THE UNIVERSITY OF KANSAS
CANCER CENTER

Investigator Initiated Trial

2015-IIT- Neoadjuvant-BRST-TNBC (NeoSTOP)

Randomized open label Phase II trial of neoadjuvant Carboplatin plus Docetaxel or Carboplatin plus Paclitaxel followed by Doxorubicin plus Cyclophosphamide in stage I-III triple-negative breast cancer (NeoSTOP: Neoadjuvant Study of two Platinum regimens in Triple negative breast cancer)

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Protocol Number: 2015-IIT-Neoadjuvant-BRST-TNBC

Study Drugs:
- Doxorubicin plus Cyclophosphamide (**AC**)
- Docetaxel
- Paclitaxel
- Carboplatin
- Pegfilgrastim

IND Number: EXEMPT

IND Holder Name: EXEMPT

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LIST OF KEY PERSONNEL

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BIOSTATISTICIAN

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 2015-IIT-Neoadjuvant-BRST-TNBC

Protocol Title: Randomized open label Phase II trial of neoadjuvant Carboplatin plus Docetaxel or Carboplatin plus Paclitaxel followed by Doxorubicin plus Cyclophosphamide in stage I-III triple-negative breast cancer (NeoSTOP: Neoadjuvant Study of two Platinum regimens in Triple negative breast cancer)

Protocol Version and Date: Version 4 dated 05-17-2016

Investigator Signature: _____ _____
Date

Print Name and Title: _____

Site Number: N/A

Site Name: The University of Kansas Cancer Center / University of Kansas Medical Center

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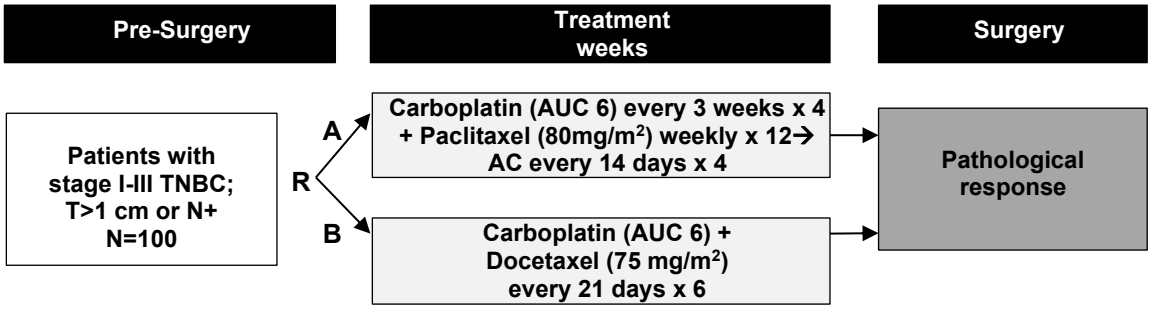
LIST OF ABBREVIATIONS

A	Anthracycline
AC	Doxorubicin plus Cyclophosphamide regimen
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BA/BE	Bioavailability/Bioequivalence
BCS	Breast Conservation Surgery
BID	Twice daily
BUN	Blood Urea Nitrogen
C	Cyclophosphamide
CAP	College of American Pathologists
Cb	Carboplatin
Cb+P	Carboplatin plus Paclitaxel
CBC	Complete Blood Count
CdD	Carboplatin plus Docetaxel regimen
CHF	Congestive heart failure
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CVAP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone regimen
D5W	5% Dextrose in Water
DCIS	Ductal carcinoma in situ
ddAC	Dose Dense Doxorubicin + Cyclophosphamide
DNA	Deoxyribonucleic Acid
ECG	Electrocardiography
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
DSMC	Data and Safety Monitoring Committee
ER	Estrogen Receptor
FA	Fanconi Anemia
FNA	Fine Needle Aspiration
GFR	Glomerular Filtration Rate
HER2	ERBB2
HR	Homologous Recombination
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IULN	Institutional Upper Limit of Normal
IV	Intravenous
LD	Longest Diameter
LFT	Liver Function Tests
LOH	Loss of Heterozygosity
LVEF	Left Ventricular Ejection Fraction
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan

N+	Lymph node positive
NCI	National Cancer Institute
PAC	Premature atrial contractions
pCR	Pathological Complete Response
PD	Progressive Disease
PFS	Progression Free Survival
PM	Promoter Methylation
po	Per os/by mouth/orally
PgR	Progesterone Receptor
PR	Partial Response
PS	Performance Status
PVC	Premature ventricular contractions
q3w	Every 3 week administration
qw	Weekly administration
RBC	Red Blood Cells
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
T	Tumor Size
Ta	Taxanes
TNBC	Triple-Negative Breast Cancer
TPN	Total parenteral nutrition
ULN	Upper Limit of Normal
US	Ultrasound
USP	United States Pharmacopeia

