in which a relatively long post-operative chemotherapy regimen would be acceptable and in which the event rate would be expected to be sufficiently high to allow significant differences in treatment outcome to be seen with an acceptable number of patients. Tissue blocks from the primary tumor will be required from all patients in order to allow correlative studies to be performed. The rationale for the study arms is discussed above.

Correlative Studies:

Tissue blocks will be obtained to serve as a resource for future correlative studies. Examples of such studies might include the following: tumor microvessel density or tumor VEGF expression by immunohistochemistry. It is anticipated that entry onto this trial will consist primarily of patients with HER2 negative tumors until NSABP B-31 is closed. If a significant proportion of accrual occurs after B-31 is closed, consideration could be made to performing HER2 and Topoisomerase II assays by fluorescence in situ hybridization in all tumors. Other correlative studies utilizing the prospectively collected data from this trial will also be considered as ancillary studies.

Prospective Evaluation of Polymorphisms in Genes that Synthesize and Metabolize Hormones and in Those that Metabolize Chemotherapeutic Drugs and Their Impact on Breast Cancer Survival

Despite lower breast cancer incidence, women of African ancestry (AA) have a significantly worse prognosis from breast cancer compared with white women, even when the stage at diagnosis is equivalent. (22, 23) The reasons for this disparity are probably multifactorial, including socioeconomic, sociocultural, and biological factors. Unfavorable biological parameters, such as negative estrogen receptor status, high nuclear grade, and high S-phase fraction, are more common in breast cancers from women of AA. (23, 24) However, it is controversial whether there are true biologic differences that explain worse survival outcomes for AAs when the analyses are controlled for similar stage and treatment. A recent pooled analysis of clinical

trials data from patients enrolled in consecutive adjuvant breast cancer trials coordinated by the Southwest Oncology Group shed significant light on this issue and raised questions that serve as the impetus for this proposal. (25) Between the years of 1975 and 1995, data from 5 clinical trials, incorporating data from 6,676 women, were analyzed for racial differences in survival. After stratifying for study and receptor status and then adjusting for age, number of positive nodes and tumor size, hazard ratios indicated a significant risk of failure of AAs to all other patients for disease-free, overall and cause-specific survival. In the premenopausal cohort, there was a 39%, 41%, and 42% greater risk of failure for these endpoints, respectively, and in postmenopausal women, the greater risk for AAs were 45%, 49% and 39%, respectively. (25) A parallel analysis of the overall SWOG database showed similar results for prostate cancer and for ovarian cancer. (26) Thus, a hormonal-biologic interaction with survival is raised as a hypothesis for the differential outcome by race/ethnicity.

The breast cancer adjuvant results form the rationale for this study. The inferior survival outcomes of AA women with breast cancer after adjustment for multiple variables, mandates exploration of treatment details, molecular biologic, pharmacogenetic and hormonal hypotheses. To lay the groundwork for future studies, we will further explore the etiology of the observed ethnic/racial differences in breast cancer outcome. This project will address differences in estrogen synthesis and metabolism and variability in chemotherapeutic drug metabolism as factors in racial differences in survival.

Specific Aims:

1. To evaluate the differential distribution of the polymorphisms for hormone metabolism across racial/ethnic groups and determine the relation of these gene polymorphisms to racial differences in breast cancer survival in patients enrolled in *SWOG S0221* (PI Budd). We hypothesize that the prevalence of alleles associated with poorer prognosis will be greater among AA women.

2. To determine if polymorphisms resulting in greater activation (*CYP3A4*) and lesser detoxification (*GSTP1* and *GSTA1*) of cyclophosphamide are associated with disease-free survival.

3. To set up serum and DNA banks that will be later used to determine if proteomic patterns in serum from cancer patients can predict response/resistance to specific drug therapies, and if racial differences exist, and to serve as a resource for future R01 applications for studies of racial differences in hormone and drug metabolism in relation to survival.

Antioxidant Study

In this trial, we will also request that women who are enrolled consent to be contacted for collection of additional data and to provide contact information. Women who consent will be contacted by telephone and queried regarding use of antioxidant supplements during treatment.

There is widespread use of antioxidants and other dietary supplements among cancer patients, used with the intentions and hopes that supplement use will maintain overall health, decrease treatment-associated toxicity, and increase treatment efficacy. However, there are no existing empirical data to support the notion that antioxidant supplement use can decrease toxicity associated with treatment, and it is unclear if vitamin use has any impact of treatment efficacy, either to inhibit it or to enhance it.

Because numerous chemotherapeutic agents exert their cytotoxic effects through generation of reactive oxygen species (ROS), it is possible that supplement use could block the effects of treatment upon the tumor. However, there are some experimental in vitro data showing that some

antioxidants (ascorbic acid, selenium) actually potentiate the effects of some specific treatments, supported by studies showing that antioxidants can act as pro-oxidants in cancer cells. Functional systemic genetic polymorphisms resulting in variability in activity of enzymes that generate ROS and that protect cells from oxidative damage, will also determine levels of cytotoxic metabolites that reach and damage tumor and normal cells.

Currently, there are no observational or clinical data to guide physicians in providing recommendations to their patients. It is not known whether use of antioxidants blocks the cell-killing capabilities of ROS in both normal and tumor cells. Before clinical trials can be ethically conducted to determine the potential effects of antioxidant supplements on toxicity and recurrence, observational data are required. If it is found that use of antioxidant supplements decreases toxicity while not interfering with the efficacy of radiation and/or chemotherapy, then clinical trials could ethically be conducted to investigate the potential synergistic effects of antioxidants and cancer therapy. Thus, we will query women enrolled in this study about supplement use, and evaluate in relation to toxicity and recurrence. We will also evaluate if variants (polymorphisms) in genes that impact levels of oxidative stress will affect toxicity and disease free survival, or modify relationships between supplement use and treatment outcomes.

Closure of Arms 1-4 and Opening of Arms 5-6.

In Fall 2010, the SWOG Data and Safety Monitoring Committee recommended suspension of randomization to Arms 2 and 4 (weekly administration of AC) due to crossing the futility boundary discussed in Section 11.4 such that **S0221** will be unable to demonstrate superiority of AC+G. Accrual to the remaining factor (paclitaxel administration) will continue in order to determine the optimal dose-schedule of paclitaxel. Patients will no longer be randomized to AC+G, and all patients hereafter will be assigned to treatment with four cycles of AC+pegfilgrastim. The number of cycles of AC is being reduced to four to be consistent with standard therapy, as the amended protocol is no longer asking a question regarding AC dose and schedule. Patients currently receiving treatment on Arms 1-4 may be transitioned to q 2 week AC+pegfilgrastim as described in Section 7.3, at the discretion of the patient and the investigator. Patients entered in the amended protocol will be randomized to receive treatment with 4 cycles of q 2 week AC followed by either 6 cycles of q 2 week paclitaxel (Arm 5) or 12 weeks of weekly paclitaxel (Arm 6). Statistical analysis will be as described in Section 16.7.

Inclusion of Women and Minorities:

Ethnic Category	Females	Males	Total
Hispanic or Latino	144	1	145
Not Hispanic or Latino	3,086	19	3,105
Total Ethnic	3,230	20	3,250
Racial Category			
American Indian or Alaskan Native	25	0	25
Asian	125	0	125
Black or African American	350	3	353
Native Hawaiian or other Pacific Islander	10	0	10
White	2,720	17	2,737
Racial Category: Total of all Subjects*	3,230	20	3,250

Differences among treatment arms are not expected to be a function of race or ethnicity. The study is not designed to detect differences within race or ethnicity subsets. This will be explored as part of the final analysis.

3.0 DRUG INFORMATION

3.1 Cyclophosphamide (Cytoxan®) (NSC-26271

a. DESCRIPTION

2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxidemonohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

b. TOXICITY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits

cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

For prescribing information and a comprehensive list of adverse events associated with cyclophosphamide, refer to the drug package insert.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W. The PO form is supplied as 50 mg and 25 mg tablets.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours. Tablets are stable at room temperature.

Administration: Cyclophosphamide should be diluted in about 150 cc of normal saline or D5W and infused IV. An increased dose of IV fluids may help prevent bladder toxicity. The tablet form of the drug may also be administered PO.

Supplier: Cyclophosphamide is commercially available and should be purchased by a third party. This drug will not be supplied by the NCI.

3.2 Doxorubicin (Adriamycin®) (NSC-123127)

a. DESCRIPTION

Mechanism of Action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from S. *Peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of

cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nailbeds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/M^2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

For prescribing information and a comprehensive list of adverse events associated with doxorubicin, refer to the drug package insert.

c. PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20 and 50 mg single-use vials, and 150 mg multidose vials as a red-orange, lyophilized powder which has a storage stability of at least two years (see expiration date on vial). Doxorubicin should be reconstituted with 5, 10, 25 and 75 ml respectively of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/ml.

Doxorubicin is also available in 2 mg/ml vials containing doxorubicin hydrochloride, sodium chloride 0.9% (to adjust to tonicity) and water for injection; pH adjusted to 3 using hyrochloric acid. This formulation is available in 10 mg, 20 mg and 50 mg single-use vials and in a 200 mg multidose vial.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2 - 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

Care in the administration of doxorubicin hydrochloride will reduce the chance of perivenous infiltration. On intravenous administration of doxorubicin, estravasation may occur with or without an accompanying burning or stinging sensation, even if flood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly

established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.3 Filgrastim (r-metHuG-CSF) (Neupogen®) (NSC-614629)

a. DESCRIPTION

Filgrastim, (recombinant human granulocyte-colony stimulating factor, r-metHuG-CSF), is a protein produced by E. coli into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not o-glycosylated. G-CSF functions as a hematopoietic growth hormone; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increased expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

Approximately 26,270 patients in U.S. and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 5,145,570. The maximum tolerated dose of filgrastim has not been determined. Efficacy has been demonstrated at doses of 4 to 8 mcg/kg/day. Patients receiving up to 138 mcg/kg/day displayed no toxic effects although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

b. TOXICOLOGY

The most frequently reported adverse effect was transitory bone pain, occurring in 20 - 25% of patients in Phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20-100 mcg/kg/day of intravenously administered filgrastim and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen. Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels. These occurred in 27-58% of patients, without clinical sequelae observed. Elevations of leukocyte alkaline phosphatase levels have also been noted but the significance is not yet known. Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis

Allergic reactions: Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dyspnea), and

cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when rechallenged.

Splenic rupture: Rare cases of splenic rupture have been reported following the administration of filgrastim in both healthy donors and patients. Some of these cases were fatal. Individuals receiving filgrastim who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult Respiratory Distress Syndrome (ARDS): Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Sickle Cell Disease: Severe sickle cell crises, in some cases resulting in death, have been associated with the use of filgrastim in patients with sickle cell disease. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disease should prescribe filgrastim for such patients, and only after careful consideration of the potential risks and benefits.

Alveolar Hemorrhage and Hemoptysis: Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing peripheral blood progenitor cell (PBPC) mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of filgrastim for PBPC mobilization in healthy donors is not an approved indication.

Pregnancy and Lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of filgrastim, (r-metHuG-CSF) during pregnancy or lactation is not recommended until further data are available.

Contraindications: Filgrastim is contraindicated in those patients with known hypersensitivity to E. coli derived proteins.

PHARMACOLOGY

Formulation: Filgrastim (Neupogen®) is supplied as a sterile, clear, colorless preservative-free liquid for parenteral administration. Filgrastim is available in single use vials and prefilled syringes. The single use vials contain either 300 mcg or 480 mcg filgrastim at a fill volume of 1 mL or 1.6 mL, respectively. The single use prefilled syringes contain either 300 mcg or 480 mcg filgrastim at a fill volume of 0.5 mL or 0.8 mL, respectively. See table below for product composition of each single use vial or prefilled syringe.

	300 mcg/ 1 mL vial	480 mcg/ 1.6 mL vial	300 mcg/ 0.5 mL syringe	480 mcg/ 0.8 mL syringe
Filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
Acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
Sorbitol	50 mg	80 mg	25 mg	40 mg
Tween® 80	0.004%	0.004%	0.004%	0.004%
Sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg
Water for injection USP q.s. ad	1 mL	1.6 mL	0.5 mL	0.8 mL

Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/mL. When diluted in 5% dextrose or 5% dextrose plus albumin (human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 mcg/mL is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

Storage and Stability: Filgrastim should be stored in the refrigerator at 2-8°C (36-46°F). Do not freeze. Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

Administration: Filgrastim is administered as a single daily injection by subcutaneous bolus injection.

Supplier: Filgrastim (G-CSF; Neupogen®) is commercially available. However, for this study it is being supplied free-of-charge by Amgen, Inc. and is available from UVI, Inc. To obtain a supply of filgrastim, complete the Filgrastim (G-CSF) Drug Request Form supplied in Appendix 19.1, and fax the form to UVI, Inc. at:

UVI Inc.
Phone: 800/370-2508
Fax: 610/745-3877

UVI, Inc. office hours are 8:00 a.m. to 1:00 p.m. PST; a phone message may be left at other times.

Orders received by 12:00 p.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 3:00 p.m. PST on Friday will be shipped for receipt the following Monday for receipt Tuesday, unless the institution specifically requests Saturday delivery, and can guarantee their institution will accept delivery. **Filgrastim orders from USA sites only will be accepted.** Patients must be registered to the study before study drug can be obtained.

For this study, filgrastim is supplied in 480 mcg/1.6 mL vials; initial order quantities will be 100 vials; reorder quantities will be in 30 vial increments.

Drug returns: Unused drug at the site upon termination of the study must be returned to UVI Inc. with a completed Return Medication Packing Slip (See Appendix 19.2).

3.4 Paclitaxel, Taxol® (NSC-673089)

a. DESCRIPTION

Chemistry: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, Taxus brevifolia. The marketed formulation is prepared in a semi-synthetic process.

Molecular Weight: 853.9

Empirical Formula: $C_{47}H_{51}NO_{14}$

Description: Clear viscous fluid

b. TOXICOLOGY

Human Toxicity:

Dose-limiting toxicity is myelosuppression with reversible granulocytopenia, anemia, and thrombocytopenia. Allergic reactions occur in up to 8% of patients receiving paclitaxel as an intravenous infusion over 6 to 24 hours. These can be acute anaphylactoid reactions to include flushing, hypotension, and bronchospasm; dermatitis and pruritus are also observed. Hypertension has also been seen, and may be related to concomitant medication with dexamethasone. Premedication with diphenhydramine, cimetidine, and dexamethasone appears to diminish the incidence of these reactions. Neurotoxicity can include distal painful paresthesias. Rarely, this toxicity has required discontinuation of drug due to pain, impairment of fine motor skills, or difficulty ambulating. Experience to date suggests that this neuropathy is reversible. Rarely, associated forms of neurotoxicity have included taste aversion, seizures, and mood changes. Some patients have reported vision abnormalities such as blurred vision, "flashing lights" and scintillating scotomata. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has also been seen. Patients reporting abdominal discomfort should be monitored closely. These events generally occurred while the patients were severely

neutropenic. They may be most consistent with neutropenic enterocolitis (typhlitis). Although increased SGOT, SGPT, bilirubin and alkaline phosphatase, as well as hepatic failure and hepatic necrosis have been seen, one patient receiving this drug has also experienced hepatic encephalopathy, and two incidences of pancreatitis have been noted. Neuroencephalopathy has also been reported. Pulmonary toxicities that have occurred are pneumonitis and radiation pneumonitis (following concomitant paclitaxel and radiation).

Other non-hematologic reactions include: diarrhea, alopecia, myalgias and arthralgias, nausea or vomiting, mucositis (stomatitis and pharyngitis), light-headedness, myopathy and fatigue. Less commonly, cardiotoxicity has been associated with paclitaxel administration, to include arrhythmias (sinus bradycardia, ventricular tachycardia, atrial arrhythmia, and heart block), and myocardial infarction. Skin reactions including erythema, induration, tenderness, ulceration, radiation recall, rash and nail changes have occurred including discoloration of fingernails and separation from nail bed.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implanatations and live fetuses, and increased resorption and embryo-fetal deaths. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

For prescribing information and a comprehensive list of adverse events associated with paclitaxel, refer to the drug package insert.

c. PHARMACOLOGY

Formulation: Sterile solution containing 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. There are also vial sizes of 100 mg and 300 mg.

Solution Preparation: Paclitaxel is reconstituted by diluting the total dose in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (D5W) to maintain a paclitaxel concentration between 0.3 and 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each vial/bottle should be prepared immediately before administration.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtrations should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II or IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Administration of Paclitaxel: Paclitaxel, at the appropriate dose, will be given as an intravenous infusion as specified in the protocol, diluted in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to

infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered.

Storage and stability: The intact vials of paclitaxel should be stored between 2 - 25°C. Based on stability data for Taxol® made from either natural or semi-synthetic paclitaxel, stored for up to 12 months at 40°C, potency losses were within the range of 2.0 to 2.4 percent per year. Samples stored for up to 3 months at 60°C lost potency at rates corresponding to 20 to 40% per year. Accordingly, vials left out in a warm place for a few days should still be satisfactory for use. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 - 1.2 mg/ml) are physically and chemically stable for 27 hours. Vials will be labeled with a firm expiration date.

Supplier: Paclitaxel is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.5 Pegfilgrastim (Neulasta™)

a. DESCRIPTION

Pegfilgrastim (Neulasta™) is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. Both pegfilgrastim and Filgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that Filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared with Filgrastim.

Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Pegfilgrastim was evaluated in 2 randomized, double-blind, active-control studies using doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles in the treatment of patients with high-risk stage II or stage III breast cancer. Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 used a weight-adjusted dose. In the absence of growth-factor support, similar chemotherapy regimens have been reported to result in a 10% incidence of severe neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/L] with a mean duration of 5 to 7 days, and a 30 to 40% incidence of febrile neutropenia.

In study 1, 157 subjects were randomized to receive a single subcutaneous (SC) dose of 6 mg of pegfilgrastim on Day 2 of each chemotherapy cycle or Filgrastim 5 μg/kg/day SC beginning on Day 2 of each cycle. In study 2, 310 subjects were randomized to receive a single SC injection of pegfilgrastim at 100 μg/kg on Day 2 or Filgrastim 5 μg/kg/day SC beginning on Day 2 of each cycle of chemotherapy.

Both studies met the primary objective of demonstrating that the mean days of severe neutropenia (ANC < 0.5 x 10^9/L) of pegfilgrastim-treated patients did not exceed that of Filgrastim-treated patients by more than 1 day in Cycle 1 of chemotherapy. The rates of febrile neutropenia were 13% and 9% for pegfilgrastim vs 20% and 18% for Filgrastim in studies 1 and 2, respectively.

Other secondary endpoints included days of severe neutropenia in Cycles 2 to 4, the depth of ANC nadir in Cycles 1 to 4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the 2 treatment groups.

