NRG ONCOLOGY
NSABP PROTOCOL B-49

A Phase III Clinical Trial Comparing the Combination of Docetaxel Plus Cyclophosphamide to Anthracycline-Based Chemotherapy Regimens for Women with Node-Positive or High-Risk Node-Negative, HER2-Negative Breast Cancer

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: Alliance, ECOG-ACRIN, and SWOG

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PROTOCOL REVISION RECORD

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Sections Changed:

Throughout the protocol, the following have been changed:

- *The NSABP and the NSABP Operations Center were changed to NRG Oncology where appropriate.*
- *All references to NSABP Biostatistical Center have been changed to NRG Oncology Statistics and Data Management Center (SDMC).*
- *Division has been changed to Department throughout the protocol where appropriate.*
- *References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)."*

Cover Page

Information Resources

Cancer Trials Support Unit (CTSU) Address and Contact Information

Glossary of Abbreviations and Acronyms

Section 1.0: 1.0

Section 4.0: 4.0

Section 5.0: 5.0 (Table 2)

Section 10.0: 10.2, 10.2.5, 10.2.6

Section 12.0: 12.0

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INFORMATION RESOURCES

NRG Oncology http://www.nsabp.pitt.edu		
NRG Oncology	Two Allegheny Center, Suite 1200 Pittsburgh, PA 15212	Phone: 412-339-5300
NRG Oncology Statistics and Data Management Center (SDMC)	One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213	Phone: 412-624-2666 Fax: 412-624-1082 (General office fax)
Questions/problems regarding IRB review & informed consent	NRG Oncology Department of Regulatory Affairs	Phone: 412-339-5300 E-mail: regulatory@nsabp.org
Submission of IRB approval	CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103	Phone: 1-866-651-2878 Fax: 215-569-0206 E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
Questions concerning eligibility and clinical aspects of the trial	NRG Oncology Clinical Coordinating Department	Phone: 1-800-477-7227 E-mail: ccd@nsabp.org
Study entry information (see Section 12.0)	NRG Oncology SDMC Patient Entry Coordinator	Phone: 412-383-4900 *Refer to the Patient Entry Guidelines in the Members' Area of the NSABP Web site.*
Submission of tumor blocks (see Section 6.0)	NRG Oncology SDMC One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 ***Note: When sending blocks, or other materials, please indicate on the package "Pathology Specimens Enclosed."***	*Questions regarding receipt of specimens:* Phone: 412-624-2666 *For all other questions:* Phone: 412-697-6611 *Refer to the B-49 Pathology and Correlative Science Instructions in the Members' Area of the NSABP Web site.*
Arrangement for return of blocks that are not to be stored	NSABP Division of Pathology	E-mail: pathology.questions@nsabp.org Phone: 412-697-6611
Questions concerning expedited adverse event reporting (see Section 10.2)	NRG Oncology SDMC B-49 AE Reporting Nurse	Phone: 412-383-2641 Fax: 412-622-2113 E-mail: SAEReporting@nsabp.pitt.edu
Submission of data forms/questions concerning data management	NRG Oncology SDMC B-49 Data Manager	Phone: 412-624-2666 *Refer to the B-49 Data Forms page in the Members' Area of the NSABP Web site.*

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the NRG Oncology unless otherwise specified in the protocol**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-2878 Fax: 215-569-0206 E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) system.	Submit study data online through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account. NRG Oncology Statistics and Data Management Center One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site Registration, Patient Enrollment, Adverse Event Reporting, and Data Submission.		
For patient eligibility and treatment-related questions, contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccd@nsabp.org. **For data submission questions**, contact the B-49 Data Manager at the NRG Oncology SDMC by calling 412-624-2666.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites, please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU Member Web site at https://www.ctsu.org.		
The CTSU Web site is located at https://www.ctsu.org.		

GLOSSARY OF ABBREVIATIONS AND ACRONYMS

AC	doxorubicin and cyclophosphamide
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer
ANC	absolute neutrophil count
ALT	alanine aminotransferase (also referred to as SGPT)
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase (also referred to as SGOT)
AT	doxorubicin and docetaxel
BCIRG	Breast Cancer International Research Group
BID	twice daily
BP	blood pressure
BSA	body surface area
CALGB	Cancer and Leukemia Group B
CAP	College of American Pathologists
CBC	complete blood count
CCD	Clinical Coordinating Department (NRG Oncology)
CHF	congestive heart failure
CI	confidence interval
CISH	chromagen in situ hybridization
CMF	cyclophosphamide, methotrexate, and fluorouracil
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP-Adverse Event Reporting System
CTEP-IAM	CTEP-Identity and Access Management
CTSU	Cancer Trials Support Unit
D/C	discontinue
DCIS	ductal carcinoma in situ
DCTD	Division of Cancer Treatment and Diagnosis
DD	dose dense
DFS	disease-free survival
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
FAC	fluorouracil, doxorubicin, and cyclophosphamide
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
G-CSF	granulocyte-colony stimulating factor
GEICAM	Grupo Español de Investigación en Cáncer de Mama
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HER2	human epidermal growth factor receptor-2

GLOSSARY OF ABBREVIATIONS AND ACRONYMS (continued)

HR	hazard ratio
IBTR	ipsilateral breast tumor recurrence
IDFS	invasive disease-free survival
IHC	immunohistochemistry
IRB	institutional review board
IV	intravenous
LCIS	lobular carcinoma in situ
LHRH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NSABP	National Surgical Adjuvant Breast and Bowel Project
OPEN	Oncology Patient Enrollment Network
OS	overall survival
p	probability
P	paclitaxel
PBI	partial breast irradiation
PET	positron emission tomography
PgR	progesterone receptor
PO	by mouth
RFI	recurrence-free interval
RT	radiation therapy
SDMC	Statistics and Data Management Center
SERM	selective estrogen receptor modulator
SN	sentinel node
SQ	subcutaneous
T	docetaxel
TAC	docetaxel, doxorubicin, and cyclophosphamide
TC	docetaxel and cyclophosphamide
TCB	docetaxel, cyclophosphamide, and bevacizumab
TID	three times a day
TOP2A	topoisomerase II alpha
ULN	upper limit of normal
USOR	US Oncology Research, Inc.
WBI	whole breast irradiation
WP	weekly paclitaxel

1.0 OVERVIEW OF THE STUDY DESIGN

Note: Accrual closed on November 21, 2013, following achievement of the sample size goal.

The B-49 study, a multicenter, open-label, randomized Phase III, adjuvant therapy trial, will compare the value of a non-anthracycline-based chemotherapy regimen relative to anthracycline-based chemotherapy regimens in women with resected node-positive or high-risk node-negative, HER2-negative breast cancer. This trial will compare invasive disease-free survival of a regimen of docetaxel and cyclophosphamide (TC) to anthracycline-based chemotherapy regimens. Secondary aims will evaluate the regimens in terms of disease-free survival, overall survival, and recurrence-free interval. The toxicities of the regimens will also be compared.

Patients in the B-49 study will be randomized to one of two treatment regimens: Arm 1 patients will receive 1 of 4 anthracycline-based chemotherapy regimens per investigator choice; Arm 2 patients will receive 6 cycles of TC administered every 21 days (docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2). Primary prophylaxis with growth factor support is required for Arm 1 Regimens A, C, and D patients (optional for patients in Arm 1 Regimen B and Arm 2). Patients will also receive adjuvant radiation therapy as clinically indicated and endocrine therapy for hormone receptor-positive tumors.

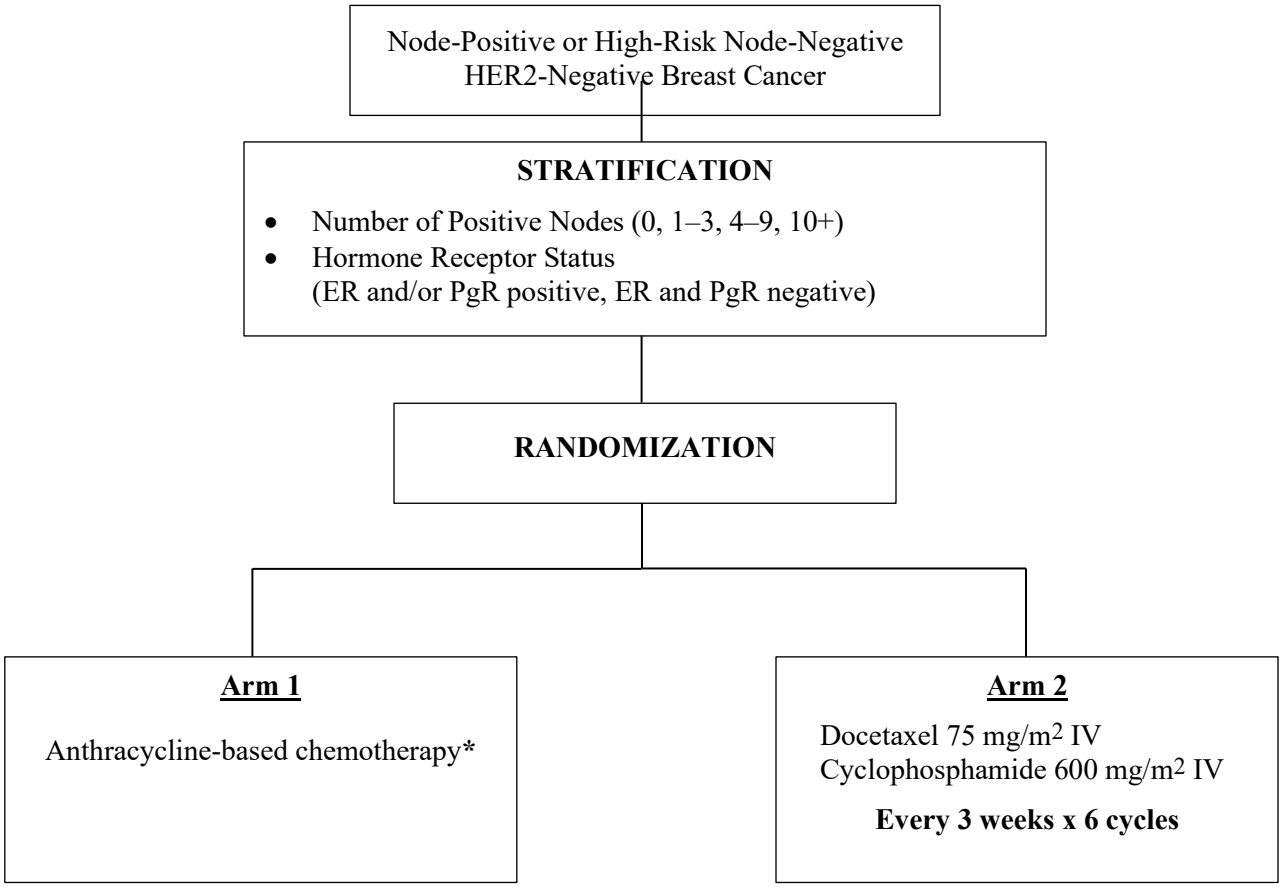
Efficacy data from the TAC/AC→P regimens and TC arms of this trial will be combined with the efficacy data from Groups 1 and 2 patients in NSABP B-46-I/USOR 07132 and the efficacy data from the USOR 06-090 study, which are comparing the TC and TAC regimens.

Tumor samples will be submitted for correlative science studies to evaluate predictors of study therapy benefit. Submission of a tumor sample is a study requirement for all patients.

The B-49 study will enroll 1843 patients (to be combined with 2357 patients from the TAC and TC groups of the NSABP B-46-I/USOR 07132 and USOR 06-090 studies for a total sample size of 4200) over a period of approximately 2 years and 4 months. It is anticipated that the initial release of study findings will be approximately 3.8 years after completion of accrual.

Figure 1

NSABP B-49 SCHEMA



* **Anthracycline-based chemotherapy** *(choice of regimen per investigator)*

- **Regimen A:**
  TAC: Docetaxel 75 mg/m^2 IV + doxorubicin 50 mg/m^2 IV + cyclophosphamide 500 mg/m^2 IV every 3 weeks for 6 cycles.
- **Regimen B:**
  AC→WP: Doxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 every week for 12 doses.
- **Regimen C:**
  DD AC→WP: Doxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 2 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 every week for 12 doses.
- **Regimen D:**
  DD AC→DD P: Doxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 2 weeks for 4 cycles followed by paclitaxel 175 mg/m^2 every 2 weeks for 4 cycles.

