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

Prognostic Impact of the Combination of Recurrence Score and Quantitative Estrogen Receptor Expression (ESR1) on Predicting Late Distant Recurrence Risk in Estrogen Receptor-Positive Breast Cancer after Five Years of Tamoxifen: Results from NRG Oncology/NSABP B-28 and B-14

Wolmark, et al

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NSABP PROTOCOL NO. B-28

A RANDOMIZED TRIAL EVALUATING THE WORTH OF PACLITAXEL (TAXOL) FOLLOWING DOXORUBICIN (ADRIAMYCIN)/CYCLOPHOSPHAMIDE IN BREAST CANCER PATIENTS WITH POSITIVE AXILLARY NODES

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

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STUDY DRUGS:

Paclitaxel	NSC#673089	NCI Supplied
Doxorubicin	NSC#123127	Commercial
Cyclophosphamide	NSC#26271	Commercial
Tamoxifen	NSC#180973	Commercial

Revised Version as of October 30, 1997 (PLEASE DESTROY ALL OTHER VERSIONS)

NSABP PROTOCOL NO. B-28

A RANDOMIZED TRIAL EVALUATING THE WORTH OF PACLITAXEL (TAXOL) FOLLOWING DOXORUBICIN (ADRIAMYCIN)/CYCLOPHOSPHAMIDE IN BREAST CANCER PATIENTS WITH POSITIVE AXILLARY NODES

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

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Protocol Revision Record

Original Version: July 14, 1995

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Sections Changed: Cover Page, Table of Contents, 1.0, 4.2.2, 5.1, 5.1.9, 5.1.12, 5.1.14, 5.2.2, 5.3, 5.3.3, 5.3.6, 7.1, 7.2, 9.1, 9.2, 10.0, 11.1.1, 11.1.2, 11.1.4, 11.1.5, 11.1.6, 11.1.7, 11.1.8, 11.2.1, 11.2.2, 11.2.3, 11.2.4, 11.2.5, 11.2.6, 11.2.7, 11.2.8, 11.3.3, 11.3.4, 12.3.3, 12.3.4, 12.4, 12.5, 13.1, 14.0, 14.1, 14.2, 14.3, 14.3.2, 14.4, 14.4.1, 15.1, 15.2, 15.3.2, 15.4, 15.6, 16.1, 16.2, Tables 4, 5, 6, 7, Appendixes A, D, F, H, and the Consent Form.

Amendment #2: October 30, 1997
Sections Changed: Cover Page, Table of Contents, 7.1.2, 18.6, 18.7, 18.8, Appendix D (Section IV), and the Consent Form.

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TABLE OF CONTENTS

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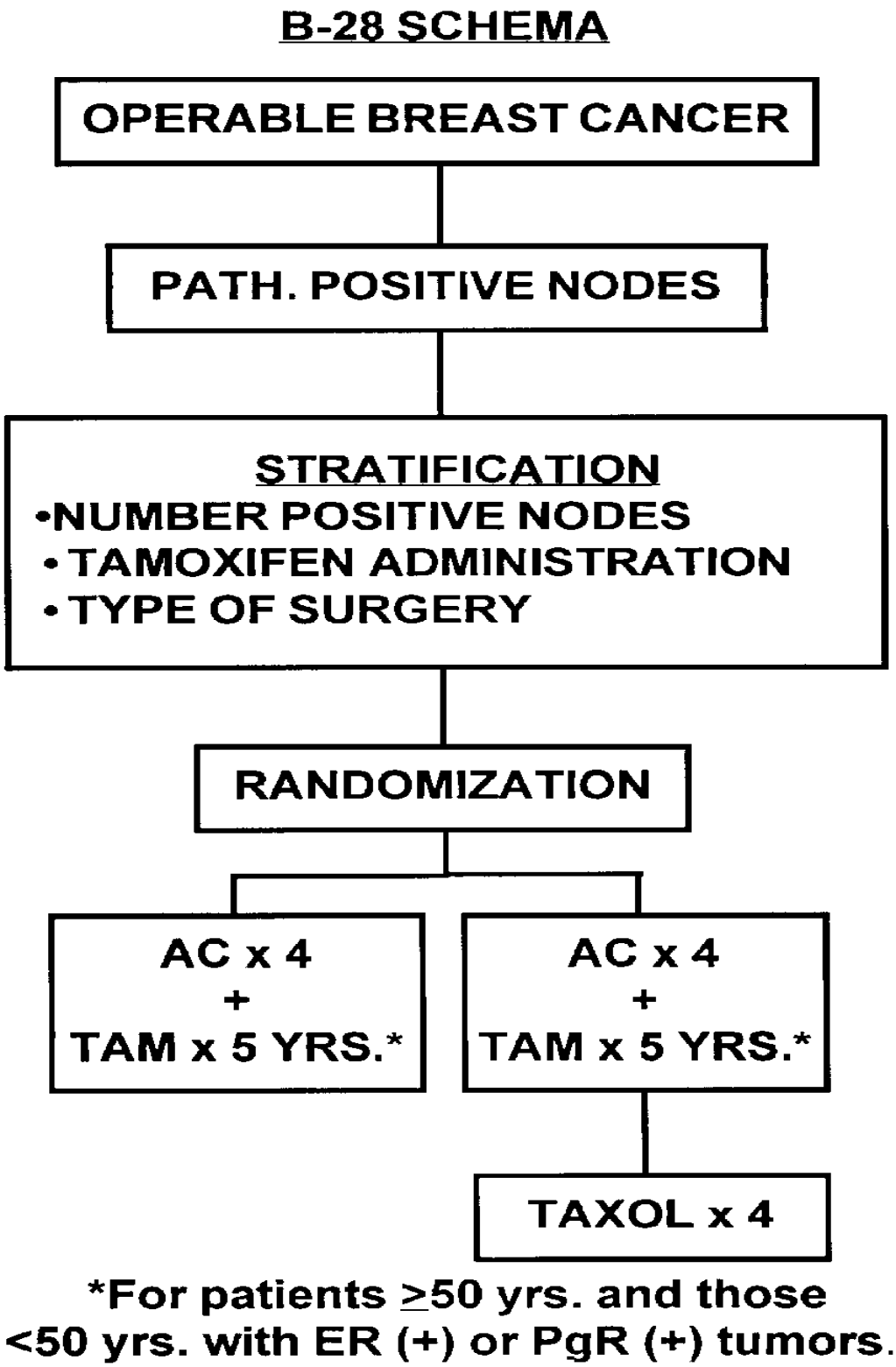
1.0 SUMMARY OF THE STUDY

3/26/97 The primary aim of this study is to determine whether four cycles of Taxol* given after four cycles of postoperative Adriamycin (A)* and cyclophosphamide (C) [AC] will more effectively prolong disease-free survival (DFS) and survival (S) than do four cycles of postoperative AC alone in patients with operable breast cancer who have one or more histologically positive axillary lymph nodes. Patients should have no evidence of metastatic disease and should have undergone either lumpectomy plus axillary node dissection or total mastectomy plus axillary node dissection. Following stratification by number of positive axillary nodes, tamoxifen administration, and type of surgery, patients will be randomly assigned to one of two groups (Figure 1). Group I will receive four cycles of A and C given at 60 mg/m^2 and 600 mg/m^2, respectively, every 21 days. Group II will receive four cycles of AC as in group I, followed by four cycles of Taxol given at 225 mg/m^2 as a 3-hour infusion every 21 days. Beginning on the first day of administration of their assigned chemotherapy, patients $\geq$50 years of age and those <50 years of age with tumors that are ER-positive or PgR-positive will receive tamoxifen at 20 mg p.o. once daily for 5 years. All patients in both groups who undergo lumpectomy will receive postoperative radiotherapy after completion of their assigned chemotherapy and after any toxicity has resolved.

3/26/97 *Note: Throughout the protcol, revision dates are listed in the left hand margin near the revised section, or at the top center of a revised page.*

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


B-28 SCHEMA
OPERABLE BREAST CANCER
PATH. POSITIVE NODES
STRATIFICATION
•NUMBER POSITIVE NODES
• TAMOXIFEN ADMINISTRATION
• TYPE OF SURGERY
RANDOMIZATION
AC x 4
+
TAM x 5 YRS.*
AC x 4
+
TAM x 5 YRS.*
TAXOL x 4
*For patients ≥50 yrs. and those
<50 yrs. with ER (+) or PgR (+) tumors.

2.0 BACKGROUND

2.1 Rationale for Evaluating New Agents in the Treatment of Patients with Node-Positive Breast Cancer

The value of adjuvant chemotherapy in node-positive breast cancer patients, who have a substantial risk for recurrence, has been incontrovertibly demonstrated. In a large meta-analysis of adjuvant clinical trials, the 10-year recurrence rate in women with positive axillary nodes who were not receiving systemic therapy was about 60%, and the overall mortality was close to 50%.[1] The administration of systemic chemotherapy in such patients was shown to reduce the rates of recurrence by about 30% over a 10-year period.[1]

In the NSABP B-15 trial,[2] node-positive, tamoxifen-nonresponsive patients treated with AC experienced a 5-year DFS of 54% and an overall S of 70%. In the NSABP B-16 trial,[3] node-positive, tamoxifen-responsive patients who were treated with AC and tamoxifen experienced a DFS and S at 5 years of 71% and 83%, respectively.

These data clearly demonstrate the need for seeking new strategies to improve the outcome in these high-risk patients. One potentially useful strategy is to manipulate the doses and schedules of the drugs currently in use. Over the past several years, one of the goals of the NSABP has been to determine the benefit of using maximally tolerated doses of chemotherapy that can be administered without bone marrow transplant support. This approach has been employed in two recent trials, B-22 and B-25. However, early results from B-22[4] suggest that increasing the dose of cyclophosphamide in a combination with standard-dose Adriamycin does not improve the DFS or S. The results of B-25, in which the doses of cyclophosphamide are even higher than in B-22 and are administered with rHu G-CSF support, will be crucial for determining whether increasing the dose of cyclophosphamide in a combination with Adriamycin is beneficial or if a plateau in the dose-response relationship has been achieved. However, the results of B-25 will not be available for several years.

Although high-dose polychemotherapy with autologous bone marrow transplantation is another option, its value over standard-dose chemotherapy has not been incontrovertibly demonstrated. Because of the significant toxicity associated with it, this approach may be acceptable only to patients at very high risk of recurrence (e.g., those with more than 10 positive nodes), and is difficult to apply in the adjuvant setting. Similarly, higher doses of doxorubicin appear to increase response rates in advanced breast cancer; this approach is currently being employed in the adjuvant setting as an Intergroup study.

An important alternative approach that has been proposed in order to increase treatment effectiveness is the introduction of new active drugs. In light of the data from B-22, the search for new agents may be more critical for the development of future adjuvant regimens to treat primary breast cancer than is the testing of higher doses of current agents. Among the agents that have become available for clinical testing in the past few years, Taxol seems to possess the most favorable antitumor properties. Preclinical data and clinical studies in advanced breast cancer indicate that this agent has significant antitumor activity and is worth evaluating in the adjuvant setting. These data are reviewed in the following section.

2.2 Rationale for the Use of Taxol

Discovered in the 1960s, Taxol had originally demonstrated activity against several murine leukemias and solid tumors.[5] Initial phase I studies were complicated by hypersensitivity reactions, which are now well controlled with premedication and longer infusions. Significant antitumor activity was first demonstrated in advanced ovarian cancer.[6] The therapeutic activity of Taxol is thought to be mediated through a profound disruption in the equilibrium of the tubulin-microtubular system.[7,8] Taxol binds to tubulin and stabilizes microtubules by prevention of disassembly; this novel mechanism of action makes Taxol a unique compound. Taxol has demonstrated activity in the metastatic setting against several neoplasms, such as ovarian,[6,9-11] breast,[12-16] nonsmall-cell lung,[17,18] and head and neck cancer.[19]

In patients with metastatic breast cancer, Taxol has demonstrated significant antitumor activity when used as first- or second-line chemotherapy[12-14] (Table 1) and as therapy following multiple prior chemotherapy regimens[15,16] (Table 2).

TABLE 1. Phase II Studies of Taxol as First- or Second-Line Chemotherapy in Patients with Metastatic Breast Cancer

Study	# Pts	Dose (mg/m^2)	Prior Chemotherapy	Duration (hrs)	Response Rate (complete & partial)
M.D. Anderson[12]	25	200-250	Adjuvant or one for mets	24	56% (12+44)
MSKCC[13]	28	250	Adjuvant	24	62% (12+50)
NCI[14]	17	120-160	One for mets	96	53% (0+53)

In a phase II trial conducted at M.D. Anderson,[12] 25 patients with metastatic breast cancer who had received one prior chemotherapy regimen, either as adjuvant therapy or for metastatic disease, were given Taxol as a 24-hour infusion at doses of 200-250 mg/m^2. All but two patients had received prior doxorubicin, and six were considered doxorubicin-refractory (progression on a doxorubicin-containing regimen or failure within 6 months from a doxorubicin-based adjuvant regimen). There were 12% complete responses, 44% partial responses, and 32% minor responses; 4% of the patients had stable disease and 8%, progressive disease. The median duration of response was 9 months (range 3-19). The median survival was greater than 20 months (range 5-28). Myelosuppression was severe and required dose reduction in 75% of the patients. Serious infection occurred in only 6% of the 297 cycles administered. Cumulative neuropathy or myalgias that were peak dose-related required dose reduction in four patients. Neither anaphylactoid reactions nor serious cardiac toxicity occurred.

In another phase II trial of Taxol as initial chemotherapy, Norton et al at Memorial Sloan-Kettering studied 28 patients with stage IV disease.[13] Patients received no prior chemotherapy for metastatic disease, had 12 or more months of elapsed time from adjuvant chemotherapy (58% of patients), and received no more than one prior hormone therapy as adjuvant and/or for metastatic disease. Taxol was given at 250 mg/m^2 as a continuous 24-hour infusion every 21 days. Recombinant G-CSF was given at 5 µg/kg/day s.c. on days 3-10. Administration of G-CSF was associated with a very short duration of neutropenia (median 2 days with granulocyte count <500 cells/mm^3). Eight of the 178 cycles of treatment resulted in admission for neutropenic fever. The median number of cycles administered per patient was six (range 1-15). Objective responses were seen in 16 of 26 available patients (62%; confidence interval 41-80). There were three complete and 13 partial responses. The median time to first objective response was 5 weeks (range 1-14).

In an NCI phase II study,[14] 17 stage IV breast cancer patients, who had previously received a doxorubicin or mitoxantrone-containing regimen for metastatic disease and had failed to either respond or to achieve a complete response, received Taxol as a 96-hour continuous infusion at doses of 120-160 mg/m^2. There were nine partial responses (53%) and four minor responses. The maximum tolerated dose (MTD) of 140 mg/m^2 in this study was significantly lower than the MTD of 250-300 mg/m^2 usually reported for 24-hour infusions. Mucositis was dose limiting on the 96-hour schedule and correlated well with steady-state concentrations. There was a suggestion that metastatic liver disease associated with elevated transaminase significantly decreases Taxol clearance and may be an important marker for dose adjustment.

TABLE 2. Phase II Studies of Taxol as a Single Agent in Patients with Metastatic Breast Cancer Who Received Extensive Prior Chemotherapy

Study	#Pts	Dose (mg/m^2)	# Prior Chemo Regimens	Duration (hrs)	Response Rate (complete & partial)
M.D. Anderson[15]	12	150	≥3	24	25% (0+25)
MSKCC[16]	72	200-250	(1-6)	24	28%

In a phase II trial[15] at M.D. Anderson, 12 patients who had previously received three or more prior chemotherapy regimens were given Taxol as a 24-hour infusion at a dose of 150 mg/m^2 (135 mg/m^2 if prior radiation was administered to ≤25% of the marrow). All patients had received prior doxorubicin as adjuvant therapy, for metastatic disease, or for both. Preliminary results demonstrated three partial responses (25%) and one minor response. Twenty-three additional patients are now being treated to better define the response rates.

At Memorial Sloan-Kettering,[16] 72 patients with metastatic breast cancer who had received a median of two cycles of prior chemotherapy (range 1-6) received Taxol as a 24-hour infusion at 200-250 mg/m^2 with G-CSF. All but two patients had received prior doxorubicin (37 were considered doxorubicin-refractory and 31 were considered initially doxorubicin-sensitive but then relapsed). The overall response rate was 28% (38% with one prior chemotherapy regimen, 32% with two prior chemotherapy regimens, and 17% with three or more prior chemotherapy regimens). Doxorubicin-refractory patients demonstrated a 30% response rate.

It is evident from the previous data that Taxol has demonstrated significant antitumor activity against metastatic breast cancer comparable to that shown by other single agents used for the treatment of breast cancer in the adjuvant setting. More important, Taxol appears to have significant antitumor activity in patients who are doxorubicin-resistant. Thus, there is ample justification for the evaluation of Taxol in the adjuvant setting and for the assessment of its worth when given in addition to other regimens (AC, CMF, etc.) currently used in the adjuvant treatment of breast cancer.

Hypersensitivity reactions observed in the early phase I studies with Taxol necessitated longer infusion and the use of a premedication regimen. Thus, until recently, most of the information on the efficacy of Taxol against breast cancer comes from studies employing 24-hour continuous infusion. Because a 24-hour infusion regimen is not considered to be practical in the adjuvant setting, strong interest has developed in evaluating shorter durations of infusion. The safety of administration of a 3-hour infusion has been shown for low and moderate Taxol doses (135 and 175

mg/m^2) in patients with relapsed ovarian and breast carcinoma[20,21] and for high doses (250 mg/m^2) in patients with breast carcinoma.[22] The MTD for Taxol as a 24-hour infusion has been determined to be 250 mg/m^2 with G-CSF support. For 3-hour infusion, in the initial phase I studies, 250 mg/m^2 were given safely with G-CSF support.[22] Recent phase II studies demonstrate that 250 mg/m^2 of Taxol as a 3-hour infusion can be given without G-CSF support with low rates of febrile neutropenia.[23] Because of reduced myelotoxicity with the shorter infusions when compared to longer infusions, some have argued that shorter infusions may be less effective. Information on the efficacy of the 3-hour infusion regimen has only recently become available.

The European-Canadian Trial compared, in a bifactorial design (135 and 175 mg/m^2), 3- and 24-hour Taxol infusions in patients with ovarian carcinoma. In the study, the groups receiving the 3-hour infusion regimen demonstrated a lower incidence of neutropenia and its related complications. However, preliminary data on response show similar response rates with the two different infusion regimens.[20]

In a randomized multicenter trial,[21] low and moderate doses of Taxol (135 and 175 mg/m^2) given as a 3-hour infusion were compared in patients with metastatic carcinoma of the breast. Seventy-seven percent of patients had been exposed to anthracyclines. Preliminary results from this study after a median of three cycles demonstrate an overall response rate of 27% (3% complete and 24% partial). For patients who had received only adjuvant chemotherapy, the overall response was 30%. For those who had received chemotherapy only for metastatic disease, the overall response was 29%, and for those who had received both, it was 22%. Among patients considered resistant to anthracyclines, 28% achieved a response with Taxol. These response rates are lower than those obtained with 24-hour infusions in similar populations of patients. However, lower doses (135 and 175 mg/m^2) have been used in this trial as compared to previous trials (220-250 mg/m^2).

The efficacy of high doses of Taxol (250 mg/m^2) given as a 3-hour infusion with rHu G-CSF support has recently been evaluated by the NSABP in a phase II study (BP-55) in patients with metastatic or locally advanced breast cancer who have not received prior chemotherapy for metastatic disease. From August 1993 until March 1994 this study accrued 100 patients. Toxicity information is available on 99 patients having received 448 cycles of Taxol (average 4.5 cycles/ per patient). Thirty percent of the patients developed at least one grade 3 toxicity, and 6% of the patients developed at least one grade 4 toxicity. There were no treatment-related deaths. The most common toxicities were neurosensory (grade 2, 40%; grade 3, 14%), neuromotor (grade 2, 12%; grade 3, 12%), arthralgia/myalgia (grade 2, 47%; grade

3, 15%), skin toxicity (grade 2, 13%; grade 3, 3%) Five percent of patients developed febrile neutropenia. Severe or life-threatening infection occurred in 2% of the patients. Hypersensitivity reactions were uncommon (grade 2, 6%; grade 3, 1%). Eighty-two patients are evaluable for response. There have been 14 complete responses (17%) and 21 partial responses (25%), for an overall response rate of 42%. Eighteen patients had stable disease (22%), and 29 had progressive disease (36%).

A phase III randomized trial (NSABP B-26) comparing 3-hour and 24-hour infusion regimens in patients with advanced breast cancer is currently being conducted.

Most of the information regarding the efficacy of Taxol in the treatment of metastatic breast cancer comes from studies employing high doses of Taxol (200-250 mg/m^2).[12,13,16] Excellent response rates have been obtained with such doses. Although a direct assessment of a dose-response relationship has not been established in metastatic breast cancer, the existence of such a relationship has been postulated in metastatic ovarian cancer.[24] In addition, preliminary findings from the European-Canadian trial in patients with refractory ovarian cancer were recently reported; these results indicated a higher response rate with Taxol given at 175 mg/m^2 when compared with Taxol given at 135 mg/m^2 (24% vs 13%).[20] For these reasons, high doses of Taxol (225 mg/m^2) were selected for this proposed adjuvant study.

2.3 Rationale for the Use of Standard Dose AC as the Control Arm

The combination of Adriamycin and cyclophosphamide at standard doses (60 mg/m^2 and 600 mg/m^2, respectively) has been found to be effective in the adjuvant setting and, when compared to the well-established CMF (cyclophosphamide, methotrexate, 5-FU) regimen, has demonstrated equivalent activity in node-positive patients who are tamoxifen-nonresponsive.[2] In addition, when compared to CMF, the AC regimen requires less time for administration, fewer clinic visits, and produces similar levels of toxicity. When added to tamoxifen, AC has also been demonstrated to be of value in node-positive patients who are tamoxifen-responsive.[3] The AC regimen is now being tested in the treatment of node-negative, ER-positive patients (NSABP B-23). The worth of intensifying the cyclophosphamide, and the worth of increasing the total dose of cyclophosphamide in the AC regimen, have been explored in a recently conducted NSABP randomized trial (B-22). Initial results from this trial[4] demonstrate that, when compared to patients receiving the standard AC regimen, there is no improvement in DFS or S in patients receiving the AC regimen with the intensified dose of cyclophosphamide or in those receiving the AC regimen with the intensified and increased total dose of cyclophosphamide. Higher intensification and higher increased total dose are being studied further in another recently completed NSABP randomized trial (B-25), but no results are yet available. Based on the above

information, there is no justification for using an intensified version of this regimen in the control group for this protocol.