The safety and efficacy of once-per-cycle pegfilgrastim was also found to be comparable to daily Filgrastim in phase 2 studies in patients with non-small cell lung cancer being treated with carboplatin and paclitaxel and patients with non Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma being treated with ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy.

b. TOXICOLOGY

The most common adverse event attributed to pegfilgrastim in clinical trials was medullary bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patients withdrew from the study due to bone pain. Reversible elevations in LDH, alkaline phosphatase and uric acid have been observed in clinical trials. Pegfilgrastim has been associated with leukocytosis (defined as WBC > 100 x 10^9/L) in <1% of 465 subjects with nonmyeloid malignancies, when observed is was not associated with any adverse event. Transient thrombocytopenia has also been noted in patients receiving Filgrastim.

Pegfilgrastim is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, Filgrastim or any other component of the product.

Rare cases of splenic rupture have been reported following the administration of the parent compound of pegfilgrastim, Filgrastim, for PBSC mobilization in both healthy donors and patients with cancer. Some of these cases were fatal. Pegfilgrastim has not been evaluated in this setting. Patients receiving pegfilgrastim who report left upper abdominal or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic-type reactions, including analyphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported with the parent compound of pegfilgrastim, Filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to pegfilgrastim have not been observed in clinical trials. If a serious allergic reaction or anaphylactic reaction occurs, appropriate therapy should be administered and further use of pegfilgrastim should be discontinued.

Severe sickle cell crisis have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle □+ thalassemia) who received Filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal.

There are no adequate and well-controlled studies in pregnant women. The risks of the study drug to an unborn or newborn child, are not known. In addition, it is not known whether pegfilgrastim is secreted in human milk. Therefore, pregnant or nursing mothers may not take part in this study.

No formal drug interaction studies between pegfilgrastim and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and pegfilgrastim should have more frequent monitoring of neutrophil counts.

The maximum amount of pegfilgrastim that can be safely administered in single or multiple doses has not been determined. Single doses of 300 mcg/kg have been administered SC to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These subjects experienced a mean maximum ANC of 55 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L with a corresponding absolute maximum WBC observed of 120 x 10^9/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis should be considered in the management of symptomatic individuals.

For prescribing information and a comprehensive list of adverse events associated with pegfilgrastim, refer to the drug package insert.

c. PHARMACOLOGY

Pegfilgrastim (Neulasta™) is a clear, colorless, sterile liquid. It is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, 1/2 inch needle with a UltraSafe® Needle Guard. The formulation is 10 mg pegfilgrastim (PEG-metHuG-CSF) per mL of solution containing acetate (0.35 mg), sorbitol (50 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP, pH 4.0. Each dispensing pack contains 1 prefilled syringe.

Storage and Stability: Pegfilgrastim should be stored refrigerated at 2 to 8°C (36 to 46°F). Syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded.

Administration: No preparation is required for administration of pegfilgrastim. Each subject will receive a fixed dose of 6 mg of pegfilgrastim. The entire contents of the 0.6 mL prefilled syringe should be administered subcutaneously irrespective of the subject's actual weight.

Supplier: Pegfilgrastim is commercially available and should be purchased by a third party. This drug will not be supplied by the NCI. However, Amgen, the manufacturer of Neulasta™ provides reimbursement/product support through its Clinical Trial Product Access program (see Appendix 19.6 for more details).

3.6 Trimethoprim Sulfa (Bactrim®)

a. DESCRIPTION

Chemistry: Trimethoprim-sulfa is an anti-bacterial compound which is a combination of a pyrimidine (trimethoprim) together with a sulfanilamide (sulfamethoxazole).

b. TOXICOLOGY

Human Toxicity: Human toxicity includes myelosuppression, allergic reactions including erythema multiforme, Stevens-Johnson syndrome, and other dermatitis, mucositis, nausea, vomiting, abdominal pain, hepatitis, headache, mental depression, convulsions, drug fever, chills and toxic nephrosis.

For prescribing information and a comprehensive list of adverse events associated with trimethoprim-sulfa, refer to the drug package insert.

c. PHARMACOLOGY

Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid and dihydrofolic acid by binding and reversibly inhibiting dihydrofolate reductase. Thus two consecutive steps in the biosynthesis of nucleic acids essential to many bacteria are inhibited.

Human Pharmacology: This drug is rapidly absorbed following oral administration. Blood levels of each component are similar to those achieved when each is given alone. Peak blood levels occur one to four hours after oral administration. Both drugs are present in the blood as free, conjugated, and protein bound forms. Free forms are considered to be the therapeutically active drug. Excretion of the compound is chiefly by the kidneys through glomerular filtration and tubular secretion.

Formulation: Tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole and suspension containing 40 mg of trimethoprim and 200 mg sulfamethoxazole per teaspoon are available. DS (double strength) tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole are white notched tablets.

Administration: PO.

Supplier: Trimethoprim sulfamethoxazole is commercially available and should be purchased through a third party. This drug will NOT be supplied by the NCI.

3.7 Trastuzumab (recombinant humanized HER2 antibody, Herceptin®) (NSC-688097)

a. DESCRIPTION

Trastuzumab is a monoclonal immunoglobulin G1 kappa antibody that acts as a mediator of antibody-dependent cellular cytotoxic (ADCC) agent through its high affinity, high specificity binding to extracellular domain of HER2 Receptor. HER2 is a proto-oncogene that encodes a transmembrane receptor protein that is structurally related to the epidermal growth factor receptor.

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks List (CAEPR) *for* Trastuzumab (NSC #688097)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2 September 29, 2011[1]

Adverse Events with Possible Relationship to Trastuzumab (CTCAE 4.0 Term)			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr. 3)***
	Febrile neutropenia[2]		
CARDIAC DISORDERS			
	Cardiac disorders - Other (cardiomyopathy)		
	Left ventricular systolic dysfunction		***Left ventricular systolic dysfunction (Gr. 2)***
	Pericardial effusion		
	Pericarditis		
	Sinus tachycardia		***Sinus tachycardia (Gr. 3)***
	Supraventricular tachycardia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Mucositis oral		***Mucositis oral (Gr. 3)***
	Nausea		***Nausea (Gr. 3)***
	Vomiting		***Vomiting (Gr. 3)***

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr. 3)***
	Fatigue		***Fatigue (Gr. 3)***
	Fever		***Fever (Gr. 3)***
	Flu like symptoms		***Flu like symptoms (Gr. 3)***
	Infusion related reaction		***Infusion related reaction (Gr. 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr. 3)***
	Pain		***Pain (Gr. 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr. 3)***
INVESTIGATIONS			
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr. 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr. 3)***
	GGT increased		***GGT increased (Gr. 3)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Back pain		***Back pain (Gr. 3)***
	Bone pain		***Bone pain (Gr. 3)***
	Myalgia		***Myalgia (Gr. 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		***Tumor pain (Gr. 3)***
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr. 3)***
	Peripheral sensory neuropathy		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome[3]	
	Allergic rhinitis		***Allergic rhinitis (Gr. 3)***
		Bronchospasm[3]	
	Cough		***Cough (Gr. 3)***
	Dyspnea[3]		***Dyspnea[3] (Gr. 2)***
	Hypoxia[3]		***Hypoxia[3] (Gr. 2)***
		Pneumonitis[3]	
		Pulmonary edema	
		Pulmonary fibrosis	

SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash acneiform		***Rash acneiform (Gr. 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr. 3)***
	Urticaria		***Urticaria (Gr. 3)***
VASCULAR DISORDERS			
	Hypertension[5]		
	Hypotension[5]		

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2 Fatal event when given in combination with Xeloda® (capecitabine) and Taxotere® (docetaxel).

3 Severe hypersensitivity reactions including angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, and acute respiratory distress syndrome) have been reported.

4 Infection may include any of the 75 sites of infection under the INFECTION AND INFESTATIONS SOC.

5 Associated with infusion reactions.

Also reported on trastuzumab trials but with the relationship to trastuzumab still undetermined:

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Myocardial infarction; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Blurred vision; Extraocular muscle paresis
GASTROINTESTINAL DISORDERS - Colitis; Dyspepsia; Enterocolitis; Esophageal ulcer; Gastritis; Pancreatitis; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Sudden death NOS
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (autoimmune hepatitis)
INVESTIGATIONS - Alanine aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Generalized muscle weakness; Muscle weakness left-sided; Muscle weakness lower limb; Muscle weakness right-sided; Muscle weakness trunk; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (myopathy)
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dizziness; Hydrocephalus; Ischemia cerebrovascular; Neuralgia; Seizure; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Fallopian tube obstruction; Prostatic obstruction; Spermatic cord obstruction; Uterine obstruction; Vaginal obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Apnea; Laryngeal edema; Pharyngolaryngeal pain; Pleural effusion; Pneumothorax; Pulmonary hypertension; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Pruritus; Skin ulceration
VASCULAR DISORDERS - Thromboembolic event

Note: Trastuzumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and Lactation: Pregnancy category B. Placental transfer of trastuzumab during early (Days 20 - 50 of gestation) and late (Days 120 - 150 of gestation) fetal development was observed in monkeys. Studies in cynomolgus monkeys using doses up to 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab have revealed no evidence of impaired fertility or harm to the fetus. HER2 protein expression, however, is high in many embryonic tissues. A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab showed that trastuzumab is secreted in milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is unknown whether trastuzumab is excreted in human milk, but human IgG is excreted in human milk and the potential for absorption and harm to the infant is unknown. Women are advised to discontinue nursing during trastuzumab therapy and for 6 months after the last dose of trastuzumab.

c. PHARMACOLOGY

Kinetics: In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean $t_{1/2}$ of 28 days was observed. Between weeks 16 and 32, mean trough and peak steady-state concentrations were 79 mcg/mL and 136 mcg/mL. In breast cancer patients with metastatic disease, short duration intravenous infusions demonstrated dose-dependent pharmacokinetics. Trastuzumab's volume of distribution is approximately that of serum volume (44 mL/kg). The disposition of trastuzumab is not altered based on age or serum creatinine. Administration of trastuzumab with paclitaxel resulted in reduction in trastuzumab clearance. Serum levels of trastuzumab in combination with cisplatin, doxorubicin or epirubicin plus cyclophosphamide did not suggest any interactions.

Formulation: Trastuzumab is supplied as a lyophilized, sterile powder containing 440 mg trastuzumab per vial under vacuum. Each carton contains one vial of 440 mg trastuzumab and one 20 ml vial of bacteriostatic water for injection, USP, 1.1% benzyl alcohol.

Storage and Stability: Prior to reconstitution the vials should be stored at 2 - 8°C (36 - 46°F). Each vial of trastuzumab should be reconstituted with 20 ml of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied (note that BWFI is supplied in a 30 ml vial). The resulting solution will contain trastuzumab 21 mg/ml and should not be used more than 28 days beyond the date of reconstitution with refrigeration. Do not freeze reconstituted trastuzumab. Diluted trastuzumab in polyvinylchloride or polyethylene bags containing 0.9% NaCl maintains both stability and sterility up to 24 hours refrigerated (2-8°C). Trastuzumab should not

be administered or mixed with dextrose solution. For patients with known hypersensitivity to benzyl alcohol, trastuzumab may be reconstituted with sterile water for injection and must be used immediately. Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Administration: Intravenous.

Supplier: Trastuzumab is commercially available and should be purchased by a third party. Trastuzumab will not be supplied by the NCI.

4.0 **STAGING CRITERIA**, AJCC 6th Edition, 2002

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The *telescoping* method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T3, T4). If other measurements, such as mammographic or pathologic, are used, the telescoped subsets of T can be used.*

Table 1. TNM Staging System for Breast Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget's disease of the nipple with no tumor
	Note: Paget's disease associated with a tumor is classified according to the size of the tumor.
T1	Tumor 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
Regional lymph nodes (pN)	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells
pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster > 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1	Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN1a	Metastasis in one to three axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent

Regional lymph nodes (pN) (contd.)	
pN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsitlateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit ≥2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
Regional lymph nodes (pN) (contd.)	
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Eligible Stage Groupings:

Stage Grouping		pN	M
I	T1*	[illegible]	M0
IIA	T0	N1a	M0
	T1	N1a	M0
	T2	N0	M0
IIB	T2	N1a	M0
	T3	N0	M0
IIIA	T0	N2a	M0
	T1	N2a	M0
	T2	N2a	M0
	T3	N1a	M0
	T3	N2a	M0
IIIC	T1-3	N3a (≥ 10 nodes)	M0

*If tumor is considered high-risk by the treating investigator and is ≥ 2 cm in greatest diameter

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0221** Breast Cancer Prestudy Form (Form #20608) and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.1 Patients must be women or men with a histologically confirmed diagnosis of operable Stage I, II or III invasive breast carcinoma with known estrogen or progesterone receptor status (see Section 7.7b and c). Patients with T4 tumors are not eligible.

_____ 5.2 Patients with bilateral synchronous breast cancer diagnosed within 1 month of each other are eligible if the higher TNM stage primary tumor meets the eligibility criteria for this trial

_____ 5.3 Patients must be high risk by meeting at least one of the following criteria (check all that apply):

_____ a. Tumor ≥ 2 cm in greatest diameter.

Size must be determined from the pathology specimen. Size is equal to the maximum diameter of entire lesion, including both invasive and intraductal components. In the case of multi-focal tumors, the largest lesion with an invasive component must be used to determine size. If the tumor is resected in pieces, the pathologist must re-orient the tumor fragments to determine maximum size.

Patients whose nodal status is "N0(i+)" (no cluster of tumor cells in any node greater than 0.2 mm) will be considered to be node-negative, and must have primary tumors ≥ 2 cm in size or have tumors ≥ 1 cm with high risk features as in "b" below. Patients registered to NCI-funded national sentinel node studies (e.g., ACOSOG Z0010, Z0011 and NSABP B-32) are eligible. **Patients who are node-negative on the basis of a sentinel node procedure may be entered even if fewer than 6 axillary nodes were removed; otherwise, at least 6 axillary or intramammary nodes must be negative for a patient to be considered node negative.**

_____ b. Tumor ≥ 1 cm in diameter and either:

(1) ER-negative and PgR-negative, or
(2) ER-positive or PgR-positive with a Genomic Health Recurrence Score of ≥ 26.

_____ c. One or more axillary or intramammary nodes are involved by metastatic breast cancer. If one or more nodes is involved, a minimum of 6 axillary or intramammary nodes must have been examined histologically. Patients with N0 (i+) disease will be considered to be node negative.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.4 Patients with HER2-positive tumors (3+ by immunohistochemical staining or amplified by fluorescence in-situ hybridization) are eligible. Such patients must be treated in compliance with Section 7.8. The use of trastuzumab should be documented in the treatment forms.

_____ 5.5 Patients must have had either a modified radical mastectomy or local excision of all tumors plus an axillary lymph node dissection or sentinel node resection prior to registration. Final resection margins for the primary tumor must be histologically negative for invasive cancer and ductal carcinoma in situ. Patients with resection margins positive for lobular carcinoma in-situ will be eligible. Patients must have at least 6 axillary or intramammary lymph nodes sampled, with the exception of patients who have a sentinel node procedure with all sampled nodes being uninvolved by malignancy.

_____ 5.6 Patients must be registered within 84 days from the final surgical procedure required to adequately treat the primary tumor and/or axilla.

_____ 5.7 Patients must not have received prior cytotoxic chemotherapy for this breast cancer. Patients must not have had prior chemotherapy with an anthracycline, anthracenedione, or a taxane for any condition.

_____ 5.8 Patients must not have received prior radiation therapy for the current malignancy, except for partial breast irradiation (PBI) following lumpectomy. PBI must have been completed at least 2 weeks prior to registration. Patients who have received prior radiation therapy for ductal carcinoma in situ are eligible, provided that radiation therapy was completed at least 2 weeks prior to registration.

Note: Patients who have had segmental mastectomy or other breast sparing procedure will be treated with radiotherapy according to standard procedure after completion of all chemotherapy, unless treated with PBI. Participation in NSABP B-39 is allowed. 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.

_____ 5.9 Patients with the clinical diagnosis of congestive heart failure or active angina pectoris are NOT eligible. All patients must have a MUGA, echocardiogram scan, or cardiac catheterization performed within 42 days prior to registration and LVEF % must be ≥ to the institutional lower limit of normal.

_____ 5.10 Patients must have a serum creatinine and bilirubin ≤ the institutional upper limit of normal, an alkaline phosphatase ≤ 2 x the institutional upper limits of normal, and an SGOT or SGPT ≤ 2 x the institutional upper limit of normal. These tests must have been performed within 28 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.11 Patients must have an ANC of ≥ 1,200/µl and a platelet count of ≥ 100,000/µl. These tests must have been performed within 28 days prior to registration.

_____ 5.12 Female patients of reproductive potential must have a negative pregnancy test determined within 28 days prior to registration due to the possibility of fetal harm or of harm to nursing infants from this treatment regimen. All patients of reproductive potential must agree to use an effective contraceptive method during the entire period of drug treatment.

_____ 5.13 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, lobular carcinoma in-situ of the breast (LCIS), or any other cancer from which the patient has been disease-free for 5 years. Patients with prior invasive breast cancer or ductal carcinoma in-situ (DCIS) are eligible if they have been disease free for 5 years.

_____ 5.14 Patients must be of age 18 or greater.

_____ 5.15 Patients must have a performance status of 0 – 2 by Zubrod criteria (see Section 10.7

_____ 5.16 Patients known to be HIV positive are not eligible due to the fact that [illegible] compromised immune system of these patients and the possibility of early death may compromise study objectives.

_____ 5.17 For patients who consent to the genetic polymorphism sample submission, a pretreatment sample of 17 mL of blood (one 10 mL red top [serum] tube for banking and 7 mL purple top [EDTA] tube for DNA extractions) must be submitted per Section 15.2.

_____ 5.18 If Day 28, 42 or 84 falls on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.

_____ 5.19 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. All patients must sign an authorization for the release of protected Health Information in accordance with institutional and federal guidelines.

_____ 5.20 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

Balancing on patient characteristics will not be necessary due to the large sample size. Thus, stratification factors are not applicable to this study. Originally patients were randomized to one of four treatment arms. With the amended protocol, patients will be randomized with equal probability to two arms.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Budd at 216/444-6480 (e-mail: buddg@ccf.org or S0221@ccf.org) or Dr. Moore at (216) 445-4624 (e-mail: S0221@ccf.org).

7.1 Good Medical Practice

The following pre-study tests/assessments are recommended within 42 days prior to registration in accordance with Good Medical Practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering. If an individual test is considered to be unnecessary, the rationale for not conducting the test must be documeneted in the medical record.

It is recommended that the following tests be done to rule out metastatic disease:

a. Chest X-ray.

b. Bone scan if patient has symptoms of bone pain.

c. CT scan of the abdomen if liver function tests (alkaline phosphatase, AST, or ALT) are elevated but without a clear cause.

d. CT scan of the chest and abdomen and a bone scan are recommended in patients at high risk for harboring metastatic disease, such as patients with Stage III disease or those with 10 or more lymph nodes involved by malignancy.

7.2 ARMS 1 AND 3: Q 2 WEEK DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) WITH PEGFILGRASTIM SUPPORT

NOTE: ACCRUAL TO THESE ARMS CLOSED EFFECTIVE 11/10/10.