NOTE: For Arm 1 and Arm 2 patients, see Section 7.7.1 for information regarding protocol requirements for primary prophylaxis with G-CSF.

2.0 BACKGROUND

2.1 Background of breast cancer

Breast cancer is the most common type of noncutaneous cancer among women in the United States, with approximately 230,480 new cases of invasive breast cancer expected in 2011. Moreover, breast cancer is second only to lung cancer as a cause of cancer deaths in women, with 39,520 expected deaths from breast cancer in 2011.[1]

The risk of breast cancer increases gradually with age, with most diagnoses occurring in women over age 50. Over age 60, the risk is especially high (median age of patients with breast cancer is between 60-65 years). Since 1990, the overall death rate for breast cancer has decreased by 2.2% per year. Improvements in breast cancer screening have resulted in more women being diagnosed with earlier stages of breast cancer, and the efficacy of treatments for early stage breast cancer has improved substantially. For instance, the 5-year survival rate for women with localized breast cancer (cancer that has not spread to lymph nodes or other locations outside the breast) has improved from 80% in the 1950s to 98.6% today.[1] Unfortunately, approximately 20% to 25% of patients still develop recurrence and ultimately succumb to their disease.

2.2 Adjuvant treatment of breast cancer

Adjuvant chemotherapy can substantially reduce the risk of breast cancer recurrence and death in early stage breast cancer,[2] and there are many chemotherapy regimens with established efficacy and safety data. The value of chemotherapy has been consistently demonstrated from the data of individual randomized trials and affirmed in the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) 15-year meta-analyses combining data from the individual chemotherapy trials. The meta-analyses have shown that anthracycline-containing therapies, such as sequential doxorubicin and cyclophosphamide (AC) followed by taxanes, and combination regimens such as docetaxel, doxorubicin, and cyclophosphamide (TAC), reduce the risk of recurrence by 11% and the risk of death by 16% compared with cyclophosphamide, methotrexate, and fluorouracil (CMF) combinations.[3] However, anthracycline-based therapies carry a low but problematic risk of serious long-term toxicities such as congestive heart failure and leukemia.[4–7]

2.2.1 *Anthracycline regimens incorporating sequential taxanes*

CALGB 9344 and NSABP B-28 established the role of taxanes as a component of adjuvant therapy of breast cancer. Between May 1994 and April 1999, the CALGB randomized 3121 patients in a 3x2 factorial design to cyclophosphamide combined with one of three doses of doxorubicin given every 3 weeks for 4 cycles followed by paclitaxel on an every-3-week schedule or observation. No differences in efficacy based on doxorubicin dose were observed. However, adding paclitaxel to the AC regimens led to reductions in hazard for recurrence and death of 17% and 18%, respectively.[8] NSABP B-28 randomized 3060 women with resected, node-positive breast cancer to receive 4 cycles of AC followed by 4 cycles of paclitaxel on the every-3-week schedule vs. 4 cycles of AC. The addition of paclitaxel significantly reduced the hazard for DFS events by 17% (relative risk 0.83; 95% CI, 0.72– 0.95; p=0.006), but OS was similar for both groups.[9]

Following C9344, the US Intergroup evaluated the utility of every 2-week dosing intervals (dose-dense) relative to standard every 3-week intervals, employing a 2 x 2 factorial design in C9741. Paclitaxel, doxorubicin, and cyclophosphamide were used in

this trial. Initial results demonstrated improvement in both DFS and OS with the every 2-week dosing interval relative to the conventional schedule. In order to administer therapy every 2 weeks, prophylactic filgrastim was used. As a result, the incidence of neutropenia was diminished in the groups receiving the shorter dosing interval. However, red blood cell transfusions were given to 13% of patients treated on one of the dose-dense arms. Non-hematologic toxicities were not increased with the more frequent dosing, and overall, the dose-dense regimens were felt to be well tolerated.[10] Based on the increased efficacy without an overall increase in toxicity, dose-dense administration of doxorubicin, cyclophosphamide, and paclitaxel (DD AC→P) can be considered as yet another alternative standard of care for women with node-positive breast cancer.

NSABP B-27 evaluated the potential benefit of administering docetaxel (T) following AC as preoperative therapy for 2411 women with palpable, operable breast cancer. The addition of preoperative or postoperative T after preoperative AC showed a non-significant trend toward improving DFS, primarily by decreasing the incidence of local recurrences, but did not improve OS. Concurrent use of tamoxifen may have limited the impact of adding T.[11]

ECOG E1199 employed a 2x2 factorial design to compare paclitaxel to docetaxel following 4 cycles of AC and a weekly schedule vs. an every-3-week schedule of the taxanes in nearly 5,000 women with node-positive or high-risk node-negative breast cancer. Patients were randomly assigned to receive one of the following taxane treatments: docetaxel 35 mg/m^2 once a week; docetaxel 100 mg/m^2 once every 3 weeks; paclitaxel 80 mg/m^2 once a week; or paclitaxel 175 mg/m^2 once every 3 weeks. The primary comparisons showed no differences between the taxanes (paclitaxel vs. docetaxel: HR 1.032; p=0.61) or schedule (q3w vs. q1w: HR 1.062; p=0.33). However, a Cox proportional hazards model, which included the taxane administered, the taxane schedule and their interaction, showed the interaction of docetaxel and the weekly schedule was significant for both DFS (p=0.003) and OS (p=0.01). This complicated the interpretation of the primary endpoints so comparisons were made between the standard every-3-week paclitaxel schedule and each of the other three arms. As compared with the group receiving paclitaxel every 3 weeks, there was better DFS in the group receiving weekly paclitaxel (HR 1.27; p=0.006) and in the group receiving every-3-week docetaxel (HR 1.23; p=0.02). However, while OS was significantly better in the group receiving weekly paclitaxel (HR 1.32; p=0.01), it was not evident in the group receiving docetaxel every 3 weeks (HR 1.13; p=0.25). Serious adverse effects of treatment developed in 71% of patients treated with docetaxel every 3 weeks, and only 28% of patients treated with paclitaxel once a week. The increase in adverse events with docetaxel was primarily due to febrile neutropenia and neutropenia-associated infections which can be substantially diminished with the use of primary prophylactic G-CSF.[12,13]

2.2.2 *Anthracycline regimens employing concurrent taxanes*

In the BCIRG 001 study, 1491 women with axillary node-positive breast cancer were randomly assigned to receive either 6 cycles of TAC (n=745) or FAC (n=746). After 55 months of follow-up, the estimated rates of 5-year DFS were 75% among the women receiving TAC vs. 68% among those receiving FAC, a significant reduction in the risk of relapse (28%; p=0.001). TAC treatment also resulted in a significant reduction in the risk of death (30%; p=0.008). The estimated rates of OS at 5 years were 87% for TAC vs. 81% for FAC.[14]

GEICAM conducted a similar trial in 1060 women with node-negative breast cancer and at least one high-risk factor for recurrence (tumor size > 2.0 cm, negative hormone receptors, tumor histology grade 2 or 3, or < 35 years) which, with a median follow-up of 77 months, demonstrated a significant improvement in DFS in the TAC arm over the FAC arm, 87.8% and 81.8%, respectively (HR 0.68; 95% CI 0.49–0.93; p=0.01). The difference in survival rates, TAC 95.2% and FAC 93.5%, was not significant (HR 0.76; 95% CI 0.45–1.26).[15]

While TAC is effective, it is associated with some increased toxicity. Comparing the TAC-treated to the FAC-treated patients, Martin et al[14] reported significantly higher incidences of grade 3 or 4 neutropenia (65.5% vs. 49.3%; p < 0.001); febrile neutropenia (24.7% vs. 2.5%; p < 0.001); and grade 3 or 4 infections (3.9% vs. 2.2%; p=0.05). Routine use of prophylactic G-CSF on NSABP B-38 reduced the rates of febrile neutropenia to 7.2% in women receiving 6 cycles of TAC.[16]

2.2.3 *Studies comparing docetaxel administered concurrently or sequentially with doxorubicin*

The NSABP recently reported the results of B-30, a trial of adjuvant therapy in 5351 women with node-positive breast cancer. The study compared AC x 4 followed by docetaxel x 4 (AC→T) vs. TAC x 4 vs. AT x 4. The primary aim of the study was to determine if there was a significant difference in OS in the AC→T vs. TAC x 4 arms. There was a trend toward superiority of AC→T vs. TAC with a HR of 0.86 (p=0.086). AC→T was superior to TAC x 4 for reduction in DFS events with a HR of 0.83 (p=0.006). Toxicities were similar in AC→T and TAC with the notable exception that febrile neutropenia was more frequent in the AC→T arm (22% vs. 16%; p=0.0001). However, primary prophylaxis with G-CSF was required in the TAC arm, but not in the AC→T arm.[17]

In BCIRG 005, TAC x 6 was compared with sequential AC x 4 followed by docetaxel x 4 (AC→T) in 3298 women with node-positive, HER2-normal breast cancer. The primary endpoint of DFS showed no difference between the arms (HR 1.002; 95% CI 0.86–1.16). The TAC arm administered without primary G-CSF prophylaxis had a significantly higher rate of febrile neutropenia (17.9% vs. 8.3%; p= < 0.0001) and thrombocytopenia (2.5% vs. 1.3%; p=0.01) than AC→T while the AC→T arm had a greater incidence of neuropathy, nail changes, and myalgias.[18]

2.2.4 *Comparison of anthracycline and non-anthracycline regimens incorporating taxanes*

USOR compared TC to standard AC in 1016 women with node-positive or high-risk node-negative breast cancer. Patients with operable invasive breast cancer were randomly assigned to 4 cycles of either standard-dose AC (60/600 mg/m^2) [n=510] or TC (75/600 mg/m^2) [n=506], administered every 3 weeks. After a median follow-up of 7 years, DFS was statistically superior for TC relative to AC (81% vs. 77%) and the survival difference between TC and AC was significant, 87% and 82% (HR=0.69; p=0.032).[19] The TC arm was associated with more myalgias, arthralgias, edema, and febrile neutropenia, while patients on the AC arm experienced more nausea and vomiting. In the AC group, 1 patient died from CHF and 4 patients from MIs. In the TC group, no cases of CHF were observed though 2 patients had MIs.[20] These results provided

justification for a Phase III trial comparing the non-anthracycline TC regimen with the anthracycline-containing regimen of TAC.

Taken together, these studies suggest that TC x 4 is at least as efficacious as AC x 4 and that the longer duration regimens of AC→T, AC→P, and TAC have similar efficacy.

2.3 Rationale for plans to combine efficacy data from the anthracycline-based chemotherapy regimens and TC arms of B-49 with USOR 06-090 and NSABP B-46-I/USOR 07132

While TAC and AC followed by a taxane are effective adjuvant chemotherapy regimens, they are associated with a higher risk of hematologic and cardiotoxic adverse effects. An evolving body of retrospective data supported by results from a single, prospective randomized Phase III trial, suggest that patients with early stage HER2-negative breast cancers will benefit similarly from non-anthracycline-based chemotherapy regimens and anthracycline-based regimens with a more favorable long-term toxicity profile.[21–23] A Phase III adjuvant trial in HER2-negative, node-positive or high-risk node-negative patients with adequate sample size to definitively answer the anthracycline question is important to both patients and physicians.

TAC/AC→P regimens and TC are established adjuvant chemotherapy regimens for early stage breast cancer.[14,20] However, because of the serious long-term toxicities associated with anthracycline-based chemotherapy, it is important to conduct an adequately powered analysis of outcomes with non-anthracycline-based chemotherapy relative to anthracycline-based chemotherapy in patient populations selected for absence of HER2 gene amplification or protein overexpression. Additionally, a larger sample size with prospective collection of tumor material will provide the opportunity to identify small subsets of patients who may still receive benefit from anthracycline even if the overall population does not benefit. While TOP2A gene alterations appear to be highly associated with HER2 gene amplification, retrospective studies have reported 0% to 9% of HER2-negative breast cancers have alterations in the TOP2A gene, which might predict for benefit from anthracycline-based chemotherapy in this small subset of patients.[24,25]

On May 29, 2007, the US Oncology Research (USOR) Network opened a Phase III trial (USOR 06-090) to directly compare TC x 6 with TAC x 6 in patients with early stage HER2-negative breast cancer. The original study was designed as a superiority trial for TAC relative to TC so was underpowered for a non-inferiority test. The projected sample size of 2000 patients was powered to detect an absolute difference of 3% in DFS (HR of 1.345 for TC versus TAC) at year 3. Failure to demonstrate superiority was to be viewed as clinical equivalence. The available funding for the trial made it necessary to limit the sample size and the duration of follow-up to 5 years.