STUDY SCHEMA



•Breast Imaging after 4 cycles

STUDY SUMMARY

Title	Randomized open label Phase II trial of neoadjuvant Carboplatin plus Docetaxel or Carboplatin plus Paclitaxel followed by AC in stage I-III triple-negative breast cancer
Short Title	Neoadjuvant Carboplatin and Docetaxel in TNBC
Phase	Phase II
Methodology	Randomized
Study Duration	24 months
Study Center(s)	Multi-center [redacted]
Objectives	**Primary Objective:** To evaluate the pathological complete response rates with two neoadjuvant chemotherapy regimens (CbDX6 and Cb+PX4 → ACX4) in patients with stage I-III TNBC. *Hypothesis:* CbD and Cb+P→AC will yield comparable pCR rates in patient with stage I-III TNBC
Number of Subjects	100 patients
Diagnosis and Main Inclusion Criteria	Newly diagnosed stage I (T>1 cm), II or III TNBC who have not undergone definitive breast surgery and have not received any systemic chemotherapy
Study Product(s), Dose, Route, Regimen	Regimen A: Paclitaxel (80mg/m^2) every week x12 weeks and Carboplatin (AUC 6, IV) every 21 days x 4 cycles, followed by Doxorubicin (60mg/m^2, IV) and Cyclophosphamide (600mg/m^2, IV) every 14 days X 4 cycles Pegfilgrastim 6mg SC Day2 during AC Regimen B: Carboplatin (AUC 6, IV) and Docetaxel (75mg/m^2, IV) every 21 days x 6 cycles Pegfilgrastim 6mg SC Day2
Duration of Administration	18 to 20 weeks
Reference Therapy	Paclitaxel (80 mg/m^2, IV) weekly x 12 weeks + Carboplatin (AUC 6, IV) every 3 weeks x 4 cycles + followed by Doxorubicin (60mg/m^2, IV) and Cyclophosphamide (600mg/m^2, IV) every 14 days x 4 cycles
Interim Monitoring	None
Statistical Methodology	Patients will be randomized 1:1 to either neoadjuvant Paclitaxel + Carboplatin → AC or Carboplatin plus Docetaxel.

	The primary objective will be to estimate the pCR rates in both arms. The estimated pCR rates in both the treatment arms is 50% with upper bound constraints for the standard errors at 7.5% and the upper bound constraint for the standard error of the difference between pCR rates of the two arms at 12%. The sample size required to satisfy these constraints is 45 patients per treatment arm (Mayo et. al. 2010). To ensure achieving 45 evaluable patients in each treatment arm, the overall maximum sample size will be inflated to 100 patients to account for patient drop outs. The pCR rates and MRD rates for each treatment arm will be estimated and 95% exact binomial confidence bounds will be calculated.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1 Triple Negative Breast Cancer

Breast cancer is the most commonly diagnosed malignancy and second leading cause of cancer mortality in American women. The lifetime risk of developing breast cancer is 12.2%, and the lifetime risk of breast cancer death is 3.3% (Harris J 1997). Triple negative breast cancer (TNBC) is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PgR), and absence of ERBB2 (HER2) over expression and/or gene amplification. TNBC accounts for 15% of all breast cancer and is associated with poor long-term outcomes compared to other breast cancer subtypes (Osborne, Kannan et al. 2006, Dent, Trudeau et al. 2007, Liedtke, Mazouni et al. 2008). Systemic neoadjuvant chemotherapy is recommended for all TNBC patients with stage I (T>1cm)-III disease (NCCN 2014). Due to the lack of specific therapeutic targets, chemotherapy remains the mainstay of systemic treatment in the adjuvant setting. However, despite receiving standard anthracycline-based adjuvant chemotherapy, a significant proportion (approximately 30-40%) of patients with early stage TNBC develop metastatic disease and succumb to the cancer (Nielsen, Hsu et al. 2004, Haffty, Yang et al. 2006, Tan, Marchió et al. 2008). To improve outcomes for this subtype, we not only need novel targeted agents, but also need to identify predictors of response/resistance to standard chemotherapy.

1.1.2 DNA damaging therapy in triple negative breast cancer

Sporadic and germline BRCA mutation associated triple-negative breast cancer (TNBC) share several pathological and molecular similarities. These similarities have led to the exploration of DNA damaging agents like platinum compounds in the general population of patients with TNBC. Growing evidence suggests that platinum compounds may be active in a significantly larger number of TNBC patients beyond germline BRCA mutation carriers (Isakoff SJ 2012, Telli 2013). Currently, anthracyclines (A), cyclophosphamide (C) and taxanes (Ta) form the backbone of systemic chemotherapy for stage I-III TNBC (www.nccn.org). Recent studies demonstrate that addition of neoadjuvant carboplatin (Cb) to A/C/Ta-based chemotherapy improves pathological complete response (pCR) in patients with stage I-III TNBC (pCR improvement form 41% to 54% with addition of Cb) (Rugo, Olopade et al. 2013, Sikov, Berry et al. 2014, von Minckwitz, Schneeweiss et al. 2014). However, this improvement in pCR rate comes at the cost of increase in toxicity (dose reductions/omissions needed in 40-50% of patients and also increases the financial cost of chemotherapy (Sikov, Berry et al. 2014, von Minckwitz, Schneeweiss et al. 2014). Furthermore, anthracyclines and cyclophosphamide although very active for treatment of breast cancer, have well known small but serious long term risks (secondary leukemia and myelodysplastic syndrome, cardiomyopathy, premature menopause) and development of effective chemotherapy regimens that are devoid of long term side effects is desirable.

Furthermore, although anthracycline agents induce double-strand breaks, repair of these lesions appears to require non-homologous end joining, an error-prone double strand break repair pathway that does not require BRCA1,

and preclinical data suggests that anthracyclines do not exhibit selective toxicity in BRCA1-deficient cells (Tassone, Tagliaferri et al. 2003, Rottenberg, Nygren et al. 2007, Schonn, Hennesen et al. 2011). Conversely, repair of platinum-induced interstrand crosslinks invokes BRCA1-mediated homologous recombination, and there is abundant clinical and in vitro evidence that BRCA1-deficient cells are hypersensitive to platinum agents (Husain, He et al. 1998, Tassone, Tagliaferri et al. 2003, Rottenberg, Nygren et al. 2007, Bolton, Chenevix-Trench et al. 2012).