Patients randomized to treatment on Arms 1 and 3 will initially receive treatment with q 2 week AC with pegfilgrastim support. The q 2 week AC regimen consists of intravenous administration of doxorubicin (Adriamycin) followed by IV cyclophosphamide (Cytoxan) every 14 days with pegfilgrastim support for 6 cycles, to be followed by treatment with paclitaxel as described in Sections 7.5 or 7.6, below.

The regimen will be administered as described below for a total of **six** cycles; ideally, therapy will be administered at the beginning of Weeks 1, 3, 5, 7, 9, and 11 of treatment.

ANC must be ≥ 1,200/µl, platelet count ≥ 100,000/µl, and all toxicity recovered to ≤ Grade 1 at the time that treatment is due. If mucositis develops, recovery to ≤ Grade 2 is allowable.

Patients who relapse at any time will be removed from protocol treatment.

Therapy will be administered on Day 1 for <u>six</u> 14-day cycles.

AGENT	DOSE	ROUTE	DAY	INTERVAL
Doxorubicin*	60 mg/m^2	IV, bolus, careful intrave-nous injection	1	Every 14 days x 6
Cyclophosphamide**	600 mg/m^2	IV, rapid intravenous infusion	1	Every 14 days x 6
Pegfilgrastim	6 mg (regardless of BSA)	Sub Q	2	Every 14 days x 6
Paclitaxel	See Section 7.5 or 7.6	See Section 7.5 or 7.6	To begin 14 days following the last cycle of AC	

* Doxorubicin should be administered into a vein with secure IV access.

** All patients should be instructed on the importance of vigorous hydration (drinking 8 - 10 glasses of water daily) during cyclophosphamide therapy.

7.3 **<u>ARMS 2 AND 4: WEEKLY DOXORUBICIN WITH DAILY ORAL CYCLOPHOSPHAMIDE AND FILGRASTIM (AC+G)</u>**

NOTE: ACCRUAL TO THESE ARMS CLOSED EFFECTIVE 11/10/10.

With this closure, the following recommendation was offered for patients who were already receiving treatment on these Arms:

Patients receiving treatment on Arms 2 and 4 may be transitioned to q 2 week AC+pegfilgrastim at the discretion of the investigator and the patient. This should be done in such a manner that, unless toxicity mandates otherwise, all patients receive at least 240 mg/m^2 of doxorubicin and no patient receives more than 360 mg/m^2 of doxorubicin. A suggested course is to discontinue treatment with AC+G and monitor blood counts weekly. Upon recovery to an ANC ≥ 1,200/mcL platelet count ≥ 100,000/mcL, and resolution of non-hematologic toxicity to Grade 0-2, patients may begin treatment with AC+pegfilgrastim, using commercial pegfilgrastim. The number of cycles of AC+filgrastim should be such that the patient receives a cumulative dose of doxorubicin between 240 and 360 mg/m^2 of doxorubicin.

Patients randomized to treatment on Arms 2 and 4 will initially receive treatment with "continuous" AC+G. The weekly AC + G regimen consists of weekly intravenous administration of doxorubicin (Adriamycin) and daily oral administration of cyclophosphamide (Cytoxan). Subcutaneous filgrastim (FILGRASTIM) is administered every day, **except the day of intravenous chemotherapy administration**. Treatment will be given weekly for 15 weeks to be followed by treatment with paclitaxel as described in Sections 7.5 or 7.6, below.

Ideally, therapy will be given at the beginning of Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15, with the final dose of oral cyclophosphamide being administered on Day 7 of Week 15.

ANC must be ≥ 1,200/µl, platelet count ≥ 100,000/µl, and all toxicity recovered to ≤ Grade 1 on Day 1 of each weekly treatment, when intravenous doxorubicin is due. If mucositis develops recovery to ≤ Grade 2 is allowable. Please see Section 8.0 for complete retreatment and dose-modification guidelines.

Patients who relapse at any time will be removed from protocol treatment.

Note: If oral cyclophosphamide is not available, the SWOG Operations Office should be contacted to determine whether an alternative supply of drug is available. If no oral cyclophosphamide can be procured, patients may be treated with <u>intravenous</u> cyclophosphamide (300 mg/m^2) on the same days as intravenous doxorubicin. Dose modifications as described in Section 8.3 will be followed for intravenous as well as oral cyclophosphamide.

Therapy will be administered for 15 weekly courses.

AGENT	DOSE	ROUTE	DAY	INTERVAL
Doxorubicin	24 mg/m^2	IV, bolus	1	Weekly x 15 weeks
Cyclophosphamide*	60 mg/m^2	PO	Daily	Continuously for 15 weeks
Filgrastim**	5 mcg/kg***	Sub Q	2 - 7	Weekly x 15 weeks
Prophylactic Trimethoprim Sulfa***	1 double-strength tablet bid	PO	4 and 5	Weekly x 15 weeks
Paclitaxel	See Section 7.5 or 7.6	See Section 7.5 or 7.6	To begin 14 days following the last dose of cyclophosphamide	

* Rounded to the nearest 25 mg dose. All patients should be instructed on the importance of vigorous hydration (drinking 8 - 10 glasses of water daily) during cyclophosphamide therapy. If oral cyclophosphamide is unavailable, see note abo (Section 7.3, page 28).

** Begin 24 hours after the administration of doxorubicin. Rounded to the nea of 00 or 480 µg. NOTE: In the event of a WBC > 50,000/µl or significant h ie ain i a WBC > 20,000/µl, the dose of FILGRASTIM will be reduced by 50 . B caus a rapid onset of neutropenia is observed when FILGRA M is held in this circumstance, FILGRASTIM should be dose-reduced rat er han held.

*** For patients who are allergic to trimeth prim sulfa, oral trimethoprim/sulfamethoxazole desensitization enta ine, o .o prophylaxis may be administered at the discretion of the treating physici n (s e Appendix 19.3).

NOTE: To order filgrastim (FILGRAST M) f patien receiving AC+ o Arms 2 and 4 of this study, please refer to the ord ing inst ctions in Section 3c and he drug order form in Appendix 19.1.

7.4 **ARMS 5 AND 6: Q 2 WE K DO XORUBICIN AND Y LOPH SPHAMIDE (AC) WITH PEGFILGRASTIM UPPOR F R 4 CYCLES**

Patients ran omized t eatment on A ms 5 nd 6 will initially receive treatment with q 2 week AC with peg grastim suppor i . q 2 we k AC regimen consists of intravenous adm istrat n o doxorubicin (driamycin) followed by IV cyclophosphamide (Cytoxan®) every 14 d ys with pegfilgrast m su port for 4 cycles, to be followed by treatment with paclitaxel as described n S ction 7.5 or 7.6, below.

The regimen will be adm istered as described below for a total of **four** cycles; ideally, therapy will be administered at the beginning of Weeks 1, 3, 5, and 7 of treatment.

ANC must be ≥ 1,200/mcL, platelet count ≥ 100,000/mcL, and all toxicity recovered to ≤ Grade 1 at the time that treatment is due. If mucositis develops, recovery to ≤ Grade 2 is allowable.

Patients who relapse at any time will be removed from protocol treatment.

Therapy will be administered on Day 1 for <u>four</u> 14-day cycles.

AGENT	DOSE	ROUTE	DAY	INTERVAL
Doxorubicin*	60 mg/m^2	IV, bolus, careful intrave-nous injection	1	Every 14 days x 4
Cyclophosphamide**	600 mg/m^2	IV, rapid intravenous infusion	1	Every 14 days x 4
Pegfilgrastim	6 mg (regardless of BSA)	Sub Q	2	Every 14 days x 4
Paclitaxel	See Section 7.5 or 7.6	See Section 7.5 or 7.6	To begin 14 days following the last cycle of AC	

* Doxorubicin should be administered into a vein with secure IV access.
** All patients should be instructed on the importance of vigorous hydration (drinking 8 - 10 glasses of water daily) during cyclophosphamide therapy.

7.5 **<u>ARMS 1, 2 AND 5: PACLITAXEL GIVEN Q 2 WEEKS X 6 (12 WEEKS) WITH PEGFILGRASTIM</u>**

After completion or removal from q 2 week AC OR AC+G therapy: Patients randomized to treatment on Arms 1 and 2 will receive chemotherapy with paclitaxel administered every 2 weeks with pegfilgrastim support.

For patients randomized to Arm 1 or Arm 5: Treatment with paclitaxel will begin 2 weeks following the final dose of intravenous doxorubicin and cyclophosphamide.

For patients randomized to Arm 2: Treatment with paclitaxel will begin 2 weeks following the final dose of oral cyclophosphamide. It is recognized that patients receiving AC+G will begin treatment with paclitaxel later relative to the onset of therapy than will patients randomized to treatment with conventional AC.

Treatment will begin on Day 1 of each of 6 cycles of treatment, with a cycle consisting of 2 weeks. Ideally, treatment will be given on Weeks 1, 3, 5, 7, 9 and 11 of the paclitaxel phase of the study.

ANC must be ≥ 1,200/µl, platelet count ≥ 100,000/µl, and all toxicity recovered to ≤ Grade 1 at the time that treatment is due.

Patients who progress at any time will be removed from protocol treatment.

Therapy will be administered on Day 1 for <u>six</u> <u>14-day</u> cycles.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Dexamethasone	20 mg	IV or po	1	30 minutes prior to paclitaxel every 2 weeks x 6
Diphenhydramine	25 - 50 mg	IV	1	30 minutes prior to paclitaxel every 2 weeks x 6
Famotidine (or equivalent H2 blocker)	20 mg	IV	1	30 minutes prior to paclitaxel every 2 weeks x 6
Paclitaxel	175 mg/m^2	IV over 3 hrs	1	Every 14 days x 6
Pegfilgrastim	6 mg (regardless of BSA)	Sub Q	2	Every 14 days x 6

7.6 **<u>ARMS 3, 4 AND 6: WEEKLY PACLITAXEL X 12 WEEKS</u>**

After completion or removal from Q 2 week AC OR AC+G therapy patients randomized to treatment on Arms 3 and 4 will receive chemotherapy with paclitaxel administered weekly.

For patients randomized to Arm 3 or Arm 6: Treatment with paclitaxel will begin 2 weeks following the final dose of intravenous doxorubicin and cyclophosphamide.

For patients randomized to Arm 4: Treatment with paclitaxel will begin 2 weeks following the final dose of oral cyclophosphamide. It is recognized that patients receiving AC+G will begin treatment with paclitaxel later relative to the onset of therapy than will patients randomized to treatment with conventional AC.

Treatment will be given on Day 1 of each of 12 weeks of treatment. Ideally, treatment will be given on Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 of the paclitaxel phase of the study.

ANC must be ≥ 1,000/ul platelet count > 100,000/ul and all toxicity recovered to ≤ Grade 1 at the time that treatment is due.

Patients who progress at any time will be removed from protocol treatment.

Therapy will be administered on Day 1 weekly x 12.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Dexamethasone	10 mg	IV or po	1	30 minutes prior to paclitaxel weekly x 12
Diphenhydramine	25 - 50 mg	IV	1	30 minutes prior to paclitaxel weekly x 12
Famotidine (or equivalent H2 blocker)	20 mg	IV	1	30 minutes prior to paclitaxel weekly x 12
Paclitaxel	80 mg/m^2	IV over 1 hr	1	Weekly x 12

7.7 **ARMS 1 - 6: HORMONAL THERAPY FOR ER+ or PR+ PATIENTS AFTER COMPLETION OF CHEMOTHERAPY**

a. Hormonal therapy will be given to patients whose tumors are estrogen receptor positive or progesterone receptor positive as defined in Section 7.7b. Hormonal therapy will begin within 1-28 days of completing adjuvant chemotherapy or, at the discretion of the investigator, within 1 - 28 days of the completion of radiation therapy, if given.

b. Definition of ER and PR "positive"

In general, the institutional definition of "positive" will be used for the estrogen and progesterone receptor assays. However, any tumor with ≥ 10% ER or PR positive cells will be classified as receptor positive, regardless of institutional definition. Borderline results should be considered positive.

c. ER-negative/PR-negative tumors

Patients with tumors that are both ER-negative and PR-negative will receive no adjuvant hormonal therapy.

d. ER-positive or PR-positive tumors in pre-menopausal women

Pre-menopausal women will be those who have had a menstrual period within one year prior to study entry. Acceptable hormonal therapies will include one of the following:

1. Tamoxifen 20 mg/day x 5 years, or
2. Medical or surgical ovarian ablation + tamoxifen x 5 years.
3. Medical or surgical ovarian ablation + an aromatase inhibitor x 5 years will be allowed.

NOTE: Standard medical ablation may include goserelin (Zoladex®) for 5 years at a dose of 3.6 mg subcutaneously monthly (or at a dose necessary to produce post-menopausal Estradiol levels).

e. ER-positive or PR-positive tumors in post-menopausal women

Post-menopausal women will be those who have had no menses for at least one year prior to study entry unless they have been pregnant within one year of study entry. In order to be considered patients who are less than age 60 and who have undergone hysterectomy without bilateral oophorectomy must have an FSH within the institutional range for post-menopausal. Patients who have undergone hysterectomy and who are age 60 or greater can be assigned to be post-menopausal. Patients achieving the above definition of post-menopausal while receiving chemotherapy will **NOT** be considered to be post-menopausal, based upon their menstrual function prior to the initiation of chemotherapy and consistent with the eligibility criteria for the adjuvant studies of aromatase inhibitors. Acceptable hormonal therapies for post-menopausal patients will be:

1. Tamoxifen 20 mg/day x 5 years, or
2. An aromatase-inhibitor x 5 years (e.g., anastrozole 1 mg/day x 5 years), or
3. Post-menopausal women completing 5 years of adjuvant hormonal therapy may receive an additional 5 years of extended adjuvant therapy with an aromatase inhibitor at the discretion of the investigator.

f. ER-positive or PR-positive tumors in male patients

Tamoxifen 20 mg/day x 5 years

7.8 **USE OF TRASTUZUMAB IN HER-2 POSITIVE CASES**

a. Trastuzumab (Herceptin) can be used in **S0221** in breast tumors which either show 3+ immunohistochemical staining or which are amplified by fluorescence in-situ hybridization. Testing should be performed in an established, high-volume laboratory using the manufacturer's or published definitions of overexpression or amplification.

b. Trastuzumab should NOT be given during the doxorubicin/cyclophosphamide phase of therapy because of the risk of cardiac toxicity.

c. Trastuzumab may be given either concurrently with the paclitaxel phase of therapy on any of the arms or sequentially, following within 3 months of the last dose of paclitaxel.

d. Trastuzumab may be given either weekly (with a loading dose of 4 mg/kg followed by 2 mg/kg weekly) or every 3 weeks (with a loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks), or a combination of these schedules at the discretion of the investigator.

e. Trastuzumab should be given for a total of 52 weeks.

7.9 Post-Treatment Follow-Up:

a. A history, physical examination, and performance status evaluation will be performed every 6 months for the first 5 years and then annually for 15 years or until death, whichever occurs first. Patients may be seen more frequently at the discretion of the investigator.

b. Additional studies to investigate and document suspected disease recurrence will be performed as clinically indicated and the results noted on the appropriate form. Biopsy confirmation of recurrence is encouraged.

c. Patients with remaining breast tissue will undergo annual mammography.

7.10 **Criteria for Removal from AC/AC+G Protocol Treatment:**

a. Breast cancer recurrence.

b. Delay of treatment for more than 3 weeks.

c. Unacceptable toxicity.

d. Completion of planned treatment.

e. The patient may withdraw from the study at any time for any reason.

f. The patient may go on to paclitaxel treatment after removal from AC/AC+G.

7.11 **Criteria for Removal from Paclitaxel q 2 weeks/weekly Paclitaxel Protocol Treatment:**

a. Breast cancer recurrence.

b. Delay of treatment for more than 3 weeks.

c. Unacceptable toxicity.

d. Completion of planned treatment.

e. The patient may withdraw from the study at any time for any reason.

7.12 **Criteria for Removal from Hormonal Therapy:**

a. Breast cancer recurrence.

b. Unacceptable toxicity.

c. Completion of planned treatment.

d. The patient may withdraw from the study at any time for any reason.

e. Patients intolerant of a particular hormonal manipulation may be switched to an alternative therapy described in Section 7.7 at the discretion of the investigator.

7.13 All reasons for discontinuation of treatment must be documented clearly on the Off-Treatment Notice (Form #61571).

7.14 All patients will be followed for 15 years or until death, whichever occurs first.

7.15 Doses will be calculated on the basis of actual body weight consistent with Southwest Oncology Group Policy #38, Dosing Principles for Patients on Clinical Trials (10/2001), available at the Southwest Oncology Group Website at http://www.swog.org/Visitors/Policies.asp. Any standard nomogram for calculating Body Surface Area will be acceptable.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 **Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used in this study.**

Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Active Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 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 3.0.

8.2 **ARMS 1, 3, 5 AND 6: TOXICITIES AND DOSE MODIFICATIONS FOR Q 2 WEEK DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) WITH PEGFILGRASTIM**

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest indicated dose reduction. Dose re-escalations are not allowed after dose reductions.

a. ARMS 1, 3, 5 AND 6 (AC): HEMATOLOGIC TOXICITIES

Toxicity	Treatment Modification
ANC < 1,200/µl on Day 1 of a treatment cycle	Hold both doxorubicin and cyclophosphamide until ANC ≥ 1,200/µl. Repeat counts at least weekly. Resume (with PEGFILGRASTIM 6 mg SQ Day 2) when counts have recovered, according to the following guidelines: IF ANC recovers to ≥ 1,200/µl in ≤ **1 week**, give both doxorubicin and cyclophosphamide at current dose. IF ANC recovers to ≥ 1,200/µl after **1 - 3 weeks**, give both doxorubicin and cyclophosphamide at 20% dose reductions for subsequent cycles. IF ANC < 1,200/µl **after the 3-week delay**, remove patient from AC treatment, but proceed to paclitaxel therapy as randomized and continue to follow the patient on study.
Platelets <100,000/µl on Day 1 of a treatment cycle	Hold both doxorubicin and cyclophosphamide until platelets are ≥ 100,000/µl. IF platelets recover to ≥ 100,000/µl in ≤ **1 week**, give both doxorubicin and cyclophosphamide at current dose. IF platelets recover to ≥ 100,000/µl after **1 - 3 weeks**, give both doxorubicin and cyclophosphamide at 20% dose reductions for subsequent cycles. IF the platelet count fails to recover to ≥ 100,000/µl **within 3 weeks**, remove the patient from AC treatment, but proceed to paclitaxel therapy as randomized and continue to follow the patient on study. See below for dose modifications for Grade 3 thrombocytopenia.
Febrile Neutropenia* Grade 3	Continue to give all remaining cycles with PEGFILGRASTIM support. At the discretion of the investigator, subsequent cycles may be given at either 1) full doses, but with prophylactic ciprofloxacin 500 mg po bid or an alternative prophylactic antibiotic regimen at the choice of the investigator, or 2) a 20% dose reduction of both doxorubicin and cyclophosphamide (either with or without prophylactic antibiotics). If a second episode occurs, both doxorubicin and cyclophosphamide will be reduced by 20% (based on the current dose) when chemotherapy is resumed in all subsequent cycles. If a third episode occurs, remove the patient from AC therapy but proceed to paclitaxel therapy as randomized and continue to follow the patient on study.
Grade 3 - 4 thrombocytopenia	Appropriate supportive care will be instituted. The doses of both doxorubicin and cyclophosphamide will be reduced by 20% (based on the current dose) for subsequent cycles. If the episode represents a recurrence of Grade 3 - 4 thrombocytopenia experienced during AC therapy, the doses of both doxorubicin and cyclophosphamide will be reduced by an additional 20% (based on the current dose) for subsequent cycles. If a third episode occurs, remove the patient from AC therapy but proceed to paclitaxel therapy as randomized and continue to follow the patient on study.