In the summer of 2007, the NSABP and USOR agreed to collaborate on a Phase III trial that would include a third arm, TC-bevacizumab (TCB), in addition to a control arm of TAC and a second control arm of TC. This study (NSABP B-46-I/USOR 07132) was developed and activated on May 8, 2009, with the support of Genentech, outside of the CTEP funding mechanism. The NRG Oncology SDMC holds the database and has provided randomization for this trial. The database for the patients accrued to USOR 06-090 is currently being held by USOR. The primary objective of B-46-I/07132 with a sample size of 3900 patients was to determine if the addition of bevacizumab to the TC regimen would improve IDFS relative to TC alone. A key secondary aim was comparison of IDFS of TCB with TAC in a hierarchical testing of pair-wise comparisons. Other secondary endpoints included OS and toxicity. The efficacy data from the TAC and TC arms of B-46-I/07132 would be sent to USOR to combine with the

efficacy data from USOR 06-090 for testing of the non-inferiority question. By combining the 2600+ women accrued to B-46-I/07132 with the 1296 women accrued to USOR 06-090, 3900 patients would have been randomized to TAC vs. TC. This would have provided sufficient power for non-inferiority testing. The analysis of the TAC vs. TC endpoints was to occur after the definitive analysis of TC vs. TCB on B-46-I/07132.

Accrual to the USOR 06-090 trial was closed on June 1, 2009, after accruing 1296 of the planned 2000 patients, in order to promptly begin accrual to B-46-I/07132. Enrollment did well until August 2010 when the FDA raised uncertainty about whether or not bevacizumab would continue to be available in the metastatic setting. At that time, all of the adjuvant bevacizumab breast cancer trials in the United States experienced a substantial drop in accrual, including ECOG E5103 and B-46-I/07132.[26] In February 2011, the DSMB (Data Safety Monitoring Board) for B-46-I/07132 recommended changes to the consent form and the protocol, to advise patients about the FDA concerns and possible worsening of cancer outcomes based on two adjuvant colon cancer trials evaluating bevacizumab, NSABP C-08 and AVANT. More recently, the Oncologic Drugs Advisory Committee (ODAC) upheld its decision to recommend the withdrawal of the approval of bevacizumab in metastatic breast cancer because of safety and efficacy concerns. On November 18, 2011, the FDA announced that bevacizumab is no longer approved for the treatment of metastatic breast cancer.

The NSABP and USOR believe the anthracycline question is compelling and needs to be answered in an adequately powered comparison of anthracycline and non-anthracycline regimens. Since B-46-I/07132 was developed, there have been several publications which have retrospectively analyzed outcomes in anthracycline-based adjuvant chemotherapy regimens. However, none of the published studies are randomized clinical trials which include or omit doxorubicin. The TC versus anthracycline-based regimens trial is a large randomized clinical trial to address the anthracycline question in women with HER2-negative breast cancer. The combined USOR 06-090 and B-46-I/07132 trials have enrolled 2357 women (as of 12/13/11) to the TC/TAC arms. With the 2357 women enrolled, we might be able to address the superiority question originally planned for USOR 06-090, if the event rate projections were correct. However, if we are able to enroll another 1843 women, we should be able to answer the non-inferiority question.

3.0 STUDY AIMS AND ENDPOINTS

3.1 Primary aim and endpoint

Aim: To determine if the TC regimen is non-inferior to the anthracycline-based chemotherapy regimens in terms of invasive disease-free survival (IDFS) by combining B-49 data with the TAC and TC arms of NSABP B-46-I/USOR 07132 and the data from USOR 06-090.

Endpoint: IDFS, defined as time to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, invasive contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer.[27]

3.2 Secondary aims and endpoints

3.2.1 *Disease-free survival (DFS-DCIS)*

Aim: To determine rates of DFS-DCIS for the TC and anthracycline-based chemotherapy regimens.

Endpoint: DFS-DCIS, defined as time to local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (invasive or non-invasive), regional recurrence, distant recurrence, contralateral breast cancer (invasive or non-invasive), second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer.[27]

3.2.2 *Overall survival (OS)*

Aim: To determine rates of OS for the TC and anthracycline-based chemotherapy regimens.

Endpoint: Time from randomization until death from any cause.

3.2.3 *Recurrence-free interval (RFI)*

Aim: To determine rates of RFI for the TC and anthracycline-based chemotherapy regimens.

Endpoint: Time from randomization until local, regional, or distant recurrence.

3.2.4 *Toxicity*

Aim: To evaluate the toxicity associated with each of the regimens.

Endpoint: Frequencies of adverse events categorized using the NCI CTCAE v4.0.

3.2.5 *Molecular predictors of efficacy*

Aim: To determine the role of TOP2A in prognosis and prediction of degree of benefit from anthracycline-based chemotherapy over TC.

Aim: To develop predictive markers for benefit from doxorubicin.

4.0 PATIENT ELIGIBILITY AND INELIGIBILITY

Note: Accrual closed on November 21, 2013, following achievement of the sample size goal.

4.1 Patient selection guidelines

Although the guidelines in Section 4.1 are not inclusion/exclusion criteria, investigators should consider each of these factors when selecting patients for the trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

- Patients should have a life expectancy of at least 10 years, excluding their diagnosis of breast cancer. (Comorbid conditions should be taken into consideration but not the diagnosis of breast cancer.)
- Women of reproductive potential must agree to use an effective non-hormonal method of contraception (for example, condoms, some intrauterine devices, diaphragms, tubal ligation, vasectomized partner, or abstinence) during therapy ***and for at least 6 months after the last dose of chemotherapy***.
- ***Submission of tumor samples from the breast surgery is required for all patients*** (see Section 6.1). Therefore, the local pathology department policy regarding submission of tumor samples for correlative science studies must be considered in the screening process. Patients whose tumor samples are located in a pathology department that by policy will not submit any samples for research purposes should not be approached for participation in the trial.

4.2 Conditions for patient eligibility

A patient cannot be considered eligible for this study unless all of the following conditions are met.

4.2.1 The patient or, if applicable, her legally authorized representative must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

4.2.2 Patients must be female.

4.2.3 The patient must be ≥ 18 years old.

4.2.4 The patient must have an ECOG performance status of 0 or 1 (see Appendix A).

4.2.5 The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.

4.2.6 The breast cancer must be HER2-negative based on current ASCO/CAP Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. If the result of the in situ hybridization testing (FISH, CISH, or other) is equivocal, the patient is eligible if there is no plan to administer HER2-targeted therapy.

4.2.7 All of the following staging criteria must be met according to AJCC criteria:

- By pathologic evaluation, primary tumor must be pT1-3;
- By pathologic evaluation, ipsilateral nodes must be pN_0, pN_1 (pN_{1mi}, pN_{1a}, pN_{1b}, pN_{1c}), pN_{2a}, pN_{3a}, or pN_{3b}.

  If pN0, at least one of the following criteria must be met:
  - ER negative ***and*** PgR negative; ***or***
  - Pathologic tumor size > 2.0 cm; ***or***

- T1c (pathologic tumor size > 1.0 cm but ≤ 2.0 cm) ***and*** ER positive (PgR status may be positive or negative) ***and either*** grade 3 histology or Oncotype DX® Recurrence Score of ≥ 25.

4.2.8 Patients must have undergone either a total mastectomy or breast-conserving surgery (lumpectomy).

4.2.9 For patients who undergo lumpectomy, the margins of the resected specimen must be histologically free of invasive tumor and DCIS as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures must be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. (Patients with margins positive for lobular carcinoma in situ [LCIS] are eligible without additional resection.)

4.2.10 For patients who undergo mastectomy, margins must be histologically free of invasive tumor and DCIS.

4.2.11 Patients must have completed ***one of the following procedures*** for evaluation of pathologic nodal status:

- Sentinel lymphadenectomy alone if pathologic nodal staging based on sentinel lymphadenectomy is pN_0, pN_{1mi}, or pN_{1b};
- Sentinel lymphadenectomy alone if pathologic nodal staging based on sentinel lymphadenectomy is pN_{1a} limited to 1 or 2 positive nodes and primary tumor is T_1 or T_2 by pathologic evaluation;
- Sentinel lymphadenectomy followed by removal of additional non-sentinel lymph nodes if the sentinel node (SN) is positive; or
- Axillary lymphadenectomy with or without SN isolation procedure.

4.2.12 The interval between the last surgery for breast cancer (treatment or staging) and randomization must be no more than 84 days.

4.2.13 Patients must have ER analysis performed on the *primary tumor* prior to randomization. Breast cancer must be assessed for ER status by current ASCO/CAP Guideline Recommendations for hormone receptor testing. If negative for ER, assessment of PgR must also be performed according to current ASCO/CAP Guideline Recommendations for hormone receptor testing. (Either a core biopsy or surgical resection specimen can be used for ER/PgR testing.)

4.2.14 The most recent postoperative blood counts, performed within 6 weeks prior to randomization, must meet the following criteria:

- ANC must be ≥ 1200/mm^3;
- platelet count must be ≥ 100,000/mm^3; and
- hemoglobin must be ≥ 10 g/dL.

4.2.15 The following criteria for evidence of adequate hepatic function must be met based on the results of the most recent postoperative tests performed within 6 weeks prior to randomization:

- total bilirubin must be ≤ ULN for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be ≤ 2.5 x ULN for the lab; *and*
- AST must be ≤ 1.5 x ULN for the lab.
- *Alkaline phosphatase and AST may not both be > the ULN*. For example, if the alkaline phosphatase is > the ULN but ≤ 2.5 x ULN, then the AST must be ≤ the ULN. If the AST is > the ULN but ≤ 1.5 x ULN, then the alkaline phosphatase must be ≤ ULN.

Note: If ALT is performed instead of AST (per institution's standard practice), the ALT value must be ≤ 1.5 x ULN; if both were performed, the AST must be ≤ 1.5 x ULN.

4.2.16 Patients with AST or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET-CT, or PET scan performed within 90 days prior to randomization) does not demonstrate metastatic disease and the requirements in criterion 4.2.15 are met.

4.2.17 Patients with alkaline phosphatase that is > ULN but ≤ 2.5 x ULN are eligible for inclusion in the study if a bone scan, PET-CT scan, or PET scan performed within 90 days prior to randomization does not demonstrate metastatic disease.

4.2.18 The most recent postoperative serum creatinine performed within 6 weeks prior to randomization must be ≤ ULN for the lab.

4.2.19 LVEF assessment by 2-D echocardiogram or MUGA scan must be performed within 90 days prior to randomization. ***The LVEF must be ≥ 50%*** regardless of the facility's LLN. (If the facility performing the assessment has not reported the LVEF as a whole number, decimals reported as ≥ 5 should be rounded up and decimals reported as < 5 should be rounded down.)

4.3 Conditions for patient ineligibility

Patients with one or more of the following conditions are ineligible for this study.

4.3.1 T_4 tumors including inflammatory breast cancer.

4.3.2 Definitive clinical or radiologic evidence of metastatic disease. (Chest imaging [mandatory for all patients] and other imaging [if required] must have been performed within 90 days prior to randomization.)

4.3.3 Synchronous or previous contralateral invasive breast cancer. (Patients with synchronous and/or previous contralateral DCIS are eligible.)

4.3.4 Any history of ipsilateral invasive breast cancer or ipsilateral DCIS.

4.3.5 History of non-breast malignancies within 5 years prior to randomization, except for the following: carcinoma in situ of the cervix, colorectal carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinomas of the skin.

4.3.6 Previous therapy with anthracyclines or taxanes for any malignancy.

4.3.7 Chemotherapy administered for the currently diagnosed breast cancer prior to randomization.

4.3.8 Continued endocrine therapy such as raloxifene or tamoxifen (or other SERM) or an aromatase inhibitor. Patients are eligible if these medications are discontinued prior to randomization.

4.3.9 Any sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy (see Section 4.1). Patients are eligible if these medications are discontinued prior to randomization.

4.3.10 Known active hepatitis B or hepatitis C with abnormal liver function tests.

4.3.11 Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens. This includes but is not confined to:

Active cardiac disease

- angina pectoris that requires the use of anti-anginal medication;
- ventricular arrhythmias except for benign premature ventricular contractions;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
- valvular disease with documented compromise in cardiac function;
- symptomatic pericarditis.