2.4 Rationale for the Sequential Administration of Adriamycin/Cyclophosphamide and Taxol

The combination of Adriamycin and cyclophosphamide has demonstrated efficacy against breast cancer in both the metastatic and adjuvant settings. Taxol has been shown in the metastatic setting to be one of the most active chemotherapeutic agents against breast cancer and has demonstrated efficacy in patients with metastatic disease who have previously been treated with doxorubicin-based regimens.[12,16]

Phase I studies sequencing doxorubicin to Taxol[25] *within the same cycle* show that there is schedule-related toxicity when Taxol is given first followed by doxorubicin. When Taxol is sequenced to follow doxorubicin within the same cycle, higher doses of both agents can be administered. Sledge et al[26] treated 12 metastatic breast cancer patients with alternating cycles of Adriamycin (75 mg/m^2) and Taxol (200 mg/m^2) every 3 weeks for a maximum of 10 cycles, demonstrating the feasibility of using the two drugs in this fashion. Taxol was associated with greater neutropenia and lesser thrombocytopenia than Adriamycin. Responses were seen in 7 of the 12 patients.

The NSABP has recently conducted a pilot trial (BP-56) evaluating the feasibility of administration of four cycles of AC (Adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2) followed by four cycles of Taxol (250 mg/m^2 given as a 3-hour infusion with prophylactic rHu G-CSF). In the first phase of accrual to this pilot trial, 17 patients with metastatic or high-risk breast cancer were entered. Sixteen of these patients were evaluable for toxicity during Taxol administration. The toxicity profile with Taxol seen in this study was acceptable and similar to that seen in BP-55 (see Section 2.2) where Taxol (250 mg/m^2 as a 3-hour infusion) was administered as first-line chemotherapy (in BP-55, 30% of patients experienced at least a grade 3 toxicity and 6% of patients experienced at least a grade 4 toxicity; in BP-56, 38% of patients experienced a grade 3 toxicity and 6% of patients experienced at least a grade 4 toxicity). No deaths due to treatment occurred. Five of the 16 patients evaluable for toxicity developed dose-limiting toxicity (DLT): 2 patients developed grade 3 myalgia/arthralgia/neurotoxicity, 1 patient developed grade 3 myalgia/arthralgia, and 2 patients developed grade 3 neurotoxicity. According to the study design, 15 more patients needed to be accrued and treated in the same fashion in order to evaluate the feasibility of administration of the regimen. However, none of the DLTs were considered life-threatening. Furthermore, based on the similarity of the toxicity profiles between this study and NSABP BP-55 (Taxol at 250 mg/m^2

given over 3-hour infusion with rHu G-CSF) it was evident that there was no cumulative toxicity during the Taxol administration secondary to the prior AC administration. In order to reduce the DLTs in the second phase of accrual, one should institute either a dose reduction of Taxol or an intervention for amelioration of the myalgias/arthralgias. In either case, this could not be considered the second phase of BP-56 since, in the second phase, the regimen would have been modified. It was also felt that it would not be appropriate to proceed with the second accrual phase of BP-56 under the same treatment since the toxicity profile seen in the first phase was acceptable from a clinical perspective (38% of patients experienced grade 3 and 6%, grade 4 toxicity). In order to further reduce the incidence of neurotoxicity, the proposed Taxol dose for this study is reduced to 225 mg/m^2.

2.5 Rationale for Tamoxifen Administration in Subgroups of Patients

The value of tamoxifen in combination with chemotherapy has been shown in postmenopausal, node-positive patients. Although an additional benefit from tamoxifen in combination with chemotherapy has not been incontrovertibly demonstrated in premenopausal, node-positive patients, most clinicians treat premenopausal, hormone-sensitive, node-positive patients, who have ER-positive or PgR-positive tumors, with that combination. Only in premenopausal, node-positive, ER and PgR-negative patients is the propriety of adding tamoxifen to chemotherapy not substantiated. Thus, tamoxifen administration in this study is limited to all patients $\geq$50 years of age and those <50 with tumors positive for ER or PgR.

2.6 Rationale for the Concomitant Administration of Tamoxifen with Chemotherapy

Although the optimal timing of tamoxifen administration in relation to chemotherapy (concomitant vs. delayed) has been extensively debated, no consensus exists to date. A randomized clinical trial currently being conducted by the Intergroup (INT 0100) is attempting to provide a definitive answer to this question. In NSABP B-16,[3] there was added benefit observed with the combination of tamoxifen and chemotherapy over tamoxifen alone (tamoxifen was given concomitantly with chemotherapy). Proponents of delayed tamoxifen administration (because of possible negative interaction between chemotherapy and tamoxifen) argue that the observed benefit in B-16 might have been greater had the tamoxifen been given following completion of the chemotherapy. There is, however, other preclinical and clinical evidence to support the concomitant administration of tamoxifen and chemotherapy. Tamoxifen has been shown in vitro to increase the sensitivity to chemotherapy of cell lines that express the multidrug resistant (MDR) phenotype.[27,28] Powles[29] recently reported on a randomized feasibility trial comparing adjuvant (postoperative) to neoadjuvant (preoperative) chemotherapy combined with tamoxifen for treatment of primary

breast cancer. The objective response with the combination in the neoadjuvant arm was over 85%, with a significant reduction in requirements for mastectomy. Although different chemotherapy was used in this study, the response rate is comparable to that achieved in NSABP B-18 with preoperative chemotherapy alone.

There are no available clinical toxicity and efficacy data on concomitant administration of Taxol and tamoxifen. The safety of concomitant administration of tamoxifen and other chemotherapeutic regimens (AC or CMF) has been repeatedly demonstrated. Whether the concomitant administration of Taxol and tamoxifen is safe is not known at present, but is likely. In the case of concomitant administration, as proposed in this protocol, the first 50 patients will be closely monitored for unusual toxicities.

In this protocol, should one chose to administer the tamoxifen in a delayed fashion (i.e., following completion of all chemotherapy), an imbalance will be created in the duration of tamoxifen administration between treatment groups I and II. Since in group I tamoxifen will be given for 4 additional months, a true benefit from Taxol administration in group II when compared to group I may become less evident or may even be eliminated.

For all the reasons provided, we propose the concomitant administration of tamoxifen and chemotherapy.

. 2.7 Rationale for Not Using Prophylactic G-CSF in All Patients.

Although in the original phase I-II studies with high-dose Taxol given as a 3-hour infusion, prophylactic use of G-CSF was employed, it soon became evident that the hematologic toxicity of Taxol given as a 3-hour infusion was not as severe as that of Taxol given as a 24-hour infusion at the same doses. Recent information[23] suggests that 250 mg/m^2 of Taxol can be given safely as a 3-hour infusion without G-CSF support. Based on these data, the NSABP is currently not employing prophylactic G-CSF in the 3-hour arm of protocol B-26 (Taxol 250 mg/m^2). Toxicity information on the first 22 patients in this arm (average 2.7 cycles of Taxol/patient) demonstrates that 59% of patients developed $\geq$grade 3 nadir neutropenia and that 96% of patients had normal granulocyte counts by day 1 of the next cycle. Only 5% of patients experienced grade 2 granulocytopenia by day 1 of the next cycle and no patients experienced $\geq$grade 3 granulocytopenia. Furthermore, no episodes of febrile neutropenia have been observed in this arm so far. For all the above reasons, prophylactic G-CSF is not employed in this study during Taxol administration. However, in patients who experience life-threatening infection, febrile neutropenia or prolonged granulocytopenia, prophylactic G-CSF will be used in all subsequent cycles.

2.8 Issues Relating to Racial and Ethnic Differences.

African-Americans are the most significant group with regard to possible racial and ethnic variation in response to the treatments under consideration. Many researchers have noted less-favorable survival rates for African-American breast cancer patients compared to Caucasians.[30,31] This has been attributed to many factors, including more advanced disease at the time of treatment,[32] social and economic factors,[33] or specific tumor characteristics such as ER positivity.[34,35] Although outcomes in general tend to be less favorable for African-Americans, significant interaction between race and treatment response has not been reported, suggesting that, where treatment efficacy is noted, both groups appear to benefit. Previous investigations of race and prognosis support these conclusions.[36,37]

Potential for enrollment of minority patients in this study is enhanced through the NSABP Minority Initiative Program, which disseminates information and provides opportunities for greater participation by under-represented racial and ethnic groups. In previous NSABP studies, African-American women have generally been represented at or slightly below the representation observed in the general population, depending on clinical eligibility criteria. Hispanic, Asian/Pacific Islander, and Native American women usually comprise about 5% of participants. A significant increase in enrollment would be required in order to meet the overall study objectives within racial groups, and accrual goals specific to racial and ethnic groups will not be specified. However, racial and ethnic background has been evaluated in the past as a prognostic discriminant, and, in this study, race and ethnicity will be examined for a relationship to the primary study endpoints through statistical modelling.

3.0 SPECIFIC AIMS

To determine whether four cycles of postoperative Taxol given after four cycles of postoperative AC will more effectively prolong DFS and S than will four cycles of postoperative AC alone in patients with operable breast cancer and histologically positive axillary nodes.

4.0 ENDPOINTS

The primary endpoints to be used for statistical analysis will be disease-free survival and survival.

4.1 Survival

Event to be used for survival analysis is death from any cause.

4.2 Disease-Free Survival

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

4.2.1 Breast Cancer Recurrence

See Sections 12.1, 12.2, and 12.3 for definitions of local, regional, and distant recurrence.

3/26/97

4.2.2 Second Primary Cancer

Any second primary cancer other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast (LCIS) will be considered an event in the analysis of disease-free survival.

4.2.3 Death from Any Cause as a First Event

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

5.0 PATIENT ELIGIBILITY AND INELIGIBILITY

5.1 Conditions for Patient Eligibility

3/26/97 Female patients who satisfy all of the following conditions are the only patients who will be considered eligible for the study:

5.1.1 The patient must consent to be in the study and must have signed an approved consent form conforming with federal and institutional guidelines (see Section 16.1 and Appendix A).

5.1.2 The interval between the initial cytologic or histologic diagnosis of breast cancer and randomization must be no more than 63 days.

5.1.3 Patients must have undergone either a total mastectomy and axillary dissection (modified radical mastectomy), or lumpectomy and axillary dissection (see Section 5.2 regarding special eligibility criteria for lumpectomy patients).

5.1.4 Patients must have a life expectancy of at least 10 years, excluding their diagnosis of cancer.

5.1.5 The tumor must be confined to the breast and ipsilateral axilla on clinical examination (T_{1-3}, $N_{0-}1$, M_0). (See Appendix B for staging information.)

5.1.6 The tumor must be invasive adenocarcinoma on histologic examination.

5.1.7 At least one axillary lymph node must demonstrate evidence of tumor on histologic examination.

5.1.8 At the time of randomization, patients must have had the following: history and physical exam including blood tests, gynecologic exam within the past year (for women who have a uterus and/or ovaries), chest X ray within the past 3 months, bone scan, bilateral mammogram within the past year, and an EKG within the past year.

3/26/97 5.1.9 At the time of randomization the postoperative WBC must be $\geq$4,000 and postoperative platelet count $\geq$100,000, and there must be postoperative evidence of adequate hepatic and renal function (bilirubin, SGOT or SGPT, and serum creatinine, all within normal limits for the laboratory).

5.1.10 Patients with skeletal pain are eligible for inclusion in the study if bone scan and/or roentgenological examination fails to disclose metastatic disease. Suspicious findings must be confirmed as benign by X ray, MRI, or biopsy.

5.1.11 Patients with prior nonbreast malignancies are eligible if they have been disease-free for ≥10 years. Patients with squamous or basal cell carcinoma of the skin that has been effectively treated, carcinoma in situ of the cervix that has been treated by operation only, or lobular carcinoma in situ of the ipsilateral or contralateral breast treated by segmental resection only are eligible, even if diagnosed within 10 years prior to randomization.

3/26/97 *Deletion of text resulted in renumbering of section.*

5.1.12 Patients must have a determination of estrogen and progesterone receptors performed on the primary tumor prior to randomization (see Section 8.0).

3/26/97 *Deletion of text.*

5.2 Special Conditions for Eligibility in Lumpectomy Patients

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

5.2.1 On physical examination, the tumor must be 5 cm or less in its greatest dimension.

3/26/97 *Deletion of text resulted in renumberbing of section.*

5.2.2 The margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS). In patients where pathologic examination demonstrates tumor present at the line of resection, additional operative procedures may be performed to obtain clear margins. This is permissible even if axillary dissection has been performed. Patients in whom tumor is still present after reexcision(s) must undergo total mastectomy to be eligible.

5.3 Conditions for Patient Ineligibility

3/26/97 Male patients are not eligible for this study. Patients with one or more of the following conditions will be ineligible for this study:

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

5.3.2 Pregnancy at the time of proposed randomization.

3/26/97 5.3.3 Ulceration, erythema, infiltration of the skin or the underlying chest wall (complete fixation), peau d'orange, or skin edema of **any** magnitude. (Tethering or dimpling of the skin or nipple inversion should **not** be interpreted as skin infiltration. **Patients with these conditions are eligible.**)

5.3.4 Ipsilateral lymph nodes that are clinically fixed to one another **or** to other structures (N_2 disease).

5.3.5 Suspicious palpable nodes in the contralateral axilla or palpable supraclavicular or infraclavicular nodes. Patients with these conditions are considered ineligible unless there is biopsy evidence that these are not involved with tumor.

3/26/97 5.3.6 Prior therapy for breast cancer, including irradiation, chemo-, immuno-, and/or hormonal therapy. Patients receiving any sex hormonal therapy, e.g., birth-control pills, ovarian hormonal replacement therapy, etc., are eligible <u>if</u> this therapy is discontinued prior to randomization and while the patient is on protocol. Patients who have received prior anthracycline therapy for any malignancy are not eligible.

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

5.3.8 Active cardiac disease that would preclude the use of Adriamycin and/or Taxol. This includes:

- any documented myocardial infarction;
- angina pectoris that requires the use of anti-anginal medication;
- any history of documented congestive heart failure;
- a cardiac arrhythmia requiring medication, or a severe conduction abnormality;
- valvular disease with documented cardiac function compromise;

- patients with cardiomegaly on chest X ray or ventricular hypertrophy on EKG, unless they demonstrate adequate left ventricular function by MUGA scan ($\geq$45%) or by echocardiogram;
- patients with poorly controlled hypertension, i.e., diastolic greater than 100 mm/Hg. (Patients with hypertension who are well controlled on medication are eligible for entry);
- patients who currently receive medications (digitalis, beta-blockers, calcium channel blockers, etc.) that alter the cardiac conduction if these medications are administered for cardiac arrhythmia, angina or congestive heart failure. If these medications are administered for other reasons (i.e., hypertension), the patients will be eligible.

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

5.4 Special Conditions for Ineligibility in Lumpectomy Patients.

For patients treated by lumpectomy with or without axillary dissection to be followed by breast radiation therapy, the presence or existence of one more of the conditions in Section 5.3 will render the patient ineligible for entry into the study. In addition, the following patients will also be ineligible:

5.4.1 Patients with tumors greater than 5 cm in size at the largest dimension on physical examination.

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

5.4.3 Patients treated with lumpectomy in whom there is another dominant mass within the ipsilateral breast remnant. Such a mass must be biopsied and demonstrated to be histologically benign prior to randomization.

5.4.4 Patients who receive breast radiation therapy following lumpectomy but prior to randomization.

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

6.0 REQUIRED ENTRY AND FOLLOW-UP STUDIES (Table 3)

6.1 Prior to Randomization

Those studies required prior to randomization are shown in Table 3, column 2. These studies are imperative to accurately stage trial participants.

6.2 Year 1 Through Year 5

Refer to Table 3, column 3, for those studies required (1) on day 1 every 3 weeks, prior to each cycle of chemotherapy administration, (2) every 6 months, and (3) every 12 months, for Years 1 through 5.

6.3 After Year 6

Refer to Table 3 column 4 for those studies required every 12 months during Year 6 and thereafter.

PROTOCOL NO. B-28
TABLE 3. Studies Required

Required Studies[a]	Prior to Randomization	Year 1 Through Year 5		Years 6+
		On Day 1 Prior To Each Cycle of Chemotherapy and Every 6 Months[b]	Every 12 Months[b]	Every 12 Months[b]
History and Physical Examination	X	X		X
Gynecologic exam[c]	X		X	X
Hematologic Studies				
CBC and Differential	X[d]	X		
Platelet Count	X[d]	X		
Chemistries				
BUN	X[d]	X		
Serum Creatinine	X[d]	X		
Bilirubin	X[d]	X		
SGOT or SGPT	X[d]	X		
Roentgenologic Exam				
Chest (PA & Lat.)	X[e]		X	X[f]
Bone Scan	X		X[f]	X[f]
Bilateral Mammogram	X[g]		X[h]	X[h]
MUGA[i]				
EKG	X[g]			

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

[b] From date of randomization.

[c] Required only for women who have a uterus and/or ovaries. Exam must be performed within 1 year prior to randomization.

[d] Postoperative testing.

[e] Within 3 months prior to randomization.

[f] Required only if symptoms are present.

[g] Within 1 year prior to randomization.

[h] Unilateral for patients with mastectomy.

[i] MUGA scan is not required, but, if performed, must show LVEF $\geq$ 45%.

7.0 REQUIRED PATHOLOGY STUDIES

Ideally, one staff pathologist at each participating institution should supervise all pathology examinations, which will be recorded on Form D-1. This form, attached to a copy of the institution's official pathology report(s), will be forwarded to the NSABP Biostatistical Center, along with the materials requested below. In cases where the tumor block is not available, the pathologist from the institution must submit Form BLR to the NSABP Biostatistical Center within 18 months stating the reason for not submitting a block.

3/26/97 7.1 Mastectomy or Lumpectomy Specimens

All cases will be reviewed by the NSABP Pathology Section to minimize the impact of interobserver variations in grading schemes. Blocks will be stored at the NSABP Pathology Section and, if required, will be returned immediately upon an institution's request.

Due to the differences in institutional policies among NSABP membership institutions, the following guidelines are provided to help identify which materials need to be submitted. **However, it needs to be stressed that the ideal material is paraffin-embedded blocks rather than unstained slides, since antigenicity of most of the markers deteriorates after sectioning, even under the most ideal storage conditions.** Submission of blocks is strongly encouraged for this reason.

7.1.1 Institution allows blocks to be sent out and stored at the NSABP Pathology Section.

- At least one representative tumor block with the least necrosis.
- At least one representative block of a positive lymph node.
- One representative block of histologically normal breast *(optional submission)*
- **No** H&E stained sections need to be submitted.

10/30/97 7.1.2 Institution allows blocks to be sent out but wants them to be returned.

Submit the same materials as in Section 7.1.1. Thirty (30) unstained sections will be made at the NSABP Pathology Section and blocks will be sent back to the institution within approximately 1 month.

7.1.3 Institution does not allow blocks to be sent out.

Submit unstained sections as described below. Slides should be 5 microns thick and mounted on charged (or silanated) slides for immunostaining procedures. It is recommended that the blocks be hydrated on top of ice water for at least 1 hour before sectioning to keep the sections mounted permanently.

- At least thirty (30) unstained sections from the representative tumor block with the least necrosis and one 50 μm cut in a tube.
- At least thirty (30) unstained sections from the representative block of a positive lymph node.
- **No** H&E stained sections need to be submitted.

7.1.4 Institution does not allow unstained materials or blocks to be sent out.

Submit Form BLR to the NSABP Biostatistical Center along with representative H&E stained slides from the following anatomical areas to verify diagnosis.

- Representative sections of the primary tumor.
- Representative sections of the positive lymph nodes.

3/26/97 7.2 Pathology Material

Submit all NSABP pathology material to:

NSABP Biostatistical Center
Suite 600
230 McKee Place
Pittsburgh, PA 15213

8.0 ESTROGEN (ER) AND PROGESTERONE (PgR) RECEPTORS

8.1 All patients must have a determination of estrogen and progesterone receptors performed on the primary tumor prior to randomization. Acceptable methods for determining ER and PgR include the Dextran-coated charcoal or sucrose-density gradient, the enzyme immunoassay (EIA) or the immunohistochemical assay.

9.0 TREATMENT REGIMEN

9.1 Group I (AC)

3/26/97 Patients randomized to this group will receive Adriamycin 60 mg/m^2 i.v. every 21 days x 4 cycles, along with cyclophosphamide 600 mg/m^2 i.v. every 21 days x 4 cycles. Adriamycin will be administered by i.v. slow push followed by cyclophosphamide infusion over 30 minutes to 2 hours. Patients ≥50 years of age and those <50 years of age with tumors that are ER-positive or PgR-positive will receive tamoxifen 20 mg p.o. once daily for 5 years, starting on day 1 of the first cycle. Chemotherapy should start no earlier than 2 weeks from the last surgical procedure. In lumpectomy patients, postoperative radiotherapy will be given after patients recover from AC chemotherapy. (See Appendixes C and D for details on surgery and radiation therapy.)

9.2 Group II (AC followed by Taxol)

3/26/97 Patients randomized to this group will receive Adriamycin 60 mg/m^2 i.v. every 21 days x 4 cycles along with cyclophosphamide 600 mg/m^2 i.v. every 21 days x 4 cycles. Adriamycin will be administered by i.v. slow push followed by cyclophosphamide infusion over 30 minutes to 2 hours. After completion of AC therapy, Taxol 225 mg/m^2 i.v. will be given as a 3-hour continuous infusion every 21 days x 4 cycles. Patients ≥50 years of age and those <50 years of age with tumors that are ER-positive or PgR-positive will receive tamoxifen 20 mg p.o. once daily for 5 years, starting on day 1 of the first AC cycle. Chemotherapy should start no earlier than 2 weeks from the last surgical procedure. In lumpectomy patients, postoperative radiotherapy will be given after patients recover from Taxol chemotherapy. (See Appendixes C and D for details on surgery and radiation therapy.)

9.3 Premedication Regimen

All patients in group II will receive the following premedication regimen before each cycle of Taxol administration:

- Dexamethasone 20 mg p.o. at 12 and 6 hours before the beginning of Taxol infusion.
- Diphenhydramine 50 mg i.v., 1 hour before the beginning of Taxol infusion.
- Cimetidine 300 mg i.v. or ranitidine 50 mg i.v., 1 hour before the beginning of Taxol infusion.

The agent used as a premedication (cimetidine or ranitidine) should be recorded on the appropriate data form.

10.0 DOSE DETERMINATIONS

3/26/97 The drug dose for each cycle of therapy will be calculated following determination of the WBC and platelet count before the onset of each cycle of therapy. THE PATIENT'S BODY SURFACE AREA (BSA) WILL BE CALCULATED BEFORE EACH CYCLE OF CHEMOTHERAPY. The patient's AC dosages will be calculated with an upper limit of 2 m^2. That is, if a patient's meter square surface area is greater than 2 m^2, all AC dosages will be calculated and administered only up to 2 m^2. The Taxol drug dosage will also be calculated according to the patient's body surface area but **with no upper limit**. (See Appendix E for Body Surface Area Nomogram.) The total dose of therapy will be adjusted as follows:

10.1 Adriamycin (60 mg/m^2 i.v.): Should be rounded to the nearest mg.

Example:	75.40 mg	=	75 mg
	75.50 mg	=	76 mg

10.2 Cyclophosphamide (600 mg/m^2 i.v.): Should be rounded to the nearest 25 mg.

Example:	1010 mg	=	1000 mg
	1015 mg	=	1025 mg

10.3 Taxol (225 mg/m^2 i.v.): Should be rounded to the nearest 10 mg.

Example:	375 mg	=	380 mg
	371 mg	=	370 mg

3/26/97 *Note: Only for patients ≥50 years of age and those <50 years of age with tumors that are ER-positive or PgR-positive.*

3/26/97 10.4 Tamoxifen 20 mg p.o., every day for 5 years

11.0 DOSE MODIFICATIONS OR DELAYS

(Refer to Appendix F for toxicity grading and to Section 15.0 for toxicity reporting information)

11.1 Dose Modification of AC

Administration of AC will be delayed as a result of hematologic or gastrointestinal toxicity on day 1 of any cycle. AC administration will be resumed when any gastrointestinal symptoms have resolved, and when granulocyte counts and platelet counts permit administration of full dose.