1.1.3 Neoadjuvant Carboplatin plus Docetaxel Pilot data

Taxanes are an integral part of chemotherapy regimens for breast cancer treatment and appear to contribute particularly among patients with early stage TNBC (Hayes, Thor et al. 2007, Jacquin, Jones et al. 2012). Several in vitro studies have demonstrated synergy between platinum compounds and taxanes in TNBC cell lines (Corkery, Crown et al. 2009). Efficacy of anthracycline-devoid neoadjuvant platinum/taxane chemotherapy combination in sporadic and BRCA-associated TNBC has not been well studied. We recently reported encouraging pCR rates with a non-anthracycline carboplatin plus docetaxel (CbD) neoadjuvant chemotherapy regimen in an observational cohort of 49 TNBC patients (Sharma P 2014). This chemotherapy regimen of CbD yielded an overall pCR rate of 65% in unselected TNBC with pCR rates of 61% in sporadic and 77% in germline BRCA-associated TNBC (Table 1).

Table 1. Carboplatin/Docetaxel pathological response

	All patients (n=49)	BRCA1/2 Wild type (n=36)	BRCA mutation carriers (n=13)
Pathological Complete Response; n (%)	32 (65%)	22 (61%)	10 (77%)
		p=0.50	
Residual Cancer Burden 0/1; n (%)	38 (78%)	27 (75%)	11 (85%)
		p=0.70	

The chemotherapy regimen of carboplatin/docetaxel is well tolerated, and is routinely used for HER2 positive and metastatic breast cancer, with well-known safety profile (Slamon DJ 2001, NCCN 2014). In our neoadjuvant experience, most common Grade 3/4 toxicities with carboplatin/docetaxel were neutropenia (4%), anemia (6%), thrombocytopenia (6%), and diarrhea (6%). Thus, we have recently demonstrated in an observational cohort that the pCR achieved with carboplatin/docetaxel chemotherapy is comparable to the pCR noted with addition of carboplatin to AC/paclitaxel chemotherapy and this regimen should be studied further in TNBC. More importantly this regimen should be compared with regimens that add carboplatin to the standard anthracycline/taxane containing regimens.

1.1.4 Neoadjuvant chemotherapy

Neoadjuvant (primary) chemotherapy refers to induction chemotherapy given before local treatment, such as surgery or radiation (Bear 1998). The biologic rationale for the use of neoadjuvant therapy in breast cancer is based on several key observations. Animal models have demonstrated that the removal of a primary tumor may increase the rate of growth of

micrometastases. Fischer suggested that this accelerated growth which is controlled by serum growth factors, could be prevented by systemic chemotherapy before tumor resection (Fisher, Gunduz et al. 1983). Goldie and Coldman have proposed that the number of tumor cells is proportional to the number of chemoresistant clones, and therefore, neoadjuvant chemotherapy would be effective in maximizing future drug response (Goldie and Coldman 1979).

Clinically, neoadjuvant chemotherapy has a number of potential advantages. Decreasing the size of the primary tumor may effectively downstage a mass to make breast preservation more likely, and may improve local control (Bear 1998). Chemotherapy may also decrease the intensity and morbidity of irradiation required to treat the breast or chest wall. Additionally, it allows for immediate objective assessment of chemotherapy response which offers prognostic information, as well as guides alterations in therapy. Finally and most importantly, neoadjuvant chemotherapy allows for rapid early assessment of new treatment approaches and to study the relationship of biologic markers and treatment response.

In the landmark phase III randomized study (National Surgical and Adjuvant Breast Project [NSABP] B-18), it was demonstrated that in patients with stage I and II disease, neoadjuvant chemotherapy was equivalent to adjuvant chemotherapy in terms of disease free survival, distant disease free survival and overall survival, however, a higher percentage of breast conservation surgeries (67% vs. 59%) was possible with neoadjuvant chemotherapy (Fisher and Mamounas 1995). For breast cancer, neoadjuvant chemotherapy was initially used in patients only with locally advanced or inoperable disease, but now is considered for patients who are candidates for adjuvant chemotherapy.

It has been demonstrated that degree of tumor response and extent of residual disease after neoadjuvant chemotherapy are associated with relapse and long term survival (Fisher, Bryant et al. 1998, Kuerer, Newman et al. 1999). Prospective trials have demonstrated that patients who achieve a pathologic complete response of the primary tumor with neoadjuvant chemotherapy have significantly improved disease free and overall survival when compared with patients who do not have a pCR (Fisher, Bryant et al. 1998, Kuerer, Newman et al. 1999, van der Hage, van de Velde et al. 2001, Green and Hortobagyi 2002, Valero V 2002, Wang, Buchholz et al. 2002). Due to its value as a surrogate for survival, response to neoadjuvant chemotherapy is being used as a primary end point in studies that examine the efficacy of new drugs and novel drug combinations (Cortazar P 2012).

1.1.5 Surgery after neoadjuvant treatment

Approximately one third of patients thought to be in complete remission on clinical grounds after neoadjuvant chemotherapy still have residual disease at the time of pathologic examination. Therefore, pathologic examination following surgical excision of the suspected area of involvement is the best indicator of response (Fisher and Mamounas 1995). Appropriate selection of patients for breast conserving surgery (BCS) following neoadjuvant chemotherapy is important. Absolute contraindications for BCS include extensive, residual, or multifocal tumor, or positive resection margins, while a

relative contraindication is predicted poor cosmetic outcome (Brenin and Morrow 1998).

1.2 Study Agent(s) Background and Associated Known Toxicities

1.2.1 Carboplatin (Paraplatin)

Please refer to carboplatin package insert for full prescribing information.

Carboplatin is a platinum analog that covalently binds to the DNA producing cross-links which leads to inhibition of DNA synthesis. It is a cell cycle non-specific chemotherapeutic agent. Single agent carboplatin is active in patients with previously untreated metastatic breast cancer, producing response rates of 20-35% (Carmo-Pereira J 1990, Kolaric and Vukas 1991, Martin, Diaz-Rubio et al. 1992, Baselga, Norton et al. 1993, O'Brien, Talbot et al. 1993). Combination regimens of carboplatin with other chemotherapy agents (taxanes, gemcitabine) are also active for treatment of advanced breast cancer (Nasr, Chahine et al. 2004, Perez 2004, Perez, Suman et al. 2005). Platinum compounds are considered to be especially active for triple negative breast cancer. Recent studies demonstrate that addition of neoadjuvant carboplatin to A/C/Ta-based chemotherapy improves pathological complete response in patients with stage I-III TNBC.