History of cardiac disease

- myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
- history of documented CHF;
- documented cardiomyopathy.

4.3.12 Whole breast RT prior to randomization or partial breast RT that cannot be completed on or before the date of randomization (see Section 7.8).

4.3.13 Intrinsic lung disease resulting in dyspnea.

4.3.14 Unstable diabetes mellitus.

4.3.15 Active infection or chronic infection requiring suppressive antibiotics.

4.3.16 History of a major organ allograft or condition requiring chronic immunosuppression, e.g., kidney, liver, lung, heart, bone marrow transplant, or autoimmune diseases. (Patients who have received corneal transplants, cadaver skin, or bone transplants are eligible.)

4.3.17 Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v4.0.

4.3.18 Conditions that would prohibit administration of corticosteroids.

4.3.19 Chronic daily treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).

4.3.20 History of hypersensitivity reaction to drugs formulated with polysorbate 80.

4.3.21 Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)***

4.3.22 Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.

4.3.23 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

4.3.24 Use of any investigational product within 30 days prior to randomization.

5.0 REQUIREMENTS FOR ENTRY, TREATMENT AND FOLLOW-UP

Note: Accrual closed on November 21, 2013, following achievement of the sample size goal.

Tests, exams and other assessments required prior to randomization are listed on Table 1. Requirements following randomization are outlined on Table 2.

TABLE 1. Tests, exams, and other requirements prior to randomization

Required Assessments	Prior to Randomization	
Consent form signed by the patient	X	
Determination of hormone receptor status (see Section 4.2.13)	X	
Complete history & physical exam	X**a**	Within 4 weeks
Menopausal status (see Appendix A)	X**b**	
Performance status (see Appendix A)	X	
Height & weight	X	
CBC/differential/platelet count	X	Within 6 weeks (must be *postoperative* testing)
Bilirubin/AST/Alkaline phosphatase	X**c**	
Serum creatinine	X	
Pregnancy test	X**d**	Within 2 weeks
2-D echocardiogram or MUGA scan	X	Within 90 days
Chest imaging (chest CT scan or chest x-ray)	X**e**	
Liver imaging	X**f**	Within 90 days *(if required)*
Bone nuclear imaging	X**g**	
Bilateral breast imaging	X**h**	Within 180 days

a The exam can be performed by a physician or other healthcare professional.
b An estradiol level may be required. Refer to the criteria in Appendix A.
c ALT may be substituted for AST if required by the institution's standard practice.
d For women of childbearing potential: Pregnancy testing should be performed according to institutional standards within 2 weeks prior to randomization.
e PET scans and PET-CT scans are permitted as an alternative to chest x-ray and CT scan of the chest.
f Liver imaging is required if alkaline phosphatase or AST is > ULN. Acceptable methods of liver imaging include CT, MRI, PET-CT, and PET scans to rule out metastatic disease.
g Bone nuclear imaging is required to rule out metastatic disease if alkaline phosphatase is > ULN or if the patient has unexplained bone pain. PET scan or PET-CT scan is permitted as a substitute for a bone scan.
h MRI is permitted as a substitute for mammogram prior to randomization (ultrasound is not permitted). Imaging may be unilateral for patients who have had mastectomy with or without reconstruction. (Breast imaging is not required for patients who had a bilateral mastectomy.)

TABLE 2. Tests, exams, and other requirements during therapy and follow-up
Note: Accrual closed on November 21, 2013, following achievement of the sample size goal.

Required assessments *(See footnote **a**)*	**After randomization**	**Within 4 days before each chemotherapy cycle** *(beginning with Cycle 2)*	**3-4 weeks following last chemotherapy dose**	**From completion of chemotherapy through Year 5 from randomization**	**Years 6 through 10 from randomization**
History & physical exam**b**		X	X	X (every 6 months)	X (every 12 months)
Performance status (Appendix A)		X	X		
Weight		X	X		
Adverse event assessment		X	X	X (every 6 months for selected late cardiac/vascular AEs)**c**	X (every 12 months for selected late cardiac/vascular AEs)**c**
CBC/differential/platelets		X (For WP, prior to doses 1, 4, 7, and 10)	X		
Serum creatinine			X		
Bilirubin/AST/ Alkaline phosphatase**d**			X		
Bilateral mammogram**e**				X (every 12 months)**f**	X (every 12 months)
Tumor sample submission	X**g**				

a H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.
b Treatment-related exams (by physician or other healthcare professional).
c See instructions in Section 10.4 for reporting selected late cardiac and vascular events on the B-49 follow-up form (after the final TRTAE form has been submitted).
d ALT may be substituted for AST if required by the institution's standard practice.
e ***Mammogram*** is required unless the patient has had a bilateral mastectomy. (Unilateral mammogram is required for patients who have had a unilateral mastectomy with or without reconstruction.) MRI is not permitted as a substitute for mammogram.
f First assessment will be 1 year from the most recent mammogram (or MRI) performed prior to randomization.
g Submission of a tumor sample is ***a study requirement for all patients*** within 3 months following randomization (see Section 4.1 and Section 6.0).

NOTE: *Tests, exams, and assessments **are not required** following a documented invasive breast cancer recurrence or diagnosis of a second primary malignancy, if treated with systemic anticancer therapy. Follow-up for subsequent cancer events and for survival continues to be required every 6 months until Year 6 from randomization and then every 12 months through Year 10. (See Section 10.0 for adverse event reporting requirements.)*

6.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

6.1 Overview of requirements

NSABP B-49 requires the submission of a tumor sample for all patients (see Section 4.1). Non-submission of the required tumor sample will be a protocol deviation.

TABLE 3. Summary of B-49 tumor sample submission requirements

Specimen	After randomization
Paraffin block from the breast cancer surgery* *(A study requirement for all patients)*	Yes *(within 3 months)*
Diagnostic H&E slides	No

* A tumor sample is required; a tumor block is strongly preferred. If the pathology department will not agree to submit a block that can be kept for research purposes, the block should be submitted and the NSABP Division of Pathology will procure samples of the tumor and return the block to the pathology department that submitted it. If the pathology department refuses to provide a tumor block for submission, contact the NSABP Division of Pathology to discuss possible alternative tumor sample submission instructions (see Information Resources on page 7).

Note: Refer to the B-49 Pathology and Correlative Science Studies Instructions in the Members' Area of the NSABP Web site for detailed instructions.

6.2 Use of specimens

The tumor samples collected in this study will be used for B-49 studies as described in Section 6.4. ***The procured specimens, including DNA samples, will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used.*** Results of the correlative science studies will not be reported to the patient or her physician and will not have any bearing on her treatment.

Patients must consent to the use of their tumor samples for the purposes of the B-49 studies as described in Section 6.4 in order to be eligible for the trial. Additionally, if any tumor sample remains upon completing the studies as described in Section 6.4, for those patients who agree, the remaining tumor sample may be used for future studies relating to patient prognostication, prediction of response to therapy, and susceptibility to drug toxicity that are not specified in the protocol document. Use of remaining tumor sample will be consistent with the patient's permission(s) granted by her responses to the consent form questions. De-identification procedures to protect the identity of the patient will be followed.

6.3 Specimen submission and identification procedures

Refer to the B-49 Pathology Instructions in the Members' Area of the NSABP Web site for details regarding submission of specimens.

Tumor blocks from all patients are initially shipped to and logged into the database at the NRG Oncology SDMC (refer to Information Resources, page 7). These samples are then stripped of patient identifiers, except B-49 Patient ID numbers, and forwarded to the NSABP Division of Pathology where they are assigned a code number for further processing and study.

6.4 Rationale for correlative science studies

The role of the TOP2A gene (encoding for topoisomerase II alpha) amplification and expression as a prognosticator or predictor of differential benefit from TAC versus TC

While many believe that TOP2A gene amplification is a predictor of preferential benefit from anthracyclines and, therefore, anthracyclines will not have any role in the treatment of TOP2A non-amplified breast cancer, scientific data do not always agree with this belief.[24] Doxorubicin is not a TOP2A-specific toxin. In a study utilizing synthetic lethality screening with a series of mutant yeast strains, Simon et al have demonstrated that most of the chemotherapeutic agents do not have single specific targets.[28] Doxorubicin was categorized as a non-selective agent when compared with mitoxantrone, which was validated as a TOP2A-specific toxin in the latter study. Furthermore, TOP2A gene expression levels do not correlate tightly with TOP2A mRNA or protein expression levels. Instead, TOP2A expression levels are associated with proliferation genes such as Ki67 and tumor histologic grade.[29] Therefore, TOP2A gene expression may have a role as a prognosticator, or even as a predictor of degree of benefit from more aggressive or potent chemotherapy.

The NSABP Division of Pathology prepared unstained tissue sections from the submitted blocks for B-46-I/07132. The unstained sections were sent to the Molecular Profiling Institute Inc. (MPI) for B-46-I/07132 research purposes. Provision of these tissue sections to MPI were limited to a cohort of B-46-I/07132 patients who were randomized to Group 1 or Group 2. These tissue sections were added to tumor samples from patients enrolled in USOR 06-090 until samples from a total of 2,000 patients were received by MPI. The correlative science study incorporated in USOR 06-090 will address some of the issues described by assaying for TOP2A gene amplification by FISH and expression of TOP2A protein and Ki67 by the IHC method. These studies will continue to be performed by the MPI.

In addition, using banked tumor blocks, we plan to examine the expression levels of other genes, using gene expression profiling methods to be determined upon completion of the trial. Due to the rapid development in gene expression profiling technology, we will not commit to a single existing method at the time of protocol development. Additional review of profiling methods will be required at the time specific methods are determined.

7.0 TREATMENT REGIMENS

7.1 Chemotherapy for Arm 1 regimen A (TAC)

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 4. Arm 1 treatment regimen A (TAC)

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	50 mg/m^2 via sidearm through a running IV over 5-15 minutes	Day 1 every 3 weeks**a**	Cycles 1-6
Cyclophosphamide (C)	500 mg/m^2 IV over 15-30 minutes		
Docetaxel (T)	75 mg/m^2 IV over 60 minutes *See footnote **b** for premedications.*		

a ***Primary prophylaxis with G-CSF is required*** (see Section 7.7.1 for instructions).

b All patients should receive premedications as follows before each docetaxel dose:

- Dexamethasone 8 mg by mouth twice daily the day before and the day of chemotherapy is recommended. At the investigator's discretion, dexamethasone may be continued on the day after chemotherapy. An equivalent dose of other corticosteroids may be substituted (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg).
- Administration of IV dexamethasone (dose at the investigator's discretion) as a substitute for oral dexamethasone prior to chemotherapy is at the investigator's discretion.
- At the investigator's discretion, other non-steroidal premedications, e.g., diphenhydramine hydrochloride 50 mg IV and H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) may be given in addition to dexamethasone.

7.2 Chemotherapy for Arm 1 regimen B (AC→WP)

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 5. Arm 1 treatment regimen B (AC→WP)

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m^2 IV over 15 minutes	Day 1 every 3 weeks[a]	Cycles 1–4
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
Initiate 3 weeks after the last dose of AC			
Paclitaxel (WP)	80 mg/m^2 IV over 60 minutes *See footnote **b** for premedications*	Weekly	12 doses[c]

a ***Primary prophylaxis with G-CSF is optional*** (see Section 7.7.1 for instructions).

b All patients should receive premedications as follows before each paclitaxel dose:

- Dexamethasone 10 mg IV, completed 30 minutes before each paclitaxel administration. (At the investigator's discretion, dexamethasone may be tapered during the paclitaxel cycles.)
- Diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before each paclitaxel administration.

c Paclitaxel therapy must stop 16 weeks after the first dose of paclitaxel. If medical or non-medical treatment delays occur during paclitaxel therapy, administer as many of the remaining doses as possible by 16 weeks.

7.3 Chemotherapy for Arm 1 regimen C (DD AC→WP)

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 6. Arm 1 treatment regimen C (DD AC→WP)

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m^2 IV over 15 minutes	Day 1 every 2 weeks[a]	Cycles 1–4
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
Initiate 2-3 weeks after the last dose of AC			
Paclitaxel (WP)	80 mg/m^2 IV over 60 minutes *See footnote **b** for premedications*	Weekly	12 doses[c]

a ***Primary prophylaxis with G-CSF is required during AC cycles*** (see Section 7.7.1 for instructions).

b All patients should receive premedications as follows before each paclitaxel dose:

- Dexamethasone 10 mg IV, completed 30 minutes before each paclitaxel administration. (At the investigator's discretion, dexamethasone may be tapered during the paclitaxel cycles.)
- Diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before each paclitaxel administration.

c Paclitaxel therapy must stop 16 weeks after the first dose of paclitaxel. If medical or non-medical treatment delays occur during paclitaxel therapy, administer as many of the remaining doses as possible by 16 weeks.