3/26/97

11.1.1 Hematologic Toxicity

- Granulocytopenia: No dose reductions of either A or C will be allowed for granulocytopenia. Administration of AC will be delayed as a result of ≥grade 2 granulocytopenia on day 1 (granulocytes <1500)[1]. AC administration will resume when granulocyte counts permit administration of full dose (granulocytes ≥1500). If delay occurs, counts should be repeated weekly. Resume AC treatment when granulocytes ≥1500, at full dose, with rHu G-CSF support at 5μg/kg s.c. beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8 (see Appendix G for rHu G-CSF administration). During rHu G-CSF administration, granulocyte counts should be monitored twice weekly beginning on day 8 to avoid extreme elevations. All remaining cycles will be administered with rHu G-CSF. Administration of AC will also be delayed as a result of ≥grade 2 granulocytopenia on day 1 despite rHu G-CSF administration (granulocytes <1500). Administration of rHu G-CSF will continue, but AC administration will resume only when granulocyte counts permit administration of the next cycle (granulocytes ≥1500). If, in any cycle, the granulocyte counts are still <1500 after a 2-week delay, the NSABP Clinical Coordinating Section should be notified (see Section 15.4).

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[1]Granulocytes<1,500 is equivalent to granulocytes <1.5 x 10^3 cells/μl or 1.5 x 10^9 cells/L.

For any cycle in which rHu G-CSF is administered, the patient should be off rHu G-CSF for at least 24 hours prior to the next dose of chemotherapy.

- Thrombocytopenia: No dose reductions of either A or C will be allowed for thrombocytopenia. Administration of AC will be delayed as a result of ≥grade 2 thrombocytopenia on day 1 (platelets <75,000). If delay occurs, counts should be repeated weekly. AC administration will be resumed when platelet counts permit administration of full dose (platelets ≥75,000). If, after a 2-week delay the platelets are still <75,000, the NSABP Clinical Coordinating Section should be notified (see Section 15.4).

3/26/97 11.1.2 Febrile Neutropenia/Infection (Please refer to Tables 4 and 5)

Patients will be classified as having febrile neutropenia if they:

- are hospitalized or receive antibiotics as an outpatient, and
- are granulocytopenic (granulocytes <2000, classified as a ≥ grade 1 toxicity) and
- are febrile (fever >38.0°C, classified as a ≥grade 2 toxicity), and/ or
- have a systemic infection.

Patients who, during a cycle, develop an episode of febrile neutropenia will have all remaining cycles of A and C given with rHu G-CSF support at 5 µg/kg s.c. beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8. During rHu G-CSF administration, granulocyte counts should be monitored twice weekly beginning on day 8 to avoid extreme elevations. Should a second episode of febrile neutropenia occur with rHu G-CSF, further cycles of AC should be given with rHu G-CSF at 5 µg/kg, along with prophylactic Cipro (ciprofloxacin HCl) at 500 mg p.o. b.i.d., beginning on day 5 and continuing for at least 7 days. Should a third such episode develop while the patient is on AC therapy, the fourth cycle of AC should be given at 75% of the originally calculated dose for both A and C, (see Section 10.0) along with rHu-G-CSF at 5µg/kg and prophylactic Cipro. Appropriate supportive therapy during the first episode of febrile neutropenia is at the discretion of the investigator.

Patients who, while on AC, develop documented grade 4 infection (life-threatening) with or without neutropenia will have all remaining cycles of AC given with rHu G-CSF support and prophylactic Cipro as previously

described. In the event of a grade 4 documented infection with or without neutropenia, despite the administration of prophylactic rHu G-CSF and Cipro, AC will be given at 75% of the originally calculated dose for both A and C, during the remaining cycles, (see Section 10.0) along with rHu G-CSF at 5μg/kg and prophylactic Cipro. If a grade 4 documented infection with or without neutropenia occurs despite all the above, further AC therapy will be discontinued.

For any cycle in which rHu G-CSF is administered, the patient should be off rHu G-CSF for at least 24 hours prior to the next dose of chemotherapy.

PROTOCOL NO. B-28

TABLE 4. Supportive Therapy During Subsequent Cycles of AC Following Febrile Neutropenia in an AC Cycle

Agents Used	Treatment Parameters for Next Cycle			
	No episodes	First episode	Second episode	Third episode
AC	100%	100%	100%	75%
RHu G-CSF	NO	YES*	YES*	YES*
Ciprofloxacin HCl	NO	NO	YES†	YES†

3/26/97

* RHu G-CSF 5µg/kg s.c beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8. Granulocyte counts should be monitored twice weekly during rHu G-CSF administration beginning on day 8 to avoid extreme elevations.

† Ciprofloxacin HCl 500 mg p.o. b.i.d. from day 5 for at least 7 days.

TABLE 5. Supportive Therapy During Subsequent Cycles of AC Following Grade 4 Infection in an AC Cycle

Agents Used	Treatment Parameters for Next Cycle			
	No episodes	First episode	Second episode	Third episode
AC	100%	100%	75%	OFF AC
RHu G-CSF	NO	YES*	YES*	N/A
Ciprofloxacin HCl	NO	YES†	YES†	N/A

3/26/97

* RHu G-CSF 5µg/kg s.c. beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8. Granulocyte counts should be monitored twice weekly during rHu G-CSF administration beginning on day 8 to avoid extreme elevations.

† Ciprofloxacin HCl 500 mg p.o. b.i.d. from day 5 for at least 7 days.

11.1.3 Gastrointestinal Toxicity

The administration of AC on day 1 will be delayed in the presence of any grade gastrointestinal toxicity until all such toxicity has resolved. AC will then be administered at full dose. Aggressive prophylactic antiemetic therapy is recommended, beginning with the initial cycle of therapy. The selection of the specific antiemetic regimen is at the discretion of the investigator.

3/26/97 11.1.4 Hepatic Dysfunction

A rising bilirubin, SGOT, or SGPT to a level >1.5 times the upper limit of laboratory normal mandates delay of AC therapy and determination of the cause. If the rise is not due to metastatic disease and the levels return to ≤1.5 times the upper limit of laboratory normal within 2 weeks, AC therapy should be resumed at full dose. If a delay of greater than 2 weeks occurs, notify the NSABP Clinical Coordinating Section (see Section 15.4) to discuss further management.

3/26/97 11.1.5 Renal Toxicity

All chemotherapy will be delayed for a serum creatinine of >1.5 times the upper limit of laboratory normal. The cause of the elevated creatinine must be determined. If the rise is not due to metastatic disease and if the creatinine returns to ≤1.5 times the upper limit of laboratory normal within 2 weeks, AC therapy should be resumed at full dose. If a delay of greater than 2 weeks occurs, notify the NSABP Clinical Coordinating Section (see Section 15.4) to discuss further management.

3/26/97 11.1.6 Cardiac Toxicity

A decrease in cardiac function is an indication to permanently stop Adriamycin. Patients will, however, continue with the other agents according to protocol. The presence of PACs or PVCs without cardiac dysfunction is **not** an indication to permanently stop Adriamycin. Acute dysrhythmias that may occur during and shortly after Adriamycin infusion should not lead to dose modification; however, in such cases the NSABP Clinical Coordinating Section should be notified (see Section 15.4).

3/26/97 11.1.7 Hemorrhagic Cystitis

All patients should be instructed on the importance of vigorous hydration during cyclophosphamide therapy. If drug-related ≥grade 2 hemorrhagic cystitis should occur despite vigorous hydration, cyclophosphamide therapy should be stopped and the NSABP Clinical Coordinating Section should be notified (see Section 15.4). If cyclophosphamide therapy is discontinued due to hemorrhagic cystitis, all other protocol therapies should be continued.

3/26/97 11.1.8 Other Toxicities

For other grade 3 and grade 4 nonhematologic toxicities except alopecia, contact the NSABP Clinical Coordinating Section to discuss further management (see Section 15.4).

11.2 Dose Modification of Taxol

Since AC and Taxol have substantial differences in toxicity and mechanism of action, any toxicity that occurs during AC administration and resolves prior to Taxol administration would not require dose reduction or delay during Taxol therapy. Thus, a patient who discontinues AC therapy due to toxicity should still proceed with Taxol as per protocol. The first Taxol dose should occur 3 weeks after the last dose of AC and after the toxicity has resolved. In the event of toxicity requiring a dose reduction of Taxol, the following dose reduction schema will be employed:

- 225 mg/m^2 (full dose)
- 200 mg/m^2 (1st dose reduction)
- 175 mg/m^2 (2nd dose reduction)
- 150 mg/m^2 (3rd dose reduction)

3/26/97 11.2.1 Hematologic Toxicity

- Granulocytopenia: Administration of Taxol will be delayed as a result of ≥grade 2 granulocytopenia on day 1 (granulocytes <1500). Taxol administration will resume when granulocyte counts permit administration of full dose (granulocytes ≥1500). If delay occurs, counts should be repeated weekly. Resume Taxol treatment when granulocytes ≥1500, at full dose, with rHu G-CSF support at 5 µg/kg s.c. beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8 (see Appendix G for rHu G-CSF administration). During rHu G-CSF administration, granulocyte counts should be monitored twice weekly beginning on day 8 to avoid extreme elevations. All remaining cycles will be administered with rHu G-CSF. Administration of Taxol will also be

delayed as a result of ≥grade 2 granulocytopenia on day 1 despite the rHu G-CSF administration (granulocytes <1500). Administration of rHu G-CSF will continue, but Taxol administration will resume only when granulocyte counts permit administration of the next cycle (granulocytes ≥1500). If this occurs in 1 week, Taxol will be given at full dose. If it takes 2 weeks, Taxol will be given at the first dose reduction level. If after 2 weeks the granulocytes are still <1500, further Taxol therapy will be discontinued and the patient will be treated at the discretion of the investigator. The NSABP Clinical Coordinating Section should be notified (see Section 15.4).

For any cycle in which rHu G-CSF is administered, the patient should be off rHu G-CSF for at least 24 hours prior to the next dose of chemotherapy.

- Thrombocytopenia: No dose reductions of Taxol will be allowed for thrombocytopenia. Administration of Taxol will be delayed as a result of ≥grade 2 thrombocytopenia on day 1 (platelets <75,000). If delay occurs, counts should be repeated weekly. Taxol administration will be resumed when platelet counts permit administration of full dose (platelets ≥75,000). If, after a 2-week delay the platelets are still <75,000, further Taxol therapy will be discontinued and the patient will be treated at the discretion of the investigator. The NSABP Clinical Coordinating Section should be notified (see Section 15.4).

3/26/97 11.2.2 Febrile Neutropenia/Infection (Please refer to Tables 6 and 7)

Patients will be classified as having febrile neutropenia if they:

- are hospitalized or receive antibiotics as an outpatient, and
- are granulocytopenic (granulocytes <2000, classified as a ≥ grade 1 toxicity) and
- are febrile (fever >38.0°C, classified as a ≥grade 2 toxicity), and/ or
- have a systemic infection.

Patients in Group II who, while on Taxol, develop an episode of febrile neutropenia will have all remaining cycles of Taxol given at full dose, with rHu G-CSF support at 5 µg/kg s.c. beginning on day 2 at least 24 hours after completion of Taxol infusion and continuing until a granulocyte count of ≥10,000 is obtained after day 8. During rHu G-CSF administration, granulocyte counts should be monitored twice weekly beginning on day 8 to avoid extreme elevations. If a second episode occurs in such patients, all remaining cycles of Taxol will be given at full dose with rHu G-CSF at 5μg/kg s.c. and prophylactic Cipro 500 mg p.o. b.i.d. beginning on day 5 and continuing for at least 7 days. Should an episode of febrile neutropenia

occur despite the rHu G-CSF and prophylactic antibiotics, the fourth cycle of Taxol will be given at the first dose reduction level (see Section 11.2), with rHu G-CSF at 5 μg/kg, and with prophylactic Cipro. Appropriate supportive therapy during the first episode of febrile neutropenia on Taxol is at the discretion of the investigator. Patients who, while on Taxol, develop documented grade 4 infection (life-threatening) with or without neutropenia will have all remaining cycles of Taxol given with rHu G-CSF support and prophylactic Cipro. In the event of a grade 4 documented infection with or without neutropenia despite the administration of prophylactic rHu G-CSF and Cipro, Taxol will be given at the first dose reduction level during the remaining cycles along with rHu G-CSF at 5 µg/kg and prophylactic Cipro. If a grade 4 documented infection with or without neutropenia occurs despite all the above, further Taxol therapy will be discontinued.

For any cycle in which rHu G-CSF is administered, the patient should be off rHu G-CSF for at least 24 hours prior to the next dose of chemotherapy.

PROTOCOL NO. B-28

TABLE 6. Supportive Therapy During Subsequent Cycles of Taxol Following Febrile Neutropenia in a Taxol Cycle

	Treatment Parameters for Next Cycle			
Agents Used	No episodes	First episode	Second episode	Third episode
Taxol	225 mg/m^2	225 mg/m^2	225 mg/m^2	200 mg/m^2
RHu G-CSF	NO	YES*	YES*	YES*
Ciprofloxacin HCl	NO	NO	YES†	YES†

3/26/97

* RHu G-CSF 5µg/kg s.c beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8. Granulocyte counts should be monitored twice weekly during rHu G-CSF administration beginning on day 8 to avoid extreme elevations.

† Ciprofloxacin HCl 500 mg p.o. b.i.d. from day 5 for at least 7 days.

TABLE 7. Supportive Therapy During Subsequent Cycles of Taxol Following Grade 4 Infection in a Taxol Cycle

	Treatment Parameters for Next Cycle			
Agents Used	No episodes	First episode	Second episode	Third episode
Taxol	225 mg/m^2	225 mg/m^2	200 mg/m^2	OFF TAXOL
RHu G-CSF	NO	YES*	YES*	N/A
Ciprofloxacin HCl	NO	YES†	YES†	N/A

3/26/97

* RHu G-CSF 5µg/kg s.c. beginning on day 2 at least 24 hours after the end of chemotherapy and continuing until a granulocyte count of ≥10,000 is obtained after day 8. Granulocyte counts should be monitored twice weekly during rHu G-CSF administration beginning on day 8 to avoid extreme elevations.

† Ciprofloxacin HCl 500 mg p.o. b.i.d. from day 5 for at least 7 days.

3/26/97 11.2.3 Gastrointestinal Toxicity

Nausea and vomiting do not occur in many patients and, when they do occur, they are mild. Administration of a prophylactic antiemetic regimen is not recommended. However, patients in both groups who develop nausea or vomiting should receive prophylactic antiemetics for subsequent cycles. The selection of the specific antiemetic regimen, including steroids, is at the discretion of the investigator but should be recorded on the treatment forms. There will be no dose reductions for patients who develop nausea and vomiting without having received a prophylactic antiemetic regimen. In the event of grade 4 vomiting, despite the administration of a prophylactic antiemetic regimen, all remaining cycles will be given at the first dose reduction level (see Section 11.2). In the event of ≥grade 3 diarrhea or stomatitis, all remaining cycles will be given at the first dose reduction level. In the event of ≥grade 3 gastrointestinal toxicity, despite the first dose reduction, all remaining cycles will be given at the second dose reduction level. Any toxicity should resolve (grade 0) before administration of the next cycle. No more than 2 weeks will be allowed for this recovery. If after 2 weeks the toxicity has not resolved, further Taxol therapy will be discontinued.

3/26/97 11.2.4 Neurologic Toxicity

In the event of grade 4 neurologic toxicity, Taxol therapy will be discontinued. Dose modifications of Taxol will be required in the event of grade 3 neurotoxicity. In such cases, all remaining cycles will be given at the first dose reduction level provided no prior dose reductions have occurred (in which case, an additional dose reduction should take place). In the event of grade 3 neurotoxicity, despite the dose reduction, further Taxol therapy will be given at the second dose reduction level. In the event of ≥grade 3 neurotoxicity, despite the second dose reduction, further Taxol therapy will be discontinued.

Any grade 2 or grade 3 toxicity should return to grade 1 or less before retreatment. No more than 2 weeks will be allowed for this recovery. If after 2 weeks the toxicity has not returned to grade 1 or less, further Taxol therapy will be discontinued.

11.2.5 Myalgia/Arthralgia

Myalgias/arthralgias will be classified as mild (muscle and joint aches), moderate (decreased function, decreased ability to perform daily tasks, but still functioning), or severe (unable to function, confined to bed).

3/26/97

For myalgias and arthralgias, patients should be given nonsteroidal anti-inflammatory medications (Toradol, ibuprofen, etc.): if this is ineffective, administer prednisone 20 mg p.o. daily for 2-5 days. If there is still no relief, narcotic pain medications should be given. In the event of grade 2 or grade 3 myalgia/arthralgia that persists in spite of the above, or for myalgia/arthralgia that is relieved by prednisone, prophylaxis with steroids should be instituted in the next cycle without dose reduction (prednisone 20 mg p.o. daily for 5 days, starting on the day of treatment). In the event of grade 3 toxicity despite administration of prophylactic steroids, there will be a dose reduction of Taxol to the first dose reduction level for all remaining cycles with additional dose reductions according to the proposed schema (see Section 11.2). Toxicity should return to grade 1 or less before retreatment. No more than 2 weeks will be allowed for this recovery. If the toxicity has not resolved after 2 weeks, further Taxol therapy will be discontinued. The NSABP Clinical Coordinating Section should be notified (see Section 15.4).

3/26/97

11.2.6 Hypersensitivity Reactions

For patients who develop severe hypersensitivity reactions (dyspnea, symptomatic hypotension, angioedema, generalized urticaria, or chest pain) during Taxol administration, the infusion will be discontinued. Patients should be treated with the necessary support measures and further Taxol therapy will be discontinued. The following management of hypersensitivity reactions is recommended:

- Administration of diphenhydramine 50 mg i.v. (or its equivalent);
- Administration of adrenaline (or its equivalent) every 15-20 minutes until the reaction subsides or until a total of six doses are given;
- If hypotension is present and does not respond to adrenaline, administration of i.v. fluids is recommended;
- If wheezing is present and is not responsive to adrenaline, administration of nebulized albuterol (or its equivalent) is recommended;
- Although corticosteroids have no effect in the initial reaction, they have been shown to block "late" allergic reactions. Thus, methylprednisolone 125 mg i.v. (or its equivalent) may be administered to prevent recurrent or ongoing allergic manifestations.

In the event of grade 1 or grade 2 hypersensitivity reactions (flushing, skin rash), the infusion will continue with further support as necessary (steroids, antihistamines, etc). There will be no dose modifications for hypersensitivity reactions, but extreme caution should be employed with subsequent cycles.

3/26/97 11.2.7 Cardiac Toxicity

There will be no dose modifications for asymptomatic (grade 1 or grade 2) cardiac toxicity or asymptomatic hypotension. In the event of first degree AV block, continue Taxol therapy at full dose under continuous cardiac monitoring. In the event of grade 3 or grade 4 cardiac toxicity, further Taxol therapy will be discontinued. If grade 4 cardiac toxicity (brady-arrhythmia) is detected in an asymptomatic patient because of continuous cardiac monitoring and does not require therapy, the NSABP Clinical Coordinating Section should be notified (see Section 15.4) and the patient will be permitted to remain on study pending a complete evaluation, performed at the NSABP Operations Center, of the clinical circumstances and the event.

3/26/97 11.2.8 Other Toxicities

For other nonhematologic toxicities except alopecia, there will be dose reduction to the first dose reduction level in the event of grade 3 or grade 4 toxicity. If grade 3 or 4 toxicity occurs despite the first dose reduction, all remaining cycles will be given with additional dose reductions according to the proposed schema (see Section 11.2). Toxicity should return to grade 1 or less before retreatment. No more than 2 weeks will be allowed for this recovery. If the toxicity has not resolved after 2 weeks, further Taxol therapy will be discontinued. The NSABP Clinical Coordinating Section should be notified (see Section 15.4).

11.3 Dose Modification of Tamoxifen

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

11.3.1 Hepatic Toxicity

Should a grade 2 or greater elevation of liver function tests (>2.5 x normal) occur at any time subsequent to the completion of the last cycle of all chemotherapy, the test will be repeated to ensure accuracy. If the

value is confirmed, tamoxifen will be discontinued for at least 4 weeks. The patientshould be evaluated carefully for other potential causes of the abnormality, including metastatic disease. The liver function tests will be repeated at monthly intervals, or more frequently, depending on the severity of the abnormality noted. When the toxicity returns to ≤ grade 1, tamoxifen therapy may be resumed. Follow-up testing will be performed one month after the patient resumes tamoxifen therapy, or sooner if indicated, to ensure that no further toxicity occurs with the rechallenge. When a grade 3 or 4 toxicity has occured and is unequivocally related to tamoxifen, the decision to rechallenge the patient with tamoxifen after a return to grade 1 range must be done only after careful deliberation regarding potential risks and benefits.

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

11.3.2 Hematologic Toxicity

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

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

3/26/97 11.3.3 Other Serious Toxicity (e.g. Deep Venous Thrombosis, Pulmonary Embolism, etc.,)

In such cases, tamoxifen therapy may be permanently discontinued only after the case has been discussed with personnel at the NSABP Clinical Coordinating Section. (See Section 15.4.)

3/26/97 11.3.4 Management of Tamoxifen-Related Toxicity

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

Hot flashes: Vitamin E, clonidine, or Bellergal is permitted for treatment of hot flashes. Other nonhormonal therapies may be used at the investigator's discretion. Megace and other hormonal therapies are not permitted.

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

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

12.0 DIAGNOSIS OF BREAST CANCER RECURRENCE OR SECOND PRIMARY CANCER

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

12.1 Local Recurrence

12.1.1 Local Recurrence of Tumor in the Ipsilateral Breast (IBTR) Following Lumpectomy

Defined as evidence of tumor (except LCIS) in the ipsilateral breast following lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. Further treatment for ipsilateral breast tumor recurrence following lumpectomy is at the discretion of the investigator.

- Acceptable: Positive biopsy or cytology

12.1.2 Local Recurrence (except IBTR)

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

- Acceptable: Positive biopsy or cytology

12.2 Regional Recurrence

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after operation. (Further treatment for regional recurrence will be at the discretion of the investigator.)