1.2.2 Doxorubicin (Adriamycin)

Please refer to doxorubicin package insert for full prescribing information.

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

Drug Interactions: For a comprehensive list of adverse events associated with doxorubicin, refer to package insert.

Toxicity/Side Effects: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2-3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulites, vesication and erythematous streaking have also been seen. Mucositis may be seen 5-10 days after administration. Ulceration necrosis of the colon, particularly the cecum, with bleeding and severe infection has been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nail beds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/m^2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Renal excretion of doxorubicin is minimal, but enough to color the urine red. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and

lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

1.2.3 Cyclophosphamide (Cytoxan)

Please refer to cyclophosphamide package insert for full prescribing information.

Description: Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

Drug Interactions: For a comprehensive list of adverse events associated with cyclophosphamide, refer to package insert.

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

Secondary malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If a patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

1.2.4 Paclitaxel (Taxol)

Please refer to paclitaxel package insert for full prescribing information.

Paclitaxel is a cytotoxic agent with proven antitumor activity in a variety of solid tumors, including breast cancer, ovarian cancer, and lung cancer. The antitumor activity of paclitaxel is based on tubulin-binding and stabilization of non-functional microtubule bundles, there by blocking normal mitotic spindle development and subsequent cell division (Ringel and Horwitz 1991).

In breast cancer, paclitaxel is used both in combination with other agents and as single agent. A weekly (qw) over a three-weekly (q3w) administration schedule has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy (Seidman, Berry et al. 2008, Sparano, Gray et al. 2009). In these two large randomized Phase 3 studies the overall toxicity profile was similar between the qw and q3w

schedule except for neuropathy (higher in qw arm) while other studies have described a more favorable toxicity profile with the qw administration (Eniu, Palmieri et al. 2005).

1.2.5 Docetaxel (Taxotere)

Please refer to docetaxel package insert for full prescribing information.

Docetaxel is an anti-microtubule agent. Randomized phase III trials have confirmed the anti-tumor activity of docetaxel in breast cancer in neoadjuvant, adjuvant and metastatic settings (Bonneterre J 1997, Gradishar 1997, Nabholtz JM 1998, Hutcheon, Heys et al. 2003, Bear, Anderson et al. 2004, Malhotra, Dorr et al. 2004, Roche H 2004, Goldstein LJ 2005, Jones, Savin et al. 2005, Martin, Pienkowski et al. 2005). Addition of docetaxel to anthracycline based chemotherapy in neoadjuvant setting has universally been associated with improved outcome in all studies (superior complete clinical and pathologic response rate in all and improved survival in the Aberdeen study). One of the largest neoadjuvant studies, NSABPB-27, investigated neoadjuvant Doxorubicin/Cyclophosphamide +/- Docetaxel in patients with early breast cancer (T>3 cm or lymph node positive). Addition of neoadjuvant docetaxel to doxorubicin and cyclophosphamide was associated with superior clinical response rate and pCR (pCR of 27% vs. 13%). The Aberdeen Breast Study investigated the use of neoadjuvant docetaxel in large or locally advanced breast cancer after treatment with induction cyclophosphamide, doxorubicin, vincristine, prednisolone (CVAP) (Hutcheon, Heys et al. 2003). Patients who were responsive to induction CVAP and subsequently treated with sequential docetaxel achieved a 94% clinical and 34% pathologic response rate versus a 66% clinical and 16% pathologic response rate in patients who received four additional cycles of CVAP therapy. Overall survival at 5 years was also superior in the docetaxel arm.

1.2.6 Docetaxel + Carboplatin

Commonly used dosing schedule of this combination in breast cancer is Docetaxel at 75mg/m^2 and Carboplatin at AUC of 6 given every 21 days. Primary toxicity of this regimen is hematologic with grade 3-4 neutropenia occurring in up to 65% of patients and febrile neutropenia occurring in 9-10% of the patients (when given without growth factor support). The incidence of grade 3-4 neutropenia and leucopenia with carboplatin/docetaxel is lower compared to AC-T based chemotherapy (Slamon, Eiermann et al. 2011). Due to the modest risk of grade 4 neutropenia and febrile neutropenia prophylactic growth factor support is generally recommended for this combination in breast cancer (NCCN 2014).

1.3 Rationale

Sporadic and germline BRCA mutation associated triple-negative breast cancer (TNBC) share several pathological and molecular similarities. These similarities have led to the exploration of DNA damaging agents like platinum compounds in the general population of patients with TNBC. Recent studies demonstrate that addition of neoadjuvant carboplatin (Cb) to A/C/T-based chemotherapy improves pathological complete response (pCR) in patients with stage I-III TNBC but also increase toxicity (dose reductions/omissions needed in 40-50% of patients). Evaluation of the carboplatin in neoadjuvant chemotherapy for TNBC

has been an area of intense exploration in the recent years and identifying the best carboplatin regimen is actively being sought.

We recently reported encouraging pCR rates with a non-anthracycline carboplatin plus docetaxel neoadjuvant chemotherapy regimen in a cohort of 49 TNBC patients (Sharma P 2014). This chemotherapy regimen of carboplatin plus docetaxel yielded an overall pCR rate of 65% in unselected TNBC with pCR rates of 61% in sporadic and 77% in germline BRCA-associated TNBC. The chemotherapy regimen of carboplatin/docetaxel is well tolerated. In our neoadjuvant experience, most common grade 3-4 toxicities with carboplatin/docetaxel were neutropenia (4%), anemia (6%), thrombocytopenia (6%), and diarrhea (6%). Thus, this regimen should be studied further and compared with regimens that add carboplatin to the standard anthracycline/taxane containing regimens.