7.4 Chemotherapy for Arm 1 regimen D (DD AC→ DD P)

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 7. Arm 1 treatment regimen D (DD AC→DD P)

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m^2 IV over 15 minutes	Day 1 every 2 weeks**a**	Cycles 1–4
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
Initiate 2-3 weeks after the last dose of AC			
Paclitaxel (P)	175 mg/m^2 IV over 3 hours *See footnote **b** for premedications*	Day 1 every 2 weeks**a**	Cycles 5–8

a ***Primary prophylaxis with G-CSF is required during AC and dose-dense paclitaxel cycles*** (see Section 7.7.1 for instructions).

b All patients should receive premedications as follows before each paclitaxel dose:

- Dexamethasone 20 mg by mouth the night before and the morning of each paclitaxel administration. Following Cycle 5, investigators may reduce the dose of dexamethasone at their discretion to manage steroid-related toxicities.
- Diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before each paclitaxel administration.

7.5 Chemotherapy for Arm 2 (TC)

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 8. Arm 2 treatment regimen (TC)

Drug	Dose	Dosing Interval	Planned Duration
Docetaxel (T)	75 mg/m^2 IV over 60 minutes *See footnote **a** for premedications.*	Day 1 every 3 weeks**b**	Cycles 1-6
Cyclophosphamide (C)	600 mg/m^2 IV over 15-30 minutes		

a All patients should receive premedications as follows before each docetaxel dose:

- Dexamethasone 8 mg by mouth twice daily the day before and the day of chemotherapy is recommended. At the investigator's discretion, dexamethasone may be continued on the day after chemotherapy. An equivalent dose of other corticosteroids may be substituted (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg).
- Administration of IV dexamethasone (dose at the investigator's discretion) as a substitute for oral dexamethasone prior to chemotherapy is at the investigator's discretion.
- At the investigator's discretion, other non-steroidal premedications, e.g., diphenhydramine hydrochloride 50 mg IV and H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) may be given in addition to dexamethasone.

b ***Primary prophylaxis with G-CSF is optional*** (see Section 7.7.1 for instructions).

7.6 Dose determinations

7.6.1 *Calculation of BSA and/or chemotherapy doses*

- Based on the patient's weight and BSA, recommended chemotherapy doses will be provided at the time of randomization.
- Recalculations of BSA and drug doses are required if the patient has a 10% or greater weight change (+/-) from baseline or from the last weight used to calculate BSA and drug doses. At the investigator's discretion, the BSA and drug doses may also be recalculated prior to each treatment.

7.6.2 *Rounding doses*

Rounding of drug doses is optional. If the investigator decides to round the dose(s), follow these guidelines. (These also apply to dose modifications.)

- ***Cyclophosphamide*** (500 mg/m^2 IV –Arm 1 Regimen A;
  600 mg/m^2 IV –Arm 1 Regimens B, C, and D and Arm 2)
  Doses should be rounded to the nearest 20 mg.
- ***Docetaxel*** (75 mg/m^2 IV)
  Doses should be rounded to the nearest 5 mg.
- ***Doxorubicin*** (50 mg/m^2 IV)
  Doses should be rounded to the nearest 2 mg.
- ***Paclitaxel*** (80 mg/ m^2 IV –Arm 1 Regimens B and C; 175 mg/m^2 IV – Arm 1 Regimen D)
  Doses should be rounded to the nearest 5 mg.

7.7 Supportive therapy

7.7.1 *G-CSF*

- Primary prophylaxis with pegfilgrastim or filgrastim is required for patients receiving **Arm 1 Regimens A, C, or D** (see Tables 4, 6, and 7). It should be administered according to the package insert for the agent used.
- If G-CSF support is required during weekly paclitaxel therapy, filgrastim ***must*** be used.
- Use of pegfilgrastim or filgrastim as primary prophylaxis (i.e., initiating G-CSF prior to febrile neutropenia or infection with neutropenia) is at the investigator's discretion for **Arm 1 Regimen B and Arm 2** patients (see Tables 5 and 8). If utilized, it should be administered according to the package insert for the agent used.
- Do not administer G-CSF within 24 hours of chemotherapy.
- If required by institutional standards, GM-CSF may be administered as an alternative to G-CSF.

7.7.2 *Prophylactic antibiotics*

At the investigator's discretion, primary prophylaxis with fluoroquinilones may be administered, e.g., levofloxacin 500 mg PO daily or ciprofloxacin 500 mg PO BID. Other antibiotics may be used in case of allergy prohibiting levofloxacin and ciprofloxacin.

7.7.3 *Erythropoietin*

Use of an erythropoiesis-stimulating agent is not permitted. (See Section 8.2 for instructions regarding ≥ grade 3 anemia.)

7.7.4 *Antiemetic therapy*

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) clinical practice guidelines.

7.8 Adjuvant radiation therapy

Choice of RT, treatment fields, and treatment schedule will be at the discretion of the radiation oncologist.

7.8.1 *Whole breast irradiation (WBI) following breast conserving surgery*

WBI should begin within 6 weeks following the last dose of chemotherapy. Regional nodal irradiation is at the radiation oncologist's discretion.

7.8.2 *Partial breast irradiation (PBI) following breast conserving surgery*

PBI utilizing 3-D conformal RT or brachytherapy is permitted only if RT is completed on or before the date of randomization.

7.8.3 *Post-mastectomy RT*

RT is at the radiation oncologist's discretion.

7.9 Adjuvant endocrine therapy

Patients with ER-positive and/or PgR-positive tumors should receive a minimum of 5 years of adjuvant endocrine therapy.

- Adjuvant endocrine therapy should be initiated 3-6 weeks following the completion of chemotherapy. At the investigator's discretion, initiation may be delayed until after completion of RT but should be initiated by 12 weeks following completion of chemotherapy.
- LHRH agonist/antagonists (e.g., Lupron® and Zoladex®) or ovarian ablation by surgery or RT are permitted for premenopausal patients.
- Adjuvant endocrine therapy should be administered according to the current ASCO guidelines. However, selection of endocrine therapy will be at the investigator’s discretion. The dose and schedule of endocrine therapy should be consistent with the drug package insert. (See Section 7.10 for prohibited therapies.)

7.10 Prohibited therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited until the time of diagnosis of the first cancer recurrence or diagnosis of a second primary malignancy.

7.10.1 *Chemotherapy*

Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited.

7.10.2 *Targeted therapy*

Administration of targeted therapy for cancer is prohibited.

7.10.3 *Endocrine therapy*

SERMs other than tamoxifen and toremifene are prohibited (see Section 7.9 for instructions regarding initiation of endocrine therapy ***following*** chemotherapy).

7.11 Participation in other clinical trials

- Patients may participate in the NSABP B-39/RTOG 0413 trial.
- If a B-49 patient is considering participation in another clinical trial (including supportive therapy trials), contact the NRG Oncology Clinical Coordinating Department (see Information Resources on page 7).

8.0 TREATMENT MANAGEMENT

8.1 General instructions

- The CTCAE v4.0 must be used to grade the severity of adverse events (AEs).
- All doses must be based on the AE requiring the greatest modification.
- Chemotherapy doses that have been reduced may not be escalated.
- Chemotherapy should be held for at least 1 week until any AE requiring dose modification returns to ≤ grade 1 unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified in Section 8.0 instructions) has not occurred after 3 weeks of delay, chemotherapy must be discontinued.
- In the event of tumor recurrence, chemotherapy should be discontinued. Further therapy is at the investigator's discretion.
- See Section 12.7 for instructions regarding investigator-initiated discontinuation of chemotherapy.

8.2 Management of anemia

Chemotherapy should not proceed with ≥ grade 3 anemia. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

8.3 Docetaxel-specific toxicities

8.3.1 *Allergic reaction or anaphylaxis*

If a docetaxel-related hypersensitivity reaction occurs despite premedication, treatment as medically indicated will be instituted. For ≤ grade 3 allergic reaction or grade 3 anaphylaxis, continuation of docetaxel is at the investigator's discretion. Following a grade 4 allergic reaction or grade 4 anaphylaxis, docetaxel must be permanently discontinued. (See Appendix B for recommended symptom management.)

8.3.2 *Fluid retention*

Docetaxel-related fluid retention will be treated as per the investigator's discretion.

(See Appendix B for recommended symptom management.)

8.3.3 *Neuropathy and musculoskeletal pain related to docetaxel*

See Tables 11 and 12 for management of neuropathy and musculoskeletal pain.

8.4 Treatment management for TAC (Arm 1 Regimen A)

Also refer to Section 8.1 for general instructions, Section 8.2 for anemia, and Section 8.3 for docetaxel-specific toxicities.

8.4.1 *Cardiac AEs during AC*

If the patient develops any of the following cardiac AEs during AC, study therapy should be discontinued and further therapy is at the investigator's discretion.

- Any ≥ grade 2 cardiac AE listed in Appendix C.
- Any ≥ grade 3 AE listed in the Cardiac Disorders section of the CTCAE v4.0.

8.4.2 *Non-cardiac toxicity*

- If AC is discontinued due to non-cardiac toxicity, study therapy should be discontinued. Further therapy is at the investigator's discretion.
- If docetaxel is discontinued due to toxicity, chemotherapy should be completed with AC. Alternatively, the investigator may discontinue study therapy and administer alternative chemotherapy at the investigator's discretion.

8.4.3 *Dose modifications for TAC*

- All TAC dose modifications are based on dose level changes noted in Table 9.
- Instructions for all other toxicities are listed in Table 10.

TABLE 9. Dose levels for TAC (Arm 1 Regimen A)

	Dose Level 0 ***Starting Dose*** **(mg/m²)**	**Dose Level-1 (mg/m²)**	**Dose Level-2**
Docetaxel (T)	75	60	Discontinue
Doxorubicin (A)	50	40	Discontinue
Cyclophosphamide (C)	500	400	Discontinue

TABLE 10. Treatment management for TAC (Arm 1 Regimen A)

Important table instructions:

- Dose modifications must be based on AEs observed during the cycle (column 2) ***and*** AEs present on scheduled Cycle Day 1 (column 3). Refer to all sections/tables within Section 8.0 for additional instructions.
- Dose modifications must be based on the AE requiring the greatest modification.
- Modifications apply to docetaxel, doxorubicin, and cyclophosphamide unless specified otherwise.
- **NOTE:** If the docetaxel dose has been reduced for docetaxel-related toxicities (see Tables 11 and 12) and a subsequent toxicity requiring dose reduction of docetaxel or AC occurs, maintain docetaxel at the reduced dose level (-1) and decrease AC to dose level -1; ***or***, at the investigator's discretion, study therapy may be discontinued. Further therapy is then at the investigator's discretion.

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, 4	Maintain dose	***ANC:*** *Hold until ≥ 1200/mm^3. If recovery takes:* 1 wk – maintain dose 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2 to 3 wks – ↓ one dose level
Grade 4	↓ one dose level	↓ one dose level
GI *(if related to chemotherapy)*: **Diarrhea** Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis oral Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting (*despite antiemetics*) Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grades 3,4	↓ one dose level or D/C	D/C
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1; then* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1; then* ↓ one dose level or D/C
Grade 4	D/C	D/C
Febrile neutropenia: Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	↓ one dose level or D/C
Infection Grade 2	Maintain dose	Maintain dose
Grade 3	Maintain dose	Maintain dose
Grade 4	↓ one dose level or DC	↓ one dose level or D/C
Other clinically significant AEs:[c] Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level or D/C
Grade 4	↓ one dose level or D/C	D/C

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle, i.e., treatment can be given without delay. (See Section 8.4.1 regarding LV dysfunction.)

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤grade 1.*** If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue chemotherapy.

c Determination of "clinically significant" AEs is at the discretion of the investigator.