*Febrile neutropenia is defined as a fever ≥ 38.5°C in the presence of neutropenia (ANC < 1,000/µl).

1. There will be no dose modifications for lymphopenia.
2. There will be no dose modifications for Grade 2 - 4 anemia. Transfusions will be given as clinically indicated.

b. ARMS 1, 3, 5 AND 6 (AC): OTHER TOXICITIES

Toxicity	Treatment Modification
GI – Nausea/Vomiting Grade 2 - 4	Hold both doxorubicin and cyclophosphamide until toxicity has resolved to Grade 0-1. When toxicities resolve to Grade 0-1, resume at the current dose**.** If Grade 2-4 nausea or vomiting recur, resume treatment at a 20% dose reduction. If, after a three week delay, the toxicity is not resolved to Grade 0-1, remove the patient from treatment with AC, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Mucositis Grade 3 - 4	Provide supportive measures and hold doxorubicin and cyclophosphamide. Resume at current dose when toxicity recovers to Grade 0-2. If the patient again experiences mucositis Grade 3-4, reduce the doses of both doxorubicin and cyclophosphamide by 20%. If, after three week delay, the toxicity is not resolved remove the patient from the AC portion of the protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Liver Function Abnormalities Grade ≥ 2 (e.g., Bilirubin > 1.5 x IULN or SGOT/SGPT > 2.5 x IULN)	Consider investigation of the cause of the liver function abnormalities. Hold chemotherapy until toxicity resolves to Grade 0-1. If delay longer than 3 weeks is required, remove the patient from the AC portion of protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Cardiac** ≥ Grade 3	Discontinue AC therapy and remove the patient from protocol treatment if the patient has symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) and a diagnosis of CHF is confirmed or if the patient has a myocardial infarction or a drop in LVEF to below the institutional limits of normal. The presence of PACs or PVCs without cardiac dysfunction is **not** an indication to stop doxorubicin. Acute dysrhythmias, which may occur during and shortly after doxorubicin infusion, are not an indication to stop doxorubicin.
Hand-foot syndrome Grade 3 - 4 (desquamation, vesicle formation or pain which interferes with walking ***)	Hold doxorubicin and cyclophosphamide for one week. Resume at current dose in one week if improved to Grade 0-1. Otherwise, reduce current dose of doxorubicin by 20%. If, after three week delay, the toxicity is not resolved remove the patient from the AC portion of the protocol therapy but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study. ***Hand-foot syndrome often begins as tenderness or mild erythema at the lateral margins of the nails (usually of the hands) or as tenderness and edema over the calluses of the feet. Patients who show these early symptoms or have persistent significant involvement should do the following: 1. Take vitamin B6 (pyridoxine) 100 mg three times daily. 2. Regularly use Bag Balm or Australian tea tree lotion or oil on the hands and feet.
Hematuria (hemorrhagic cystitis) Grade 2	If hematuria is felt to be secondary to cyclophosphamide therapy, delay treatment until Grade 0-1. Provide adequate hydration and other supportive measures. Mesna can be used at the discretion of the investigator. If not, three week delay, the toxicity is persistent remove the patient from the AC portion of the protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Hematuria (hemorrhagic cystitis) Grade 3 - 4	If hematuria is felt to be secondary to cyclophosphamide therapy, discontinue cyclophosphamide treatment and contact the Study Coordinator.
Other toxicities Grade 1	Proceed without dose modification but with appropriate supportive measures.
Other toxicities Grade 2	At the discretion of the investigator, therapy can be resumed at full dose, otherwise hold therapy until recovery to Grade 0-1, then resume at current dose with appropriate supportive measures (except alopecia).
Other toxicities Grade 3	Hold therapy until recovery to Grade 0-2. At the discretion of the investigator, doses of doxorubicin and cyclophosphamide will either be resumed at full dose or reduced by 20%. If the Grade 3 toxicity occurred or recurred despite appropriate supportive measures, reduce the doses of both doxorubicin and cyclophosphamide by 20% for subsequent cycles. If more than 3 weeks is required for recovery, remove the patient from q 2 week AC therapy, but proceed to paclitaxel therapy and continue to follow the patient on study.
Other toxicities Grade 4	Discontinue q 2 week AC treatment. (If the investigator wishes to continue therapy, treatment may continue with a 20% dose reduction and institution of appropriate supportive measures with the consent of the Study Coordinator.) Patients will proceed to paclitaxel therapy at the discretion of the investigator and will continue to be followed on study.

8.3 ARMS 2 AND 4: TOXICITIES AND DOSE MODIFICATIONS FOR WEEKLY DOXORUBICIN AND DAILY CYCLOPHOSPHAMIDE + FILGRASTIM (AC+G)

Chemotherapy dose modifications and delays for toxicities shall be based on the guidelines below.

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest indicated dose reduction. Dose re-escalations are not allowed after dose reductions.

The total duration of treatment will be 15 weeks. "Lost" weeks will not be made up.

a. ARMS 2 AND 4 (AC+G): HEMATOLOGIC TOXICITIES

Toxicity	Treatment Modification
ANC < 1,200/µl on Day 1 of a treatment cycle	Hold both doxorubicin and cyclophosphamide for **1 week**; continue FILGRASTIM. Then proceed as follows: IF ANC recovers to ≥ 1,200/µl in ≤ **1 week**, resume both doxorubicin and cyclophosphamide **at current doses.** IF ANC recovers to ≥ 1,200/µl in ≤ after **1 - 3 weeks**, resume treatment with the doses of both doxorubicin and cyclophosphamide **reduced by 20%.** IF ANC fails to recover to ≥ 1,2000/µl **within 3 weeks**, remove the patient from the AC+G treatment, but proceed to paclitaxel as randomized and continue to follow the patient on study.
Platelets < 100,000/µl on Day 1 of a treatment cycle	Hold both doxorubicin and cyclophosphamide, but continue FILGRASTIM. Hold until platelets are ≥ 100,000/µl. Resume at **current dose**. If platelet count fails to recover to ≥ 100,000/µl **within 3 weeks**, remove the patient from AC+G treatment, but proceed to paclitaxel as randomized and continue to follow the patient on study. See below for Grade 3 - 4 thrombocytopenia.
Febrile Neutropenia* Grade 3	Give all remaining cycles with ciprofloxacin (500 mg po, bid) + antibiotic of choice. If a second episode occurs, the doses of both doxorubicin and cyclophosphamide will be reduced by 20% (based on current dose) when chemotherapy is resumed. If a third episode occurs, remove patient from AC+G treatment, but proceed to paclitaxel as randomized and continue to follow the patient on study.
Grade 3 - 4 thrombocytopenia	Hold both doxorubicin and cyclophosphamide until platelets are ≥ 100,000/µl but continue FILGRASTIM. Appropriate supportive care will be instituted. The doses of both doxorubicin and cyclophosphamide will be reduced by 20% (based on the current dose) for subsequent cycles. If the episode represents a recurrence of Grade 3 - 4 thrombocytopenia experienced during AC+G therapy, the doses of both doxorubicin and cyclophosphamide will be reduced by an additional 20% (based on the current dose) for subsequent cycles. If a third episode occurs, remove the patient from AC+G therapy but proceed to paclitaxel therapy as randomized and continue to follow the patient on study.
WBC > 50,000 or WBC > 20,000 with significant bone pain	Because a rapid onset of neutropenia is observed when filgrastim is held in this circumstance, filgrastim should be dose-reduced rather than held. A dose reduction of 50% is recommended.

*Febrile neutropenia is defined as a fever ≥ 38.5°C in the presence of neutropenia (ANC < 1,000/µl).

1. There will be no dose modifications for lymphopenia.
2. There will be no dose modifications for Grade 2 - 4 anemia. Transfusions will be given as clinically indicated.

b. ARMS 2 AND 4 (AC+G): OTHER TOXICITIES

Toxicity	Treatment Modification
GI – Nausea/Vomiting Grade 2 - 4	Hold both doxorubicin and cyclophosphamide until toxicity has resolved to Grade 0 - 1. When toxicities resolve to Grade 0 - 1, resume at the current dose**.** If Grade 2 - 4 nausea or vomiting recur, resume treatment at a 20% dose reduction. If, after a three week delay, the toxicity is not resolved to Grade 0 - 1, remove the patient from treatment with AC+G, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Mucositis Grade 3 - 4	Hold doxorubicin; hold cyclophosphamide **only** if patient is unable to take oral medication. Resume at current dose the following week if mucositis is Grade 0 - 2. If patient continues to have mucositis Grade 3 - 4 the next week, reduce the doses of both doxorubicin and cyclophosphamide by 20%. If, after three week delay, the toxicity is not resolved remove the patient from the AC+G portion of the protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Liver Function Abnormalities Grade ≥ 2 (e.g., Bilirubin > 1.5 x IULN or SGOT/SGPT > 2.5 x IULN)	Consider investigation of the cause of the liver function abnormalities. Hold chemotherapy until toxicity resolves to ≤ Grade 1. If delay longer than 3 weeks is required, remove the patient from the AC+G portion of protocol therapy, but proceed to paclitaxel and continue to follow the patient on the study.
Cardiac ** Grade 3 - 4	Discontinue AC+G therapy and remove the patient from protocol treatment if the patient has symptoms of CHF (e.g. dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) and a diagnosis of CHF is confirmed or if the patient has a myocardial infarction or a drop in LVEF to below the institutional limits of normal. **The presence of PACs or PVCs without cardiac dysfunction is **not** an indication to stop doxorubicin. Acute dysrhythmias, which may occur during and shortly after doxorubicin infusion, are not an indication to stop doxorubicin.
Hematuria (hemorrhagic cystitis) Grade 2	If hematuria is felt to be secondary to cyclophosphamide therapy, delay treatment until Grade 0 - 1. Provide adequate hydration and other supportive measures. If, after three week delay, the toxicity is not resolved remove the patient from the AC+G portion of the protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study.
Hematuria (hemorrhagic cystitis) Grade 3 - 4	If hematuria is felt to be secondary to cyclophosphamide, discontinue cyclophosphamide and contact the Study Coordinator.
Hand-foot syndrome Grade 3 - 4 (desquamation, vesicle formation or pain which interferes with walking***)	Hold doxorubicin, cyclophosphamide and G-CSF for one week. Resume at current dose in one week if improved to Grade 2. If not improved to Grade 2 in one week, reduce the dose of doxorubicin by 20% (based on current dose) for subsequent cycles. If, after three weeks delay, the toxicity is not resolved remove the patient from the AC+G portion of the protocol therapy, but proceed to treatment with paclitaxel as randomized and continue to follow the patient on study. *** Hand-foot syndrome often begins as tenderness or mild erythema at the lateral margins of the nails (usually of the thumbs) or as tenderness and edema over the palmar surfaces of the feet. Patients who show these early symptoms or have persistent significant involvement should: Take vitamin B6 (pyridoxine) 100 mg three times daily. Regularly use Eucerin Balm or Australian tea tree lotion or oil on the hands and feet.
Other toxicities Grade 1	Proceed without dose modification but with appropriate supportive measures.
Other toxicities Grade 2	At the discretion of the investigator, therapy can be resumed at full dose, otherwise hold therapy until recovery to Grade 0 - 1, then resume at current dose with appropriate supportive measures (except alopecia).
Other toxicities Grade 3	Hold therapy until recovery to Grade 0 - 2. At the discretion of the investigator, doses of doxorubicin and cyclophosphamide will either be resumed at full dose or reduced by 20%. If the Grade 3 toxicity occurred or recurred despite appropriate supportive measures, reduce the doses of both doxorubicin and cyclophosphamide by 20% for subsequent cycles. If more than 3 weeks is required for recovery, remove the patient from AC+G therapy, but proceed to paclitaxel therapy and continue to follow the patient on study.
Other toxicities Grade 4	Discontinue AC+G treatment. (If the investigator wishes to continue therapy, treatment may continue with a 20% dose reduction and institution of appropriate supportive measures with the consent of the Study Coordinator.) Patients will continue to be followed on study.

8.4 **ARMS 1, 2 AND 5: TOXICITIES AND DOSE MODIFICATIONS FOR PACLITAXEL GIVEN EVERY 2 WEEKS WITH PEGFILGRASTIM**

Dose reduction of paclitaxel should follow the guidelines below.

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest indicated dose reduction. Dose re-escalations are not allowed after dose reductions.

a. ARMS 1, 2 AND 5 (Q 2 WEEK PACLITAXEL + PEGFILGRASTIM): HEMATOLOGIC TOXICITIES

Toxicity	Treatment Modification
ANC < 1,200/µl on Day 1 of a treatment cycle	Hold paclitaxel until ANC ≥ 1,200/µl. Repeat counts at least weekly. Resume **at current dose** with PEGFILGRASTIM 6 mg SQ Day 2 when counts have recovered. If despite growth factor support, ANC < 1,200/µl on Day 1 of subsequent cycles, do the following: IF ANC recovers to ≥ 1,200/µl in ≤ **1 week**, give paclitaxel at current dose. IF ANC recovers to ≥ 1,200/µl after **1 - 3 weeks**, give paclitaxel at a 20% dose reduction for subsequent cycles. IF ANC < 1,200/µl **after the 3-week delay**, remove patient from protocol treatment.
Platelets < 100,000/µl on Day 1 of a treatment cycle	Hold paclitaxel until platelets are ≥ 100,000/µl. IF platelets recover to ≥ 100,000/µl in ≤ 1 **week**, give paclitaxel at current dose. IF platelets recover to ≥ 100,000/µl after **1 - 3 weeks**, give paclitaxel at a 20% dose reduction for subsequent cycles. IF the platelet count fails to recover to ≥ 100,000/µl **within 3 weeks**, remove the patient from protocol treatment.
Febrile Neutropenia* Grade 3	Continue to give all remaining cycles with PEGFILGRASTIM support. At the discretion of the investigator, subsequent cycles may be given at either 1, full dose but with prophylactic ciprofloxacin 500 mg po bid or an alternative prophylactic antibiotic regimen at the choice of the investigator, or 2, a 20% dose reduction for paclitaxel. If a second episode occurs the remaining cycles of paclitaxel will be reduced by 20% (based on the current dose) when chemotherapy is resumed. If a third episode occurs, remove the patient from paclitaxel therapy but continue to follow the patient on study.
Grade 3 - 4 thrombocytopenia	Appropriate supportive care will be instituted. The dose of paclitaxel will be reduced by 20% for subsequent cycles. If the episode represents a recurrence of Grade 3 - 4 thrombocytopenia experienced during paclitaxel therapy, the dose of paclitaxel will be reduced by an additional 20% (based on the current dose) for subsequent cycles. If a third episode occurs, remove the patient from paclitaxel therapy but continue to follow the patient on study.

*Febrile neutropenia is defined as a fever ≥ 38.5°C in the presence of neutropenia (ANC < 1,000/µl).

1. There will be no dose modifications for lymphopenia.

2. There will be no dose modifications for Grade 2 - 4 anemia. Transfusions will be given as clinically indicated.

b. ARMS 1, 2 AND 5 (Q 2 WEEK PACLITAXEL + PEGFILGRASTIM): OTHER TOXICITIES

Toxicity	Treatment Modification
Neurotoxicity Grade 1	No dose modification. Institute or continue appropriate supportive care measures.
Neurotoxicity Grade 2	If Grade 2 neurotoxicity resolves to Grade 0 - 1 by the day of scheduled therapy, proceed with treatment without dose modification. If Grade 2 neurotoxicity is present on the day of scheduled drug administration, reduce the dose of paclitaxel by 20%.
Neurotoxicity Grade 3	Hold therapy until recovery to Grade 0 - 1 and reduce the dose of paclitaxel by 20%. Patients who have not recovered to Grade 0 - 1 after 3 weeks of withholding paclitaxel will have chemotherapy discontinued, but will continue to be followed on study.
Neurotoxicity Grade 4	Discontinue paclitaxel therapy, but continue to follow the patient on study.
GI – Nausea/Vomiting Grade 2 - 4	Hold paclitaxel until toxicity has resolved to Grade 0 - 1. When toxicities resolve to Grade 0-1, resume at the current dose. Grade 2 - 4 nausea or vomiting recur, resume treatment at a 20% dose reduction. If, after a three week delay, the toxicity is not resolved to Grade 0 - 1, remove the patient from treatment with paclitaxel, but continue to follow the patient on study.
Mucositis Grade 3 - 4	Provide supportive measures and hold paclitaxel. Resume at the current dose when toxicity recovers to Grade 0 - 2. If the patient again experiences mucositis Grade 3 - 4, reduce the dose of paclitaxel by 20%. If delay longer than 3 weeks is required, remove the patient from the paclitaxel portion of protocol therapy, but continue to follow the patient on the study.
Liver Function Abnormalities Grade 2 - 4 (e.g., Bilirubin > 1.5 x IULN or SGOT/SGPT > 2.5 x IULN)	Consider investigation for the cause of the liver function abnormalities. Hold chemotherapy until toxicity resolves to Grade 0-1. If a delay longer than 3 weeks is required remove the patient from the paclitaxel portion of protocol therapy, but continue to follow the patient on the study.
Other toxicities Grade 1	Proceed without dose modification but with appropriate supportive measures.
Other toxicities Grade 2	At the discretion of the investigator, therapy can be resumed at full dose, otherwise hold therapy until recovery to Grade 0 - 1, then resume at current dose with appropriate supportive measures (except alopecia).
Other toxicities Grade 3	Hold therapy until recovery to Grade 0 - 2. At the discretion of the investigator, therapy will either be resumed at full dose or reduced by 20%. If the Grade 3 toxicity occurred or recurred despite appropriate supportive measures, reduce the dose of paclitaxel by 20% for subsequent cycles. If more than 3 weeks is required for recovery, remove the patient from paclitaxel therapy, but continue to follow the patient on study.
Other toxicities Grade 4	Discontinue paclitaxel treatment **or** contact the study coordinator and remove the patient from paclitaxel treatment. (If the investigator wishes to continue therapy, treatment may continue with a 20% dose reduction and institution of appropriate supportive measures with the consent of the Study Coordinator.) Patients will continue to be followed on study.