Thus, a randomized neoadjuvant open label phase II study to further estimate and compare pCR rates of carboplatin plus docetaxel x 6 cycles to carboplatin plus paclitaxel x 4 cycles→doxorubicin plus cyclophosphamide x 4 cycles in stage I-III TNBC is proposed. Carboplatin plus paclitaxel → AC is chosen as a comparator regimen since this was the regimen used in the largest randomized neoadjuvant trial which evaluated addition of carboplatin to A/C/Ta based chemotherapy.

1.4 Correlative Studies

[redacted]

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To evaluate the pathological complete response (pCR) rates with neoadjuvant chemotherapy regimens of carboplatin plus paclitaxel x 4 cycles→ doxorubicin plus cyclophosphamide (AC) X 4 cycles (CbP→AC) and carboplatin plus docetaxel X 6 cycles (CbD) in subjects with stage I-III TNBC.

Hypothesis: CbD and CbP→AC will yield comparable pCR rates in subjects with stage I-III TNBC.

2.2 Secondary Objectives

To evaluate minimal residual disease (MRD) rates (Residual Cancer Burden score of 0/1) with two neoadjuvant chemotherapy regimens (CbP→AC and CbD) in subjects with stage I-III TNBC.

Hypothesis: CbP→AC and CbD regimens will yield comparable MRD rates in subjects with stage I-III TNBC.

2.3 Exploratory Objectives

1. To compare pCR and MRD rates in subjects with germline BRCA associated and BRCA wild type TNBC with the two neoadjuvant chemotherapy regimens.
2. Exploratory assessment of cost associated with the delivery of the two chemotherapy regimens.

2.4 Endpoints

1. Primary end point: To estimate the rates of pathological complete response in breast and axilla (pCR) in the two treatment arms.
2. Secondary end point: To estimate the rates of MRD in the two treatment arms

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

3.1.1 Ability to understand and the willingness to sign a written informed consent

3.1.2 Subjects with newly diagnosed stage I (T>1cm), II or III TNBC who have not undergone definitive breast surgery and have not received systemic chemotherapy will be eligible.

3.1.3 The invasive tumor must be hormone receptor-poor, defined as both estrogen receptor (ER) and progesterone receptor (PgR) staining present in $\leq$ 10% of invasive cancer cells by IHC.

3.1.4 HER- 2 negativity will be based on the current ASCO-CAP guidelines for HER testing (Wolff, Hammond et al 2013)

3.1.5 No previous chemotherapy, endocrine, therapy or radiation therapy with therapeutic intent for this cancer

3.1.6 Female subjects age 18 - 70 years

3.1.7 Performance Status of 0-1

3.1.8 Adequate organ and marrow function as defined below:

- Leukocytes ≥ 3,000/uL
- Absolute neutrophil count ≥ 1500/uL
- Platelets ≥ 100,000/uL
- Total bilirubin ≤ 1.5mg/dL
- AST(SGOT)/ALT(SPGT) ≤ 2 x institutional upper limit of normal
- Creatinine ≤ 1.5mg/dl and/or Creatinine Clearance ≥ 60mL/min
- Serum albumin $\geq$ 3.0 g/dL

3.1.9 Women of child-bearing potential must agree to use adequate contraception (barrier method of birth control or abstinence – hormonal contraception is not allowed while participating in this study) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9.1 A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)

3.1.10 Subjects must be informed of the investigational nature of the study, and must sign an informed consent in accordance with the institutional rules.

3.1.11 Pretreatment lab values must be performed within 14 days of treatment initiation, and other baseline studies performed within 30 days prior to registration

3.1.12 Subjects should have LVEF ≥ 50% by echocardiogram or MUGA scan performed within 4 weeks prior to treatment initiation

3.1.13 Subjects should have breast and axillary imaging with breast MRI (preferred) or breast and axillary US within 4 weeks prior to treatment initiation

3.1.14 Subjects with clinically/radiologically abnormal axillary lymph nodes should have pathological confirmation of disease with image guided biopsy/fine needle aspiration.

3.1.15 Subjects must be already enrolled in P.R.O.G.E.C.T observational registry (HSC #12614)

3.1.16 Staging to rule out metastatic disease is recommended for subjects with clinical stage III disease

3.1.17 Subjects with bilateral disease are eligible if they meet other eligibility criteria.

3.1.18 Neuropathy: No baseline neuropathy grade > 2

3.1.19 Cardiac function

Subjects with congestive heart failure are not eligible, nor are subjects with myocardial infarction, unstable angina pectoris, an arterial thrombotic event, stroke or transient ischemia attack (TIA) within the past 12 months, uncontrolled hypertension (Systolic BP>160 or Diastolic BP>90), uncontrolled or symptomatic arrhythmia, or grade 2 or greater peripheral vascular disease.

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Current or anticipated use of other investigational agents

3.2.2 Subject has received chemotherapy, radiotherapy or surgery for the treatment of breast cancer

3.2.3 Subject with metastatic disease

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, docetaxel, doxorubicin, cyclophosphamide, paclitaxel, or other agents used in the study.

3.2.5 Subjects with inflammatory breast cancer

3.2.6 Uncontrolled intercurrent illness including, but not limited to; ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris,

cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.7 Subject is pregnant or nursing. There is a potential for congenital abnormalities and for this regimen to harm nursing infants.

3.2.8 Subjects with concomitant or previous malignancies within the last 5 years are excluded from the study. Exceptions include: adequately treated basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and ductal carcinoma in situ (DCIS).