TABLE 11. Treatment management for docetaxel-related neuropathy (Arm 1 Regimen A [TAC] and Arm 2 [TC])

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	**1-7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Cycle to be Delayed**
Grade 1	Maintain docetaxel dose	
Grade 2	Maintain docetaxel dose[a]	Decrease docetaxel one dose level[b]
Grade 3	**First episode:** Decrease docetaxel one dose level[a] **Second episode:** Discontinue docetaxel	Discontinue docetaxel
Grade 4	Discontinue docetaxel	

a Must be resolved to ≤ grade 1 on Day 1 of the next cycle.

b Hold chemotherapy for ***persistent*** grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification for docetaxel (no dose reduction for cyclophosphamide and doxorubicin [Arm 1 Regimen A] or cyclophosphamide [Arm 2]). If grade 2 toxicity persists after 3 weeks of delay, discontinue docetaxel.

TABLE 12. Treatment management for docetaxel-related musculoskeletal pain (Arm 1 Regimen A [TAC] and Arm 2 [TC])

Note: The treatment management instructions in Table 12 apply to patients with **musculoskeletal pain not controlled by analgesics**. Use of narcotics and NSAIDs is encouraged to maintain the docetaxel dose if possible.

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	**1 – 7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Cycle to be Delayed**
Grade 1 *(despite analgesics)*	Maintain docetaxel dose	
Grade 2 *(despite analgesics)*	Maintain docetaxel dose	Maintain docetaxel dose or Decrease docetaxel one dose level*
Grade 3 *(despite analgesics)*	**First episode:** Decrease docetaxel one dose level **Second episode:** Discontinue docetaxel	**First episode:** Decrease docetaxel one dose level* or Discontinue docetaxel **Second episode:** Discontinue docetaxel

* Hold docetaxel for ***persistent*** grade 2 or 3 musculoskeletal pain. ***(While docetaxel is held, other study therapy should continue.)*** When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue docetaxel.

8.5 Treatment management for AC (Arm 1 Regimens B, C, and D)

8.5.1 *Cardiac AEs during AC*

If the patient develops any of the following cardiac AEs during AC, study therapy should be discontinued and further therapy is at the investigator's discretion.

- Any ≥ grade 2 cardiac AE listed in Appendix C.
- Any ≥ grade 3 AE listed in the Cardiac Disorders section of the CTCAE v4.0.

8.5.2 *Non-cardiac toxicity*

- If AC is discontinued due to non-cardiac toxicity, paclitaxel (WP or DD P) should be initiated.
- If AEs occurring during dose-dense AC have resulted in treatment delays, the AC therapy should be converted to the every 3-week treatment schedule.
- All dose modifications for AC are based on Table 13 dose level changes. Instructions for management of non-cardiac AC toxicities are listed on Table 14. The dose levels on Table 13 and the instructions on Table 14 apply to both AC treatment schedules (every 3-weeks and every 2-weeks [dose-dense]).

TABLE 13. Dose levels for AC and DD AC (Arm 1 Regimens B, C, and D)

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level-1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Doxorubicin (A)	60	50	40	Discontinue
Cyclophosphamide (C)	600	500	400	Discontinue

TABLE 14. Treatment management for AC and DD AC (Arm 1 Regimens B, C, and D)

Important table instructions:

- Dose modifications must be based on AEs that occurred during the cycle (column 2) and AEs present on the scheduled Day 1 of Cycles 2-4 (column 3). Refer to all sections/tables within Sections 8.0.
- All modifications in dose levels apply to both doxorubicin and cyclophosphamide (AC).
- Dose modifications must be based on the AE requiring the greatest modification.
- **If the dose-dense schedule for AC is used, primary prophylaxis with G-CSF is required.**

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, 4	Maintain dose	***ANC:*** *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose and add G-CSF**c** *If receiving G-CSF and recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2 to 3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI *(if related to chemotherapy)*: **Diarrhea**		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis oral		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting *(despite antiemetics)*		
Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigation (hepatic): **Bilirubin, AST, alk phos**		
Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia:		
Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles if neutropenia was present.**d**	
Grade 3	Maintain dose and add G-CSF**c** prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose and add G-CSF**c** prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	
Other clinically significant AEs:[e]		
Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** If toxicity has not resolved after 3 weeks of delay, discontinue AC and proceed to paclitaxel.

c Pegfilgrastim, at a fixed dose of 6 mg SQ on Day 2, is preferred. Filgrastim, if used, should be administered according to the drug package insert.

d If grade 2 criteria for infection include topical and/or systemic antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.

e Determination of "clinically significant" AEs is at the discretion of the investigator.

8.6 Treatment management for WP (Arm 1 Regimens B and C) and DD P (Arm 1 Regimen D)

8.6.1 *Treatment decisions when paclitaxel must be held or discontinued*

- Unless otherwise specified, paclitaxel that is held due to toxicity will not resume until the toxicity has resolved to ≤ grade 1.
- Weekly paclitaxel (WP) must be completed within 16 weeks. Any of the 12 doses remaining after 16 weeks following the first paclitaxel dose should not be administered.

8.6.2 *Instructions for dose modifications and treatment delays during paclitaxel*

- Dose modifications for paclitaxel are based on the dose level changes outlined on Tables 15 and 16.
- Dose modifications and instructions for management of neuropathy related to paclitaxel are outlined on Table 18.
- Dose modifications and instructions for management of musculoskeletal pain related to paclitaxel are outlined on Table 19.
- Dose modifications for other toxicities are outlined on Table 17.

TABLE 15. Dose levels for weekly paclitaxel (Arm 1 Regimens B and C)

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level-1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Weekly paclitaxel (WP)	80	60	45	Discontinue

TABLE 16. Dose levels for dose-dense paclitaxel (Arm 1 Regimen D)

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level-1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Dose-dense paclitaxel (DD P)	175	135	100	Discontinue

TABLE 17. Treatment management for WP and DD P (Arm 1 Regimens B, C, and D)

Important table instructions:

- Dose modifications must be based on AEs that occurred between treatments (column 2) and AEs present on the scheduled treatment day (column 3). Refer to all sections/tables within Sections 8.0 for additional instructions.
- Dose modifications must be based on the AE requiring the greatest modification.
- **If the dose-dense schedule for paclitaxel is used, primary prophylaxis with G-CSF is required.**

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, 4	Maintain dose	***ANC:*** *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose and add G-CSF**c** *If receiving G-CSF and recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2 to 3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI *(if related to chemotherapy)*:		
Diarrhea		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis oral		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting *(despite antiemetics)*		
Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigation (hepatic): **Bilirubin, AST, alk phos**		
Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia:		
Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles if neutropenia was present.**d**	
Grade 3	Maintain dose and add G-CSF**c** prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose and add G-CSF**c** prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	
Other clinically significant AEs:[e]		
Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level or D/C
Grade 4	↓ one dose level or D/C	D/C

a ***Treatment may not proceed until clinically significant AEs are ≤grade 1*** (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade).

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue paclitaxel.

c Only filgrastim on Days 2-6 may be used for WP; pegfilgrastim is prohibited duringWP.

d If grade 2 criteria for infection include topical and/or systemic antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.

e Determination of "clinically significant" AEs is at the discretion of the investigator.

TABLE 18. Treatment management for paclitaxel-related neuropathy (Arm 1 Regimens B, C, and D)

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	**1–7 Days Duration**	**Persistent for> 7 Days *or* Caused the Next Treatment to be Delayed**
Grade 1	Maintain paclitaxel dose	
Grade 2	Maintain paclitaxel dose[a]	Decrease paclitaxel one dose level[b]
Grade 3	**First episode:** Decrease paclitaxel one dose level[a] **Second episode:** Discontinue paclitaxel	Discontinue paclitaxel
Grade 4	Discontinue paclitaxel	

a Must be resolved to ≤ grade 1 on the next treatment day.

b Hold paclitaxel for ***persistent*** grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification for paclitaxel. If grade 2 toxicity persists after 3 weeks of delay, discontinue paclitaxel.

TABLE 19. Treatment management for paclitaxel-related musculoskeletal pain (Arm 1 Regimens B, C, and D)

Note: The treatment management instructions in Table 19 apply to patients with **musculoskeletal pain not controlled by analgesics**. Use of narcotics and NSAIDs is encouraged to maintain the paclitaxel dose if possible.

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	**1–7 Days Duration**	**Persistent for> 7 Days *or* Caused the Next Treatment to be Delayed**
Grade 1 *(despite analgesics)*	Maintain paclitaxel dose	
Grade 2 *(despite analgesics)*	Maintain paclitaxel dose	Maintain paclitaxel dose or Decrease paclitaxel one dose level*
Grade 3 *(despite analgesics)*	**First episode:** Decrease paclitaxel one dose level **Second episode:** Discontinue paclitaxel	**First episode:** Decrease paclitaxel one dose level* or Discontinue paclitaxel **Second episode:** Discontinue paclitaxel

* Hold paclitaxel for ***persistent*** grade 2 or 3 musculoskeletal pain. When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue paclitaxel.

8.7 Treatment management for TC (Arm 2)

Also refer to Section 8.1 for general instructions, Section 8.2 for anemia, and Section 8.3 for docetaxel-specific toxicities.

- If docetaxel is discontinued due to toxicity, chemotherapy should be completed with cyclophosphamide. Alternatively, the investigator may discontinue study therapy and administer alternative chemotherapy at the investigator's discretion.
- All dose modifications for docetaxel are based on the dose level changes outlined in Table 20. Instructions for TC toxicities are listed in Table 21.

TABLE 20. Dose levels for TC (Arm 2)

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level-1 (mg/m^2)**	**Dose Level -2**
Docetaxel (T)	75	60	Discontinue
Cyclophosphamide (C)	600	500	Discontinue

TABLE 21. Treatment management for TC (Arm 2)

Important table instructions:

- Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled cycle Day 1 for Cycles 2–6 (column 3). Refer to all sections/tables within Section 8.0 for additional instructions.
- Modifications apply to both docetaxel and cyclophosphamide unless specified otherwise.
- Dose modifications must be based on the AE requiring the greatest modification.
- **NOTE:** If the docetaxel dose has been reduced for docetaxel-related toxicities (see Tables 11 and 12) and a subsequent toxicity requiring dose reduction of docetaxel or TC occurs, maintain docetaxel at the reduced dose level (-1) and decrease cyclophosphamide to dose level -1; ***or***, at the investigator's discretion, study therapy may be discontinued. Further therapy is then at the investigator's discretion.

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, 4	Maintain dose	***ANC:*** *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose and add G-CSF *If receiving G-CSF and recovery takes:* 1 wk – maintain dose 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2 to 3 wks – ↓ one dose level
Grade 4	↓ one dose level	↓ one dose level
GI *(if related to chemotherapy)*: **Diarrhea**		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis oral		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting *(despite antiemetics)*		
Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigation (hepatic): **Bilirubin, AST, alk phos**		
Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1; then* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1; then* ↓ one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia:		
Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF prophylaxis for subsequent chemotherapy cycles if neutropenia was present.[c]	
Grade 3	Maintain dose and add G-CSF prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose or ↓ one dose level and add G-CSF prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	
Other clinically significant AEs:[d]		
Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle, i.e., treatment can be given without delay.

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤grade 1.*** If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue chemotherapy.

c If grade 2 criteria for infection include topical and/or systemic antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.

d Determination of "clinically significant" AEs is at the discretion of the investigator.

9.0 DRUG INFORMATION

There are no investigational agents in the B-49 study and none of the drugs included in the B-49 treatment regimens will be provided through the study. Cyclophosphamide, docetaxel, doxorubicin, and paclitaxel must be obtained by the investigator from commercial sources. Please refer to the current FDA-approved package insert provided with each drug for toxicity information and instructions for drug preparation, handling, and storage.

10.0 ADVERSE EVENT REPORTING REQUIREMENTS

Please refer to Coordinator Online in the Members' Area of the NSABP Web site for general information regarding AE reporting.

10.1 B-49 definitions for AE reporting

10.1.1 *Investigational agent*

There are no investigational agents in B-49.

10.1.2 *Commercial agents*

The commercial agents in B-49 are cyclophosphamide, docetaxel, doxorubicin, and paclitaxel.

10.1.3 *Adverse event characteristics*

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

10.2 Expedited reporting of adverse events

NRG Oncology follows procedures for centralized reporting of adverse events. Centralized reporting requires that adverse events be reported to the NRG Oncology SDMC. NRG Oncology forwards reports to the appropriate regulatory agencies. Expedited reporting for B-49 utilizes the CTEP Adverse Event Reporting System (CTEP-AERS).