8.5 ARMS 3, 4 AND 6: TOXICITIES AND DOSE MODIFICATIONS FOR WEEKLY PACLITAXEL

Dose reductions of paclitaxel should follow the guidelines below.

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest indicated dose reduction. Dose re-escalations are not allowed after dose reductions.

a. ARMS 3, 4 AND 6 (WEEKLY PACLITAXEL) - HEMATOLOGIC TOXICITIES

Weekly paclitaxel 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, it is suggested that all 12 doses be completed within 15 weeks of the initiation of paclitaxel therapy.

Toxicity	Treatment Modification
ANC < **1,000**/µl on Day 1 of treatment	Hold paclitaxel until ANC ≥ **1,000**/µl. Repeat counts at least weekly. Resume when counts have recovered. If the ANC recovers to ≥ 1,000/µl in ≤ 7 days, retreat at current dose if dose reduction is not otherwise indicated. If recovery to an ANC of ≥ 1,000/µl requires > 7 days, the dose of paclitaxel should be reduced by 20%. IF ANC < 1,000/µl **after a 3-week delay**, remove the patient from paclitaxel therapy but continue to follow the patient on study. Filgrastim may be given at the discretion of the investigator
Platelets < 100,000/µl On Day 1 of treatment	Hold paclitaxel until platelets are ≥ 100,000/µl If the platelet count recovers to ≥ 100,000/µl in ≤ 7 days, retreat at the current dose if dose reduction is not otherwise indicated. If recovery to a platelet count of ≥ 100,000/µl requires > 7 days, the dose of paclitaxel should be reduced by 20% for the next cycle. If the platelet count should be < 100,000/µl on Day 1 of treatment on a second or subsequent occasion, the dose of paclitaxel should be reduced by 20%. If platelet count fails to recover to ≥ 100,000/µl within 3 weeks, remove the patient from paclitaxel therapy but continue to follow the patient on study.
Febrile Neutropenia* Grade 3	Reduce paclitaxel by 20% for all subsequent cycles or give ciprofloxacin (500 mg po, bid) or antibiotic of choice during the anticipated periods of neutropenia. If a second episode occurs, reduce the dose of paclitaxel by 20% for all subsequent cycles. If a third episode occurs, remove the patient from paclitaxel treatment. FILGRASTIM may be given at the discretion of the investigator.
Grade 3 - 4 thrombocytopenia	Appropriate supportive care will be instituted. The dose of paclitaxel will be reduced by 20% for subsequent cycles.

*Febrile neutropenia is defined as a fever ≥ 38.5°C in the presence of neutropenia (ANC < 1,000/µl).

1. There will be no dose modifications for lymphopenia.

2. There will be no dose modifications for Grade 2 - 4 anemia. Transfusions will be given as clinically indicated.

b. ARMS 3, 4 AND 6: (WEEKLY PACLITAXEL) - OTHER TOXICITIES

Toxicity	Treatment Modification
Neurotoxicity Grade 1	No dose modification. Institute or continue appropriate supportive care measures.
Neurotoxicity Grade 2	If Grade 2 neurotoxicity resolves to Grade 0 - 1 by the day of scheduled therapy, proceed with treatment without dose modification. If Grade 2 neurotoxicity is present on the day of scheduled drug administration, reduce the dose of paclitaxel by 20%.
Neurotoxicity Grade 3	Hold therapy until recovery to Grade 0 - 1 and reduce the dose of paclitaxel by 20%. Patients who have not recovered to Grade 0-1 after 3 weeks of withholding paclitaxel will have chemotherapy discontinued, but will continue to be followed on study.
Neurotoxicity Grade 4	Discontinue paclitaxel therapy, but continue to follow the patient on study.
GI – Nausea/Vomiting Grade 2 - 4	Hold paclitaxel until toxicity has resolved to Grade 0 - 1. When toxicities resolve to Grade 0 - 1, resume at the current dose. If Grade 2 - 4 nausea or vomiting recur, resume treatment at a 20% dose reduction. If, after a three week delay the toxicity is not resolved to Grade 0 - 1, remove the patient from treatment with paclitaxel, but continue to follow the patient on study.
Mucositis Grade 3 - 4	Provide supportive measures and hold paclitaxel. Resume at the current dose when toxicity recovers to Grade 0 - 2. If the patient again experiences mucositis Grade 3 - 4, reduce the dose of paclitaxel by 20%. If a delay longer than 3 weeks is required, remove the patient from the paclitaxel portion of protocol therapy, but continue to follow the patient on the study.
Liver Function Abnormalities Grade 2 - 4 (e.g., Bilirubin > 1.5 x IULN or SGOT/SGPT > 2.5 x IULN)	Consider investigation of the cause of the liver function abnormalities. Hold chemotherapy until toxicity resolves to Grade 0 - 1. If a delay longer than 3 weeks is required, remove the patient from the paclitaxel portion of protocol therapy, but continue to follow the patient on the study.
Other toxicities Grade 1	Proceed without dose modification but with appropriate supportive measures.
Other toxicities Grade 2	At the discretion of the investigator, therapy can be resumed at full dose, otherwise hold therapy until recovery to Grade 0 - 1, then resume at current dose with appropriate supportive measures (except alopecia).
Other toxicities Grade 3	Hold therapy until recovery to Grade 0 - 2. At the discretion of the investigator, therapy will either be resumed at full dose or reduced by 20%. If the Grade 3 toxicity occurred or recurred despite appropriate supportive measures, reduce the dose of paclitaxel by 20% for subsequent cycles. If more than 3 weeks is required for recovery, remove the patient from paclitaxel therapy, but continue to follow the patient on study.
Other toxicities Grade 4	Discontinue paclitaxel treatment **or** contact the study coordinator and remove the patient from paclitaxel treatment. (If the investigator wishes to continue therapy, treatment may continue with a 20% dose reduction and institution of appropriate supportive measures with the consent of the Study Coordinator.) Patients will continue to be followed on study.

8.6 **TRASTUZUMAB IN HER2 POSITIVE CASES: TOXICITIES AND DOSE MODIFICATIONS**

a. Cardiac monitoring is mandatory for all patients receiving treatment with trastuzumab. Monitoring by MUGA scan or echocardiogram should be performed according to the following schedule: 1) following completion of doxorubicin and cyclophosphamide and prior to treatment with trastuzumab, 2) after 3 months of therapy with trastuzumab, 3) after 6 months of therapy with trastuzumab, 4) after 12 months of therapy with trastuzumab.

b. Dose Modifications of trastuzumab for cardiac toxicity will be patterned after those used in N9831.

c. Trastuzumab will be permanently discontinued for documented symptomatic congestive heart failure.

d. The following guidelines will be followed for patients with asymptomatic changes in left ventricular ejection fraction:

Asymptomatic Decrease in LVEF Percentage Points from Baseline			
Relationship of LVEF to the facility's lower limits of normal (LLN)	Decrease of <10 percentage points	Decrease of 10-15 percentage points	Decrease of ≥16 percentage points
Within normal limits	Continue	Continue	**Hold** and repeat LVEF after 4 weeks
1-5 percentage points below the LLN	Continue and repeat LVEF after 4 weeks	**Hold** and repeat LVEF after 4 weeks	**Hold** and repeat LVEF after 4 weeks
≥6 percentage points below the LLN	Continue and repeat LVEF after 4 weeks	**Hold** and repeat LVEF after 4 weeks	**Hold** and repeat LVEF after 4 weeks

- Trastuzumab must be permanently discontinued when two consecutive "hold" categories occur.
- Trastuzumab must be permanently discontinued when three intermittent "hold" categories occur (at the discretion of the investigator), trastuzumab may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories).
- If the LVEF is maintained at a "continue and repeat LVEF" or improves form a "hold" to a "continue and repeat LVEF" category, additional LVEF determinations prior to the next scheduled LVEF determination will be at the discretion of the investigator.

8.7 For treatment or dose modification related questions, please contact Dr. Budd at 216/444-6480 (e-mail: buddg@ccf.org) or Dr. Moore at (216) 445-4624 (e-mail: S0221@ccf.org).

8.8 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting serious adverse events is outlined in Section 16.0. The procedure for institutions participating through the CTSU is included in Section 19.4.

9.0 STUDY CALENDAR

9.1

THE STUDY CALENDAR IS UNDER DEVELOPMENT.

9.2

THE STUDY CALENDAR IS UNDER DEVELOPMENT.

9.3

THE STUDY CALENDAR IS UNDER DEVELOPMENT.

9.4

THE STUDY CALENDAR IS UNDER DEVELOPMENT.

9.5

To be inserted

9.6

To be inserted

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 **Local or regional recurrence:** Recurrence of breast cancer involving the involved breast, chest wall, ipsilateral axilla or ipsilateral supraclavicular region.

10.2 **Contralateral breast cancer:** The development of a cancer confined to the contralateral breast.

10.3 **Distant Recurrence:** The development of a metastatic recurrence at a site not defined as local, regional, or the contralateral breast.

10.4 **Disease-Free Survival:** Time from date of registration to date of documentation of first treatment failure (local or regional recurrence, contralateral breast cancer, distant recurrence, or death due to any cause).

10.5 **Distant Disease-Free Survival:** Time from date of registration to date of first documentation of distant recurrence or death due to any cause.

10.6 **Survival:** Time from date of registration to date of death due to any cause.

10.7 **Performance Status**: Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 The original sample size for this trial was based on accruing 2,000 patients per year for 2.25 years with additional follow-up for 6 years. It was projected that 1/3 would be high risk node negative patients with the remainder being node positive. The actual accrual rate has been approximately 480 per year, but is expected to increase as NCIC endorses the study in early 2006. Based on an average accrual of 500 patients per year for 6.5 years with 5 years of additional follow-up, a total of 3,250 patients will be accrued. The entire duration of the study would be 11.5 years compared to the original 8.25 years. The observed proportion of node positive patients is 75%, rather than the projected 67%. Due to the longer study duration and a higher proportion of patients who have positive nodes, the target accrual is reduced from 4,500 to 3,250.

11.2 The primary outcome is disease-free survival (DFS). There are no stratification factors in this study. Cox regression will be performed including the two main treatment factors and their interaction. The interaction will be tested at level α=0.10. If there is no significant interaction, we will drop the interaction term and perform two-sided tests of each treatment factor in the joint model using α levels as prescribed in 11.4. In the first comparison, continuous AC (AC+G) will be compared to AC every two weeks (AC2). The second comparison will compare weekly paclitaxel (T1) to paclitaxel every two weeks (T2). Secondary analyses include log-rank tests of each treatment factor stratified by the other treatment factor and a Cox regression analysis adjusting for nodal status (positive or negative), receptor status (either ER or PgR positive versus both negative), and Her2 status (positive or negative). If there is a significant interaction (P<0.10), each treatment factor will be compared in separate Cox regression analyses at each of the two levels of the other treatment factor.

11.3 Power is estimated assuming exponential survival. We assume that the hazard ratio for AC2 versus AC+G is 1.22 and that the hazard ratio for T2 to T1 is 1.22 as well. For the purpose of the power calculations we assume no interaction between the two comparisons. The hazard rate for Arm 1 (standard treatment AC2 and T2) is estimated to be 0.06 based on DFS in similar clinical trials. This is equivalent to an estimated 5-year DFS of 74%. The hazard rates for Arm 2 (AC+G and T2) and for Arm 3 (AC2 and T1) would be 0.049 for both, corresponding to an estimated 5-year DFS of 78%. The hazard rate for Arm 4 (AC+G and T1) would be 0.04 or a 5-year DFS of 82%. With stratification by the other treatment factor, power is 90.2% for testing both factors given the accrual specified in 11.1. Interaction of the two treatment factors could slightly decrease power. On the other hand if one factor shows no significant difference, more events would be observed and power would be increased. Only 13% of the patients to date have been HER2 positive. A sensitivity analysis considering the additional impact of bevacizumab on the trial showed power to decrease by at most 1 to 2% (see modification in Section 11.7).

11.4 Under the alternative hypotheses specified in 11.3, the expected number of events would be 1072 among the 3,250 patients enrolled. Because of the long planned duration of this trial we will perform annual interim analyses starting after 30% of the expected events have occurred (approximately April 2009). Six interim analyses will be performed after approximately 30%, 41%, 54%, 66%, 77%, and 88% of the events have occurred. One-sided efficacy tests will be performed using truncated O'Brien-Fleming boundaries and a one-sided cumulative level of 0.025. The one-sided p-values to be used at the seven analyses that would cause rejection of the null hypothesis are 0.00001, 0.00042, 0.00213, 0.00507, 0.00876, 0.01331, and 0.01925 (final). If the interim analysis is significant, consideration will be given to (1) ending accrual for the inferior treatment if accrual is not yet complete or (2) reporting the result if accrual is complete. Additionally, at each interim analysis a 99% 2-sided confidence interval on the hazard ratio will be constructed. If the confidence interval lies entirely below the alternative hypothesis (HR 1.22), then consideration will be given to (1) termination of accrual to arms with the higher toxicity if accrual is incomplete or (2) publication of the result if accrual is complete. Therefore, the trial may be stopped early due to efficacy or due to failure to demonstrate that the alternative is plausible.

11.5 As discussed in Section 7.3, shortages of oral cyclophosphamide have occurred during the course of the trial. To date the shortages have not impacted the trial, though it is possible in the future that IV cyclophosphamide may have to be used instead of oral cyclophosphamide for patients already randomized if the shortage becomes acute. Nonetheless, the intent-to-treat principle requires these patients to be analyzed by their randomization assignment although the number of patients affected will be reported. For patients not yet randomized, randomization to arms with oral cyclophosphamide may have to be suspended temporarily or permanently. If the suspension is temporary, then subsequent randomization probabilities can be changed slightly so that the groups are balanced at the end of accrual. Permanent suspension will slightly lower power for the relevant comparison. If accrual to two of the arms is suspended, then ramifications of this for power and trial duration will be discussed with the Data Safety and Monitoring Committee and CTEP, though the impact would need to be strong before recommending a change in the accrual goal.

11.6 A secondary endpoint of overall survival will be analyzed using the same method as outlined in 11.2 for DFS. Using data from similar clinical trials, we estimate a baseline hazard rate of 0.035 for overall survival. Under the same alternative hypotheses and model of 11.3, power for each treatment factor will be 74% for a 2-sided 0.05 test.

11.7 In October 2010, the Data and Safety Monitoring Committee recommended suspension of randomization to Arms 2 and 4 (weekly administration of AC) due to crossing the futility boundary discussed in Section 11.4. Accrual to the remaining factor (paclitaxel administration) will continue. Since four-cyle q 2 week administration is becoming common (and may become standard of care), it was decided to reduce the number of cycles of AC from 6 to 4. This complicates the analysis since the AC factor is no longer randomized and survival may differ by calendar period or changes in the patient population. For the comparison of AC arms and the assessment of interaction between AC and paclitaxel administration, only patients accrued before this protocol change can be used in the analysis. Accordingly, in this analysis we use the 2x2 factorial analysis specified in Section 11.2 including all patients randomized prior to the protocol change. However, the comparison for paclitaxel is more complex since randomization to the paclitaxel arms continues beyond the protocol change. To adjust as completely as possible for AC administration as well as secular time changes in the population, we will stratify by the three levels of AC administration. This will be done by using a stratified log-rank test comparing the two paclitaxel arms as well as a stratified Cox regression analysis of paclitaxel administration. Interaction of the three AC strata with the paclitaxel effect will be tested in the Cox model. Kaplan-Meier plots comparing paclitaxel arms will be constructed for each level of AC administration as well as overall. The original power calculations gave 90% power under the specified design conditions. We do not redo the power calculations since the sample size goal remains the same for the paclitaxel comparison. However, if there is no difference in efficacy for the paclitaxel factor, then comparison for approximate equivalence of the two administrations becomes important. In this analysis we will be considering hazard ratios in close proximity to 1.0 as evidence that the paclitaxel administration does not affect survival. Since this is a post hoc hypothesis, we do not propose formal statistical rules for this comparison. If the two administrations of paclitaxel are similar with respect to outcome, then a comparative effectiveness analysis will be performed that accounts for IV administration times and drug costs for the pegfilgrastim. Demonstration of similarity of paclitaxel comparisons across all three platforms of AC administration will increase generalizability of these results.

11.8 An exploratory analysis of the impact of both antioxidant supplements and of reactive oxygen species (ROS) associated polymorphisms on toxicity and disease-free survival will be performed. A total of 3,000 patients are expected to be administered a questionnaire regarding antioxidant use both prior to and after protocol treatment. For each general category of antioxidant, Kaplan-Meier estimates of disease-free survival will be generated for high vs. low levels of antioxidant use. For each ROS-associated gene, Kaplan-Meier estimates of disease-free survival for the subgroups of patients with common and variant alleles will be generated. Differences between the levels will be tested using logrank tests. In order to adjust for other known prognostic factors, Cox regression models will be used. Standard methods for binary data (chi-square tests, logistic regression models) will be used for the toxicity analysis. For a given binary factor with 50% of patients in each subgroup, 3,000 patients is sufficient to detect a hazard ratio of 1.4 between the poor and good performing groups with 92% power. In the case where ≥ Grade 4 toxicity occurs with overall 50% frequency, 3,000 patients is sufficient to detect a difference between two groups of 6% in the proportion of patients with ≥ Grade 4 toxicity with 90% power. Power will be greater when toxicity frequency varies from 50%.

Interactions of lifestyle factors, such as smoking, exercise, and body mass index, with antioxidant use and ROS-associated polymorphisms, as well as interactions between antioxidant use and ROS-associated polymorphisms, will also be explored.

11.9 A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the Southwest Oncology Group, three Southwest Oncology Group members, three non-voting representatives from the NCI, and the Group Statistician (non-voting). The members of the Committee will receive confidential reports every 6 months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and early reporting of the study.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 For either method of registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to this therapeutics study using the SWOG registration program. To access the registration program go to the SWOG Website (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/Visitors/logon.asp). The Web program is available at any time

except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For any method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

13.5 Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 19.4.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2, call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@swog.org*.

b. If you need to submit data that are not available for on-line data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-0207 or 210/342-1680 locally. Please do not use cover sheet for faxed data.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 18.4.

14.4 WITHIN 7 DAYS OF REGISTRATION:

Submit copies of the following:

a. **S0221** Breast Cancer Prestudy Form (Form #20608)

b. All pre-registration breast cancer pathology reports

14.5 AT PRESTUDY (PRIOR TO INITIATION OF TREATMENT):

a. If patient consent is obtained, submit tissue, whole blood, and serum as outlined in Sections 15.1 and 15.2.

b. If patient consent is obtained, fax the page from the consent that includes patient contact information for the antioxidant questionnaire to Dr. Christine Ambrosone per Section 15.3b.