- Acceptable: Positive biopsy or cytology

12.3 Distant Recurrence

Defined as evidence of tumor in all areas, with the exception of those described in Sections 12.1 and 12.2. Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

12.3.1 Skin, Subcutaneous Tissue, and Lymph Nodes (other than local or regional)

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

12.3.2 Bone Marrow

- Acceptable: Positive cytology, aspirate, or biopsy

3/26/97 12.3.3 Lung

- Acceptable: (i) Positive cytology, aspirate, or biopsy or (ii) the presence of multiple pulmonary nodules on chest X ray that are felt to be consistent with pulmonary metastases.

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

3/26/97 12.3.4 Skeletal

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

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

12.3.5 Liver

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

  Note: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy would be mandatory.

12.3.6 Central Nervous System

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

3/26/97 12.4 Second Primary Cancer

Any second primary cancer other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or LCIS will be considered an event in the analysis of disease-free survival. The diagnosis of a second primary cancer must be confirmed histologically whenever possible. Representative slides should be submitted to the NSABP Biostatistical Center for review.

3/26/97 12.5 Postmortem Examination

Autopsy reports should be secured whenever possible and be submitted to the NSABP Biostatistical Center. A copy of the death certificate should be forwarded to the Biostatistical Center if it is readily available or if it contains important cause-of-death information not documented elsewhere.

13.0 NONPROTOCOL THERAPY

Patients may **not** receive any cancer therapy other than that specified in the protocol until time of development of first breast cancer recurrence or second primary cancer (see Section 4.2.2).

3/26/97

13.1 Sex Hormonal Therapy

Patients may not receive any sex hormonal therapy such as birth-control pills, replacement therapy, etc., before the first event (breast cancer recurrence, or second primary cancer).

13.2 Radiation Therapy

Patients may not receive any radiation therapy other than that specified in the protocol until time of first event. (See Appendix D for details on radiation therapy.)

14.0 DRUG INFORMATION

3/26/97 The following subsections describe the individual drugs used in this trial, list their potential side effects, and outline general recommendations concerning their preparation and delivery. The FDA-approved package insert should be reviewed for specific directions regarding preparation and a more complete discussion of adverse reaction information. As with any research study, there is also the potential that unforeseeable or unexpected risks, including death, may occur.

3/26/97 14.1 Adriamycin (Generic Name: doxorubicin) [NSC#123127]

Adriamycin is an antineoplastic antibiotic. Although it has anti-infective properties, its cytoxicity precludes its use as an anti-infective agent. The drug also has immunosuppressive activity. It is available in parenteral form for injection. Please refer to the current FDA-approved package insert provided with the medication, or the *Physicians' Desk Reference*, for instructions regarding preparation, handling, dosing, and storage.

14.1.1 Clinical Safety and Adverse Effects

Toxic side effects include bone marrow suppression (thrombocytopenia, anemia, and particularly leukopenia), hair loss, nausea, vomiting, diarrhea, anorexia, mucositis, changes in nails, and anaphylactic reactions. Discoloration of urine can occur. Cardiotoxicity, the major dose-limiting toxicity, usually occurs with total cumulative dose ≥ 550 mg/m^2. In addition, acute life-threatening arrhythmias have been reported to occur during or within a few hours after drug administration. Acute or subacute left ventricular dysfunction or a pericarditis/myocarditis syndrome has been reported. The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported rarely in patients concurrently treated with Adriamycin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 years) latency period. Severe local tissue necrosis will occur if there is extravasation during administration. Adriamycin should not be taken during pregnancy because it could potentially harm a fetus.

14.1.2 Procurement

Adriamycin is available commercially and should be obtained from such sources.

3/26/97 14.2 Cyclophosphamide [NSC #26271]

Cyclophosphamide is a nitrogen mustard-derivative, polyfunctional alkylating agent that interferes with DNA replication and transcription of RNA, and ultimately results in the disruption of nucleic acid function. It is available in both oral form and parenteral form for injection. In this trial, cyclophosphamide will be administered by intravenous injection. Please refer to the current FDA-approved package insert provided with the medication, or the *Physicians' Desk Reference,* for instructions regarding preparation, handling, dosing, and storage.

14.2.1 Clinical Safety and Adverse Effects

Toxic side effects include bone marrow suppression (thrombocytopenia, anemia, and particularly leukopenia), hair loss, nausea, vomiting, diarrhea, anorexia, mucositis, hemorrhagic cystitis, second cancers of the urinary bladder, leukemia, hepatotoxicity, irregularities in/cessation of menses, skin rash, skin discoloration, changes in nails, SIADH-like syndrome with impaired water excretion and hyponatremia, headache, dizziness, and anaphylactic reactions. Pulmonary fibrosis, cardiotoxicity, acute myopericarditis, and pneumonitis have been associated with cyclophosphamide therapy, usually when given at higher doses than those to be used in this study. Cyclophosphamide should not be taken during pregnancy because it could potentially harm a fetus.

14.2.2 Procurement

Cyclophosphamide is available commercially and should be obtained from such sources.

3/26/97 14.3 Taxol (Generic Name: paclitaxel) [NSC#673089]

Taxol for Injection Concentrate is a clear, colorless-to-slightly-yellow, viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Taxol is available in 30 mg (5 ml) single-dose vials. Each ml of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor® EL (polyoxyethylated castor oil), and 49.7% (v/v) dehydrated alcohol USP. Paclitaxel is a white-to-off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at about 216-217°C.

Taxol is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling it. The use of gloves is recommended. If Taxol solution comes in contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If Taxol comes in contact with mucous membranes, these should be flushed thoroughly with water.

Taxol should be stored between 2°-25°C (36°-77°F). Based on stability data for Taxol made from either the 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% per year.

Samples stored for up to 3 months at 60°C (140°F) 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. Taxol will be labeled with an expiration date (final use date).

Taxol for Injection Concentrate must be diluted prior to infusion. Taxol should be diluted in 0.9% sodium chloride injection, USP; 5% dextrose injection, USP; 5% dextrose and 0.9% sodium chloride injection, USP; or 5% dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/ml. The solutions are physically and chemically stable for up to 24 hours at ambient temperature (approximately 25°C) and lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The 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 Taxol. Therefore, in-line filtration is necessary for administration of Taxol solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g., IVEX-HP or IVEX-II, Abbott) into the i.v. 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.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted Taxol solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and be administered through polyethylene-lined administration sets. Use of filter devices such as IVEX-2 filters, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

14.3.1 Clinical Safety and Adverse Effects

Taxol as a single agent has been given in doses of 135-250 mg/m^2 and as a 3-hour or 24-hour infusion. The main toxicities include hematologic toxicity, neurologic toxicity, cardiac toxicity, and hypersensitivity reactions.

Hematologic Toxicity: Neutropenia is the DLT but is not cumulative and rarely delays therapy.[38] With G-CSF, 250 mg/m^2 of Taxol can be administered repetitively. Neutropenia usually occurs by day 8, and the granulocyte nadirs occur on days 8-11, with recovery by days 15-21.

Severe neutropenia is of short duration, with only 7% of the patients having a neutrophil count below 500/mm^3 for 7 days or more.[39] The principal predisposing factor for neutropenia is the extent of prior myelotoxic therapy. Myelosuppression seems to be more frequent and more severe for patients who receive prior radiotherapy.[39] Thrombocytopenia and anemia are rarely significant problems, even in heavily pretreated patients.[38] Only 5% of patients treated at the recommended dose (135 mg/m^2) had a platelet nadir count below 50,000/mm^3, which occurred around day 8 or 9.[39] Although mild anemia (<11 g/dL) is frequent, severe anemia (8 g/dL) is much less common. The incidence and severity of anemia seem to increase with prolonged exposure to Taxol.[39]

Neurologic Toxicity: Peripheral neuropathy becomes a DLT with G-CSF and higher doses of Taxol. Peripheral neuropathy has been observed in 62% of all patients treated with Taxol, with mild paresthesia occurring most frequently.[39] Severe neurologic symptoms are infrequent (4%). The neuropathy is of the stocking-and-glove distribution and is characterized by sensory symptoms such as numbness, paresthesias, and burning.[40] Symptoms may begin as early as 24-72 hours after administration; they often occur after multiple cycles of conventional doses. Involvement of both motor and autonomic nerves may also occur, especially at high doses and with preexisting neuropathies (e.g., ethanol abuse, diabetes).[38] Although symptomatic motor and autonomic neurotoxicity are rare with conventional single-agent doses, subclinical evidence of motor neurotoxicity is frequently noted on objective electrophysiological testing. Examination often reveals distal sensory loss to both large (proprioception, vibration) and small (temperature, pinprick) fiber modalities.[38] Neurotoxicity is rare at doses less than 170 mg/m^2; at higher doses ($\geq$250 mg/m^2), it is dose limiting. Neurotoxicity is an even more critical effect when Taxol is used in combination with cisplatin.[41] Peripheral neuropathy is rarely (2%) the cause of Taxol discontinuation.[39] Sensory symptoms usually improve or resolve within several months of Taxol discontinuation.

Cardiac Toxicity: Cardiac abnormalities associated with Taxol therapy first became apparent during routine cardiac monitoring because of concerns regarding anaphylactoid reactions.[42] Asymptomatic hypotension and bradycardia, which occur in 25% and 12% of patients, respectively, are generally without clinical significance in those with no potential cardiac risk factors and, thus, are not an indication to discontinue Taxol. The incidence of severe cardiac toxicity is low (1.5%)[39] in patients with no potential cardiac risk factors; there is no

evidence of cumulative cardiac toxicity. Although Taxol therapy is associated with cardiac conduction abnormalities, the precise mechanism of its effect is unknown. Bradyarrhythmias such as Wenckebach's disease and third-degree block have been observed. Fatal myocardial infarction and atypical chest pains have also been reported. Asymptomatic left-bundle-branch block and ventricular tachycardia have been observed in patients receiving cisplatin and Taxol in combination but have not been seen in those receiving Taxol as a single agent.[43]

Hypersensitivity Reactions: Hypersensitivity reactions, which were severe and frequent during the early trials,[44] are now infrequent with adequate premedication (dexamethasone-cimetidine-diphenhydramine) and longer continuous infusions.[43-45] Hypersensitivity reactions have been reported in 19% of all cycles of Taxol therapy.[39] These generally occur within the first 10 minutes of infusion and may consist of flushing, rash, dyspnea, angioedema, hypotension, and chest pain. Since the introduction of premedication and the 24-hour continuous infusion regimens, severe hypersensitivity reactions requiring therapeutic intervention and/or discontinuation of Taxol infusion have occurred infrequently (2%).[39] Even with the 3-hour continuous infusion regimen and adequate premedication, hypersensitivity reactions are infrequent and, in most cases, not severe.[46]

Other Toxicity: Myalgias, arthralgias, and fatigue become more frequent with moderate and high doses (>170 mg/m^2). These reactions usually begin 2-3 days after treatment and resolve in 5 days. It has been suggested that the myalgia may be related to toxic effects on skeletal muscles.[41] Elevations in muscle enzymes have not been documented. Alopecia is complete and occurs in most patients. Mucositis (stomatitis, pharyngitis, typhlitis), nausea, vomiting, and diarrhea may occur; mucositis is more frequent with higher doses and longer infusions. Instances of ischemia and infarcted colon have been reported. Changes in liver function have been demonstrated by patients while on therapy. Rare cases of hepatic necrosis and hepatic encephalopathy have been reported. Other toxicities include pruritus, pancreatitis, sensory changes (taste), visual changes, seizures, mood changes, and myopathy. Extravasation with Taxol may result in erythema, induration, tenderness, and, rarely, ulceration.

14.3.2 Procurement

Taxol will be supplied free-of-charge to patients from Bristol-Myers Squibb through the Drug Management Authorization Section (DMAS) of the NCI (NSC #673089). Taxol will be shipped using priority ("First class") mail at 'room temperature' with a 2-3 day delivery time. Institutions requiring expedited delivery must provide an appropriate billing account number.

Drug Ordering: Once the patient's eligibility is established and the individual has been registered, a supply of drug may be ordered. Drug may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Pharmaceutical Management Branch, CTEP, DCTDC, NCI, 9000 Rockville Pike, EPN Room 707, Bethesda, MD 20892, or by sending a FAX to (301) 480-4612. For questions call (301) 496-5725.

Drug Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain careful record of the inventory and disposition of all drugs received from DCT, using the NCI Drug Accountability Record Form. (Refer to Appendix A of this protocol and the NCI's Investigator's Handbook for procedures for Drug Accountability and Storage.)

3/26/97 14.4 Tamoxifen [NSC #180973]

Tamoxifen is a nonsteroidal antiestrogen. The precise mechanism(s) of action of the drug is not known. Tamoxifen is supplied as 10 mg and 20 mg tablets, which should be stored at room temperature and protected from heat and light. Please refer to the current FDA-approved package insert provided with the medication, or the *Physicians' Desk Reference,* for instructions regarding preparation, handling, dosing, and storage.

3/26/97 14.4.1 Clinical Safety and Adverse Effects

Adverse effects include hot flashes, nausea (vomiting is rare), vaginal bleeding, discharge or dryness, menstrual irregularities, and skin rash. Other rarely seen adverse effects are hypercalcemia, peripheral edema, leukopenia and transient thrombocytopenia, loss of appetite, distaste for food, pruritus vulvae, depression, dizziness, headache, leg cramps, lightheadedness, confusion, and fatigue. There is a small risk of ovarian cysts occurring. Hair thinning and/or hair loss has also been reported in women taking tamoxifen. Liver cancer and other liver toxicities have been reported in women taking tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to cause such cancer in humans. Tamoxifen can sometimes cause other liver toxicities in women, such as fatty liver, cholestasis, hepatitis and hepatic necrosis, which rarely can be severe or life-threatening. A few of these serious cases have resulted in death, but whether tamoxifen was the cause of these problems remains uncertain. Women taking tamoxifen may be at a slightly increased risk for developing cataracts. Eye surgery may be required to remove the cataract and improve vision. Women who have a cataract before begining to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients. Tumor flare can appear in patients being treated for metastatic disease. Tamoxifen should not be taken during pregnancy due to potential hazard to the fetus. This includes miscarriage, birth defects, or long-term effects on sexual development (which could be similar to the long-term effects caused by diethylstilbestrol [DES]). Women whose mothers took DES during pregnancy have an increased risk of developing cancer of the vagina or cervix, and may have trouble bearing children. The relevance of findings from animal studies to women who may accidentally take tamoxifen during pregnancy is unknown, but it is essential that effective contraceptive methods be used while taking tamoxifen therapy, and for 2 months after completing or discontinuing therapy. Tamoxifen may cause changes in the lining of the uterus which could potentially lead to uterine cancer. An early sign of abnormal changes in the uterus may be abnormal vaginal bleeding or pelvic discomfort. An increased risk of uterine cancer has been reported with the use of tamoxifen; however, the level of risk is still uncertain. After an average of 8 years of follow-up, the annual risk observed in a large-scale trial of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women (approximately three times greater than that of a similar group of women in the general population.) Uterine cancer is potentially life-threatening, and some breast cancer patients who developed uterine cancer while taking tamoxifen have subsequently died from that disease. Most of the uterine cancers that have occurred have been diagnosed at an early stage when treatment is highly effective. Tamoxifen may cause changes in the lining of the uterus, such as polyps and hyperplasia, and endometriosis. Data from the NSABP B-14 study show no increase in other (nonuterine) cancers among patients receiving tamoxifen. However, other data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. Whether an increased risk for other (nonuterine) cancers is associated with tamoxifen is still uncertain and will continue to be evaluated. Women on tamoxifen have an increased risk for developing phlebitis and blood clots. Some studies, but not all, have shown that tamoxifen causes about a 1% increase in the incidence of thrombotic events. These include superficial phlebitis, deep vein thrombosis, and pulmonary embolism. Rarely, death has occurred from such events in these studies.

3/26/97 [As a result of information provided as of March 1997, the following ophthalmic toxicity information has been provided as an update to the NSABP B-14 trial at the request of the National Cancer Institute. Two additional publications which provide updated results from the NSABP B-14 trial can be found in the following: 1) Endometrial Cancer In Tamoxifen-Treated Breast Cancer Patients: Findings from NSABP B-14 (*Journal of the National Cancer Institute*, 86:527-537, 1994) and 2) Five Versus More Than Five Years of Tamoxifen Therapy for Breast Cancer Patients With Negative Lymph Nodes and Estrogen Receptor-Positive Tumors (*Journal of the National Cancer Institute*, 88: 1529-1540, 1996).]

In 1993, the NSABP began Protocol P-1E, with the aim of estimating the prevalence of adverse ocular changes associated with the long-term use of tamoxifen. The P-1E study was a cross-sectional, single-masked evaluation of women from NSABP Protocol B-14 who had been entered from eight selected NSABP centers. A total of 303 women participated and comprised three groups: 1) those who had never taken tamoxifen (n=85 TAM-NONE), 2) those who had taken tamoxifen for an average of 4.8 years and were off tamoxifen for an average of 2.7 years (n=140 TAM ON-OFF), and 3) those who had taken tamoxifen for an average of 7.8 years (n=78 TAM-CONT).

Adverse changes in visual function were measured by subjective and psychophysical tests; adverse changes in the cornea, lens, retina, and optic nerve were determined by ophthalmic examination. The results demonstrated no vision-threatening ocular toxicity among tamoxifen-treated participants. When compared with nontreated participants, tamoxifen-treated women had no differences in their activities of daily vision, visual acuity, or other tests of visual function except for color screening. No abnormalities of either the cornea or the optic nerve were identified.

There was a trend toward an increasing frequency of intraretinal crystals reported with tamoxifen use; reports were more frequent in those women who had taken tamoxifen for the longest period of time (TAM-NONE, 1.2%; TAM ON-OFF, 2.8%; and TAM-CONT, 6.5%). However, the occurrence of intraretinal crystals was not associated with either macular edema or with loss of visual acuity.

The overall rate of occurrence of cataracts was similar for the placebo and tamoxifen-treated groups (40% vs. 43%, respectively). In the TAM-NONE group, 2.5% of the women had posterior subcapsular opacities, as compared with 9.2% in the TAM ON-OFF group and 9.3% in the TAM-CONT group; this was a statistically significant difference. The other lens opacities, i.e., cortical and nuclear sclerosis, were more frequent than were posterior subcapsular opacities in all groups, but no statistically significant differences were noted.

The findings from P-1E were presented to the members of the BCPT Data Monitoring Committee, who felt that the data suggested a potential association between tamoxifen use and posterior subcapsular opacities. With the approval of the committee, the BCPT cataract data were evaluated in October 1996; only a 0.5% difference between the tamoxifen and placebo groups was found at that time. Women in the tamoxifen group who reported having a cataract before entering the BCPT had an increased likelihood of undergoing cataract surgery.

As a result of these findings, women who are currently taking, or who previously took, tamoxifen or placebo in an NSABP study received updated information with regard to potential eye toxicity. Consent forms for accruing trials involving tamoxifen therapy were modified, but no changes were made in the follow-up care of patients taking tamoxifen in NSABP studies. Specifically, an eye examination is still not required as part of the routine follow-up care. However, women are encouraged to follow the normal guidelines for eye care established by the American Academy of Ophthalmology, which includes a complete eye examination at least every 2 years for people 40 years of age or older. Women with cataracts or other eye problems should be monitored according to their doctor's recommendation, and those taking tamoxifen or placebo should report any changes in their vision.

14.4.2. Procurement

Tamoxifen is available commercially and should be obtained from such sources.

15.0 REPORTING OF TOXICITY

3/26/97 ### 15.1 Investigator's Obligations

Complete and timely reporting of adverse drug reactions (ADRs) is required to ensure the safety of patients enrolled in current studies, as well as to those who will enroll in future studies using similar agents. This reporting also enables the NCI and/or FDA to notify the scientific community about new information concerning investigational agents.

As indicated in FDA Form 1572 (Statement of Investigator), by signing the form, an investigator accepts the responsibility for conducting investigational agent trials; this includes reporting ADRs to the appropriate agencies.

ADRs that need to be reported to the NCI are defined as: 1) previously unknown toxicities (not included in the list of known toxicities presented in the scientific literature, protocol, or consent form), and 2) life-threatening or fatal toxicities (regardless of whether or not previously unknown). (See Table F1 in Appendix F.)

Investigators should submit such reports even if there is only a suspicion of drug effect. Investigators should be prepared to provide additional information if requested by the governmental agency.

Any investigator who is uncertain about whether a particular adverse reaction needs to be reported should call the NCI Investigational Drug Branch at (301) 230-2330. A recorder will be available after normal working hours.

Any toxicity, regardless of grade, or whether known or unknown, must ultimately be reported to the NSABP Biostatistical Center on an NSABP ADR form. The submission of the NSABP ADR form should follow the schedule outlined in Table 8.

3/26/97 ### 15.2 Report Content

ADR reporting should be based on the NCI Common Toxicity Criteria (see Appendix F).

Reports and supporting documentation sent to the Investigational Drug Branch of the NCI should have patient names and identifiers such as social security number, address, etc., removed. In addition, all phone calls and/or written reports should reference the Division of Cancer Treatment, Diagnosis, and Centers (DCTDC) protocol number, which is the same as the NSABP protocol number. The data required on the form should be printed, typed, or written legibly.

15.3 Reporting Requirements (Please refer to Table F1 in Appendix F.)

15.3.1 Events in this trial must be reported to three groups: 1) the Investigational Drug Branch of the NCI, 2) the NSABP, and 3) the local IRB.

3/26/97 15.3.2 This trial involves administration of both commercially available and investigational drugs; therefore, in reporting to the NCI Investigational Drug Branch, use Form No. 391R (See Appendix F). Additionally, the NSABP ADR Form must be used for submissions to the NSABP Biostatistical Center (See Appendix F).

Addresses used for toxicity reporting are provided below:

[All ADR correspondence for Protocol B-28 must include the identifier DCTDC# NSABP B-28.]

Investigational Drug Branch
Post Office Box 30012
Bethesda, MD 20824
Phone: (301) 230-2330
Fax: (301) 230-0159

NSABP Biostatistical Center
Suite 600
McKee Place
Pittsburgh, PA 15213
Phone: (412) 624-2666
Fax: (412) 624-1082

3/26/97 15.4 Toxicity Requiring Dose Modification or Delay

For information regarding dose modifications or delays due to toxicity (see Section 11.0), contact the NSABP Clinical Coordinating Section at 1-800-477-7227.

15.5 NCI/CTEP Secondary AML/MDS Reporting

Please refer to Appendix F for instructions and forms required for the reporting of AML/MDS events.

3/26/97 15.6 Pregnancy Occurring While Patient is on Protocol Therapy

Should a patient become pregnant while she is receiving protocol therapy, the NSABP Clinical Coordinating Section should be notified immediately.