3.2.9 Ejection Fraction <50% on ECHO or MUGA

4.0 TREATMENT PLAN

Protocol treatment is to begin within 14 days of randomization.

4.1 Pre-chemotherapy surgical evaluation

Prior to beginning drug therapy, the subject will be seen and examined by the treating surgeon. This will include a clinical breast and lymph node examination and review of the imaging studies (MRI or other radiographic method) of the breast and axilla. After examining the subject and reviewing the pertinent radiographic studies, the surgeon will determine whether the subject is a breast conservation candidate. If the subject is not a breast conservation candidate, the reason(s) will be documented on the surgical evaluation form **(APPENDIX A).**

4.2 Treatment Dosage and Administration

NEOADJUVANT THERAPY:
In general chemotherapy premeditations and at home supportive medications to prevent anticipated side effects are to follow institutional guidelines. Appendix D describes the suggested pre-medication use with each arm of the treatment.

4.2.1 Chemotherapy Regimen Arm A

Carboplatin plus Paclitaxel followed by dose dense AC (Cb+P→AC)					
Agent	**Pre-medications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Paclitaxel	Per institutional guidelines	80 mg/m^2	IV over 1 hours	Day 1	weekly x 12*
Carboplatin[#]	Per institutional guidelines	AUC 6	IV over 30 min	Day 1	every 3* weeks x 4
The total duration of the above treatment should not exceed 12 weeks. Missed doses (for any reason) of either paclitaxel or carboplatin should not be made up at the end of the 12 week treatment period. Doxorubicin/cyclophosphamide (see below) to start 3 weeks (+ 7 days) after the last dose of carboplatin and/or one week (+ 7 days) after the last dose of paclitaxel.					
Doxorubicin	Per institutional guidelines	60 mg/m^2	IV push over 3-5 min	Day 1	Every 14* days x 4 cycles
Cyclophosphamide	Per institutional guidelines	600 mg/m^2	IV over 30 min	Day 1	
Pegfilgrastim		6mg	SC	Day 2	

[#]The SWOG ((South West Oncology Group) guidelines **must** be followed for carboplatin dose calculation: 1) Use of Modified Cockcroft-Gault formula for calculating renal function, 2) Calculating

Modified Cockcroft-Gault with serum creatinine set to 0.8 mg/dL if actual serum creatinine < 0.8 mg/dL, 3) Maximum GFR is 125 ml/min, 4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance, 5) Maximum carboplatin dose to be given is 900mg
*+/- one day

4.2.2 Chemotherapy Regimen Arm B

Carboplatin plus Docetaxel (CbD)					
Agent	**Pre-medications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Docetaxel	Per institutional guidelines	75mg/m^2	IV over 60 minutes	Day 1	Every 21* days x 6 cycles
Carboplatin[#]	Per Institutional guidelines	AUC 6	IV over 30 minutes	Day 1	
Pegfilgrastim		6mg	SC	Day 2	

[#]The SWOG (South West Oncology Group) guidelines **must** be followed for Carboplatin dose calculation: 1) Use of Modified Cockcroft-Gault formula for calculating renal function, 2) Calculating Modified Cockcroft-Gault with serum creatinine set to 0.8 mg/dL if actual serum creatinine < 0.8 mg/dL, 3) Maximum GFR is 125 ml/min, 4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance, 5) Maximum carboplatin dose to be given is 900mg
*+/- one day

4.2.3 Growth factor support: Erythropoietic growth factor support for fatigue/anemia is not allowed. Packed RBC transfusion is allowed per the discretion of the treating physician. Pegfilgrastim growth factor support as described above is included in the treatment plan.

4.3 Surgery

After completion of neoadjuvant therapy, subjects will proceed with either modified radical mastectomy or lumpectomy. Breast conservation eligibility as “Yes”/”No” should be documented prior to surgery. Surgery should take place between 3-6 weeks after the last chemotherapy cycle.

All subjects with pretreatment lymph node positive disease and positive sentinel lymph node will undergo complete axillary lymph node dissection and/or axillary radiation. Histopathological examination of the surgical specimen will be done to determine the extent of residual disease. Pathological complete response (pCR) will be defined as no evidence of disease in the breast and axilla at the time of pathology review except for DCIS.

Prior to neoadjuvant therapy and at the end of neoadjuvant chemotherapy (prior to breast surgery), the surgeon will assess the subject and assess whether the subject is a candidate for breast conserving surgery. This must be documented in the medical record and on the study specific surgical assessment form (**APPENDIX A**).

4.4 Adjuvant Therapy:

Adjuvant chemotherapy: as per recommendations of treating physician.
Adjuvant radiation therapy: As per recommendations of the treating physician. In general adjuvant radiation is recommended for patients who undergo BCS, have tumors > 5 cm, have skin or chest wall involvement, or have pathologically positive lymph node(s) after neoadjuvant chemotherapy.

4.5 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the Schedule of Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose modifications for chemotherapy in event of toxicity (sections 4.5-4.8, tables 4.6.1– 4.8.5) are applicable only if the toxicity is deemed "treatment-related." This is in accordance with standard clinical practice. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.6 Carboplatin + Paclitaxel

Carboplatin Dose Levels
Level 0: AUC 6
Level -1: AUC 5
Level -2: AUC 4

Paclitaxel Dose Levels
Level 0: 80mg/m^2
Level -1: 70mg/m^2
Level -2: 60mg/m^2

There are no paclitaxel dose reductions below dose level -2. If dose reduction below dose level -2 is required, discontinue paclitaxel and carboplatin and begin ddAC when ANC > 1,000/uL (and platelets≥> 75,000/uL).