14.6 WITHIN 7 DAYS AFTER COMPLETION OR REMOVAL FROM AC TREATMENT OR AC + G TREATMENT AND AFTER COMPLETION OF SINGLE AGENT PACLITAXEL TREATMENT :

Submit copies of the **S0221** AC Treatment Form (Form #49303) or **S0221** AC+G Treatment Form (Form #35457) and the **S0221** Paclitaxel Treatment Form (Form #46970) as appropriate documenting required parameters as specified in the Study Calendar. After completion or removal from treatment and resolution of acute toxicities, submit adverse event forms **S0221** Paclitaxel Adverse Event Form (Form #29134) and **S0221** AC or AC+G Adverse Event Form (Form #40563).

14.7 WITHIN 14 DAYS OF DISCONTINUATION OF PACLITAXEL TREATMENT:

Submit copies of the Off Treatment Notice (Form #1974).

14.8 AFTER OFF-TREATMENT: EVERY SIX MONTHS FOR FIVE YEARS AND THEN ANNUALLY UNTIL YEAR 15 OR UNTIL DEATH, WHICHEVER COMES FIRST:

Submit the Follow-Up Form (Form #61519) and **S0221** Supplemental Follow-Up Form (Form #11593).

14.9 WITHIN 14 DAYS OF DISCONTINUATION OF TRASTUZUMAB TREATMENT (IF RECEIVED).

Submit the **S0221** Trastuzumab Use Form (Form #58998).

14.10 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of the Follow-Up Form (Form #61519) documenting date, site, and method for determining progression/relapse, and **S0221** Supplemental Follow-Up Form (Form #11593).

14.11 WITHIN 4 WEEKS OF KNOWLEDGE OF SUBSEQUENT MALIGNANCY:

Submit copies of the Follow-Up Form (Form #61519) documenting date, site and method for determining malignancy and **S0221** Supplemental Follow-Up Form (Form #11593).

14.12 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death (Form #38060) and the Follow-Up Form (Form #61519) if death occurs after off treatment.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for Banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) optional for patient:

a. With patient's consent specimens must be submitted at the following times (see Sections 9.5 and 9.6)

One block of the primary tumor should be submitted Prestudy. If the institution is not able to release the block, a punch of the block plus 25 unstained 5 micron sections on plus slides would be acceptable. The tissue bank will send a disposable punch instrument at the request of the submitting institution. At minimum, if no other tissues are available for submission, the tissue bank will accept 25 unstained 5 micron sections of the tumor block on plus slides.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0221** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; shipping will be via institutional supplies.

15.2 Blood Submission Instructions

a. **Institutions are <u>required to</u> seek additional patient consent to submit serum for banking. (NOTE: The specimen collection instructions below for the serum sent for banking differ from the instructions on the specimen submission webpage. The collection instructions below are to be followed for this submission; shipping instructions on the specimen submission webpage should be followed.) Institutions are <u>encouraged</u> to seek additional patient consent to submit whole blood for genetic polymorphism testing.**

b. Directions for obtaining blood collection kits

1. Prior to patient registration, institutions should order blood collection kits, by contacting Dr. Warren Davis, Roswell Park Cancer Institute (716/845-8165; email: Warren.Davis@RoswellPark.org).

2. Each blood collection kit contains:

- One blood processing sheet and specimen submission form
- One red-top Vacutainer® tube (for serum)
- One purple-top Vacutainer® tube (for DNA extractions)
- Eighteen (18) cryovials; eight (8) with tan caps for serum and ten (10) with green caps for whole blood
- Two (2) absorbent pads
- Biohazard label
- UN 3373/Diagnostic specimen label
- One FedEx shipping form
- One ice pack
- One shipping container

c. Blood Collection:

1. <u>Timing</u>: If patient consent is obtained, serum and whole blood should be drawn at prestudy (prior to initiation of treatment).

2. The date and time of the blood draw should be noted on the Specimen Submission Form. Subjects should be seated for at least five minutes prior to blood collection.

3. Complete the specimen submission form and enter the requested information: visit number, collection date and time, initials of phlebotomist and participant study ID number. The date of onset of the menstrual cycle should be noted, if relevant.

4. Remove the red top Vacutainer® tube and the eight tan capped vials. Label the vials with the date of the draw, patient ID number, and patient initials.

5. Using the red-top Vacutainer® blood collection tube and a double ended needle, draw 10 mLs of blood. Invert the tube five times to initiate clotting. The red-top tubes should sit at room temperature from a minimum of 30 to a maximum (preferred) of 60 minutes to allow the clot to form and then be refrigerated (4°C) from a minimum of 30 to a maximum (preferred) of 60 minutes before centrifugation.

6. Centrifuge the red-top Vacutainer® tube for for 15 – 20 minutes at ≤ 1,300 g (rpm will roughly = 10,000/square root of the radius in cm from the center of the centrifuge rotor to the bottom of the tube), preferably using a refrigerated centrifuge. <u>Use of a non-refrigerated centrifuge should be noted on the specimen submission form</u>.

7. Using a plastic, disposable pipet, transfer 0.5 mL of serum to each of the eight (8) tan capped vials. Close the vials securely.

8. Write on the matching serum log sheet any comments such as problems with blood draw, insufficient volume, spills, etc.

9. Freeze the tan capped vials in a -20°C freezer.

10. Use the purple-top Vacutainer® blood collection tube and a double-ended needle, draw 7 mLs of blood. Invert the tube five (5) times to ensure adequate mixing of the anticoagulant. Using a plastic, disposable pipet, transfer the well mixed contents of the purple-top tube to the labeled, green capped cryovials. Freeze the green capped vials in a -20°C freezer.

11. Institutions should also complete the appropriate Specimen Collection Tracking Form available in the "CRA Workbench" at http://www.swog.org.

d. Shipping Instructions

1. Place the frozen tan capped cryovials into a biohazard bag containing an absorbent pad. Place the green capped cryovials into a second biohazard bag containing an absorbent pad.

2. Add dry ice to the shipping container (preferable). If dry ice is not available, the frozen ice pack (included in the kit) may be used. Place the biohazard bags containing the cryovials on top of the dry ice (or ice pack) and place the lid on the Styrofoam container. Place the completed specimen submission form on top of the Styrofoam container, inside the shipping box. Close the shipping box and seal with packing tape. Place the UN 3373/Diagnostic Specimens and Biohazard labels on the outside of the box and use the FedEx label that was included in the kit to ship the box.

3. Do not ship on Friday. If a patient is drawn on Friday, please place the cryovials in a -20°C freezer and ship the following week and then ship.

4. Please fax a copy of the FedEx form to 716/845-1356, so that the receiving laboratory can expect shipment and is able to track the package if any shipping problems occur. **Please note that the laboratory will replace all blood collection kits sent with a new kit so that institutions will always have a kit available for future blood draws.**

5. Fax the page from the patient consent that includes the patient contact information for the antioxidant substudy (if consent is obtained) to the attention of Dr. Christine Ambrosone at 716/845-8125 (see Section 15.3).

6. Ship all specimens by overnight delivery to:

Lab #110: **SWOG Breast Lab – DNA Analysis**
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263

Contact: Warren Davis, Ph.D.
Phone: 716/845-8165
Fax: 716/845-1356
E-mail: Warren.Davis@RoswellPark.org

15.3 Antioxidant Use Questionnaire

a. **Institutions are <u>encouraged</u> to seek additional patient consent to submit information for the following substudy:**

Patient questionnaire regarding patient lifestyle habits and patient use of medications, vitamins, and supplements while on protocol treatment.

b. Directions

1. Fax the page from the patient consent that includes patient contact information for the antioxidant substudy (if consent is obtained) to 716/845-8125, Attn: Dr. Christine Ambrosone. Write the SWOG patient ID number on the page as well as the institute study coordinator name. Patients will then be contacted by a representative of Roswell Park Cancer Institute (RPCI) regarding lifestyle habits and the use of certain medications, vitamins, and supplements while on protocol treatment at the following timepoints:

i. Prestudy (prior to beginning protocol treatment);

ii. At the end of protocol treatment;

iii. Annually (from the date of initial registration) according to the follow-up timeframe outlined in Section 7.14.

Note: Current **S02** patients that have consented to the antioxidant questionnaire schedule as originally planned may opt out of the annual questionnaire at any time. If this occurs, please contact the staff at Roswell Park Cancer Institute (RPCI) at 716/845-8103 so that the RPCI staff can update their database accordingly and stop further questionnaire contacts.

Instructions for institutions that <u>do not</u> allow patients to be contacted directly RPCI will provide a brief questionnaire regarding lifestyle habits and the use of certain medications, vitamins, and supplements while on protocol treatment. The antioxidant use questionnaire can be provided in the blood collection kit <u>upon request</u> (see Section 15.2). The Study Coordinator should write the patient's ID number on the inside of the questionnaire before giving it to the patient and then fax the questionnaire administration form to 716/845-8125, Attn: Dr. Christine Ambrosone. The patient should complete the form (the questionnaire takes about 20-30 minutes to complete). The patient should then return the questionnaire in the stamped envelope that will be provided. Except for the information used to contact the patient, the information provided in the questionnaire will not have the patient's name or other personal identifying information on them.

3. Additionally, institutions are encouraged to seek additional patient consent to allow the whole blood specimen collected above (See Section 15.2) to be used to evaluate if genetic polymorphisms that impact levels of oxidative stress will affect toxicity and disease free survival (or modify relationships between antioxidant use and treatment outcomes).

NOTE: In order to expedite the local IRB approval of the Antioxidant Use Questionnaire, the document can be downloaded from the Southwest Oncology Group website link for this study, http://www.swog.org.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also **Appendix 19.7** for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the Southwest Oncology Group Operations Office by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, **or**
- **Only if submitting electronically is not possible**, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents – paper template, located at http://ctep.cancer.gov, to 210/614-0006.

c. When to report an event in an expedited manner

Some adverse events may require 24 hour notification (refer to Table 16.1) via AdEERS and/or to designated recipient(s) and method of reporting, i.e., phone or fax.

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

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

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**AdEERS**	**AdEERS**
Possible, Probable, Definite	**AdEERS**		**AdEERS**	**AdEERS**

AdEERS: Indicates an expedited report is to be submitted via NCI AdEERS within 10 calendar days of learning of the event[b].

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

b Submission of the on-line AdEERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

f. **Reporting secondary AML/MDS/ALL**

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in AdEERS.

   i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

   - Leukemia secondary to oncology chemotherapy
   - Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)" and insert MDS as the specify term.
   - Treatment related secondary malignancy

   ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as "Secondary malignancy-Other (specify, ___)". Report MDS as "Myelodysplasia," in the BLOOD/BONE MARROW category.

   iii. Secondary malignancies <u>other than</u> AML/ALL/MDS that are related to protocol treatment must also be reported in AdEERS.

   iv. <u>Non</u>-treatment related cases of AML/ALL/MDS must be reported as follows:

   In protocols using CTCAE Version 4.0 for SAE reporting, report as "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify"

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as "Myelodysplasia" and Leukemias as "Blood/Bone Marrow - Other (Specify, __)"

For more information see:
http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

Submit the Report and documentation to:

Investigational Drug Branch **and** Southwest Oncology Group
by fax at 301-230-0159 ATTN: SAE Program
4201 Medical Drive, Suite 230
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial

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18.0 MASTER FORMS SET

18.1 Attached are copies of all data forms which must be completed for this study. The Model Informed Consent form is also included, and must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 Forms to be used for patients treated on this study include:

a. **S0221** Registration Form (Form #53454) (3/15/08); Southwest Oncology Group Registration Form Code Sheet (10/24/06)

b. **S0221** Breast Cancer Prestudy Form (Form #20608) (8/1/11)

c. **S0221** AC Treatment Form (Form#49303) (1/7/11)

d. **S0221** AC + G Treatment Form (Form #35457) (2/15/06)

e. **S0221** Paclitaxel Treatment Form (Form #46970) (1/7/11)

f. **S0221** AC or AC + G Adverse Event Form (Form #40563) (11/[illegible])

g. **S0221** Paclitaxel Adverse Event Form (Form #29134) (3/[illegible]5/08)

h. Off Treatment Notice (Form #1974) (10/15/[illegible])

i. Notice of Death (Form #38060) (10/[illegible]/02)

j. Follow-Up Form (Form #615[illegible]) (5/1/[illegible]1)

k. **S0221** Supplemental Follow-Up Form (Form #115[illegible]8) ([illegible]3/15/[illegible]8)

l. **S0221** Trastuzumab Use Form (Form #58[illegible]98) ([illegible]/15/[illegible])

For IRB use only, not to be included in patient information.

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. (Institutions should attempt to use sections of this document which are in bold type 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 the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	Flesch Reading Ease	64.0 (targeted above 55)
	Flesch-Kincaid Grade Level	8.7 (targeted below 8.5)

S0221, "Phase III Trial of Continuous Schedule AC + G Vs. Q 2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer"

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your family and friends.

You are being asked to take part in this study because you have breast cancer that is considered high-risk.

WHY IS THIS STUDY BEING DONE?

The main purpose of this study is to compare the effects (good and bad) of two different treatments (or "regimens") for breast cancer. *(11/12/10)* **These two treatments include essentially the same drugs given in different ways and on different schedules.** *(11/12/10)* **All of the treatments use standard, commercially available medicines that are known to be effective for treating breast cancer. The chance that your cancer will return or spread depends on a number of factors and you should discuss with your health care provider and/or the study doctor what the chance for return or spread is in your particular case both with and without various treatments.**

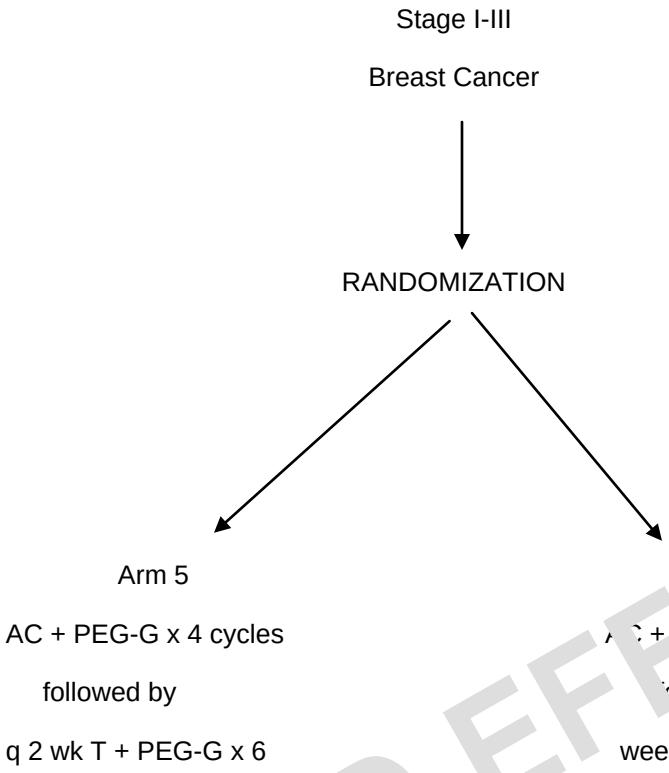
The researchers would also like to learn whether there is any link between DNA or protein patterns from racial/ethnic groups and how your body metabolizes drugs and hormones. By analyzing your DNA or protein, researchers may be able to predict whether racial/ethnic groups with breast cancer will respond to specific drug therapies and whether this information can predict breast cancer survival. If you agree to submit to blood samples for this purpose, small amounts of your blood will be sent to a central laboratory where the DNA or protein will be extracted and analyzed. The studies done on your blood may lead to discoveries that may help future patients with breast cancer. *(paragraph added 9/22/04)*

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 3,250 people will take part in this study. *(9/15/06)*

WHAT IS INVOLVED IN THE STUDY?

SCHEMA *(updated 11/12/10)*



A = doxorubicin; C = cyclophosphamide; T = paclitaxel; PEG-G = pegfilgrastim

NOTE: Women with HER-2 positive tumors may have trastuzumab (Herceptin®) added to their treatment.

NOTE: Hormonal therapy (such as tamoxifen, anastrozole or goserelin) will be given if your tumor is estrogen receptor-positive or progesterone receptor positive. Trastuzumab (Herceptin®) may be added to your treatment if your tumor tests positive for the human epidermal growth factor receptor-type 2 (or HER-2). *(added 9/15/06)*

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in each group.

Regardless of which group you are assigned to, you will receive three chemotherapy drugs that are commonly used to treat breast cancer: Doxorubicin (also called Adriamycin), cyclophosphamide (also called Cytoxan) and paclitaxel (also called Taxol). The doxorubicin and cyclophosphamide are given the same

way to all patients. The paclitaxel is given differently in Arms 5 and 6. The numbers of the arms start at 5 because the study has been changed, and arms 1-4 are no longer being studied. *(11/12/10)*

If you are assigned to Arm 5, you will receive the chemotherapy drugs doxorubicin and cyclophosphamide through a needle in your vein on Day 1 and pegfilgrastim as a shot under the skin on Day 2 every 14 days for four cycles (with each cycle being a 14-day timeframe). *(11/12/10)* Two weeks after completing your last doxorubicin/ cyclophosphamide treatment, you will begin to receive the drug paclitaxel through a needle in your vein for 3 hours on Day 1 and on Day 2 pegfilgrastim is given as a shot under the skin every 14 days for six cycles.

(paragraph deleted 11/12/10)

If you are assigned to Arm 6, you will receive the chemotherapy drugs doxorubicin and cyclophosphamide through a needle in your vein on Day 1 and pegfilgrastim as a shot under the skin on Day 2 every 14 days for four cycles (with each cycle being a 14-day timeframe). *(11/12/10)* Two weeks after completing your last doxorubicin/ cyclophosphamide treatment, you will receive the drug paclitaxel through a needle in your vein for one hour on one day every week for 12 weeks.

(paragraph deleted 11/12/10)

(deleted 11/12/10)

Regardless of which study arm you are assigned, you should drink 8 - 10 glasses of water per day while you are on cyclophosphamide.

Hormonal therapy will be given to you if your tumor is estrogen receptor-positive or progesterone receptor-positive as defined in the treatment plan. Hormonal therapy will be given within 1-28 days of completing adjuvant chemotherapy or at the discretion of your physician, within 1-28 days of the completion of radiation therapy, if given.

If you have tumors that are estrogen receptor-negative and progesterone receptor-negative, you will receive no adjuvant hormonal therapy.

If your tumor is estrogen receptor-positive or progesterone receptor-positive and you are a pre-menopausal woman (you have had your period within one year prior to entering the study) you could receive the following hormone treatments:

- Tamoxifen 20 mg once a day for five years, or
- Tamoxifen 20 mg once a day for five years plus removal of your ovaries or receive medical treatment to stop your ovaries from functioning for five years *(9/15/06)*
- An aromatase-inhibitor for five years plus removal of your ovaries or receive medical treatment to stop your ovaries from functioning for five years. *(9/15/06) (sentence deleted 11/14/11) (added 10/7/05) (9/15/06)*

If your tumor is estrogen receptor-positive or progesterone receptor-positive and you are a post-menopausal woman (you have not had your period for at least one year before entering the study but not because of pregnancy) you could receive the following hormone treatments:

- Tamoxifen 20 mg a day for five years, or
- An aromatase-inhibitor (such as anastrozole, femara or aromasin) for five years, or
- *(sentence deleted 11/14/11)*
- If you completed 5 years of hormonal therapy, you may receive an additional 5 years of therapy with an aromatase inhibitor at the discretion of your doctor. *(added 9/15/06)*

If you are a male whose tumor is estrogen receptor positive or progesterone receptor positive you could receive tamoxifen 20 mg a day for five years as your hormone treatment.