16.0 PATIENT ENTRY PROCEDURES

3/26/97 ### 16.1 Patient Consent Form

Before the patient is randomized, the consent form (see Appendix H), including all updated information known at the time of consent, must be signed and dated by: 1) the patient, 2) a witness to the patient's signature, and 3) the investigator. [Please note that (2) and (3) cannot be the same person.] ***In addition, prior to randomization a copy of the signed, witnessed, dated consent form must be faxed to the NSABP Biostatistical Center. Please note that all pages of the consent form are to be initialed by the patient.*** All institutional and government regulations concerning informed consent and peer judgment must be fulfilled (see Appendix A).

Those patients who provided informed consent before the creation of any consent form addendum are to be presented with the additional information covered in the consent form addendum at the time of their next follow-up visit. Informed consent must be obtained in order for patients to continue their participation in the trial.

3/26/97 Deletion of text resulted in renumbering of section.

3/26/97 ### 16.2 Randomization

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

- A completed Form A (Entry and Eligibility Form)
- A properly signed and dated consent form

In addition to the above materials, the NSABP Biostatistical Center will verify that you have current IRB approval of this study. Randomization will not take place if the IRB approval is not current for the instituion with IRB oversight responsibility.

At least 1 hour must be allowed after receipt of the faxed material to assign the patient's treatment. NSABP Biostatistical Center personnel will notify the institution about the assigned treatment and dose of drugs. **The material must be faxed before 4:00 p.m. EST.**

16.3 Patient Study Number

A nine-digit identification number will be assigned to the patient at the time of randomization. The first two digits of this number refer to the protocol identification number, the next four are assigned sequentially, and the last three refer to the institution randomizing the patient.

17.0 RECORDS TO BE KEPT (See Table 8)

TABLE 8
NSABP PROTOCOL B-28
REQUIRED FORMS AND MATERIALS

FORM/MATERIAL	DESCRIPTION	SUBMISSION
PRE-ENTRY		
Consent Form	Signed/dated informed consent	Prior to randomization
Form A	Patient entry and eligibility	Prior to randomization
EP Lab Report	Lab report for ERt and for PR (primary tumor only)	Prior to randomization
ENTRY		
Form B-6	History and physical exam	Within 30 days of randomization
Form OR-1	Operative report form	Within 30 days of randomization
Dictated Operative Report	Typed operative report	Within 30 days of randomization
Form D-1	Pathology report form	Within 30 days of randomization
Dictated Pathology Report	Typed pathology report	Within 30 days of randomization
Pathology Materials	Pathology block and slides	Within 30 days of randomization
	Form BLR (if block is unavailable)	Within 18 months of randomization
RADIATION THERAPY (Lumpectomy patients only)		
Form E-1	Radiation therapy report	Submit all radiation therapy materials, as one packet, at the completion of radiation therapy.
Treatment Sheets	Treatment prescription and daily record sheet	
Isodose Breast Contour	Isodose distribution for treatment plan & a breast contour	
Portal Films	Copies of field verification films (portal film)	
Dosimetry	Copies of dosimetry calculations	
Treatment Position Photographs	Photographs of patient in treatment position with field markings	

(continued)

TABLE 8
NSABP PROTOCOL B-28
REQUIRED FORMS AND MATERIALS (cont.)

FORM/MATERIAL	DESCRIPTION	SUBMISSION
TREATMENT		
Form T28-A	Treatment form for AC (Cycles 1-4)	At the end of each 3-week AC cycle
Form T28-B	Treatment form for Taxol (Cycles 5-8)	At the end of each 3-week Taxol cycle
Form ADR	Toxicity/adverse drug reaction report form	• At the end of each chemotherapy cycle; • with Form F while on tamoxifen (until first event); • 3 months after termination of all protocol therapy; • immediately in event of severe or unusual toxicity.
Form OFF	OFF protocol therapy	When indicated. (See instructions on Form OFF.)
FOLLOW-UP		
Form F	Follow-up form with attached documentation when indicated	Every 6 months for first 5 years; every 12 months thereafter.
Form GYN	Gynecologic follow-up form	Every 6 months for first 5 years; every 12 months thereafter.
ALL NSABP REPORT FORMS MUST BE SENT TO: **NSABP Biostatistical Center** **Suite 600, 230 McKee Place** **Pittsburgh, PA 15213** **Fax no.: (412) 624-1082** **Phone no.: (412) 624-2666**		

18.0 STATISTICAL CONSIDERATIONS

18.1 Randomization and Treatment Assignments

Assignment of treatments to patients will be balanced with respect to number of positive nodes (1-3, 4-9, 10+), tamoxifen assignment (yes, no), type of surgery (mastectomy, lumpectomy), and institution, using a biased-coin minimization algorithm.[47]

18.2 Endpoints

The primary endpoints for analysis are survival (S) and disease-free survival (DFS). The S endpoint is defined as death from any cause. DFS endpoints are local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, second primary cancer other than squamous or basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, and death from any cause other than cancer. See Section 4.0 for details.

18.3 Statistical Analyses

Differences in S and DFS between the Taxol and control arms will be assessed by stratified log-rank tests, controlling for number of positive nodes, tamoxifen administration, and type of surgery. Two-sided tests will be used with control of Type 1 error rate at the .05 level.

As a diagnostic check, treatment comparisons using Cox modeling will control for additional prognostic variables (age, clinical tumor size, and estrogen receptor status) by including terms in the models corresponding to these prognostic variables. This will be done even though the method of balanced randomization used in the assignment of treatments (Section 18.1) makes it highly unlikely that prognostic factors could confound the treatment comparison.

Flow cytometry analyses will be available for a subset of tumor specimens obtained in this trial. Within this subset, treatment comparisons will be carried out which further control for S-phase and nuclear grade by means of Cox proportional hazards modeling. The demographics of those patients for whom flow data are available will be compared to those of the general patient population in order to determine comparability.

The sample size specified below may be inadequate to support detailed subgroup analyses. Such subgroup analyses will be carried out only in the event that preliminary tests of treatment-by-group interactions are strongly ($\alpha \leq .01$) significant, based on the addition of appropriate cross-product terms to Cox models. It is possible that a treatment-by-method of surgery interaction could result from the asymmetry of breast irradiation scheduling for patients receiving lumpectomy, since patients in the AC + Taxol arm will have delayed radiation relative to those in the AC-only arm. This could conceivably result in a higher loco-regional relapse rate, resulting in an interaction in

DFS. Surgical method has been included as a stratification variable to insure balanced rates within either treatment arm, and to optimize our ability to detect such an interaction.

18.4 Estimates of Annual Accrual

Patients to be enrolled in this trial will be drawn from the pool of patients who would have been eligible for the node-positive trial, B-25, which closed on February 28, 1994. In 1993, Protocol B-25 had an average monthly accrual of 118 patients. We, therefore, project an average monthly accrual of 118 ($\approx$ 1400 patients/year) to this trial.

18.5 Baseline Hazard Rates

In patients who received standard AC therapy in NSABP node-positive trials, the annual death rates are: B-15 (AC without tamoxifen in tamoxifen-nonresponsive patients), 0.07; B-16 (AC + tamoxifen in tamoxifen-responsive patients), 0.04; and B-22 (AC + tamoxifen if age $\geq$50), 0.04. The annual DFS failure rates on these trials were: B-15, 0.11; B-16, 0.07; and B-22, 0.10. Based on this information, it is reasonable to use 0.045 and 0.095 as projected annual hazard rates for death and DFS failure, respectively, in the control arm of the current trial.

10/30/97 18.6 Original Sample Size Estimates**

We require that the power for detecting a "material" survival difference using a two-sided test be $\geq$0.80 and that the Type 1 error rate be $\leq$0.05. We consider a 25% decrease in death rate to be material. Furthermore, it is desired that the definitive survival analysis be completed within roughly 5 years of the date on which the trial is opened.

Based on these considerations, a total accrual of 2,450** patients will be required. Accrual is projected to require 21 months. Definitive analysis will be completed after 380** deaths have occurred, at which time a two-sided test at the .05 level will have power equal to 0.80 in detecting a 25% reduction in death rate. Based upon the projected rates of accrual and death, this analysis will take place approximately at year 5.25 (i.e., after 3.5 years of additional follow-up).

Since DFS failure rate is projected to equal 0.095/year in the control arm, tests of differences in DFS will be more powerful than survival comparisons. Specifically, a test of DFS at year 5.25 will have a power of 80% to detect a treatment reduction in DFS failure rate of as little as 19%.

The waiting time to definitive analysis (380 deaths)** is rather robust to mispecification of the accrual rate. Even in the unlikely case that accrual proceeds only half as quickly as anticipated, and the accrual goal is not reached until year 3.5, definitive analysis would still be expected by year 6.0, assuming that death rates remain as predicted. However, if it is established that death rates are considerably less than anticipated, NSABP may elect to amend the protocol in favor of an earlier definitive analysis whose primary endpoint is DFS.

**Modified 10/30/97 per Section 18.8

10/30/97 18.7 Original Interim Analyses Scheduled**

Four interim analyses are scheduled prior to the definitive analysis, after 40, 152, 228 and 304** deaths have been reported. Using the O'Brien-Harrington-Fleming[48] boundary at the overall 0.05 level, these five analyses will be carried out at nominal levels of significance of 0.0024, 0.0030, 0.0035, 0.0043, and 0.0458**. This allocation of Type 1 error corresponds to permitting a 0.01 probability of early declaration of significance under the null hypothesis. Based on projected rates of accrual and death, these analyses will occur approximately at years 1.25, 2.5, 3.5 and 4.25.

Only the first interim analysis is liable to occur during the accrual period of the trial. Termination of accrual will be considered only in light of a significant S difference at this time, and not for a significant DFS difference alone.

10/30/97 18.8 Sample Size Adjustment for Compliance

As initially approved, the B-28 protocol called for definitive analysis after 380 deaths are reported on both arms combined. This specification followed from the requirement that the test of the primary hypothesis (survival difference) have at least 80% power against the alternative hypothesis that the AC+Taxol arm has a 25% reduction in mortality rate relative to the AC-only arm. However, as of October 20, 1997, compliance in cycles 5-8 (Taxol administration) has been somewhat lower than expected. Specifically, it is estimated that, while 98.5% of patients on the AC+Taxol arm complete all four AC cycles (similar to the compliance seen in the AC-only arm), only 91.6% complete one or more Taxol courses, 85.2% complete two or more, 81.7% complete three or more, and only 78.5% complete all four Taxol courses. This lack of compliance will attenuate any treatment effect that may exist, leading to a decrease in power.

Even if the AC+Taxol regimen were an established treatment regimen (i.e., had already been proven to be superior to the current AC standard regimen), it is unrealistic to suppose that compliance would be perfect. As a crude estimate of what compliance might be expected under this hypothetical scenario, one might suppose that withdrawals that have been intiated by the physician would still be considered to be necessary, but that those which were patient-initiated would generally not occur if the treatment were well established. If it is assumed that these withdrawals could be prevented, then the proportion of patients completing cycles 5, 6, 7, and 8 may be estimated from current compliance data to be 97.8%, 94.0%, 91.8%, and 90.1%, respectively, a significant improvement on the actual compliance to date in B-28.

Under the simplifying assumption that the reduction in mortality rate is linearly related to the number of cycles of Taxol received, and further assuming that the regimen with idealized compliance (as estimated in the previous paragraph) results in a 25% reduction in mortality rate relative to the administration of AC alone, it can be computed that the AC+Taxol regimen, with compliance similar to that seen in Protocol B-28 to date, will result in only a 22.6% reduction in mortality on an intent-to-treat basis. That is, the relatively low compliance seen in the protocol will result in a 2.4% attenuation in treatment effect.

**Modified 10/30/97 per Section 18.8

To preserve the intended power characteristics of the study design, the sample size will be increased to provide 80% power against the alternative hypothesis of a 22.6% decrease in mortality rate. This requires 490 deaths prior to definitive analysis. To achieve this number of deaths within 3.5 years of study closure, 600 additional patients will be accrued. At the current rate of accrual, this will require 5-6 additional months. The sample size requirements, timing of the definitive analysis, and interim analysis schedule originally specified as in paragraphs 18.6 and 18.7 are, therefore, modified as follows:

1) the total accrual is increased from 2450 patients to 3050 patients;

2) definitive analysis will occur after 490 deaths are observed, rather than 380 as originally stipulated; and

3) interim analyses will take place after 50, 130, 250, 370, and 490 deaths, rather than 40, 152, 228, 304, and 380 deaths, as originally stipulated. These analyses will be carried out at nominal levels of significance of 0.0025, 0.0028, 0.0031, 0.0037, and 0.0452. These boundaries are based on the O'Brien-Harrington-Fleming boundary at the 0.05 level (adjusted for nonconstant time intervals by the method of Armitage), and correspond to spending .0025 alpha at each of the first four looks.

19.0 PUBLICATION INFORMATION

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning Taxol, Bristol-Myers Squibb shall be provided thirty (30) days to review the proposed publication or disclosure to ensure that confidential and proprietary data are protected. The investigators will send any proposed publication or disclosure to the Protocol and Information Office of CTEP at the following address:

Protocol and Information Office
Cancer Therapy and Evaluation Program, DCT, NCI
Executive Plaza North, Room 730
Bethesda, MD 20892

Please note that the NCI Division of Cancer Treatment (DCT) investigators maintain the full right to the timely publication and presentation of the data from DCT-sponsored studies conducted with Taxol.

Following study completion, the NSABP agrees to make the raw data available exclusively to NCI and Bristol-Myers Squibb for use in obtaining regulatory approval for the commercial marketing of Taxol. All contacts with the company will be arranged through CTEP staff.

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The following principles must be observed to comply with Food and Drug Administration (FDA) 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). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations. In seeking informed consent, the following information will be provided in a language understandable to the subject.

1. Basic Elements of Informed Consent

   The following are the basic elements of informed consent which should be provided to each subject:

   a. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

   b. A description of any reasonably foreseeable risks or discomforts to the subject.

   c. A description of any benefits to the subject or to others which may reasonably be expected from the research.

   d. A disclosure of appropriate alternative procedures or cycles of treatment, if any, that might be advantageous to the subject.

   e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.

   f. For research involving more than minimal risk, an explanation regarding compensation and the availability of medical treatments in the event of injury, what these treatments consist of, or where further information may be obtained.

   g. An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury to the subject.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

2. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information will also be provided to each subject:

a. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject (or to the embryo or fetus, if the subject is, or may become, pregnant).

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

f. The approximate number of subjects involved in the study.

A subject (or the subject's legally authorized representative) must give his/her written consent to participate in the study. This consent must be witnessed and dated and retained by the investigator as part of the study records.

If Experimental Subject's Bill of Rights is applicable in the state, this form must also be prepared and signed by each subject and retained as part of the required study records.

A copy of the proposed consent form must be submitted together with the protocol to the Institutional Review Board (IRB) for approval. Each subject's signed informed consent form must be kept on file by the investigator for FDA inspection at any time.

3. Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 56).

The protocol and informed consent form for this study must be approved in writing by the appropriate IRB. Prior to study implementation, a consent form which has been approved by the National Cancer Institute (NCI) will be provided to each clinical center as a guideline for preparation of consent forms for individual IRB approval, which must be obtained for each participating clinical center to take part in the trial. Local IRB review of this protocol and consent form must adhere to the policy guidelines set forth by The Office for Protection from Research Risks (OPRR) in their directive of November 9, 1992. These procedures complement the informed consent requirements of Department of Health and Human Services (DHHS) regulations as follows:

- The OPRR now requires that each local IRB receive a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document.

- Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

- The justification for and approval of such deletions or modifications must be reflected in the IRB minutes. For trials sponsored by the NCI, investigators must forward copies of such IRB-approved changes, with their justifications, to the appropriate cooperative group headquarters. [Lin, MH and Miller, JG. NIH-OPRR letter to institutional officials and IRB chairpersons, 9 November, 1992.]

A memorandum directed to local IRBs detailing these responsibilities has been provided with the consent form as part of this protocol.

The letter of approval from the Board must include the statement that "The Institutional Review Board is in compliance with the requirements in Part 56, Subchapter D, Part 312 of the 21 Code of Federal Regulations published January 27, 1981." Providing the assurance number of the named institution would also serve to fulfill this requirement. If the IRB uses an approval form which does not contain this or a similar statement, the investigator should request from the chairperson of the IRB a separate letter or memo which does include this statement.

3/26/97 Significant changes to the protocol, as well as a change of principal investigator, must also be approved by the Board and documentation of this approval provided to the NSABP Regulatory Compliance Coordinator. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the IRB at least yearly, as well as notification of completion of the study and a final report within three months of study completion or termination. The investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

4. Drug Accountability

An accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained for each drug supplied for a study.

The ledger will be maintained routinely for all studies, regardless of study design, and will identify for each shipment the subject number (as applicable) and the quantity of drugs contained in the shipment. The ledger will consist of Drug Accountability Records Forms supplied by the NCI. One form will be kept for each investigational drug used on each research protocol. If a protocol contains more than one investigational drug, a separate Accountability Form should be used. A separate Drug Accountability Form should also be maintained for each different strength or dosage form of the particular drug being used.

The Drug Accountability Form will be used at each location at which the drug is stored for patient administration, i.e., main pharmacy, satellite pharmacy, physician's office or other dispensing areas. The form is also designed to accommodate both dispensing accountability and any other types of drug transactions (receipts, transfers, returns, broken vials, etc.). The Drug Accountability Form requires information related to the specific protocol and drug transactions such as dispensing to individual patients, drug receipts, transfers to and returns from satellite pharmacies, and drug returns.

Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger: the quantity of drug dispensed to the subject and the date(s) and quantity of drug returned by the subject. Subjects should return empty containers to the investigator, and the return should be noted in the ledger. These Drug Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

One copy of all Drug Accountability Forms and the return statement are retained by the investigator for his or her files; the ledger containing copies of the inventory sheets is included in the return shipment of drug supplies.

5. Adverse Experiences

3/26/97

The prompt reporting of adverse drug reactions (ADRs) is the responsibility of each investigator engaged in clinical research with investigational drugs. Reporting must take place within the time frame associated with the seriousness and severity of the reaction. For further details, refer to the protocol section which outlines the reporting of adverse events. Failure to report adverse reactions in accordance with government regulations may result in discontinuation of the study, and, in some cases, revocation or suspension of the investigator's permission to perform clinical research using investigational agents. All adverse reactions should also be reported to the appropriate local IRB.

TNM Nomenclature for Breast Cancer

Tumor (T)

T_0 No evidence of primary tumor
T_{is} Carcinoma in situ
T_1 ≤2 cm
- **T_{1a} ≤0.5 cm**
- **T_{1b} >0.5 cm-1 cm**
- **T_{1c} >1 cm-2 cm**

T_2 >2 cm-5 cm
T_3 >5 cm
T_4 Any size, with direct extension to chest wall or skin (excluding pectoral muscle)
- **T_{4a} Extension to chest wall**
- **T_{4b} Edema or ulceration of skin or presence of satellite nodules**
- **T_{4c} Both T_{4a} and T_{4b}**
- **T_{4d} Inflammatory carcinoma**

Nodes (N)

N_0 No regional lymph node metastasis
N_1 Metastasis to movable ipsilateral axillary lymph node or nodes
N_2 Metastasis to ipsilateral axillary lymph node or nodes fixed to one another or to other structures
N_3 Metastasis to ipsilateral internal mammary lymph node or nodes

Metastasis (M)

M_0 No distant metastases
M_1 Distant metastasis, including metastasis to ipsilateral supraclavicular lymph node or nodes

Stages of Primary Breast Cancer

	T	*N*	*M*
Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage IIA	T_0	N_1	M_0
	T_1	N_1	M_0
	T_2	N_0	M_0
Stage IIB	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIIA	T_0	N_2	M_0
	T_1	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1,N_2	M_0
Stage IIIB	T_4	Any N	M_0
	Any T	N_3	M_0
Stage IV	Any T	Any N	M_1

Adapted with permission from Beahrs P, et al (eds): *Staging of Cancer*, ed 3. Philadelphia. JB Lippincott Company, 1988, pp 146-147.

NSABP SURGICAL GUIDELINES

I. Operative Considerations for Lumpectomy

The following statements are guidelines to assist the surgeon in selecting the type of operative incision for a lumpectomy. These guidelines have evolved from the NSABP experience with over 2,000 patients to date; their implementation will result in improved cosmesis. **These statements are to be regarded as suggestions and are not mandatory for patient entry or protocol compliance.**

A. For lesions located in the upper half of the breast, it is recommended that circumferential curvilinear or transverse incisions be performed. In the lower half, however, radial incisions tend to provide superior cosmesis.

Incisions to be avoided include radial incisions in the upper half of the breast. NSABP experience has indicated that such incisions tend to result in unacceptable cosmesis. Similarly, circumferential curvilinear or transverse incisions in the lower half of the breast may result in unacceptable deformity.

B. It is recommended in the majority of instances that the incision for the tumor excision and that for the axillary dissection be separate. A single, continuous incision is to be avoided. An exception to this recommendation might be for those lesions in the axillary tail where a continuous incision could be used.

C. Regardless of the incision used, extensive undermining of the skin should be avoided. The dissection of thin skin flaps adjacent to the incision is not part of the recommended operation and may result in unsatisfactory cosmesis.

D. Following excision of the tumor, it is urged that the breast tissue not be reconstructed. The use of breast sutures in an attempt to obliterate the dead space has resulted in unnecessary deformity.

E. Drainage of the breast wound, either with penrose drains or suction catheters, is not recommended. Drainage of the axilla, however, is necessary.

F. Careful approximation of the skin incision is essential. It is recommended that a subcuticular closure be used in all cases.

G. Surgeons should contemplate biopsy incisions so as to conform to the above-mentioned guidelines.

H. A biopsy should be performed as if it were a lumpectomy, i.e., precautions should be taken to ensure that the margins of the resected tissue are free of tumor. This will obviate the need for a reexcision of breast tissue if the biopsy is positive for cancer.

II. Operative Considerations for Axillary Dissection

An axillary dissection as defined by this protocol consists of the excision of the axillary contents at levels I and II. An anatomic delineation of the scope of dissection is the latissimus dorsi muscle laterally, the axillary vein superiorly, and the medial margin of the pectoralis minor muscle medially. The nerves to the serratus anterior and latissimus dorsi muscles should be identified and preserved. The axillary vein should be visualized and followed under the pectoralis minor muscle to the medial border. These are minimal limits for dissection. The extent of axillary dissection should not vary with the operative procedure performed for the resection. Axillary sampling, i.e., partial nonanatomic removal of axillary contents, is not in compliance with NSABP operative criteria.

CTOMY

Radiation following lumpectomy is intended to be delivered in a cancerocidal dose to all remaining ipsilateral breast tissue. The dose level was chosen to produce sterilization of occult tumor foci which may possibly be present in the residual breast tissue following lumpectomy. The dose level described in this protocol was chosen in order to avoid distortion or fibrosis of the breast as a result of irradiation.

I. Area to be Treated and Technique

It is the intent of radiation therapy to treat the skin, breast tissue, muscle, lymphatics and entire scar of the breast using parallel opposed tangential fields. No attempt will be made to include axillary, supraclavicular, interpectoral and internal mammary lymph nodes. The latter lie at the medial edge of the treatment field and may sometimes be either partially or wholly included. No special attempt should be made to exclude these nodes since this would interfere with irradiation of the entire breast.