4.6.1 Hematologic Toxicities:

Toxicity	Treatment Modifications
ANC < 1,000/uL (prior to each treatment)*	-Skip paclitaxel. Skipped doses are not made up. -On week 4, 7 or 10, delay carboplatin for ANC < 1000/uL. When treatment resumes (ANC ≥1000uL) continue with carboplatin every 3 weeks. If delays result in a carboplatin dose being scheduled on wk 12, that dose will be skipped; carboplatin will not be given on wk 12. -If paclitaxel is skipped for 1 week, resume paclitaxel at previous dose level when ANC ≥ 1000/uL -If paclitaxel is skipped for 2 consecutive weeks for ANC ≤ 1000/uL, decrease paclitaxel and carboplatin by one dose level for all subsequent doses. -If paclitaxel is skipped for 3 consecutive weeks for ANC ≤ 1000/uL, discontinue paclitaxel and carboplatin and begin ddAC when ANC ≥ 1000/uL (and platelets ≥ 75,000/uL)
ANC <100 or febrile neutropenia** (at any time)	Reduce carboplatin and paclitaxel by one dose level for all subsequent cycles
Thrombocytopenia* • For platelets < 25,000/uL, at any time, decrease carboplatin by one dose level for all subsequent doses. • For platelets < 50,000/uL* on weeks 2, 3, 5, 6, 8, 9, 11 or 12 skip paclitaxel and decrease carboplatin by one dose level for all subsequent doses. Skipped doses	

are not made up. • For platelets < 75,000/uL on weeks 4, 7 or 10 delay carboplatin until platelets ≥ 75,000/uL, then resume carboplatin with one dose level reduction for all subsequent doses. • When treatment with carboplatin resumes, continue with carboplatin every 3 weeks. However, if delays result in a carboplatin dose being scheduled on week 12, that dose will be skipped; carboplatin will not be administered on week 12. • For platelets ≥ 50,000/uL and < 75,000/uL, continue paclitaxel at previous dose. • If paclitaxel is skipped for 2 consecutive weeks for platelets < 50,000/uL, reduce paclitaxel by one dose level for all subsequent doses. • There are no carboplatin dose reductions below dose level -2. If dose reduction below dose level -2 is required, discontinue carboplatin, and resume weekly paclitaxel when platelets are ≥ 50,000/uL. • If paclitaxel is skipped or carboplatin delayed for 3 consecutive weeks for thrombocytopenia, discontinue paclitaxel and carboplatin, and begin ddAC when platelets ≥ 75,000/uL (and ANC ≥ 1,000/uL).	
Anemia	During the twelve weeks of weekly paclitaxel and carboplatin, if the patient requires more than 2 units of packed red blood cells for symptomatic anemia, all subsequent doses of carboplatin will be reduced one dose level. The doses of paclitaxel will not be changed, nor will the doses for subsequent treatment with ddAC.

*If the ANC is < 1000/uL or the platelet count is < 75,000/uL when drawn > 24 hours prior to the scheduled treatment, the CBC should be re-checked on the day of the treatment to see if the blood counts have recovered sufficiently to allow the scheduled treatment to be given.
** Febrile neutropenia = ANC < 1000/uL and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour.

4.6.2 Non hematologic toxicities:

Peripheral neuropathy	• Grade 1: continue treatment • Grade 2: decrease the dose of paclitaxel by one dose level for all subsequent doses. The dose of carboplatin is not reduced. • Grade 3: skip paclitaxel and delay carboplatin (week 4, 7 or 10). Skipped doses are not made up. • When neuropathy improves to ≤ grade 2, resume treatment with one dose level reduction of both paclitaxel and carboplatin. • If a carboplatin dose was delayed, the remaining doses of carboplatin will continue every 3 weeks. However, if delays result a carboplatin dose being scheduled on week 12, that dose will be skipped; carboplatin will not be administered on week 12. • If grade 3 peripheral neuropathy, does not improve within 3 weeks, discontinue paclitaxel + carboplatin and begin ddAC. • For grade 3 peripheral neuropathy that has recurred after recovery to ≤ grade 2, discontinue paclitaxel + carboplatin and begin ddAC. • Grade 4: discontinue paclitaxel + carboplatin and begin ddAC. Recovery of neuropathy is not

	required to begin ddAC.
Other non-hematologic toxicities	•Delay all treatment for any toxicity ≥ grade 3 (with the exception of fatigue), until toxicity improves to ≤ grade 2. When treatment is resumed, reduce the dose of both paclitaxel and carboplatin • If toxicity does not improve to ≤ grade 2 within 3 weeks, discontinue paclitaxel + carboplatin and begin ddAC when non-hematologic toxicities (including sequelae of hypersensitivity reactions) have improved to ≤ grade 2.
Hepatic dysfunction (prior to each treatment)	•For total bilirubin > 1.5 x IULN or ALT > 5 x IULN, skip paclitaxel. Skipped doses are not made up. Recheck LFTs the following week. Paclitaxel can be resumed when total bilirubin ≤ 1.5 x IULN and ALT ≤ 5 x IULN • For total bilirubin > 1.5 x IULN or ALT > 5 x IULN on week 4, 7 or 10, delay carboplatin until total bilirubin ≤ 1.5 x IULN and ALT ≤ 5 x IULN, then, resume treatment with carboplatin at previous dose. Continue with carboplatin every 3 weeks. However, if delays result in a carboplatin dose being scheduled on week 12, that dose will be skipped; carboplatin will not be administered on week 12. • If treatment is skipped or delayed for 3 consecutive weeks for hepatic dysfunction, discontinue paclitaxel + carboplatin and begin ddAC when total bilirubin ≤ 1.5 x IULN and ALT ≤ 2.5 x IULN.