(paragraph added below 10/7/05)
If you have tumors that are HER-2 positive (HER-2, human epidermal growth factor receptor 2; protein involved in the growth of some cancer cells), you may receive trastuzumab (Herceptin) either concurrently with the paclitaxel phase of therapy on any of the arms or sequentially (within 3 months of the last dose of paclitaxel). If trastuzumab is administered, you will first receive an initial loading dose of the drug through a needle in your vein, then you will receive one (1) weekly dose of trastuzumab or a dose every three weeks (or a combination of these schedules), depending on the decision of your study doctor. Regardless of dosing schedule, you would be given trastuzumab for a total of 52 weeks. The addition of trastuzumab is considered optimal treatment for patients with HER-2 positive tumors. The drug is not a specific part of this study and will not be supplied through the study. *(sentence deleted 9/15/06)*

If you agree to submit samples for DNA polymorphism and/or serum analysis the following will be done:

A total of 17 mL of blood will be collected (one 10-mL tube for serum protein analysis and one 7 mL tube for DNA analysis). Blood samples will be submitted before you begin treatment. The samples will be sent to a central laboratory for testing. *(last two paragraphs added 9/22/04) (last sentence deleted 10/7/05)* This is not mandatory. You can still take part in the treatment study if you do not submit specimens for this testing. *(last two sentences added 8/23/10)*

HOW LONG WILL I BE IN THE STUDY?

(sentence deleted 11/12/10)

We expect that your initial treatment will take about 20 weeks. *(11/12/10)* Patients with estrogen receptor-positive or progesterone receptor-positive tumors will receive five years of hormonal therapy after their initial treatment.

After your initial treatment is done we would like to examine you every six months for the first 5 years and then once a year for a maximum of 15 years to see how you are doing. *(9/22/04) (10/7/05) (9/15/06)*

(paragraph deleted 9/15/06)

The researcher may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of drug supply or lack of funding.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drug therapies are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks and side effects related to the doxorubicin, cyclophosphamide, and pegfilgrastim treatment include: *(1/20/11)*

Likely: (doxorubicin, cyclophosphamide, pegfilgrastim) *(1/20/11)*

- **Nausea and vomiting**
- **Loss of appetite**
- **Heartburn**
- **Hair loss**
- **Low white blood cell counts which may make you more susceptible to infection**
- **Low platelet counts which may make you bruise more easily and bleed longer if injured**
- **Low red blood cell counts which may cause tiredness, shortness of breath or fatigue**

Less Likely:

- **Sores in the mouth**
- **Hand-foot syndrome (tingling pain and redness of the hands and feet)**
- **Change in color of fingernails and toenails**
- **Loosening of fingernails and toenails**
- **Inflammation or damage to the skin and around the IV tubing.**
- **Bladder inflammation (prevent this by drinking 8 - 10 glasses of water each day and emptying your bladder frequently)**
- *(deleted 1/20/11)*
- **Bone or joint pain** *(9/22/04) (7/14/11)*
- **Cramps in the legs or back** *(9/22/04) (7/14/11)*

Rare but Serious: *(section updated 1/1/08)*

- **Heart damage**
- **Increased risk of blood cancer or other secondary cancers**
- **Spleen Rupture (related to pegfilgrastin use): Your spleen may become enlarged and can rupture while taking pegfilgrastin. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. This pain could mean your spleen is enlarged or ruptured.** *(1/20/11)*
- **Serious Allergic Reactions (related to pegfilgrastin use): Pegfilgrastin can cause serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating.** *(1/20/11)*
- **A serious lung problem called acute respiratory distress syndrome (ARDS) resulting in shortness of breath, trouble breathing, or a fast rate of breathing have been reported in patients using pegfilgrastin.** *(1/20/11)*

Risks and side effects related to the pacitaxel treatment schedule:

Likely

- **Low white blood cell counts which may make you more susceptible to infection**
- **Low platelet counts which may make you bruise more easily and bleed longer if injured**
- **Low red blood cell counts which may cause tiredness, shortness of breath or fatigue**
- **Mild to severe allergic reaction, which may be life threatening with hives**
- **Wheezing and low blood pressure**
- **Numbness and pain of the hands and feet that sometimes worsens with additional treatment and may not disappear after the drug is stopped. This may lead to difficulty walking, buttoning clothes, etc.**
- **Hair loss**
- **Muscle weakness and muscle loss**
- **Muscle and joint aches**

Less likely:

- **A slowing of the heart rate (a slow pulse is not harmful; however if you should develop any other changes in heart rate during treatment, tests may be required)**
- **Irregular heartbeats**
- **Heart attack**
- **Nausea and/or vomiting**
- **Diarrhea**
- **Sores in the mouth or throat**
- **Fatigue**
- **Lightheadedness**
- **Headaches**
- **Kidney damage**
- **An increase in blood lipid levels which could increase risk of hardening of the arteries**
- **Liver damage**
- **Confusion**
- **Mood changes**
- **Skin irritation and swelling if the drug leaks from the vein in which it is being injected into the surrounding skin**
- **Changes in taste**
- **Irritation of the skin at a site of previous radiation**
- **Rash**
- **Inflammation of the colon, pancreas or lungs**
- **Blurred vision or other changes in eyesight such as sensation of flashing lights or spots.**

Rare but Serious.

- **Liver failure**
- **Swelling of the brain**
- **Seizures**

The following are risks that may or may not be associated with three different types of hormonal therapies (tamoxifen, anastrozole, and goserelin).

Tamoxifen

Likely: *(9/22/04)*

- **Hot flashes**
- **Nausea (vomiting is rare)**
- **Vaginal bleeding**
- **Vaginal discharge and dryness**

- **Menstrual irregularities**
- **Skin rash**

Less Likely

- **Increase in calcium in the body**
- **Swelling in the arms, legs, hands and feet**
- **Loss of appetite**
- **Distaste for food**
- **Genital itching**
- **Depression**
- **Dizziness**
- **Headache**
- **Leg cramps**
- **Lightheadedness**
- **Hair thinning or partial hair loss**
- **Confusion**
- **Tiredness**
- **Abdominal pain or cramping** *(9/22/04)*

Rare, but Serious *(section added 9/22/04)*

- **Blood clots in areas such as the lungs, legs and eyes** *(10/7/05)*
- **Cataracts**
- **Secondary malignancy such as endometrial cancer** *(added 10/7/05)*

Anastrozole

Likely *(9/22/04)*

- **Nausea and/or vomiting**
- **Sore throat**
- **Hot flushes**
- **Weakness**
- **Joint pain**
- **Depression**
- **Rash**
- **Tiredness**

Less Likely

- **Diarrhea**
- **Trouble breathing**
- **Back pain or bone pain**

- **Constipation**
- **Cough**
- **Chest Pain**
- **Dizziness**
- **Flu syndrome**
- **Fever**
- **Headache**
- **Loss of appetite**
- **Stomach pain**
- *(item deleted 12/13/04)*
- **Numbness and tingling in hands and feet**
- **Fluid retention**
- **Sweating**
- **Urinary tract infections**
- **Muscle pain**
- **Increased blood pressure**
- **Abnormal liver function test** *(10/7/05)*
- **Bone fractures**
- **Vaginal bleeding**
- **Decreased red blood cell count**
- **Difficulty sleeping**
- **Thinning hair**
- **Vaginal dryness**
- **Sleepiness**
- **Increased cholesterol**
- **Dry mouth**

Rare but Serious *(S 12/04)*

- **Blood clots**
- **Skin reactions involving ulcer**

Goserelin

Likely:

- **Menstrual periods stop for a while**
- **Hot flashes**
- **Headache**
- **Mood change**
- **Loss of libido**
- **Change in breast size**
- **Vaginal dryness**
- **Sweating**
- **Loss of bone density**

Less Likely: *(9/22/04)*

- **Menstrual periods stop often and for a long time**
- **The influence of goserelin on breast cancer recurrence risk is unknown.**

(new sections added 9/15/06)
Risks and side effects related to the trastuzumab (for patients with HER-2 positive tumors) include the following:

Likely **(occurring in > 20% of patients):** *(sentence deleted 5/21/10)*

- *(updated and moved to Rare but Serious 5/21/10)*
- *(deleted 5/21/10)*
- *(updated and moved to Less Likely 5/21/10)*
- *(updated and moved to Less Likely 5/21/10)*
- *(updated and moved to Less Likely 5/21/10)*
- *(updated and moved to Less Likely 5/21/10)*

Less Likely **(occurring in ≤ 20 % of patients)** *(section updated 5/21/10)*

- **A condition in which the heart muscle is abnormally enlarged or thickened.** *(updated 5/21/10)*
- *(deleted 5/21/10)*
- **Loss of appetite** *(updated 5/21/10)*
- **Diarrhea**
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)** *(updated 5/21/10)*
- **Lack of enough red blood cells (anemia)** *(updated 5/21/10)*
- *(deleted 5/21/10)*
- **Decreased heart's ability to pump blood during the "active" phase of the heartbeat (systole)** *(added 5/21/10)*
- **Fluid in the sac around the heart** *(added 5/21/10)*
- **Inflammation (swelling and redness) of the sac around the heart** *(added 5/21/10)*
- **Fast heartbeat; regular rhythm** *(added 5/21/10)*
- **Fast heartbeat usually originating in an area located above the ventricles** *(added 5/21/10)*
- **Belly pain** *(added 5/21/10)*
- **Irritation or sores in the lining of the mouth** *(added 5/21/10)*
- **Nausea or the urge to vomit** *(updated and moved from Likely 5/21/10)*
- **Vomiting** *(added 5/21/10)*
- **Chills** *(added 5/21/10)*
- **Fatigue or tiredness** *(updated and moved from Likely 5/21/10)*

- **Fever** *(added 5/21/10)*
- **Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)** *(added 5/21/10)*
- **Chest pain not heart-related** *(added 5/21/10)*
- **Pain** *(added 5/21/10)*
- **Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing** *(added 5/21/10) (updated 1/5/12)*
- **Infection** *(added 5/21/10)*
- **Increased blood level of a liver and bone enzyme (alkaline phosphatase)** *(added 5/21/10)*
- **Increased blood level of a liver enzyme (AST/SGOT)** *(added 5/21/10)*
- *(deleted 1/5/12)*
- **Increased blood level of a liver enzyme (GGT)** *(added 5/21/10)*
- **Decreased number of a type of white blood cell (neutrophil/granulocyte)** *(added 5/21/10)*
- *(deleted 1/5/12)*
- **Joint pain** *(added 5/21/10)*
- **Back pain** *(added 5/21/10)*
- **Bone pain** *(added 5/21/10)*
- **Muscle pain** *(updated and moved from Likely 5/21/10)*
- **Pain in the area of the tumor** *(added 5/21/10)*
- **Headache or head pain** *(added 5/21/10)*
- **Inflammation (swelling and redness) or [illegible] of the peripheral nerves (those nerves outside of [illegible] and spinal cord) causing numbness, tingling, burning** *(added 5/21/10)*
- *(moved to Rare but Serious 1/5/12)*
- **Stuffy or runny nose, sneezing** *(added 5/21/10)*
- *(moved to Rare but Serious 1/5/12)*
- **Cough** *(added 5/21/10)*
- **Shortness of breath** *(added 5/21/10)*
- **Decrease in the oxygen supply to tissue** *(added 5/21/10)*
- *(deleted 1/5/12)*
- *(moved to Rare but Serious 1/5/12)*
  Acne *(added 5/21/10)*
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** *(updated and moved from Likely 5/21/10)*
- **Hives** *(added 5/21/10)*
- **High blood pressure** *(added 5/21/10)*
- **Low blood pressure** *(updated and moved from Likely 5/21/10)*

Rare, But Serious **(occurring in < 3% of patients)**

(paragraph deleted 5/21/10)

- **Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing** *(updated and moved from Likely 5/21/10) (updated 1/5/12)*
- **Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing and loss of consciousness.** *(added 5/21/10) (9/30/11) (updated 1/5/12)*
- **Abnormal build up of fluid in the lungs** *(added 5/21/10)*
- **Scarring of the lungs that can cause shortness of breath and interfere with breathing** *(added 5/21/10)*
- **Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs** *(added 5/21/10) (updated and moved from Less Likely 1/5/12)*
- **Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath** *(added 5/21/10) (updated and moved from Less Likely 1/5/12)*
- **Inflammation of the lungs that may cause difficulty breathing and can be life-threatening** *(added 5/21/10) (updated and moved from Less Likely 1/5/12)*

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. Women should not nurse a baby while on this study. Ask about counseling and more information about preventing pregnancy. Doxorubicin and cyclophosphamide may also damage reproductive cells (eggs) and if you are a menstruating woman may begin having irregular menstrual periods or stop menstruating altogether.

Very rarely, severe bleeding or infection may result from lowered blood counts and could be fatal.

For more information about risks and side effects, ask the researcher or contact _____.

Risks from venipuncture (needed for drawing blood samples for DNA polymorphism/serum analysis): The risk from venipuncture is very small. There may be some bruising or bleeding at the site the blood is drawn. *(paragraph added 9/22/04)*

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We cannot and do not guarantee that you will benefit if you take part in this study. The treatment you receive may even be harmful. Your doctors feel

that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope the information learned from this study will benefit other patients with breast cancer in the future.

The possible benefits of taking part in the study are the same as receiving similar chemotherapy without being in the study.

There is no benefit to taking part in the DNA polymorphism/serum analysis portion of the protocol. There may be some benefit to patients with breast cancer in the future. *(paragraph added 9/22/04)*

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

You may be able to receive the same treatment combinations in this study without being in the study. You may choose to receive other chemotherapy combinations commonly used for this type of breast cancer without being in a study. You may be eligible for other treatment studies. You may also choose to have no anti-cancer treatment at this time (with care to make you feel more comfortable).

There may be other ways (besides the DNA polymorphism/serum analysis used in this study) of determining breast cancer survival. The methods used in this study are comparable to others that may be available. You also have the option of not having this procedure done on your blood samples. Please talk to your doctor about these and other options. *(paragraph added 9/22/04)*

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute or its authorized representatives, the Food and Drug Administration, Amgen Pharmaceutical Company, and the Southwest Oncology Group. *(last sentence deleted 9/22/04)*

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

(paragraph deleted 9/22/04)

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge.

(local institutions must choose one of the options below that best fits the hospital's situation:)

Funds have been set aside by the hospital to compensate you in the event of injury. Although no government or drug company funds have been set aside to compensate you for injury or illness, you do not give up any of your legal rights for compensation by signing this form.

-OR-

Although no funds have been set aside to compensate you for injury or illness, you do not give up any of your legal rights for compensation by signing this form.

You may find a National Cancer Institute guide: "Clinical Trials and Insurance Coverage - a Resource Guide" helpful in this regard. You may ask your doctor for a copy, or it is available on the world wide web at http://cancer.gov/clinicaltrials/insurance

You or your insurance company will be charged for continuing medical care and/or hospitalization.

Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). *(local institutions must choose the option that best fits the hospital's situation)*

Doxorubicin, cyclophosphamide, paclitaxel, trimethoprim sulfa, and pegfilgrastim are commercially available and must be paid by you or your insurance company. Filgrastim will be provided by Amgen Pharmaceutical. Pegfilgrastim may be provided free of charge through Amgen's Clinical Trial Product Access Program. *(12/13/04)* Additionally (if needed), tamoxifen, goserelin, anastrozole, and trastuzumab are commercially available, and must be paid by you or your insurance company *(last two sentences added 9/22/04) (9/15/06)*

In the case of injury from venipuncture blood draws for the DNA polymorphism/serum analysis: other than medical care that may be provided at the discretion of the treating institution, and any other payment specifically stated in this consent form, there is no other compensation available for your participation in this part of the study. *(paragraph added 9/22/04)*

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the Continental US only).

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigator: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following information resources]

You may call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Visit the NCI's Web site…
www.cancer.gov

For comprehensive clinical trials information go to
http://cancer.gov/clinicaltrials

For accurate cancer information go to http://cancer.gov/cancerinformation

You will get a copy of this form. Upon request, you will also receive a copy of the protocol (full study plan).

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.

We are also interested in whether or not use of certain medications, vitamins and supplements and other lifestyle habits during chemotherapy has any effect on your health while you are receiving treatment and afterwards. *(10/7/05)* Right now, there are no strong data to guide decisions about whether or not to take supplements during treatment. It is unknown whether supplements will affect how well the treatment kills cancer cells (if it hurts or helps it), or how many side effects you may experience. We would like your permission to call you on the telephone and to send you a questionnaire to complete in a stamped envelope we will provide. *(10/7/05)* This questionnaire asks about your use of medications, vitamins and supplements during your treatment and other lifestyle habits. *(10/7/05)* *(sentence deleted 10/7/05)* We will ask you to complete the questionnaire at the beginning of treatment, at the end of treatment, and annually (from your date of registration) for a maximum of 15 years. *(10/7/05)* *(sentence deleted 10/7/05)* *(1/1/08)*

We would also like to use your blood specimen (if you consented to DNA polymorphism testing) to look at common forms of genes that may affect how antioxidants work in relation to your chemotherapy. *(10/7/05)* There are very common differences in how active these genes are (for example, 25% of Caucasians have a more active form of an antioxidant gene), and we would like to look at whether or not these common differences affect how taking supplements may interact with your treatment.

We do not know whether taking supplements has any affect on treatment outcomes. We do not know if taking vitamins or supplements will make your treatment work better or worse. Therefore, this study should not interfere with your normal habits, and we would like you to continue either using or not using supplements according to your and your doctors decisions.

Except for the information we receive to contact you, the samples and the information you give to us will not have your name or any other personal identifying information on them. *(10/7/05)* They will have only an ID number that will be assigned to you. The information that links your name with the code number and the signed consent forms will be kept in a locked file the SWOG statistical center, that only certified investigators will have access to.

We need to ask your permission to contact you regarding use of supplements during treatment, and to use your blood sample to look at how inherited differences may affect how supplements impact treatment outcomes. *(section added 12/13/04)*

(Please initial 'yes' or 'no' for each question)

(Section updated 1/10/11)

1. Do you give permission for a researcher to telephone you for a short interview and to mail you a brief questionnaire regarding medications, vitamins, supplements, and lifestyle habits before you begin protocol treatment, following completion of protocol treatment, and annually for 15 years? *(10/7/05) (1/1/08)*

   Yes _____ No _____

   Please provide your contact information below:
   Name_____
   Address_____
   _____
   Telephone Number_____

(section below added 9/22/04) (section below moved from SIGNATURE section 1/20/11)

Consent for submission of blood samples for DNA polymorphism and serum analysis: This is not mandatory. You can still take part in the treatment study if you do not submit specimens for this testing. *(paragraph updated 8/23/10)*

2. Do you agree to submit blood samples for DNA polymorphism and serum analysis which will analyze how your body metabolizes drugs and hormones? (See page 9 for background.)