When lumpectomy + axillary dissection is performed through separate incisions, if the scar of the axillary dissection is extrinsic to the breast, no irradiation will be specifically directed to that scar.

If the axillary dissection scar is in continuity with that of the lumpectomy, no special attempt will be made to irradiate that portion of the scar which is beyond the breast tissue.

A. Position of the Patient. The patient lies supine, or a posterior shoulder wedge may be used if the dorsal convexity of the patient is extreme. The upper arm is abducted 90° with the forearm supported in an upright position by a vertical arm board.

B. Description of the Radiation Field. The breast (and the chest wall) are treated through opposing tangential fields to avoid direct irradiation of the lung.

C. Breast Field Boundaries. The medial border usually lies along the mid-sternal line. However, this border may be moved laterally, especially in women with small breasts.

The lateral border usually lies along the mid-axillary line. If the scar extends beyond this line, the lateral border may, within limits, be moved posteriorly to include the entire scar. The extent to which this line may be moved posteriorly should be guided by the amount of lung tissue which would be irradiated if this border is parallel-opposed to the medial border. If the irradiated slice of lung tissue exceeds a width of 3 cm, the lateral portal should be left along the mid-axillary line

and the end of the surgical scar treated by superficial irradiation. The lateral border may be moved more anteriorly and still encompass the entire breast, especially in women with small breasts.

The inferior border of the tangential field is drawn horizontally across the hemithorax at a level at least 1 cm below the inframammary fold.

The superior border is usually located along a horizontal line which bisects the sterno-manubrial junction (angle of Louis). If necessary, this border may be moved superiorly to be sure that the entire breast and the tail of the breast are included. If the scar extends above this boundary, the line should be moved superiorly so as to include the scar entirely.

3/26/97 D. Angle of Tangential Fields. The central axis of the medial and lateral fields lie on the same line. A correction for tissue inhomogeneity is not required. One or both of the tangential fields may be angled 5 degrees anteriorly if necessary to avoid irradiating an excessive amount of lung tissue.

E. Localization Films. Localization films should be taken in treatment position with the therapeutic beam; if more than 3 cm of lung tissue is included in the beam, the lateral field boundary is probably located too far posteriorly. For the purpose of blocking normal tissue, an inferior corner block is permitted.

F. SSD. 80 cm or more

II. Dosage and Time of Onset

A. Time of Onset of Therapy. No patient will begin radiation until the patient is randomized.

Timing of radiation therapy varies from protocol to protocol based on whether surgery and/or chemotherapy is involved. Please refer to appropriate sections of the protocol for more specific information.

Radiation therapy should not be initiated until the surgical scar is healed. If the entire scar has healed except for a single area of oozing and/or crusting (less than 1-2 cm), treatment can be started without compromising the residual healing.

If, however, the scar shows evidence of early necrosis along its edges, the onset of treatment should be postponed since breakdown of the entire scar may occur.

3/26/97 B. Dose. A dose of 5,000 cGy should be delivered calculated at a depth of two-thirds distance between the skin overlying the breast and the base of the tangential fields at mid-separation. This depth generally ranges from 3-7 cm. In small breasts where the 2/3 depth would be in lung, the point of calculation can be moved anteriorly to the level of the rib cage.

3/26/97 C. Dose Fractionation. The dose is given at a rate of 1,000 cGy per week in daily increments of 200 cGy per day, 5 days per week, calculated at the dose point. Both tangential fields will be treated daily, 100 cGy T.D. given to each.

D. Skin Reaction. Dry desquamation with pigmentation and/or erythema at the end of treatment are desirable; limited patches of moist desquamation are acceptable. Extensive areas of moist desquamation are to be avoided.

III. Treatment Modality

A. Equipment. Cobalt-60 or linear accelerator X rays are to be used. Superficial irradiation may only be used only to treat or boost portions of the surgical scar as described.

B. Special Equipment. For treatment with Cobalt-60, the use of a beam blocking device ("breast gadget") greatly facilitates treatment of the breast. Since the lower half of the beam is blocked near its central axis, the tangential fields do not diverge into the lung.

C. Use of Bolus. For most patients, bolus will not be necessary. The extent to which bolus should be used depends greatly on the details of the treatment situation at each institution. Bolus is added to reach the desired skin reaction, i.e., dry desquamation and erythema. Any accessories which enhance secondary electron scatter will increase the dose to the skin and thus limit the need for buildup. Plastic blocking trays or shields may enhance skin dose to the extent that the use of additional bolus is neither necessary nor desirable. Bolus may be used in clinical situations where high energy (>10 MV) beams are used.

D. Wedge Compensators. Wedge compensators should be considered to achieve dose uniformity.

E. Use of Boosts. External beam boosts to the tumor site are neither urequired nor suggested as part of the standard radiation therapy of these lumpectomy patients but may be utilized at the discretion of the treating physician. **The use of interstitial boosts is not permitted.**

IV. Reports to be Submitted.

3/26/97 *Deletion of text.*

10/30/97 Report of the radiation therapy administered will be submitted to the NSABP Biostatistical Center on Form E-1. This form will be accompanied by:

A. Treatment prescription and daily record sheet.

B. Copies of any dosimetry calculations.

C. Isodose distributions and breast contours for treatment plans.

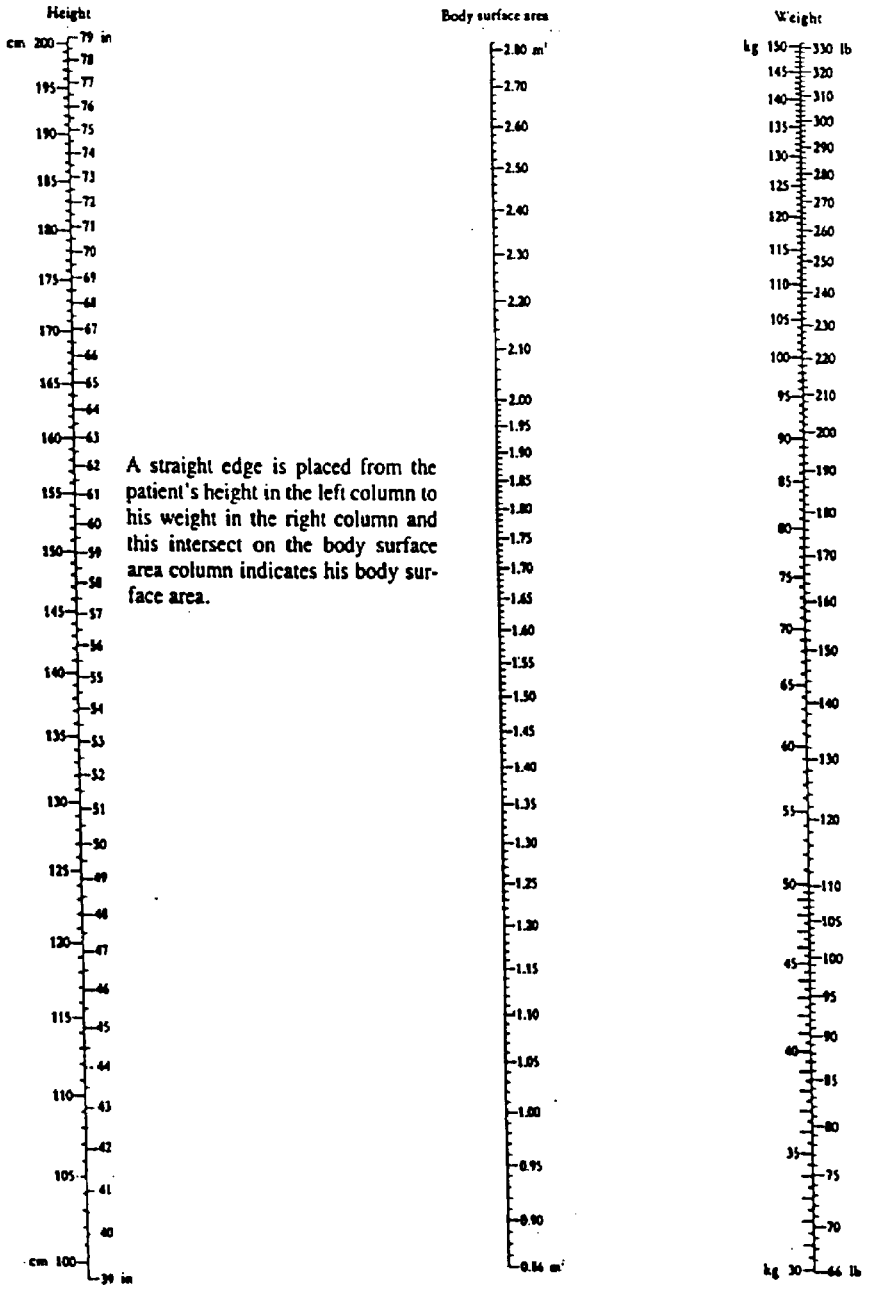
D. Copies of field verification (portal) films.

E. Photographs of patient in treatment position with field markings (two photographs may be necessary in order to see all 4 field boundaries).

3/26/97 The NSABP Operations Center radiation oncologist is to be notified of any problems or unusual situations which would interfere with administering radiotherapy per protocol. Please contact Melvin Deutsch, M.D., at (412) 647-3600.

Body Surface Area of Adults

Nomogram for determination of body surface area from height and weight



A straight edge is placed from the patient's height in the left column to his weight in the right column and this intersect on the body surface area column indicates his body surface area.

From the formula of Du Bois and Du Bois, *Arch. intern. Med.*, 17, 863 (1916): $S = W^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log W \times 0.425 - \log H \times 0.725 + 1.8564$ (S = body surface in cm^2, W = weight kg, H = height in cm)

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Table F1. Reporting Instructions for Adverse Drug Reactions for Phase II/III Trials
(For Trials Involving Investigational Drugs or a Combination of Investigational & Commercial Drugs)

ACTION REQUIRED (within specified time frame)		UNEXPECTED[1]		EXPECTED	
		Grades 2 & 3	Grades 4 & 5[2]	Grade 4	Grade 5[2]
24 HRS	• Report by fax to the **NCI and the NSABP Biostatistical Center**, using the NSABP 24-Hour Alert Form. • Follow local IRB reporting requirements.		X		X
10 DAYS	• Report to the NCI, using the NCI Form No. 391 Adverse Reaction (ADR) Form[3] for Investigational Drugs. Forward a copy of the report to the NSABP Biostatistical Center. • Send a completed NSABP ADR Form[3] with supporting documentation to the NSABP Biostatistical Center. • Notify the local IRB and forward a copy of the notification to the NSABP Biostatistical Center.	X	X	X[4]	X

[1]An unexpected toxicity is one that is not reported in the protocol, consent form, scientific literature, or the package insert, as well as any increased incidence of a known ADR reported in the protocol, consent form, package insert, or scientific literature.

[2]Any death from any nonbreast-cancer cause while a patient is receiving any treatment (including placebo) specified on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended, but is felt to be treatment-related.

[3]See Appendix F.

[4]Institutions do not have to report to the NCI Grade 4 myelosuppression for agents known and expected to cause myelosuppression at the dose used.

3/26/97 Note: All unexpected grade 1 and expected grade 1, 2, and 3 toxicities must also be reported to the NSABP Biostatistical Center on an NSABP ADR Form according to the required data submission schedule.

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COMMON TOXICITY CRITERIA

	GRADE				
TOXICITY	**0**	**1**	**2**	**3**	**4**
WBC	≥4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
PLT	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	<25.0
Hgb	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	<6.5
Granulocytes/Bands	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
Lymphocytes	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
Hemorrhage (clinical)	none	mild, no transfusion	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, >4 units transfusion per episode
Infection	none	mild	moderate	severe	life-threatening
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	---
Vomiting	none	1 episode in 24 hrs	2-5 episodes in 24 hrs	6-10 episodes in 24 hrs	>10 episodes in 24 hrs, or requiring parenteral support
Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence, or severe cramping	increase of ≥10 stools/day, or grossly bloody diarrhea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema, or ulcers, and cannot eat	requires parenteral or enteral support
Bilirubin	WNL	---	<1.5 x N	1.5 - 3.0 x N	>3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Alk Phos or 5'nucleotidase	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Liver (clinical)	no change from baseline	---	---	precoma	hepatic coma
Creatinine	WNL	<1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
Proteinuria	no change	1+ or <0.3 g% or <3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or >1.0 g% or >10 g/l	nephrotic syndrome
Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion

	GRADE				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Alopecia	no loss	mild hair loss	pronounced or total hair loss	---	---
Pulmonary	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
Cardiac dysrythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia, or fibrillation
Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Cardiac - ischemia	none	non - specific T-wave flattening	asymptomatic, ST and T wave changes suggest-ing ischemia	angina without evidence for infarction	acute myocardial infarction
Cardiac - pericardial	none	asymptomatic, effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to >150/100 if pre-viously WNL. No treatment required	recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if pre-viously WNL. No treatment required	requires therapy	hypertensive crisis
Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitaliza-tion; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for >48 hrs after stopping the agent
Neuro - sensory	none or no change	mild paresthesias, loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	---
Neuro - motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis

TOXICITY	GRADE 0	1	2	3	4
Neuro - cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis
Neuro - cerebellar	none	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuro - mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neuro - headache	none	mild	moderate or severe but transient	unrelenting and severe	---
Neuro - constipation	none or no change	mild	moderate	severe	ileus>96 hrs
Neuro - hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro - vision	none or no change	---	---	symptomatic sub-total loss of vision	blindness
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Allergy	none	transient rash, drug fever <38c, 100.4F	urticaria, drug fever=38c, 100.4F mild bronchospasm	serum sickness, bronchospasm, req parenteral meds	anaphylaxis
Fever in absence of infection	none	37.1 - 38.0c 98.7 - 100.4F	38.1 - 40.0c 100.5 - 104.0F	>40.0c >104.0F for less than 24 hours	>40.0c (104.0F) for more than 24 hrs or fever accompanied by hypotension
Local	none	pain	pain and swelling, with inflammation or phlebitis	ulceration	plastic surgery indicated

	GRADE				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Weight gain/loss	<5.0%	5.0 - 9.9%	10.0 - 19.9%	>20.0%	---
Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or keto - acidosis
Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤6.0
Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤0.24 x N
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	>2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	>3.00 x N

AUTOLOGOUS BONE MARROW OR BLOOD STEM CELL SUPPORT STUDIES
SUPPLEMENTARY TOXICITY CRITERIA

Grade 5 Death due to bacterial or fungal infection or hemorrhage associated with neutrophils <500/ul or platelets <10,000/ul more than 8 weeks after marrow transplantation.

Grade 4 Neutrophils <500/ul and/or platelets <10,000/ul for a duration in excess of 8 weeks.

Grade 3 Neutrophils <500/ul and/or platelets <10,000/ul for a duration of 4 to 8 weeks.

Grade 2 Neutrophils <500/ul and/or platelets <10,000/ul for a duration up to 4 weeks.

Grade 1 Neutropenia and/or thrombocytopenia, but neutrophils never <500/ul and platelets never <10,000/ul.

All other nonhematologic toxicities should be graded by the Common Toxicity Criteria.

NSABP 24-HOUR ALERT FOR ADVERSE DRUG REACTIONS

FORM: ALERT
10-10-95

This report must be completed and faxed to the NSABP Biostatistical Center (412-624-1082) and the NCI (301-230-0159) within 24 hours of the occurrence of an unexpected life-threatening toxicity or any death. Please provide as complete a report as possible with all information known at the time of the report.

Protocol No: _____

Study Number ☐☐☐☐☐☐☐☐☐ First 3 Letters of Last Name ☐☐☐

Institution Name: _____ Institution No. _____

Name of Treating Physician: _____
(Please Print)

Name of Person Completing This Form: _____

Telephone Number: _____

Date of Event ☐☐ ☐☐ ☐☐ (Mo Day Yr) Date of Report ☐☐ ☐☐ ☐☐ (Mo Day Yr)

Patient's Age at Time of Event ☐☐ Sex: ☐ Male ☐ Female

Adverse Event Classification (check one box):

Grade 4 (Life-threatening): ☐ Unexpected

Grade 5 (Death): ☐ Expected ☐ Unexpected Date of Death ☐☐ ☐☐ ☐☐ (Mo Day Yr)

☐ Other (Describe): _____

Describe Event or Problem (including relevant medical history and supporting laboratory data):

Suspect Medication(s):

Name _____ Dose _____ Route _____ Date(s) of Therapy _____

Concurrent Medication(s) and dose(s) (if known):

1. Name _____ Dose _____
2. Name _____ Dose _____
3. Name _____ Dose _____

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[redacted] **GS** Page 1 of 2

Instructions: This form should be completed for all Adverse Reactions. It should be mailed according to the instructions of the Cooperative Group.

Patient's Initials _____ Protocol No. _____ Patient Sequence No. _____

Institution/Affiliate _____

Intergroup Protocol No. _____ Intergroup Patient Sequence No. _____

Name of Treating Physician _____ Diagnosis _____

Name of Person Completing This Form _____Telephone Number(_____)-_____-_____

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

☐☐ Toxicity grading criteria used (01-Common Toxicity Criteria, 02-Other, (specify)_____

☐☐ Toxicity category (01-death, 02-unusual, 03-expected)

☐ Treatment arm code

DEMOGRAPHICS

☐☐ ☐☐ Date of birth (M,Y)

☐☐ Sex

01=male
02=female

☐☐ ECOG performance status, day 1 of Rx

☐☐ ☐☐ Date of initial diagnosis (M,Y)

Please record site(s) of metastatic disease if appropriate.
01=no
02=yes
-1=unknown/not applicable

☐☐ Nodal involvement

☐☐ Osseous involvement

☐☐ Visceral involvement

specify_____

☐☐ Was the patient taking nonprotocol medications at the time of ADR?
01=no, 02=yes, -1=unknown

If YES, specify meds and any concurrent disease
_____
_____
_____

ADVERSE REACTION

Specify drug(s) suspected of causing reaction.

IF RELEVANT:

_____

☐☐ Was any drug supplied by NCI?
01=no, specify source _____
02=yes
-1=unknown

Specify toxicity type _____

(e.g., cardiac, infection, or note if disease progression)

☐☐ Toxicity grade of ADR

☐☐ ☐☐ ☐☐ Date adverse reaction started (M,D,Y)

☐☐ ☐☐ ☐☐ Date adverse reaction ended (M,D,Y)

☐☐ ☐☐ ☐☐ Date protocol Rx started (M,D,Y)

☐☐ ☐☐ ☐☐ Date last dose of protocol Rx (M,D,Y)

☐☐ No. of cycles given (complete and partial)

☐☐ ☐☐ ☐☐ Date of Rx associated with the ADR (M,D,Y)

☐☐ ☐☐ ☐☐ Date of death (if patient died)

PRIOR TREATMENT Please list below any prior treatment for this malignancy (01=no, 02=yes, -1=unknown)

	Description	Start Date	Date End
☐☐ Prior chemotherapy/immunotherapy and/or hormonotherapy			
☐☐ Prior radiotherapy			
☐☐ Prior surgery			

CURRENT PROTOCOL TREATMENT (INCLUDE ALL AGENTS)

Drug	Dose	Schedule	Route	Relation to ADR**	Action Taken***	Total Dose To Date

**Options-unrelated, unlikely, possible, probable, definite, unknown/not applicable.
***Action Taken-dose reduced, dose withheld, dose discontinued.

DOCUMENTATION OF REACTION

Please complete Part A and/or Part B

Part A - Complete this section if the patient had either a nonhematologic reaction OR an unexpected hematologic reaction.

1. Give a brief description of the reaction and its temporal relationship to the Rx administration.

2. Give a brief description of any relevant physical findings or laboratory data which documents the ADR.

	Baseline Date/Value	Nadir Date/Value	Recovery or Most Recent Date/Value
ADR Lab	_____/_____	_____/_____	_____/_____

3. Give a brief description of how the ADR was treated.

4. Please list any complications and sequelae (if death, was autopsy done? Please submit report.)

5. Please describe any medical history of the patient which might be relevant to this event.

6. If the suspected agent(s) was given again, please describe dose and reactions.

Part B - Complete this section if the patient had a hematologic reaction - expected OR unexpected.

1. Laboratory Data Documenting ADR

	Baseline Date/Value	Nadir Date/Value	Recovery or Most Recent Date/Value
ADR	_____/_____	_____/_____	_____/_____
Platelets	_____/_____	_____/_____	_____/_____
HGB/HCT	_____/_____	_____/_____	_____/_____

2. Please give a brief description of any complications, treatment and sequelae if Part A HAS NOT already been completed.

☐☐☐☐☐☐ Date telephoned Cooperative Group

If relevant:

☐☐☐☐☐☐ Date telephoned NCI (301-230-2330)

Name of NCI contact:_____

☐☐☐☐☐☐ Date telephoned drug company

☐☐ Reported to local IRB (01=no, 02=yes)

☐☐☐☐☐☐ Date form sent to Cooperative Group

☐☐☐☐☐☐ Date form sent to NCI

☐☐☐☐☐☐ Date form sent to drug company

☐☐ Report by
01=Institution
02=Statistical center ☐☐☐☐☐☐
03=Study chairman
04=Statistical Center, but later documented as no report needed

_____
Signature of Treating Investigator (M.D.)

Investigator: Keep a copy for your files and submit original form.

NSABP TOXICITY REPORT FORM

FORM ADR (Rev. 8/91)

Complete this form for **ALL** patients even if no toxicity is experienced. Submit one form to correspond to each course of therapy while the patient is on therapy and up to 3 months after protocol therapy ends. "COURSE #" refers to *chemotherapy cycle. For tamoxifen or placebo given without chemotherapy, code course = 77. If post-therapy, code course = 88.* Complete and submit forms immediately if the patient experiences a Grade 3, 4, or 5 toxicity. If these more severe reactions occur, also complete the top portion of the reverse side of this form. All hematologic and chemistry data should be reported on the protocol therapy form. For appropriate dose modifications, refer to protocol.