NRG Oncology is identified in CTEP-AERS as the Lead Group for NRG Oncology protocols that require CTEP-AERS reporting. Expedited AE reporting for this study must be submitted to the NRG Oncology Lead Group using CTEP-AERS, accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to the NRG Oncology SDMC by telephone at 412-624-2666. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

10.2.1 *Expedited reporting methods*

- **CTEP-AERS-24 Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted to the NRG Oncology Lead Group **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report (see Table 22).
- **CTEP-AERS 5 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 5 calendar days** of learning of the AE.
- **Supporting documentation** is required for all expedited (CTEP-AERS) reports. Include the protocol number, patient's ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology SDMC (412-622-2113).

10.2.2 *Expedited reporting requirements – CTEP-AERS-24, CTEP-AERS, and other protocol requirements/exceptions*

- Expedited reporting requirements begin with the administration of the first chemotherapy dose. Expedited reporting requirements for all patients are provided in Table 22.
- There may be protocol specific requirements and exceptions for expedited reporting. Refer to Table 22 for instructions.

10.2.3 *Other recipients of adverse event reports*

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

TABLE 22. CTEP-AERS expedited reporting requirements for adverse events that occur **within 30 days of the last dose of chemotherapy**

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

CTEP-AERS-24: Indicates an AdEERS 24-hour notification must be electronically submitted to the NRG Oncology Lead Group *within 24 hours* of learning of the event.

CTEP-AERS: Indicates a complete expedited report must be electronically submitted to the NRG Oncology Lead Group *within 5 calendar days* of learning of the event.

Hospitalization: An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

All Reports: On all reports, use the NCI protocol number, CTEP-AERS ticket number, and the protocol-specific patient ID provided during trial registration. **Fax supporting documentation to the NRG Oncology SDMC.**

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

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

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

c Any event that results in a persistent or significant disability/incapacity or a congenital anomaly/birth defect, or is an important medical event which based upon medical judgment may jeopardize the patient and require intervention to prevent a serious adverse event, must be reported via CTEP-AERS if the event occurs following chemotherapy administration.

d Protocol-specific expedited reporting requirements: For this study, the adverse events listed below, regardless of attribution, require expedited reporting via CTEP-AERS to the NRG Oncology Lead Group within 5 calendar days of learning of the event:

- All AEs requiring expedited reporting per Table 22 instructions should continue to be reported via CTEP-AERS **until 30 days after the last dose of study therapy**.
- Cardiac disorders regardless of attribution: ≥ grade 3 acute coronary syndrome; ≥ grade 2 heart failure; ≥ grade 3 left ventricular systolic dysfunction; ≥ grade 3 myocardial infarction. ***(NOTE: Requires expedited reporting via CTEP-AERS from the first dose of study therapy until 30 days after the last dose of study therapy. Also, refer to Section 10.4 for additional instructions.)***
- ***From the first dose of study therapy until the end of patient follow-up, the following require expedited reporting via CTEP-AERS:*** (See Section 10.2.4 and 10.5.)
  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome
  - Treatment-related secondary malignancy

e Protocol-specific expedited reporting exceptions: For this study, the adverse events listed below, including hospitalizations for these events, do not require expedited reporting via CTEP-AERS:

- Neoplasms-malignant (i.e., a second primary malignancy) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy (see footnote d and Section 10.5).

10.2.4 *Reporting a secondary malignancy*

A ***secondary malignancy*** is a cancer caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur on NCI-sponsored trials either during or following treatment must be reported via CTEP-AERS within 5 days of learning of the secondary malignancy (see Table 22). Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Supporting documentation, including pathology and cytogenetics reports which confirm the secondary malignancy, must be faxed to the NRG Oncology SDMC expedited fax at 412-622-2113. Each page of supporting documentation must include the NCI protocol number, the CTEP-AERS ticket number, and the protocol-specific patient ID number provided during trial registration.

Note: All secondary malignancies should also be reported on the B-49 Form F (see Section 10.5).

10.2.5 *Second malignancy*

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting on the B-49 Form F (see Section 10.5).

10.2.6 *Expedited reporting of pregnancy, fetal death, and death neonatal occurring during study therapy*

Any pregnancy, fetal death, or death neonatal occurring while the patient is receiving study therapy or within 6 months following the last dose of study therapy must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

Upon learning of a pregnancy, fetal death, or death neonatal that occurs during study or within 6 months following the last dose of study therapy the investigator is required to:

- Call the NRG Oncology Clinical Coordinating Department (see Information Resources**).** ***Patients must immediately discontinue receiving study therapy.***
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6):
  - Create and submit an CTEP-AERS report;
  - Complete the Pregnancy Information Form (located in the NSABP Members' Area in Protocol B-49 "Forms and Supporting Documents"); and

- Fax the completed Pregnancy Information Form with all available supporting documentation to the NRG Oncology SDMC's expedited fax number at 412-622-2113.

- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Information Form used for the initial report.
- For questions concerning AE reporting, contact the AE Reporting Nurse (see Information Resources).

10.3 Routine reporting of adverse events

10.3.1 *Online reporting on the B-49 Treatment and Adverse Event form (Form TRTAE)*

- Direct online reporting of adverse events is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site.
- **All ≥ grade 2 adverse events not reported via CTEP-AERS** that occurred during study therapy or during the 30 days following the last dose of study therapy must be reported on the B-49 Treatment and Adverse Event form (Form TRTAE).
- Reporting of AEs is **not required** following a documented invasive breast cancer recurrence or diagnosis of a second primary malignancy, if treated with systemic anticancer therapy.
- Supporting documentation for each AE reported online on Form TRTAE must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

10.3.2 *Schedule for submission of the B-49 Form TRTAE*

Form TRTAE is submitted online to the NRG Oncology SDMC, **even if no AEs were experienced by the patients**, according to the following schedule:

All patients receiving chemotherapy

- *During chemotherapy:* Submit Form TRTAE at the end of each cycle of chemotherapy beginning with cycle 1.
- *During weekly paclitaxel:* Submit Form TRTAE after every 3 doses.
- *During dose-dense paclitaxel:* Submit Form TRTAE at the end of each cycle beginning with cycle 5.
- *After the final dose of chemotherapy:* Submit Form TRTAE 30 days after the final dose of chemotherapy.

10.4 Reporting selected late cardiac and vascular events on the B-49 follow-up form

- After submission of the final Form TRTAE, the following ≥ **grade 2 selected late cardiac and vascular events will be reported online on the follow-up form (Form F)** for all patients regardless of treatment assignment:

  Cardiac

  - ≥ grade 3 acute coronary syndrome
  - ≥ grade 2 heart failure
  - ≥ grade 3 left ventricular systolic dysfunction
  - ≥ grade 3 myocardial infarction
  - Definite cardiac death defined as death due to congestive heart failure, myocardial infarction, or documented primary arrhythmia
  - Probable cardiac death defined as sudden death without documented etiology.

  Vascular

  - ≥ grade 3 peripheral ischemia
  - ≥ grade 3 thromboembolic event
  - ≥ grade 3 visceral arterial ischemia

  Note: Reporting late cardiac and vascular events is **not required** for patients who have initiated systemic therapy for a breast cancer recurrence or second primary cancer.

- Supporting documentation for the late cardiac and vascular events reported on Form F must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. **Fax this transmittal form with the supporting documentation to 412-622-2111.** Remove patient names and identifiers, such as social security number, address, telephone number, etc., from reports and supporting documentation.

10.5 Reporting breast cancer recurrence, secondary malignancies, and second primary cancer

Report breast cancer recurrence, secondary malignancies (including leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, and treatment-related secondary malignancy previously reported through CTEP-AERS), and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) online on the B-49 Form F. Fax supporting documentation, unless previously faxed to the NRG Oncology SDMC with a CTEP-AERS report, that confirms the breast cancer recurrence or second primary cancer diagnosis with the transmittal form (provided by the online software and printed) to 412-622-2111.

11.0 DOCUMENTATION OF BREAST CANCER RECURRENCE AND SECOND MALIGNANCIES

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. Suspicious findings do not provide adequate documentation of a breast cancer recurrence and should not be an indication to alter protocol therapy.
- Tumor marker evaluations alone do not document breast cancer recurrence.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.
- See Section 12.7 for instructions regarding investigator-initiated discontinuation of chemotherapy.

11.1 Local recurrence

Note: If the first local recurrence is non-invasive breast cancer, the first invasive breast cancer must also be reported.

Recurrent local tumor is defined as evidence of invasive or non-invasive breast cancer in the ipsilateral breast or invasive breast cancer in the skin of the ipsilateral breast. Patients who develop clinical evidence of local recurrence in the ipsilateral breast must have a biopsy confirmation of recurrence. However if a patient also meets criteria for regional or distant metastatic disease, results of clinical exams alone will be sufficient to document local recurrences.

11.1.1 *Ipsilateral breast tumor recurrence (IBTR)*

An IBTR event is defined as recurrent invasive or non-invasive breast cancer in the ipsilateral breast parenchyma or invasive breast cancer in the skin of the breast occurring after lumpectomy. Acceptable documentation includes core, incisional or excisional biopsy. Cytology alone will not be adequate to establish IBTR.

11.1.2 *Other local recurrence*

Defined as recurrence in the skin of the chest wall (exclusive of the breast) or chest wall. Acceptable documentation includes core, incisional or excisional biopsy, as well as cytology.

11.2 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, following surgery. Recurrence must be confirmed by biopsy or cytology. However if a patient meets criteria for distant metastatic disease, results of clinical exams alone will be sufficient to document regional recurrences.

11.3 Distant recurrence

Defined as evidence of tumor in all areas, with the exception of those described in Sections 11.1 and 11.2. Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

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

Acceptable documentation includes positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease.

11.3.2 ***Bone marrow***

Acceptable documentation includes positive cytology, aspirate, biopsy, or MRI scan.

11.3.3 ***Lung***

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

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

11.3.4 ***Skeletal***

Acceptable documentation includes (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 or PET scan clearly positive for bone metastases.

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

11.3.5 ***Liver***

Acceptable documentation includes: (i) abdominal CT scan, liver scan, ultrasound, MRI, or PET scan 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 is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

11.3.6 ***Central nervous system***

Acceptable documentation includes: (i) positive CT scan or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology.

11.4 **Second primary breast cancer**

Defined as evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed by core, incisional or excisional biopsy. Cytology alone will not be adequate to document a second breast cancer primary.

11.5 **Second primary cancer**

Second primary cancer is defined as any *invasive* non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

11.6 **Documentation requested following death**

- Autopsy reports should be secured whenever possible and should be submitted to the NRG Oncology SDMC.
- A copy of the death certificate should be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

12.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

Note: Accrual closed on November 21, 2013, following achievement of the sample size goal.

12.1 Investigator requirements

This study is supported by the NCI CTSU.

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Member Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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

Requirements for B-49 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- IRB-approved consent form

12.2 Patient consent form

Before the patient is enrolled, the consent form (see Appendix D), including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

12.3 Required submission of tumor samples

As part of the B-49 consent form, all patients have agreed to allow the submission of tumor blocks (see Section 6.1).

12.4 Patient enrollment

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

12.5 Oncology Patient Enrollment Network (OPEN)

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study.

12.5.1 ***NSABP Investigators***

Note: NSABP investigators who also are registered with the CTSU must enroll patients in B-49 through the NSABP; they are not permitted to enroll patients through the CTSU.

Study entry instructions can be found in the "Patient Entry Guidelines" section of the Members' Area of the NSABP Web site, https://members.nsabp.pitt.edu.

12.5.2 ***CTSU Investigators***

CTSU investigators can access OPEN at https://open.ctsu.org or from the OPEN tab on the CTSU Members' side of the Web site at https://www.ctsu.org.

12.5.3 ***Prior to accessing OPEN site staff should verify the following:***

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the NSABP or CTSU Web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

12.5.4 ***Access requirements for OPEN***

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU Member Web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the NSABP, you must have an equivalent 'Registrar' role on the NSABP roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU Member Web site. This will allow them to assign staff the 'Registrar' role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. Additionally, a transmittal form to be used when faxing the signed consent form to the NSABP Biostatistical Center will be provided.

Further instructional information is provided on the OPEN tab of the CTSU Member side of the CTSU Web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

12.6 Patient study number

After randomization, the institution will receive the Patient ID number for the study.

12.7 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drug or other treatments for breast cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws from the study (see Section 12.9).

12.8 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, she may stop study therapy or withdraw from the study at any time. If study therapy is stopped but she still allows the investigator to submit information, study data and other materials should be submitted according to the study schedule.