   Yes _____ No _____

3. Do you give permission for the samples to be used to examine whether differences in genes that affect antioxidants may affect treatment outcomes?

   Yes _____ No _____

(section above was added and section below moved 12/23/04)

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

Participant _____ Date _____

(section moved under question #1 above 1/20/11)

(addresses deleted 11/14/11)

Consent Form for Use of Specimen For Research

About Using Specimens for Research

You have had a biopsy (or surgery) as part of your treatment. Your doctor has 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 plan your care. You have also had blood taken for special testing on this study.

We would like to keep some of the tissue and blood that is left over for future research. If you agree, this tissue and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the question and answer sheet (attached) called "How are Specimens Used for Research" to learn more about tissue research.

The research that may be done with your tissue and blood probably will not help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood 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 left over tissue and blood 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 tissue and blood 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 tissue or blood. Then the tissue and blood will no longer be used for research.

In the future, people who do research may need to know more about your health. When the Southwest Oncology Group gives them reports about your health, it will not give them your name, address, or phone number.

Sometimes tissue and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue or blood is used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new products in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, how to treat them, and how to cure them.

There are very few risks to you. The greatest risk is the release of information from your health records. The Southwest Oncolog y Group will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small.

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No." **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse. For questions about your rights as a research participant, contact the *name of center* Institutional Review Board (which is a group of people who review the research to protect your rights) at *telephone number*.

---

1. My tissue and blood may be kept for use in research to learn about, prevent, treat, or cu cancer.

(items below updated 8/23/10)
Yes, both tissue and blood _____

Blood only _____

Tissue only _____

No _____

---

2. My tissue and blood may be ke t fo research about other he lth prob ems (for example: causes of diabetes, Alzheim 's isea e, and heart disea e)

(items below update 8/23/1
Yes, both tissue and _____

Blood only _ __

Tissue only _____

_____

---

3. Someone from the Southwest Oncology Group may contact me in the future to ask me to take part in more research.

Yes _____ No _____

Please sign your name here after you check your answers.

Participant _____ Date _____

Tissue Consent Supplemental Sheet

How is Tissue Used for Research?

Where does tissue come from?

After a person has had a biopsy (or surgery) and all tests have been done, there may be some left over tissue. Sometimes, this tissue is thrown away because it is not needed for the patient's care. Instead, a patient can choose to have the tissue kept for future research. People who are trained to handle tissue and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect tissue from many patients. Many doctors across the country are helping in the same way. If you agree, only left over tissue will be saved for research. Your doctor will not take more tissue during surgery than needed for your care.

Why do people do research with tissue?

Research with tissue can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using tissue can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my tissue?

Many different kinds of studies use tissue. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your tissue may look for genetic causes and signs of disease.

How do researchers get the tissue?

Researchers from universities, hospitals, and other health organizations conduct research using tissue. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the tissue and information about you or your hospital, and sends the tissue samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my tissue?

You will receive the results of your biopsy, but you will not receive the results of research done with your tissue. This is because research can take a long time and must use tissue samples from many people before results are known. Results from research using your tissue may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your tissue, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

19.0 APPENDIX

19.1 FILGRASTIM Drug Order Form

19.2 Returned Medication Packing Slip

19.3 Oral Trimethoprim/Sulfamethoxazole Desensitization Procedure

19.4 Cancer Trials Support Unit (CTSU) Participation Procedures

19.5 Supplemental Background Information

19.6 Reimbursement/Product Support for Neulasta™

19.7 Determination of Expedited Adverse Event Reporting Requirements

19.1 Study Title: S0221, "Phase III Trial of Continuous Schedule AC + G Vs. Q 2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer"

Filgrastim (G-CSF) Drug Request Form

Requested by: **Ship To:**

Pharmacist:_____ Name:_____

Institution:_____ Address*:_____

_____

Principal Investigator:_____ *** Please do not use P.O. Box numbers**

Phone #:_____ Fax:_____

				Check One	
Southwest Oncology Group **Protocol**	**Pt. ID**	**Pt Initials (Last, First)**	**# Of Vials ** 480 µg**	**Initial (For this Pt.)**	**Reorder (For this Pt.)**

**** Reminder: See protocol section on drug formulation for instructions regarding amounts of drug to order**

FILGRASTIM will be shipped (refrigerated) on Monday through Thursday for next day delivery.

Orders received by 12:00 pm pacific time Monday through Thursday will be shipped the same day.

_____ _____

Date of Drug Request Pharmacist Signature

Return Completed, Signed, and Dated form to:

UVI, Inc.
Fax: 650-745-3877

19.2 **S0221** G. Thomas Budd, M.D.

RETURNED MEDICATION PACKING SLIP

Institution Name:

Address:

Principal Investigator: Phone No.:

Amgen Study No: Cooperative Group No.: **S0221**

Study Title: "**S0221**, "Phase III Trial of Continuous Schedule AC + G Vs. Q 2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer"

Instructions:
Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to UVI, Inc. c/o UPS Logistics, 11698 San Marino Drive, Rancho Cucamonga, CA 91730, ATTN: Greg Parsons. Questions may be directed to (800) 370-2508, Monday through Friday 8:00 am - 1:00 pm, Pacific Standard Time. Voice Mail is available at all other times.

Study in progress?

❑ Yes ❑ No

Study completed per protocol?

❑ Yes ❑ No

Reason drug returned? (Please check one)

❑ Drug Expired

❑ Unused drug being returned

Person Shipping Drug:_____

Drug being returned by:

❑ Fed Ex ❑ UPS ❑ US Mail

Date:_____ No. of cartons:_____

Data Manager/Pharmacist's Signature:

_____ Date:_____

Return receipt requested: ❑ Yes ❑ No

Fax number:_____

DESCRIPTION OF RETURN SHIPMENT

Drug Name & Vial Description ____mcg/___ml/vial	Lot Number	Number of vials
Comments:		

TO BE COMPLETED BY AMGEN

Returned shipment received on_____ and checked by:_____
(Date) (Name)

19.3 **ORAL TRIMETHOPRIM/SULFAMETHOXAZOLE DESENSITIZATION PROCEDURE**

This is completed over six days with oral doses of TMP/SMX (trimethoprim/sulfamethoxazole, or "Bactrim"). One standard double-strength (DS) Bactrim tablet contains 160 mg of TMP and 800 mg of SMX. Desensitization is performed with solutions made from a standard oral suspension of TMP/SMX, which consists of 40 mg TMP and 200 mg SMX per 5 ml. The dilutions and final concentrations for TMP and SMX components are given below.

Day 1	1:100,000 dilution	(0.0004 mg SMX in 1 cc) (0.00008 mg TMP in 1 cc)
1 cc*		
2 cc*	QID	
4 cc		
8 cc		

* The first two doses should be administered in the clinic and patients should be observed for anaphylaxis for one hour after each of these two doses, with appropriate medications and equipment available for resuscitation. **Someone must be present who can observe and summon help if anaphylaxis occurs.**

Day 2	1:10,000 dilution	(0.004 mg SMX in 1 cc) (0.0008 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

Day 3	1:1,000 dilution	(0.04 mg SMX in 1 cc) (0.008 TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

Day 4	1:100 dilution	(0.4 mg SMX in 1 cc) (0.08 TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

Day 5	1:10 dilution	(4.0 mg SMX in 1 cc) (0.8 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

19.4 Cancer Trials Support Unit (CTSU) Participation Procedures

Registration/Randomization

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an 'active' investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member website or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. EST.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at https://www.ctsu.org.

All forms and documents associated with this study can be downloaded from the **S0221** web page on the CTSU registered member Web site (https://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for **S0221 site registration**:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for **patient enrollment** on **S0221**:
- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consent and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888/462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 301/7[illegible]3780.

2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - SWOG Registration Form (Complete all sections of form except for SWOG-specific data fields)

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the Southwest Oncology Group to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site and follow up with a confirmation via e-mail or fax.

Patients must begin study treatment within five working days of registration.

Data Submission and Reconciliation

1. All case report forms (CRFs) associated with this study must be downloaded from the **S0221** web page located on the CTSU registered member website (https://www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007, (large volumes of data may be sent via post, see contacts table for mailing address). Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the SWOG data center.

Special Materials or Substudies

1. All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol Section 15.2c.

2. You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0221** protocol page and click on the link provided under the Case Report Forms header.

3. Specimen collection for correlative studies (see protocol Section 15.0)

   - **Tissue banking**: Tissue blocks or slides for banking should be submitted with patient's consent to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab 101. Submit materials as specified in Section 15.1.

   - **Serum banking**: Serum for banking should be submitted with patient's consent to the Roswell Park Cancer Institute (RPCI). Submit materials as specified in Section 15.2.

   Whole blood banking: Whole blood for genetic polymorphism studies will be banked and should be submitted with patient's consent to the Roswell Park Cancer Institute (RPCI). Submit materials as specified in Section 15.2.

   - **Antioxidant substudy**: Institutions are encouraged to seek patient consent for participation in the antioxidant questionnaire. Fax a copy of the patient's consent to participate in the antioxidant substudy (if consent is obtained) as specified in Section 15.3.

Serious Adverse (AE) Reporting (Section 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (https://www.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the **S0221** web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (Section 3.0)

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 3.0 of the protocol.

Commercial Agents: cyclophosphamide, doxorubicin, *G-CSF, paclitaxel, pegfilgrastim

All agents used in this study are commercially available; however, *G-CSF (filgrastim) will be provided free of charge by Amgen and distributed by UVI, Inc. To obtain G-CSF, complete the Filgrastim Drug Order Form (Appendix 19.1 of protocol) and fax to UVI, Inc. at the number provided on the form. Filgrastim orders from U.S. sites only will be accepted. Patients must be registered to the study before study drug can be obtained.

Regulatory and Monitoring

Study Audit

To assure compliance with Federal regulatory requirements (CFR Parts 50, 54, 56, 312, 314 and HHS 45 CFR 46) and National Cancer Institute (NCI, Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validation, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member website.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

19.5 Supplemental Background Information

Hormone metabolism and breast cancer. Because of the important role of estrogens in breast cancer etiology, as well as the observations that AA women have higher levels of estrogens, it is possible that higher levels of estrogens result in more aggressive disease and subsequently, poorer survival. Thus, differential ethnic/racial distribution of polymorphisms in genes involved in the synthesis and metabolism of steroid hormones could account for a portion of racial disparities in breast cancer survival. Although there are a number of other factors that will impact endogenous steroid hormone levels, such as diet and obesity, functional polymorphisms in genes that synthesize and metabolize hormones have been shown to impact ultimate hormone levels, including CYP11A, CYP17, CYP1B1, and CYP19. *(27 - 31)* Because of the differences in distribution of variant alleles by race/ethnicity (Table 1), it is possible that greater prevalence of alleles resulting in higher estrogen levels could account for the more aggressive disease and poorer prognosis among African-American women.

As shown in the simplified schema in figure 1, estrogens are biosynthesized from cholesterol, to androstendione and testosterone, with aromatization of androgens to form estrone and estradiol. Estradiol can be further metabolized to form the catechol estrogens. Enzymes involved in this biotransformation process are polymorphic, and we will evaluate the role of these variants in relation to racial differences in survival. Specifically, we will assess variants in CYP11A, which has a pentanucleotide repeat (TTTTA)n, which is associated with serum testosterone levels, and $P450_{17\alpha}$ (CYP17), which yields the C_{19} steroids androstenedione, Polymorphisms in CYP17 (A2 allele) are associated with higher levels of estrogens, and with earlier age at menarche. Aromatase is encoded by (CYP19), and patients with the variant were more likely to present with large, high stage breast tumors. *(27 , 29, 32, 33)* The T allele is associated with a significantly greater estrogen to androgen ratio, indicating that it is likely associated with elevated aromatase activity.

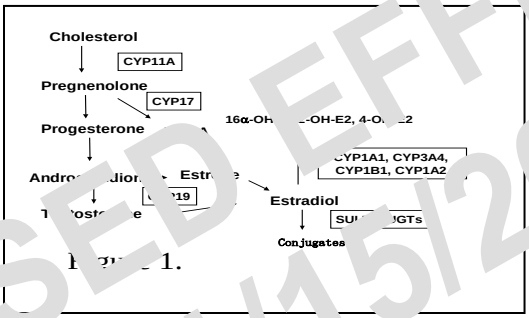


Figure 1.

Estrogens are extensively metabolized by a number of oxidative and conjugative reactions, mediated by the major hepatic P450s 1A2 and 3A4 and the extrahepatic 1A1 and 1B1. *(33)* The polymorphic CYP3A4 is the major P450 expressed in human liver and 2 studies have reported that the CYP3A4 *1B polymorphism was over-represented in prostate tumors of higher stage and grade, and more prevalent in AAs. *(34, 35)* There are four CYP1A1 variants, and both the m1 and m2 polymorphisms are associated with greater CYP1A1 inducibility. *(36)* AAs are more likely to have the m1 MspI allele, and in a case-control study of AA and white women, Taioli noted that among AA women, this CYP1A1*2A/B polymorphism significantly increased breast cancer risk [odds ratio (OR)=9.7, confidence interval (CI), 2.0-47.9)]. CYP1B1 has two variants with associated function. *(37, 38)*

GENE Polymorphism	AA	White
CYP11A (TTTTA)n	UNK	.26
CYP17 A2/A2	.13	.15
CYP19 T/T	UNK	.27
CYP1A1 M1		
M/M & M/W	.42	.18
M2		
M/M & M/W	.05	.10
CYP1B1 m1 Leu/leu	.04	.41
m2 Ser/Ser	.03	.17

Therapeutic drug metabolism. Cyclophosphamide is activated by cytochrome P450 3A4, and its metabolites are detoxified by the glutathione *S*-transferases (GSTs). In a pilot study, we found that women with genetic polymorphisms encoding lower or no activity in detoxifying enzymes (*GSTP1, GSTM1, GSTT1, GSTA1*) had better survival than those with common alleles, putatively because more damaging agents could reach the cell and cause damage. *(34 - 41)* Because of differences in racial distributions of these alleles, differences in drug metabolism could, in part, explain the poorer survival among African-American women.

CYP3A4 has a single base substitution in the 5' promoter region of the gene present in 9% of Caucasians. *(42. 43)* The importance of CYP3A4 in the metabolism of cyclophosphamide and other drugs, its high expression in liver, and phenotype/genotype correlations, all support the hypothesis that *CYP3A4* genotype may affect outcomes in breast cancer patients treated by cyclophosphamide. *GSTA1*, the GST enzyme most active in glutathione conjugation reactions with cyclophosphamide intermediates, has a polymorphism in the 5' promoter region of the gene with the *GSTA1*B* variant having decreased GSTA1 expression. *GSTP1* has a single base substitution in exon 5 that results in a variant protein with an amino acid substitution, Ile105Val. *(44)* In our pilot study, we found that women with genotypes associated with lower detoxifying activity in both genes had better survival. *(35)* Because of the importance of these genes in hormone and cyclophosphamide metabolism, and the differential distribution of the polymorphisms across racial/ethnic groups, these genetic polymorphisms clearly need to be evaluated in relation to racial differences in breast cancer survival.

Methods:

Operative Adjuvant Therapy in Node-Positive or High- Risk Node Negative Breast Cancer (PI Ludd) will be asked to give a general tissue and serum consent form. This proposal will fund the establishment of the serum bank for this study in the first 500 pts and provide the preliminary data for an R01 to fund the additional collection.

Two 10ml tubes of blood will be drawn from all participating patients. 1 serum tube will be banked for later assessment of proteomic patterns that are associated with better survival, and evaluated among African-American and Caucasian women. The second tube of blood will be used for extraction of DNA for evaluation of polymorphisms involved in hormone and cyclophosphamide metabolism, and the assessment of 'high-risk' alleles in relation to survival. The samples will be shipped overnight to the Ambrosone laboratory at Roswell Park, where they will be processed and stored. Blood components will be aliquotted into small straws that are barcoded for scanning into computerized storage and inventory software and banked in liquid nitrogen. Serum samples will be shipped periodically to the University of Michigan for storage (to establish the Breast Correlative

Science Committee's new serum bank in early breast cancer under supervision of D. Hayes), and DNA will be extracted and analyzed at the Roswell Park Cancer Institute laboratory for the polymorphisms . NOTE: Drs. Hayes and Ambrosone have determined that there will be only one bank (University of Michigan) but the collaboration will be efficient to allow the DNA analyses at Dr. Ambrosone's laboratory. The primary goals of this proposal are to test differences in outcome with respect to common variant alleles of hormone metabolism in women with breast cancer. The variants are hypothesized to be associated with longer disease-free survival. Standard descriptive statistics will be used to summarize baseline patient characteristics, genotype frequencies and baseline characteristics by genotype. Standard time to event methods (log-rank tests, Cox models, Kaplan-Meier estimates) will be used for the disease-free survival analysis. Standard methods for binary data (chi-square tests, logistic regression models) will be used for the toxicity analysis.

Dr. Ambrosone will oversee the DNA extraction and genotyping. Dr Hershman will assist with the analysis and study coordination. Dr. Daniel Hayes, Chair, Breast Correlative Sciences has enthusiastically endorsed the need for this project to serve as the nidus for establishment of the Breast Committee Serum Bank and will oversee the establishment of this serum bank for this and future projects. Dr. Albain (as mentor and as Chair of the sponsoring committee, CSP) will supervise the overall conduct of this aspect of the proposal.

19.6 Reimbursement/Product Support for Neulasta™

Amgen has established a Clinical Trial Product Access Program ("CTPAP") which supports product access for Neulasta® (pegfilgrastim) and Aranesp® (darbepoetin alfa) to qualified subjects or study sites who have agreed to participate in NCI Cooperative Group clinical trials utilizing these Amgen products where the use of the Amgen product is considered to be IND exempt.

Under CTPAP, Amgen product used in an Amgen-approved clinical trial is available without charge to subjects in the following circumstances:

(i) if a subject is uninsured and financially unable to afford the Amgen product, or is insured but the insurance does not cover payment for the Amgen product and the subject is financially unable to afford the Amgen product, or is insured but financially unable to afford the required co-pay applicable to the Amgen product (as certified by the study physician);
(ii) if the study physician certifies that the Amgen product to be supplied is not an approved product on his or her institution or practice formulary;
(iii) if the study physician certifies that the Amgen product to be supplied is difficult to obtain through his or her institution or practice formulary because of formulary preferences or access difficulties.

If the study site believes that either the site or a subject may be eligible to receive Amgen product under CTPAP, the site should contact Amgen's Reimbursement Connection® at 1-800-272-9376 (Monday through Friday, 9:00 A.M. - 8 P.M. EST) prior to administration of the requested Amgen product. An Amgen representative will contact the study site to confirm the qualification of the site or subject and proceed with enrolling the site or subject in CTPAP.

19.7 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1.

Note: This includes all events that occur within 30 days after the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.