STUDY NUMBER [ ] 1-9 COURSE# [ ] 10-11 PATIENT NAME _____

1st 3 LTRS. OF PT's LAST NAME [ ] 12-14 ANY TOXICITY ? [ ] 15 (1 = YES, 2 = NO) REPORT DATE [ ] Mo. [ ] Day [ ] Yr. 16-21 TO [ ] Mo. [ ] Day [ ] Yr. 22-27

CODE MAX. GRADE FOR INTERVAL*

↓	CRITERIA	TOXICITY GRADE** (Code "5" if Toxicity-Related Death) 1	2	3	4
[ ] 28	HEMORRHAGE	Mild	1-2 Units	3-4 Units	>4 Units
[ ] 29	INFECTION/SEPSIS	Mild	Moderate	Severe	Life-threatening
[ ] 30	NAUSEA	Able to eat	Decr. intake	No intake	--------
[ ] 31	VOMITING	1 q. 24 hrs.	2-5 q. 24 hrs.	6-10 q. 24 hrs.	Parenteral support
[ ] 32	DIARRHEA	Incr. 2-3 q. 24 hrs.	Incr. 4-6 q. 24 hrs. *Moderate*	Incr. 7-9 q. 24 hrs.; *Severe*	Incr.10+ q. 24 hrs; bloody; *support*
[ ] 33	STOMATITIS	Mild	Ulcers	Cannot eat	Support required
[ ] 34	HEMATURIA	Micro	No clots	Gross with clots	Transfusion
[ ] 35	ALOPECIA	Mild	Pronounced	Total	--------
[ ] 36	PULMONARY	Asympt.w/abn.PFTs	Exertion Dyspnea	Normal Activity Dyspnea	Rest Dyspnea
[ ] 37	PHLEBITIS/PULM. EMB.	Superficial	Deep Vein Thrombosis w/o Hosp.	DVT w/ Hospitalization	Pulmonary Embolism
[ ] 38	CARDIAC DYSRHYTHM.	*Transient*	Recurrent	Therapy Required	Monitoring
[ ] 39	CARDIAC FUNCTION	Asympt.;<20% Decr., in Lt. V.F.	>20% Decr. in Lt. V.F.	Mild C.H.F.	Severe C.H.F.
[ ] 40	CARDIAC ISCHEMIA	Flat T-wave	Addn. EKG changes	Angina	Myocardial Infarction
[ ] 41	CARDIAC PERICARDIAL	Asymptomatic	Pericarditis	Drainage	Tamponade
[ ] 42	HYPERTENSION	Transient	20+ Incr. Diastolic	Therapy Required	Crisis
[ ] 43	HYPOTENSION	No Therapy	Outpt.; fluids required	Rx. Req./Hosp.	Rx/Hosp. Req. >48 hrs.
[ ] 44	*NEURO-SENSORY*	*Mild*	*Moderate*	Severe	--------
[ ] 45	NEURO-MOTOR	Subjective	Mild Objective	Impaired Function	Paralysis
[ ] 46	NEURO-CORTICAL	Mild	Moderate	Severe	Coma/Seizures
[ ] 47	NEURO-CEREBELLAR	Slight incoord.	Tremor, slurred speech, nystagmus	Ataxia	Necrosis
[ ] 48	NEURO-MOOD	Mild	Moderate	Severe	Suicidal
[ ] 49	NEURO-HEADACHE	Mild	Moderate	Unrelenting	--------
[ ] 50	*NEURO-CONSTIPATION*	*Mild*	*Moderate*	*Severe*	*Ileus >96 hrs.*
[ ] 51	NEURO-HEARING	Loss on Audiometry	Tinnitus	Impaired Function	Deafness
[ ] 52	NEURO-VISION	Transient	Asympt.,Measurable Change	Subtotal Loss	Blindness
[ ] 53	SKIN	Eruption	Eruption w/pruritis	Gen'lized Eruption	Ulcerative Dermatitis
[ ] 54	ALLERGY	Rash	Urticaria	Therapy Required	Anaphylaxis
[ ] 55	FEVER	<38°C	38-40°C	>40°C	With Hypotension
[ ] 56	LOCAL COMPLICATION or EXTRAVASATION	Pain	Pain w/inflam.	Ulceration	Surgery
[ ] 57	OTHER, Describe				
[ ] 58	OTHER, Describe				

[ ] (OVER)

* GRADE 3, 4 or 5 = Complete Reverse Side

** GRADE 5 = DEATH

59-75 [ ] [ ] [ ] [ ]

STUDY NUMBER ____________________

FORM ADR
Rev. 8/91

COMPLETE THIS SECTION ONLY IN THE EVENT OF A GRADE 3, 4 OR 5 TOXICITY AS REPORTED ON FORM ADR AND FORWARD IMMEDIATELY TO NSABP BIOSTATISTICAL CENTER. ATTACH ANY PERTINENT DOCUMENTATION.

REPORTING DATE ____________ REACTION ONSET DATE ____________

DESCRIPTION OF SUSPECTED REACTION(S):

INCLUSIVE DATES OF REACTION(S):

SEVERITY. 1 - MILD 2 - MODERATE 3 - SEVERE 4 - LIFE THREATENING 5 - DEATH ☐ 76

OUTCOME OF REACTIONS TO DATE:

- ☐ Alive With Sequela
- ☐ Recovered
- ☐ Still Under Treatment For Reaction
- ☐ Died (Report Cause and Date)

WAS OUTPATIENT TREATMENT FOR REACTION REQUIRED?
1 - Yes 2 - No ☐ 77

WAS HOSPITALIZATION TREATMENT FOR REACTION REQUIRED?
1 - Yes 2 - No ☐ 78

SUSPECTED DRUG(S), DOSES AND DATES OF ADMINISTRATION:

IF HOSPITALIZED, NUMBER OF DAYS (Count day of admission <u>and</u> day of discharge.)
888 - Still Hospitalized ☐☐☐ 79-81

TESTS/LABORATORY DATA CONFIRMING REACTION:

☐☐☐☐ 82-85

FOR BIOSTATISTICAL CENTER USE
(TO BE COMPLETED BY HEADQUARTERS MEDICAL REVIEWER)

<u>PRIMARY-PROBLEM</u>

Date of Primary Problem ☐☐☐☐☐☐ 86-91 (Mo. Day Yr.) ICDA-8 CODE ☐☐☐.☐ 92-95

Description of Primary Problem ☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 96-129

Was protocol therapy stopped? 1 - Yes; 2 - No ☐ 130

Was this problem related to protocol therapy? 1 - Yes; 2 - No ☐ 131

GRADE OF TOXICITY ☐ 132

If reviewed for "septic episode", indicate result of review. (If judged to be septic episode, ICDA-8 code should be "038.9".)

1 = Septic Episode
2 = <u>Not</u> Septic Episode ☐ 133

REVIEWER'S INITIALS ____________

DATE OF REVIEW ☐☐☐☐☐☐ 134-139 (Mo. Day Yr.)

NCI/CTEP SECONDARY AML/MDS REPORTING INSTRUCTIONS

All cases of Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) which occur in patients being treated on NCI-sponsored clinical trials must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program. The NCI/CTEP Secondary AML/MDS Report Form (included in Appendix F) must be completed and submitted to the IDB within 30 days of the AML/MDS diagnosis. Copies of the pathology reports confirming the AML/MDS diagnosis and cytogenetics reports must be submitted with the AML/MDS Report Form. A copy of all reports should also be sent to the NSABP Biostatistical Center.

For patients developing secondary AML/MDS on NSABP studies, bone marrow aspirate should be cryopreserved whenever possible. **Do not send blood or bone marrow aspirate to the Biostatistical Center or Operations Center. As for all second cancers, stained pathology slides should be submitted to the Biostatistical Center.**

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

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NCI/CTEP SECONDARY AML/MDS REPORT FORM

INSTRUCTIONS: Submit this form **within 30 days** of AML/MDS diagnosis following treatment for cancer on NCI-sponsored trials. The form should be completed for the most recent NCI-sponsored trial on which the patient received treatment. Submit a copy of the **pathology report** confirming the AML/MDS diagnosis and of the **cytogenetic report** (if available) with this form. *See reverse side for submission mailing address.*

PLEASE ANSWER ALL QUESTIONS.

I. PATIENT IDENTIFICATION AND CHARACTERISTICS (Complete all that apply):

Patient ID# (Group):_____ _ _____
Patient ID#(Coordinating Group)*: _____
Date of Birth (*mo/day/yr*): _____
Sex (*please check*): ☐ Male ☐ Female
Initial Diagnosis:_____
*** For intergroup studies only.**

NCI Protocol #: _____
Cooperative Group Name & Protocol#:_____
Coordinating Group Name & Protocol#*:_____
Treatment Arm:: _____

II. AML/MDS DIAGNOSIS AND CHARACTERIZATION

Date of AML/MDS diagnosis (*mo/day/yr*):_____

AML subtype (*please check*):

☐ M1 ☐ M2 ☐ M3 ☐ M4 ☐ M5 ☐ M6 ☐ M7
☐ MDS ☐ Unknown ☐ Other (*specify*):_____

Cytogenetics performed? ☐ No ☐ Yes; *please check all that apply*:

☐ 11q23 abnormality
☐ Chromosome 5 and/or 7 abnormality
☐ Other chromosome abnormality (*specify*):_____
☐ Normal

Is cryopreserved marrow specimen available for biology studies? ☐ No ☐ Yes

III. CHEMOTHERAPY FROM LAST/CURRENT NCI-SPONSORED PROTOCOL PRIOR TO AML DIAGNOSIS
(i.e. therapy for protocol listed in Section I.)

First Day Protocol Chemotherapy Taken (*mo/day/yr*):_____

Last Day Protocol Chemotherapy Taken (*mo/day/yr*) :_____

Agent Received	**Actual Cumulative Dose Received (mg/m²)**
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Received RT? ☐ No ☐ Yes; *please specify site*:_____
total dose:_____

Received growth factor? ☐ No ☐ Yes; *please check all that apply*:
☐ G-CSF ☐ GM-CSF ☐ Other (*specify*):_____

IV. CANCER THERAPY RECEIVED PRIOR TO LAST/CURRENT NCI SPONSORED PROTOCOL

Did the patient receive any cancer therapy (*protocol or non-protocol*) **prior to last/current NCI protocol therapy** (*i.e. protocol listed in Section III*)?

☐ No; *if No, go to section V.* ☐ Yes

Identify agents/modalities given prior to the NCI sponsored protocol therapy listed in Section III (*check those which apply*):

☐ Alkylators ☐ Epipodophyllotoxins ☐ Platinum ☐ Anthracyclines ☐ Growth Factors

☐ Other cytotoxic drugs

☐ RT; *if checked, specify site:*_____ *total dose:*_____

Was any of this prior therapy on an NCI-sponsored trial?

☐No ☐Yes

*If yes, list NCI (Group) protocol #:*_____

Treatment arm: _____

V. CANCER THERAPY RECEIVED SUBSEQUENT TO LAST/CURRENT NCI SPONSORED PROTOCOL

Did the patient receive any cancer therapy prior to the AML/MDS diagnosis, but after completing the NCI sponsored protocol therapy described in Section III?

☐No; *if No, go to section VI.* ☐Yes

Identify agents/modalities given subsequent to the NCI sponsored protocol therapy listed in Section III, but preceding the AML/MDS diagnosis *(check those which apply)*:

☐ Alkylators ☐ Epipodophyllotoxins ☐ Platinum ☐ Anthracyclines ☐ Growth Factors

☐ Other cytotoxic drugs

☐ RT; *if checked, specify site:*_____ *total dose:*_____.

VI. INVESTIGATOR RESPONSIBLE FOR COMPLETING REPORT

Investigator Name (*please print*):_____

Phone: (**)** _____ **FAX: (** **)**_____

Institution:_____.

Address:_____

Investigator's Signature:_____ **Date:** _____

Submit this form instead of an FDA #3500 (MedWatch) form for cases of secondary AML/MDS. The **FAX #** for submission of the forms **(including the pathology and cytogenetic reports)** to NCI/CTEP is **(301) 230-0159.** Because of the poor quality of some FAX transmissions, please send a hard copy of all AML/MDS reports to the mailing address given below:

Investigational Drug Branch (NCI/CTEP)
P.O. Box 30012
Bethesda, Maryland 20824

and

NSABP Biostatistical Center
230 McKee Place, Suite 600
Pittsburgh, Pennsylvania 15213

IMPORTANT: Cryopreserved leukemia cells and extra cytogenetic material in fixative (for fluorescence *in situ* hybridization) are an invaluable resource. Contact your Cooperative Group Operations Office or CTEP (301-496-2522) for information about how leukemia cell specimens should be collected, preserved, and submitted for biology studies.

INSTRUCTIONS FOR SELF-ADMINISTERING G-CSF

A. General Information

1. This is useful information if you are required to take a medication called G-CSF. It is given as a daily injection under the skin. The first injection will be administered at least 24 hours after your chemotherapy and will continue until you are instructed to stop by your physician.

2. The injection should be given at approximately the same time each day.

3. Store the G-CSF in the refrigerator but not the freezer. Remove the vial of G-CSF from the refrigerator about 30 minutes before administration so it can reach room temperature. Do not shake the vial.

4. Collect the necessary supplies for administration, such as a vial, sterile disposable syringe with needle, alcohol pads, and puncture-proof disposal container. The container can be a coffee can or leak-proof, reclosable milk jug.

5. Wash your hands well and take any pre-medication.

B. Preparation of G-CSF for Administration

1. Remove the cap from the vial and wipe with an alcohol pad. Use each vial only once and then discard into the disposal container.

2. Use only the syringes and needles recommended or given to you by your nurse/physician. Do not reuse syringes or needles.

3. Pull back on the plunger of the syringe to allow air to enter. The amount of air should equal your dose of G-CSF.

4. Remove the needle cap carefully.

5. Place the needle through the rubber stopper on the vial and push the plunger down so that all the air goes into the vial.

6. Turn the vial and syringe upside down. Draw back on the plunger until the syringe is filled with the correct dose of G-CSF.

7. If air bubbles are present, tap the syringe so that the air floats to the top, then push the air back into the vial.

8. Remeasure until the correct dose of G-CSF is achieved.

9. Remove the needle from the vial.

C. Self-Administration of G-CSF

1. Select the site for injection.

   The best sites for injection have a layer of fat between skin and muscle:

   - thigh
   - outer surface of the upper arm
   - abdomen, except the navel or waistline

   Please refer to Diagram 1.

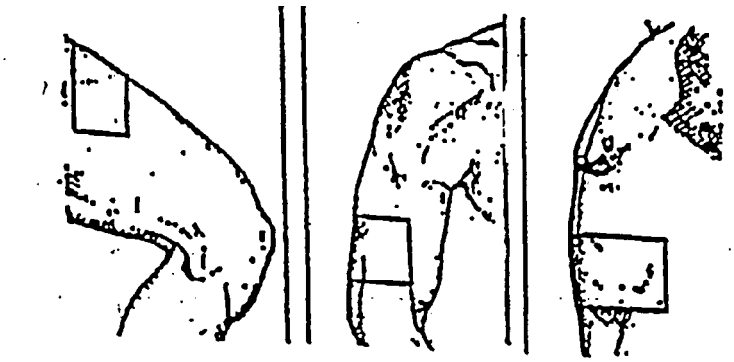

Diagram 1

   If you are exceptionally thin, use only the thigh or outer surface of the arm as injection sites.

2. Do not inject medication into the same site repeatedly.

3. Rotate your injection sites in a regular pattern.

4. Cleanse the injection site with a fresh alcohol pad.

5. Wait for the site to dry.

6. If you have not already done so, remove the needle cap.

7. Pinch a 2" fold of skin between your thumb and index finger.

8. Hold the needle at a 45° to 90° angle to the pinched skin. Please refer to Diagram 2.

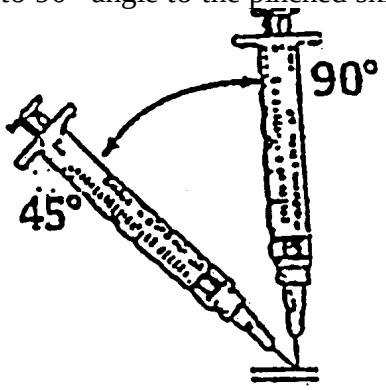

Diagram 2

9. Insert the needle into the skin fold. Please refer to Diagram 3. If you do this quickly, you will feel very little discomfort.

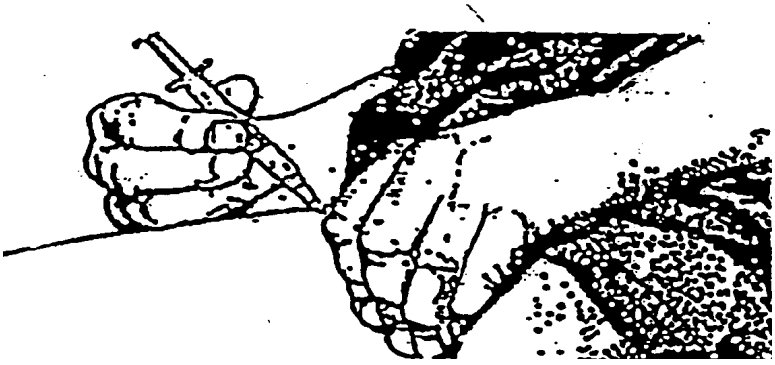

Diagram 3

10. Hold the syringe with one hand. With the other, pull back on the plunger to check for blood. If you see blood in the solution in the syringe, do not inject. Withdraw the needle and start again at a new site.

11. If you do not see blood, slowly push the plunger to inject the medication. Press the plunger all the way down.

12. Remove the needle from the skin and gently hold an alcohol pad on the injection site. Do not massage or apply heat to the site.

13. If there is bleeding, apply a bandage.

14. Immediately put the syringe, needle, and vial into the disposal container. Never recap your needle. Discard the container when it is full according to your nurse's/physician's instructions.

D. Post-Injection Information

1. Call your nurse or physician promptly for any signs or symptoms of infection (chills, fever, persistent cough, etc.). Call whenever you have a temperature greater than 101°F or 38 °C.

2. Notify your nurse/physician if you experience any local reaction to G-CSF. This would consist of persistent redness, swelling, or itching at an injection site.

3. Immediately notify your physician or go to an emergency room if you exhibit any symptoms of a systemic reaction to G-CSF. These would include difficulty breathing, sweating, or a rash over your body.

4. If you experience any bone pain or discomfort which may occur with G-CSF, please notify your nurse/physician. He/she will instruct you regarding medication to take to alleviate this pain.

5. Inform your nurse/physician of all medications you are taking (prescription and over-the-counter).

6. Take your G-CSF about the same time each day. If you miss a dose by a few hours, take your regular dose as soon as you can. However, if you miss the dose by more than a few hours, call your nurse/physician for further instructions.

Remember, if you have any problems or questions, please call your nurse or physician.

(Study Coordinator _____)

Dr. _____ Phone # _____

Nurse_____ Phone # _____

[*To be included with submission of consent form document to local IRB*]

TO: Local Institutional Review Boards

FROM: NSABP Operations Center

EFFECTIVE DATE: April 5, 1993

RE: Local IRB Review of Multicenter Clinical Trials

The NSABP understands and agrees with the position of the Office for Protection from Research Risks (OPRR) that, "Only the local IRB is familiar with the particular circumstances of its research setting and is in a position to weigh critical considerations like state and local laws, professional and community standards, institutional policies, and the needs of differing patient or subject populations." In order to conform to OPRR guidelines regarding local IRB review of multicenter clinical trials (effective November 9, 1992), and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial:

The protocol and model consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment, Diagnosis, and Centers/National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the model consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. The investigator is responsible for forwarding copies of such IRB-approved changes with their justifications to the NSABP Operations Center at the address provided below immediately following such changes. It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

NSABP Operations Center
East Commons Professional Bldg.
4 Allegheny Center - 5th Fl.
Pittsburgh, PA 15212-5234

Phone: (412) 330-4600
Fax: (412) 330-4661

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality-Assurance staff and government agencies.

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(This consent form was previously revised on March 26, 1997.)

Revision as of 10/30/97
IRB Approved: 00/00/00

MODEL CONSENT

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: A Randomized Trial Evaluating the Worth of Paclitaxel (Taxol) Following Doxorubicin (Adriamycin)/Cyclophosphamide in Breast Cancer Patients with Positive Axillary Nodes

INVESTIGATOR(S): **(supply appropriate information specific for your institution)**

DESCRIPTION: You are being invited to participate in this study because you have been diagnosed with breast cancer that has spread to one or more of the lymph nodes in your armpit. These findings indicate that you are at increased risk for recurrence and that surgery alone may not permanently cure your breast cancer.

This research study is being conducted by the National Surgical Adjuvant Breast & Bowel Project (NSABP), an organization with significant experience in conducting research studies in patients with breast cancer. The study described here will involve approximately 3,050 women at sites across the United States and Canada.

Background: The standard approach to treating breast cancer is to give several "cycles" (repeated doses at regularly specified intervals) of a combination of two or more chemotherapy drugs (drugs that kill cancer cells). Recent information suggests that it may be more beneficial to give several cycles of one drug followed by several cycles of another drug. Some researchers think that the second approach may kill more cells that are resistant to chemotherapy.

This study will involve four drugs: doxorubicin (Adriamycin), cyclophosphamide (Cytoxan), tamoxifen (Nolvadex), and paclitaxel (Taxol). The doxorubicin, cyclophosphamide, and tamoxifen, when given in the standard doses used in this study, have been approved by the Food and Drug Administration (FDA) for the treatment of breast cancer. Over a number of years, they have all been shown to be effective in the treatment of breast cancer. Doxorubicin, cyclophosphamide, and tamoxifen, when used as an adjuvant (additional) treatment following surgery for breast cancer, can significantly reduce the risk of the cancer returning. Some research studies have indicated that adjuvant treatment with tamoxifen (after surgery for breast cancer) can also reduce the risk of developing a new cancer of the opposite breast. In addition to these standard treatments, this study will involve a new treatment, paclitaxel, that is still considered to be investigational for patients with your type of breast cancer. An investigational drug or therapy is one that is still in the testing phase and has not received the approval of the FDA.

(Revised page 3/26/97)
Paclitaxel works differently from previously used chemotherapy drugs. Paclitaxel has been found to be effective in treating patients with advanced breast cancer. It has been approved by the FDA at a lower dose (than used in this study) for the treatment of such patients. More important, it has been found to be effective in treating patients who have received chemotherapy with doxorubicin and have developed a recurrence of their tumor. Paclitaxel is now being evaluated in this and other studies as an adjuvant therapy following surgery for breast cancer.

Study Purpose: The approach being tested in this study is to administer four cycles of standard chemotherapy (doxorubicin/cyclophosphamide) followed by four cycles of the investigational drug, paclitaxel. Researchers hope to show that cancer cells resistant to the doxorubicin/cyclophosphamide chemotherapy may be sensitive to paclitaxel. This may then result in prolonged patient survival and result in a decrease in the number of patients experiencing a recurrence.

Treatment Groups and Dosing Procedures: If you agree to participate in this study, you will be assigned to receive one of the following treatments (Group I or II). Since it is not known at this time which treatment is best, you will be placed by chance in one of the two groups. This chance selection process is called *randomization* and is frequently used in research studies. The drugs involved in each treatment group will be given as described.

Group I: **Chemotherapy (doxorubicin and cyclophosphamide).**
Doxorubicin will be given intravenously (into a vein in the arm) over a period of about 15-20 minutes, followed by cyclophosphamide given intravenously over a period of 30 minutes to 2 hours. The drugs will be given once every 21 days, for a total of four doses. (21 days = 1 cycle).

Group II: **Chemotherapy (doxorubicin, cyclophosphamide and paclitaxel).**
Doxorubicin and cyclophosphamide will be given as described for Group I. In addition, after completion of the four cycles of doxorubicin/cyclophosphamide therapy, paclitaxel will be given intravenously over 3 hours once every 21 days, for a total of four doses.