12.9 Patient-initiated withdrawal from the study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to the NRG Oncology), the investigator must provide the NRG Oncology SDMC with written documentation of the patient’s decision to fully withdraw from the study.

13.0 REQUIRED DATA COLLECTION

13.1 Data collection

B-49 data collection will include the following elements:

- Patient characteristics
- Characteristics of the breast cancer
- AJCC TNM stage
- Study treatment administered
- Other treatment including RT and hormonal therapy
- Adverse events as described in Section 10.0
- Breast cancer events (local, regional, and distant)
- Second primary cancer events
- Survival

13.2 Instructions for completion of B-49 forms and materials

- Data form worksheets and specimen transmittal forms, as well as instructions for completion and submission of data and materials, are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu or on the CTSU Member Web site, https://www.ctsu.org. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account to access the NSABP Web site.
- Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

13.3 Instructions for submission of B-49 forms and materials

- Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the NRG Oncology SDMC.
- Submission of study data directly to the NRG Oncology SDMC is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. When submission of supporting documentation to the NRG Oncology SDMC is required, fax to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.
- The NRG Oncology SDMC will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the NRG Oncology SDMC and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.

14.0 STATISTICAL CONSIDERATIONS

14.1 Primary endpoint

The primary endpoint for efficacy analysis is invasive disease-free survival (IDFS) for the comparison of TC vs. anthracycline-based chemotherapy regimens, defined as time to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, **invasive** contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer.

14.2 Secondary endpoints

Secondary endpoints for the comparison of TC vs. anthracycline-based chemotherapy regimens will include disease-free survival (DFS-DCIS), overall survival (OS), and recurrence-free interval (RFI). DFS-DCIS is defined as time to local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (invasive or non-invasive), regional recurrence, distant recurrence, contralateral breast cancer (invasive or non-invasive), second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. OS is defined as time from randomization until death from any cause. RFI is defined as time from randomization until local, regional, or distant recurrence.

14.3 Stratification and randomization

Assignment of treatments to patients will be balanced with respect to pathologic nodal status (0, 1-3, 4-9, 10+) and hormone receptor status (ER-negative, ER and/or PgR positive) using a biased-coin minimization algorithm that is based on the method described by White and Freedman[30] and incorporates the biased-coin approach proposed by Efron.[31]

14.4 Sample size calculation

The assumptions used in the previous sample size determination for B-46-I/07132 were those available when the original 3-arm trial was designed. Our present estimate of the expected hazard rate in the TAC group was updated using information from the USOR 01062 study.[32] The NSABP and USOR believe the results of these trials provide reliable event rate estimates for the population described in the eligibility criteria for B-46-I/07132.

From the USOR 01062 study, the average annual hazard rate for the AC→T group (used as an estimate for TAC) derived from the 5-year DFS rate (90.6%) is 0.0197 for node-negative patients. The average annual hazard rate for the TAC group derived from the 5-year DFS rate (86.5%) for node-positive patients is 0.029. In addition, we have revised our expectations of accrual to be 75 patients per month which was actually observed from our B-46-I/07132 study at the time that announcements were made about bevacizumab. However, the accrual pattern will be closely monitored and, if necessary, appropriate steps will be taken to follow the NCI guidelines for slow accruing studies.

We also make the following additional assumptions:

- The weighted proportion of node-negative patients is about 35% from B-46-I/07132 and USOR 01062, so that the average annual hazard rate for the TAC/AC→P regimens arm would be 0.0257 [= (0.35 x 0.0197 + 0.65 x 0.029)].

- The non-inferiority (NI) margin in terms of the hazard ratio comparing TC to TAC/AC→P regimens would be 1.18, which corresponds to the hazard ratio of 0.85 to compare TC to TAC/AC→P regimens in the usual superiority test. A hazard ratio > 1.18 implies TC is inferior to TAC/AC→P regimens. With a hazard ratio of 1.18, the absolute difference between treatment groups in the 5-year IDFS rate would be 0.02.
- The error probability of incorrectly concluding that TC is inferior to TAC/AC→P regimens under the alternate hypothesis that the true hazard ratio is 1.0 is 20%.
- The error probability of incorrectly concluding TC is non-inferior to TAC/AC→P regimens under the null hypothesis that the true hazard ratio is 1.18 is 10%.

Under the above scenario, the test of the primary hypothesis would require a total number of 668 events. Currently, the combined USOR 06-090 and B-46-I/07132 trials have enrolled 2357 patients as of 12/13/2011 to the TAC or TC arms. With 2.3 more years of accrual to add 1843 additional patients and thereby, achieve a total sample size of 4200, the definitive analysis would occur about 3.8 years after completion of accrual.[33–35]

14.5 **Statistical analysis**

The appropriate analysis cohort for a non-inferiority study consists of the patients who were treated according to their random assignment. Accordingly, the primary analysis will be performed on all patients with follow-up who began their assigned treatment and will use the treatment assignments made at randomization. These analyses will be repeated with the further restriction that patients are eligible for the study as a form of secondary sensitivity assessment.

Let X represent the log hazard ratio for treatment (TC to TAC/AC→P regimens) estimated by a Cox proportional hazard model stratified by nodal status and hormone receptor status, and $s(X)$ represent the standard error of the estimate. Under the null hypothesis that the hazard ratio is 1.18, the test statistic $Z = [X - \log(1.18)] / s(X)$ is asymptotically distributed as standard normal. We will reject the null hypothesis of inferiority and conclude TC is non-inferior to TAC/AC→P regimens if the test statistic Z is less than the 10th percentile of the standard normal distribution ($z_{90} = -1.2816$)

Secondary endpoints will not be tested for non-inferiority, standard superiority testing will be done instead. The cohort for these analyses will be based on intention to treat regardless of treatment actually received and excluding only patients without clinical follow-up.

Distribution of time-to-event for the primary and secondary endpoints will be estimated by Kaplan-Meier[36] and life-table methods[37] and compared by stratified log-rank tests[38–40] (using only the stratification variables) and Cox proportional hazards models.[41] We will also use Cox models to test associations between the primary endpoints and the stratification variables. Tests for treatment by covariate interactions will be performed.[42] Detailed subgroup analyses will be carried out if treatment by covariate interactions are strongly significant ($p < 0.01$). Any subset analysis of endpoints will be considered to be exploratory since the sample size specified below yields inadequate power to detect moderate differences in outcome for sub-cohorts. We will test the proportional hazard assumptions by creating an artificial time-dependent covariate and testing its interaction with other covariates as described by Klein and Moeschberger.[43] A two-sided p-value of 0.05 will be used to evaluate all secondary endpoints.

14.6 Interim analysis

There will be only one interim analysis which will occur at 50% of the expected information time, i.e., when the number of events reaches 334. If there is any indication that the observed test statistic $Z = [X - \log(1.18)] / s(X)$ is greater than 0, toward an inferiority of TC to TAC/AC→P regimens, a recommendation will be made to the NRG Oncology Data Monitoring Committee (DMC) to consider a possibility of stopping the study for futility.[44]

14.7 Issues relating to racial and ethnic differences

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians.[45,46] This difference has been attributed to many factors, including more advanced disease at the time of diagnosis,[47] social and economic factors,[48] or specific tumor characteristics such as ER positivity.[49,50] Although outcomes tend to be less favorable for African-Americans, significant race-by-treatment interactions have not been previously reported suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.[51,52]

Potential for the enrollment of minority patients in this protocol is enhanced by the NSABP's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NSABP investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distributions of ethnicity and race for B-49 are projected from the NSABP B-46-I/USOR 07132 study. The ethnicity distribution of the NSABP B-46-I/USOR 07132 population consisted of 10% Hispanic and 90% non-Hispanic. The racial distribution in the NSABP B-46-I/USOR 07132 study was 84% white; 12% black, not of Hispanic origin; 3% Asian or Pacific Islander descent; and 3% American Indian or Alaskan Native. The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

TABLE 23. Expected racial and ethnic composition of NSABP B-49

Ethnic Category	Total
Hispanic or Latino	184
Not Hispanic or Latino	1659
Ethnic Category: Total of all subjects	1843
Racial Category	
American Indian or Alaskan Native	6
Asian	55
Black or African American	221
Native Hawaiian or other Pacific Islander	7
White	1554
Racial Category: Total of all subjects	1843

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

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APPENDIX A

DETERMINATION OF MENOPAUSAL STATUS AND PERFORMANCE STATUS

1.0 MENOPAUSAL STATUS DETERMINATION

The following criteria will be used to define ***postmenopausal***:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry, **or**
- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) AND with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard, **or**
- A prior documented bilateral oophorectomy.

Women failing to meet one of these criteria will be classified as ***pre-menopausal***.

2.0 DETERMINATION OF PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

APPENDIX B

SYMPTOM MANAGEMENT RECOMMENDATIONS

Regimens found to be effective in the management of **non-hematologic toxicities of docetaxel** are listed below.

A. Fluid retention

Suggested interventions include:

- Hydrochlorothiazide/triamterene (Dyazide®) 1 capsule PO daily, up to BID
- Furosemide (Lasix®) 40 mg PO daily if edema progresses despite Dyazide (or equivalent) therapy. Potassium supplementation will be given as needed.
- If, after a 2-week trial, furosemide 40 mg PO every day is ineffective, the patient may be treated with furosemide 20 mg PO daily plus metolazone (Zaroxolyn®) 2.5 mg PO daily with potassium supplementation as needed.

B. Arthralgia/myalgia

- Gabapentin (Neurontin®) should be initiated at 300 mg BID (100 mg BID for elderly patients) and may be increased to TID over the next few days. (Gabapentin causes somnolence and ataxia so it is recommended that most of the dose be given at night before bed, e.g., 300 mg in the morning and 600 mg in the evening.) With attention to sedation and ataxia, the dose may be increased, if effective, to a maximum of 3600 mg per day, although this is rarely required.
- Hydrocodone bitartrate and acetaminophen tablets (Lortab®) may be prescribed if gabapentin does not relieve the arthralgia/myalgia.
- Pregabalin (Lyrica CV®) may also be prescribed at the discretion of the Treating Physician. The maximum recommended dose of pregabalin is 100 mg TID (300 mg/day) in patients with normal renal function. Initiate dosing at 50 mg TID (150 mg/day) and increase to 300 mg/day within 1 week based on efficacy and tolerability.

C. Skin rash

This characteristic rash typically occurs in the anatomic snuffbox of the hand (the web space between the thumb and forefinger) and the arch of the foot, though it can occur anywhere. It is generally very responsive to continuation of oral steroids and topical steroids/emollients. Patients will be premedicated with dexamethasone premedications as described in Section 7.0 (Tables 4 and 8).

D. Acute hypersensitivity reactions

Table B1 outlines treatment guidelines for the management of acute hypersensitivity reactions.

TABLE B1. Management of acute hypersensitivity reactions

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	• Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient; then, complete infusion at the initial rate.
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mmHg	• Interrupt infusion. • Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms. • Resume infusion after recovery of symptoms; depending on the physician's assessment of the patient, infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the 1-hour infusion rate). • Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse at 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, administer at the 1-hour infusion rate).
Severe symptoms: any reaction such as bronchospasm, generalized urticarial, systolic BP ≤ 80 mmHg, angioedema	• Immediately discontinue infusion • Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms. • The same treatment guidelines outlined under moderate symptoms (i.e., the third and fourth bullets) should be followed.
Anaphylaxis (CTCAE grade 4 reaction)	• No further study drug therapy.

APPENDIX C

CTCAE GRADE 2 CARDIAC DISORDER ADVERSE EVENTS THAT PROHIBIT AC THERAPY

AC will be discontinued (Arm 1 Treatment Regimens A, B, C, and D) following any **grade 2** cardiac AE listed in the table below. (AC should be administered following any of the other grade 2 AEs listed in the Cardiac Disorders section of the CTCAE v4.0 but not listed in this appendix.)

Note: AC will be discontinued for any ≥ grade 3 AE listed in the Cardiac Disorders section of CTCAE v4.0.

CARDIAC DISORDERS – CTCAE v4.0	
Adverse Event	**Grade 2 Criteria**
Acute coronary syndrome	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable
Chest pain - cardiac	Moderate pain; limiting instrumental ADL
Heart failure	Symptoms with mild to moderate activity or exertion
Myocardial infarction	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
Myocarditis	Symptoms with mild to moderate activity or exertion
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Right ventricular dysfunction	Symptoms with mild to moderate activity or exertion
Ventricular tachycardia	Non-urgent medical intervention indicated