The precise amount of these drugs for each patient is adjusted based on the woman's height and weight. The abbreviations used to indicate this dose adjustment are mg/m^2 or µg/kg. The doses for the chemotherapy drugs are as follows: doxorubicin (60 mg/m^2), cyclophosphamide (600 mg/m^2), and paclitaxel (225 mg/m^2).

- In both groups, any patient 50 years of age or over, or any patient under 50 years of age who has a tumor positive for estrogen receptors or progesterone receptors, will take 20 mg of tamoxifen either as one 20 mg tablet or two 10 mg tablets once daily by mouth for 5 years, beginning on the first day of chemotherapy.

Revised 10/30/97

- Patients assigned to receive paclitaxel in Group II will also be given additional drugs to control possible allergic reactions to the paclitaxel. Dexamethasone (20 mg), a steroid drug similar to cortisone, will be given by mouth 12 and 6 hours before the beginning of paclitaxel administration. The antihistamine drugs, cimetidine (300 mg) or ranitidine (50 mg), and diphenhydramine (50 mg), will be given intravenously at 1 hour before the beginning of paclitaxel administration.

All drugs may be given on an outpatient basis and will not require special hospitalization for their administration. Doses may be adjusted if severe side effects develop.

Patients having a lumpectomy will receive radiation therapy to the breast following completion of the assigned chemotherapy and after any side effects from the chemotherapy have resolved.

Chemotherapy kills cancer cells but can also affect normal cells, resulting in side effects. Lowered blood counts, particularly a lowered white blood cell count, are common side effects of chemotherapy. These lowered white counts can make patients more susceptible to infection and can also limit the amount of chemotherapy they can be given during a certain time. A drug called *recombinant human granulocyte colony-stimulating factor* (rHu G-CSF), approved by the FDA, appears to stimulate the production and the function of white cells that protect against infection. (RHu G-CSF is also known by the trade name Neupogen.) G-CSF is a protein that is normally made in the body. New technology has made possible the production of large quantities of rHu G-CSF. Previous studies have shown that rHu G-CSF can increase the white blood cell count and reduce the risk of hospitalization for infection.

You will be given rHu G-CSF if, after the previous cycle of therapy, you develop an infection or low white blood count that does not return to normal by the time you need to receive the next cycle of chemotherapy; the rHu G-CSF will then be given during all remaining courses of your therapy. RHu G-CSF is given by injection under the skin beginning on day 2 of each chemotherapy cycle and must be given daily until your white blood cells have recovered. This usually occurs after day 8, at which time the rHu G-CSF will be discontinued for the remainder of that cycle. From blood tests taken between chemotherapy cycles, you will be instructed when you may stop the rHu G-CSF injections in each cycle. RHu G-CSF will be given at home by you or by your family/friends. You will be fully instructed on how to administer this treatment.

If you develop serious side effects during the course of your therapy, your doctor may need to prescribe additional medications to treat your condition. The medications required will depend on the type of side effect that you experience. If additional medications are necessary, any questions regarding them will be answered by your doctor.

Duration of Participation: The time involved for your chemotherapy could vary from about 3 months (Group I) to 6 months (Group II). Radiation therapy given to lumpectomy patients will require an additional 5-6 weeks to be completed. Women assigned to take tamoxifen are expected to take the drug daily for 5 years. At this time the NSABP wishes to follow your medical condition for life.

(Revised page 3/26/97)

RISKS AND BENEFITS: The drugs used in this study may cause certain discomforts and risks, which are described below.

Risks Associated with Doxorubicin, Cyclophosphamide, and Paclitaxel: Chemotherapy will cause side effects in varying degrees, and some might be serious enough to require your being admitted to the hospital for supportive care. Doxorubicin, cyclophosphamide, and paclitaxel depress the function of the bone marrow and lower the white blood cell count, red blood cell count, and the platelet count. These conditions increase the susceptibility to bruising, bleeding, or infections, which occasionally may be serious or even life-threatening. Deaths from this type of condition have been reported. These drugs also cause nausea, vomiting, diarrhea, and weight loss in some patients. Inflammation of mucosal tissue (the moist membranes lining the mouth, throat, esophagus, and other areas) can occur. This inflammation can result in irritation and ulceration of this tissue. These effects can usually be kept to tolerable levels by adjusting the chemotherapy dosages, and the problems usually disappear after the course of treatment is stopped. These medications will produce complete hair loss, but regrowth usually begins once treatment has stopped. Changes in values of liver function tests, which could indicate potentially serious liver problems, have been observed with chemotherapy. Also, allergic reactions have been reported with these medications. These drugs could possibly cause harm to an unborn child and should not be administered to a pregnant woman or to a woman who is breastfeeding. Other side effects include skin rash, skin discoloration, sensitivity to sunlight, visual changes and eye inflammation, changes in nails, headache, dizziness, and fatigue.

Doxorubicin and cyclophosphamide have been associated with damage to the heart muscle, resulting in congestive heart failure in some patients. This association is dose-related, and such heart damage usually occurs at a greater dosage than is being given in this study. The dose for doxorubicin being used in this study has resulted in damage to a small fraction of heart muscle cells when they were examined under the microscope. This occurred in only a small percentage (less than 1%) of patients. It is believed that these microscopic changes will not result in noticeable symptoms and will not lead to heart failure. Assessment of these changes has not, however, been carried out over a prolonged period of time. Additionally, there have been reports of severe, life-threatening, irregular heartbeats occurring during or within a few hours of doxorubicin administration. Doxorubicin can cause your urine to become pink or red in color.

If doxorubicin or paclitaxel leak out at the injection site, redness, hardening of tissue, and tenderness may occur. Rarely with doxorubicin, ulceration, sometimes serious enough to require a skin graft, can occur. You will be closely monitored during treatment, and all precautions will be taken to avoid this.

Some chemotherapy agents, including cyclophosphamide and doxorubicin, have been associated with a small increase in the risk for developing leukemia (a life-threatening cancer of the blood cells) following therapy. The risk for developing leukemia following treatment with the chemotherapy used in this study is thought to be less than 1%.

(Revised page 3/26/97)
In addition to the side effects already described, cyclophosphamide may cause irritation of the bladder lining which may result in bloody urine. Drinking enough fluids will prevent this side effect, but, if it does occur, you should contact your physician immediately. Cyclophosphamide can cause water retention that can potentially lead to more serious side effects if not treated. Cyclophosphamide may cause irregular menstrual cycles and may stop them entirely. In some patients, normal menstrual function returns after completion of therapy. However, there is a chance that the therapy may make it impossible for you to conceive a child naturally. Second cancers of the urinary bladder have developed in some patients treated with cyclophosphamide.

Other reactions experienced by patients receiving paclitaxel include numbness, tingling, and burning in the extremities. More uncommon adverse effects include flushing, rash, shortness of breath, swelling, itching, lowered or increased blood pressure, chest pain, pancreatitis (inflammation of the pancreas), ischemic colitis (reduced blood supply to the large bowel), neutropenic enterocolitis (inflammation of the large bowel as a result of decrease in the white blood cell count), infarcted large bowel (blood clots in the vessels of the large bowel), changes in taste, seizures, visual abnormalities (flashing lights, blurred vision), mood changes, or muscle weakness. Also, changes in the heart rhythm have been observed; these usually do not require any therapy. One patient was reported to have had a fatal heart attack while taking paclitaxel. Temporary elevations in the values of liver function tests have been observed, leading on occasion to hepatic necrosis (death or decay of liver tissue) or hepatic encephalopathy (confusion caused by liver insufficiency) and death. Fatigue, and pain in the muscles and joints, can occur occasionally but are not usually severe. In areas of previous radiation, redness and inflammation may develop after paclitaxel administration.

Risks Associated with Tamoxifen: *(To be given to all women who are 50 years of age or over, and those under 50 who have a tumor positive for estrogen receptors or progesterone-receptors.)*
Adverse reactions to tamoxifen are infrequently severe enough to require discontinuing treatment.

The following information documents the side effects that have been observed.

Serious Side Effects:

Uterine Cancer: Tamoxifen may cause changes in the lining of the uterus (endometrium) that could potentially lead to uterine cancer. An early sign of abnormal changes in the uterus may be abnormal vaginal bleeding or pelvic discomfort (pressure/pain). Patients should report such symptoms to their physician immediately and seek evaluation in a timely fashion. The level of increased risk of uterine cancer associated with tamoxifen is still uncertain. After an average of 8 years of follow-up, the annual (per-year) risk observed in a large-scale study (NSABP B-14) of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women. This means that, on the average, 2 cases of endometrial cancer were diagnosed among every 1,000 women receiving tamoxifen during each year of study participation and follow-up. This level of risk is approximately three times greater than that of a similar age group of women in the general population. Uterine cancer is a potentially life-threatening illness. Some breast cancer patients who developed uterine cancer while taking tamoxifen have subsequently died from

(Revised page 3/26/97)
uterine cancer. However, most of the uterine cancers that have occurred have been diagnosed at an early stage when treatment is highly effective. The treatment for early-stage uterine cancer usually involves a hysterectomy (surgical removal of the uterus) as well as removal of the fallopian tubes and ovaries, and may include radiation therapy. In view of this risk, it is currently recommended that all patients receiving tamoxifen have a gynecologic exam before starting treatment and at least yearly thereafter. For women who have had a total hysterectomy, there is no risk of getting uterine cancer.

Other gynecologic side effects reported with tamoxifen include changes in the lining of the uterus that lead to polyps and hyperplasia (abnormal cell growth). Endometriosis (endometrial cells outside the uterus) has also been reported. Endometriosis can result in abdominal or pelvic pain. There is also a small risk of ovarian cysts occurring.

Other Cancers: Published data from one large U.S. study have not shown an increase in other (nonuterine) cancers in women taking tamoxifen. However, other data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been a few reports of liver cancer occurring in women taking tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (nonuterine) cancers is associated with tamoxifen is still uncertain and will continue to be evaluated.

Thrombotic Events (abnormal occurrences of blood clots): Some studies, but not all, have shown that tamoxifen causes about a 1% increase in the incidence of thrombotic events. These include superficial phlebitis (a painful but non-life-threatening inflammation of the veins close to the skin's surface), deep vein thrombosis (blood clots in large veins that could potentially travel to the lungs), and pulmonary embolism (a blood clot that has travelled to the lungs). Death has rarely occurred from such events in these studies. Patients with a preexisting history of such problems should discuss this carefully with their physician before starting tamoxifen therapy.

Eye Problems: Women taking tamoxifen may be at a slightly increased risk for developing cataracts (a clouding of the lens inside the eye). As women age, they are more likely to develop cataracts whether or not they take tamoxifen. Cataracts may lead to a decrease in vision. Eye surgery may be required to remove the cataract and improve vision. Women who have a cataract before beginning to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients.

Liver Toxicity: In addition to a few reports of liver cancer, mentioned previously, there have been reports of other liver toxicities that have occurred in women taking tamoxifen. These liver toxicities include abnormal liver function tests indicating serious problems, such as fatty liver, cholestasis (back-up of bile), hepatitis (inflammation of the liver), and hepatic necrosis (nonreversible damage to liver tissue). A few of these serious cases have resulted in death, but whether tamoxifen was the cause of these problems still remains uncertain. Blood tests to check liver function will be done at regular intervals during the study to detect liver toxicity. Should significant changes in liver function be identified, tamoxifen therapy will be suspended or discontinued.

(Revised page 3/26/97)
Typical Side Effects:

The most common side effect of tamoxifen is hot flashes. Some studies have noted increased reporting of nausea and/or vomiting. Less frequently, vaginal bleeding, discharge or dryness, menstrual irregularities, elevated blood calcium levels, lowered platelet counts, lowered white blood cell counts, fluid retention, and skin rash may occur. In the NSABP B-14 study, the number of women experiencing these side effects while taking tamoxifen was about equal to, or slightly more than, the number of women experiencing these side effects while taking a placebo. Rarer side effects associated with tamoxifen use include loss of appetite, distaste for food, vaginal itching, leg cramps, dizziness, lightheadedness, headache, mental depression, confusion, and fatigue. Hair thinning and/or hair loss has also been reported in women taking tamoxifen. Tumor flare appearing as bone or tumor pain and sometimes associated with elevated blood calcium levels can appear in patients being treated for metastatic disease (disease that has spread beyond the breast). Patients with increased pain may require additional pain relievers. Often such symptoms signal a good response to treatment, and these symptoms usually subside rapidly.

Risks Associated with the Premedication Therapy: For patients assigned to Group II, the drugs dexamethasone, cimetidine or ranitidine, and diphenhydramine will be given to control possible allergic reactions to the paclitaxel therapy. It is not expected that you will experience any side effects from these medications because they will be given for a short time (12 hours or less) at standard doses.

Risks Associated with rHu G-CSF: RHu G-CSF may cause bone pain and musculoskeletal symptoms such as muscle cramps, back and/or leg pain. Occasional skin rashes have also been reported. RHu G-CSF may also cause a recurrence of preexisting inflammatory conditions such as psoriasis, eczema, and inflammation of blood vessels. Hair thinning and an increase in the size of the spleen, with an associated lowered platelet count, have been shown to occur with prolonged administration of rHu G-CSF. The length of administration within this study would ***not*** be considered prolonged administration. Temporary elevations in blood enzyme values may occur, but these are not clinically significant and will not result in noticeable symptoms.

Risks Associated with Radiation Therapy: Side effects of breast irradiation are redness and irritation of the skin with peeling. Increased pigmentation of the skin may be persistent. There may be some increased firmness of the breast for a period of time. Very rarely, a transient dry cough with or without fever may develop a month or two after irradiation is completed. Also, in rare instances, a rib may develop a small fracture in the area of the chest that was treated, and a sharp pain may suddenly develop. This is highly unusual with modern radiation therapy techniques, and, if it should occur, heals on its own in a month or two without any local treatment required. Even more rarely, a second cancer may develop in the tissues exposed to radiation. The use of tamoxifen together with radiation is not known to cause side effects. Your radiation therapy physician may ask you to sign an additional consent form outlining the possible side effects.

(Revised page 3/26/97)
Other Risks: Mild pain or bruising may result from the needle sticks required for drug injection and blood collections in this study. The risk of infection is minimal.

Precautions:

For Women of Childbearing Potential: Women should not become pregnant while participating in this study. Doxorubicin, cyclophosphamide, and paclitaxel may cause harm to an unborn child.

While no clinical evidence is available to prove that tamoxifen may cause harm to an unborn child when given to a pregnant woman, due to its effect on estrogen (hormone) levels, tamoxifen may affect the ability of the woman's offspring to bear children. Information from studies conducted on mice has demonstrated some fetal deformities, including miscarriage, birth defects, or long-term effects on sexual development (which could be similar to the long-term effects caused by diethylstilbestrol (DES), a hormone medication that was given to pregnant women in the past). Women whose mothers took DES during pregnancy have an increased risk of developing cancer of the vagina or cervix and may have trouble bearing children. The relevance of these findings from animal studies to women who may accidentally take tamoxifen during pregnancy is unknown. To date, exposure of unborn infants to tamoxifen has not been shown to cause cancer later in the lives of these children. However, it is essential that you use effective methods to avoid pregnancy while taking protocol therapy, and for two months after completing or discontinuing therapy. Not all contraceptive measures have been approved for use in this study; you should discuss appropriate birth-control methods with your physician before entering the study. *By signing this consent form, you indicate that you have been informed of this potential risk.*

If you feel that you may be pregnant even though you have used contraceptive methods, you must notify your physician immediately and a pregnancy test may be performed.

For All Women in the Study: You must report any unusual vaginal bleeding or pelvic discomfort, which may be a sign of a uterine abnormality, to your physician. A yearly gynecologic examination should be performed.

Because estrogens may negate the effects of tamoxifen and can stimulate the growth of breast cancer cells, while you are receiving the protocol medication you must not use any intrauterine devices containing hormones, take any birth-control pills, or take any postmenopausal estrogen-replacement therapy, including estrogen pills, estrogen skin patches, or estrogen vaginal creams. You should discuss with your doctor any nonhormonal treatments for any menopausal (change-of-life) symptoms that you have or may develop.

You should report any changes in your vision, or other eye problems, to your study physician.

If any physician other than the study physician prescribes medication for you for another condition, you should inform the study staff so they can confirm that it will not conflict with your study medications.

As with any research study, unexpected side effects, some possibly life-threatening, may occur with any of these drugs. It is ***extremely*** important that you report all symptoms that you experience to your physician.

Benefits: Chemotherapy with doxorubicin/cyclophosphamide has been shown in many previous studies to be of benefit in patients with breast cancer. Paclitaxel, although not used before in a population of patients similar to yours, has been found to shrink tumors in some patients with advanced breast cancer. It is not known if you will personally benefit from participating in this study, although the knowledge gained in this study may benefit others.

Tamoxifen has been shown to decrease the risk of breast cancer recurrence after appropriate surgery. For this reason, it has been approved by the FDA for the treatment of women with breast cancer localized to the breast and for postmenopausal women with breast cancer localized to the breast and lymph nodes under the arm. It has also been approved for the treatment of metastatic breast cancer in women and men. Studies have also shown that tamoxifen can reduce the occurrence of second breast cancers in women who are taking the drug to prevent recurrence of their original tumor. In addition, it has been shown to lower the level of cholesterol and other fats in the blood, and this may reduce the risk of heart disease.

TESTING & EXAMINATION: Before entering the study, you must have a physical examination and some or all of the following tests:

- mammogram,
- blood tests,
- chest X ray,
- gynecologic exam (not required if patient has had a hysterectomy with removal of both ovaries),
- electrocardiogram,
- bone scan,
- MUGA scan (an X ray to evaluate how well the heart contracts).

Laboratory tests will be done during your course of treatment to determine drug dose modifications or delay, and to monitor any side effects you may experience. Should rHu G-CSF be required, a few drops of blood from a finger stick will be collected, or about 1-2 teaspoons of blood will be drawn from a vein in your arm with a needle, to monitor the effect of the drug on your white blood cell count.

Additional blood samples may be collected at any time should your physician feel they are medically necessary.

Years 1 through 5: A physical exam and blood tests requiring about 3 teaspoons of blood will be performed at your first visit, before each cycle of chemotherapy, and every six months.

Every 12 months you must have a gynecologic exam, a chest X ray, and a mammogram. A bone scan is required at 12 months only if your symptoms indicate it is necessary.

(Revised page 3/26/97)
From Year 6 On: Every 12 months you must have a physical exam, gynecologic exam, and a mammogram. A bone scan and/or a chest X ray is required every 12 months only if your symptoms indicate they are necessary.

Special Studies: At times it may be possible to do special research tests on samples of tissue, body fluids, or other specimens obtained from you during the normal course of your treatment and care. Samples of this nature will be sent to the NSABP's central specimen bank for storage. These samples will be used as needed for special tests that are part of other laboratory studies that have been or will be approved in the future by the NSABP. These special tests will allow researchers and doctors to learn more about how cancer works and how it can be treated.

ALTERNATIVE TREATMENTS: Alternative treatments for breast cancer that has spread to axillary lymph nodes include mastectomy alone, mastectomy and radiotherapy to the chest wall, or lumpectomy with removal of the lymph nodes plus radiotherapy without any drug treatment. In addition, other chemotherapy drugs or drug combinations are equally as effective as the doxorubicin/cyclophosphamide regimen you will be receiving. Your physician will discuss these alternatives with you and answer any of your questions.

You should understand that standard treatment with doxorubicin, cyclophosphamide, and tamoxifen is available to you without your having to participate in this study. Although paclitaxel is commercially available, the manner in which it will be given in this study is not considered to be standard therapy. It should be administered this way only as part of an approved research study.

NEW INFORMATION: If any significant new information about the study drugs or therapies develops, or if another therapy is proven to be effective, your doctor will tell you, and your options concerning your care will be discussed at that time. After being told of any new information, it may be necessary for you to sign an additional form providing your consent to continue to participate in the study. In order for the study doctor to provide you with new information, it is important that you keep him/her aware of any change in your address.

COSTS AND PAYMENTS: Physical examinations and lab tests (blood studies, X rays, mammograms, and electrocardiograms) will be done at intervals as outlined previously. These tests are felt to be part of good medical care. Your physician or his/her staff will advise you of any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs, and some of the costs may or may not be covered by your insurance company. Medications (other than paclitaxel) and all physicians' or hospital costs will be billed to you in the same manner as if you were not part of this study. No other monetary compensation will be provided.

Through Bristol-Myers Squibb Company, the makers of paclitaxel, the National Cancer Institute (NCI) will provide paclitaxel free-of-charge for this study. However, during the course of this study, if the drug is no longer supplied free to the NCI, you may be asked to purchase subsequent doses of the medicine.

There will be no cost to you for any specimens collected and stored in the NSABP specimen storage bank.

CONFIDENTIALITY: Any information about you or your treatment obtained from this research will be kept confidential and will never be identified in any report. In order to evaluate your overall health, your personal physician(s) will be asked to provide information concerning your medical care to the group of physicians responsible for coordinating this research study. It may also be necessary to send samples of your tumor tissue to a central facility for further medical review. The information included with your tissue will not identify you by name, but rather by your study code. Your study records, just like hospital records, may be subpoenaed (requested) by court order. When results of a study such as this are reported in medical journals or at meetings, the identification of participants remains confidential. Authorized representatives of the NCI, the FDA, the NSABP, and Bristol-Myers Squibb Company may examine and copy your medical records relating to this research, but all information examined will be kept confidential.

RIGHT TO WITHDRAW: You are free to refuse to participate in the study or to withdraw at any time for any reason. Your decision to do so will not adversely affect your care at this institution or cause a loss of benefits to which you might otherwise be entitled.

If you withdraw from further therapy, there may be potential adverse effects, which would depend on your individual condition. You should discuss these with your physician before stopping treatment.

At any time, your doctor can withdraw you from this study because further participation would not be in your best interest. Your doctor can stop the treatments even if you are willing to continue.

You should understand that, by signing this consent form, you are giving permission for samples of your tissue, body fluids, or other specimens to be stored in the NSABP storage bank; however, you can withdraw your permission at any time regarding this storage. Your decision to withdraw your permission will not adversely affect your participation in this study.

COMPENSATION FOR ILLNESS OR INJURY: You will not be compensated for any injury or illness resulting from your participation in this study, but any emergency medical treatment which may be necessary will be made available to you at your expense. In the case of injury related to this research study, you should contact _____at _____.

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VOLUNTARY CONSENT: I certify that I have read this consent form, or that it has been read to me, and any questions I had, including explanation of all terminology, have been answered to my satisfaction. I also understand that any future questions I may have pertaining to the research will be answered by Dr(s). _____ at _____. Any questions I have concerning my rights as a research subject will be answered by the following:

Office/Person:
Address:
Phone:

A copy of this consent form will be given to me.

My signature below means that I have freely agreed to participate in this research study.

_____ _____
Date Patient's Signature

_____ _____
Date Witness's Signature

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the patient indicated, and that any questions about this information have been answered.

_____ _____
Date Investigator's Signature