4.6.3 Hypersensitivity and/or infusion reactions

During paclitaxel infusion:

- Grade 1: Continue paclitaxel infusion. Consider more intensive premedication prior to subsequent doses.
- Grade 2: Interrupt paclitaxel infusion. Manage reaction according to institutional procedures. Resume paclitaxel when reaction has completely resolved. Consider more intensive premedication prior to subsequent doses.
- Grade 3: Stop paclitaxel infusion. Manage reaction according to institutional procedures. Do not resume paclitaxel infusion that day; delay carboplatin (if patient is due to receive carboplatin). It is up to the treating physician to decide whether to attempt re-treatment with paclitaxel the following week with more intensive premedication or to discontinue paclitaxel +carboplatin and begin ddAC.
- Grade 4: Stop paclitaxel infusion. Manage reaction according to institutional procedures. Discontinue paclitaxel + carboplatin and begin ddAC.

During carboplatin infusion

- Grade 1 or 2: Stop carboplatin infusion. Manage reaction according to institutional procedures. Do not resume carboplatin infusion that day. It is up to the treating physician to decide whether to re-attempt carboplatin infusion

with next weekly paclitaxel (with or without desensitization) or to discontinue carboplatin and continue treatment with weekly paclitaxel only.

- Grade 3 or 4: Stop carboplatin infusion. Manage reaction according to institutional procedures. Discontinue carboplatin and continue treatment with weekly paclitaxel only.

4.7 Dose dense Doxorubicin and Cyclophosphamide (ddAC)

*******Growth factor support is required during ddAC (see section with title *Treatment Dosage and Administration / NEOADJUVANT THERAPY)***

Doxorubicin and cyclophosphamide cannot be reduced below dose level -2 for toxicity. If dose reductions below dose level -2 are required, discontinue ddAC and proceed to surgery when feasible.

Doxorubicin dose level		Cyclophosphamide dose level	
Level 0	60 mg/m^2	Level 0	600 mg/m^2
Level -1	50 mg/m^2	Level -1	500 mg/m^2
Level -2	40 mg/m^2	Level -2	400 mg/m^2

Hematologic Toxicities:

- For ANC < 1000/uL or platelets < 75,000/uL, re-check CBC weekly and delay doxorubicin and cyclophosphamide until ANC ≥ 1000/uL and platelets ≥ 75,000/uL. If cycles 2 or 3 of doxorubicin and cyclophosphamide are delayed for more than 1 week for hematologic toxicity, decrease doxorubicin by one dose level and decrease cyclophosphamide by one dose level for all subsequent doses.
- For febrile neutropenia (a single temperature ≥ 38.3^{0}C or a sustained temperature of ≥ 38^{o}C in the presence of ANC < 1,000/uL) that occurs following treatment with ddAC, decrease doxorubicin by one dose level and decrease cyclophosphamide by one dose level for all subsequent doses.
- There will be no dose modifications for anemia of any grade.

Non hematologic toxicities

Mucositis (grade 3-4)	•Provide supportive measures and hold doxorubicin and cyclophosphamide. •Resume at current dose when toxicity recovers to grade 0-2. •If the subject again experiences mucositis grade 3-4, reduce the doses of both doxorubicin and cyclophosphamide by one dose level. •If, after three week delay, the toxicity is not resolved discontinue AC chemotherapy
Hepatic toxicity	See below for dose reductions •For total bilirubin 1.5 – 3.0 mg/dL, decrease doxorubicin by one dose level. • For total bilirubin > 3.0 mg/dL, decrease doxorubicin to dose level -2.

	• There are no dose modifications for cyclophosphamide for total bilirubin ≤ 5.0 mg/dL. • For total bilirubin > 5.0 mg/dL, delay all treatment until bilirubin ≤ 5.0 mg/dL.
Cardiac Dysfunction (grade 3-4)	Discontinue AC therapy and remove the subject from protocol treatment if the subject has symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distension, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) and a diagnosis of CHF is confirmed, or if the subject has a myocardial infarction or a drop in LVEF to below the institutional limits of normal. **The presence of PACs or PVCs without cardiac dysfunction is not an indication to stop doxorubicin. Acute dysrhythmias, which may occur during and shortly after doxorubicin infusion, are not an indication to stop doxorubicin.
Hemorrhagic cystitis (grade 2-4)	If hematuria is felt to be secondary to cyclophosphamide therapy, delay treatment until grade 0-1. Provide adequate hydration and other supportive measures. Mesna can be used at the discretion of the investigator. If, after three week delay, the toxicity is not resolved, discontinue AC chemotherapy.
Other non-hematologic toxicities	For any other grade 3 or 4 toxicity (with the exception of fatigue, nausea or vomiting), delay doxorubicin and cyclophosphamide until toxicity improves to ≤ grade 2. When treatment is resumed, reduce the doses of doxorubicin and cyclophosphamide by one dose level. • If toxicity does not improve to ≤ grade 2 within 3 weeks, discontinue doxorubicin and cyclophosphamide and proceed to surgery when feasible

4.7.1 Hepatic dysfunction (dose modifications based on Day 1 liver function tests)

Liver Function Tests	Dose Modification
Total bilirubin < IULN **AND** AST/ALT > IULN but ≤ 3 x IULN	Doxorubicin dose reduced 25%.
Total bilirubin ≥ IULN but ≤ 3 mg/dL **OR** AST/ALT > 3 x IULN	Doxorubicin dose reduced 50%.
Total bilirubin 3.1-5 mg/dL	Doxorubicin dose reduced 75%. Cyclophosphamide dose reduced 25%.
Total bilirubin > 5 mg/dL	Do **not** administer doxorubicin or cyclophosphamide. Recheck labs every week. Resume when Total bilirubin < IULN AND AST/ALT > IULN but ≤ 3 x IULN. If does not resolve to this level within 3 weeks stop doxorubicin and cyclophosphamide and proceed to surgery when feasible

4.8 Docetaxel and Carboplatin

Carboplatin Dose Levels
Level 0: AUC 6
Level -1: AUC 5
Level -2: AUC 4

Docetaxel Dose Levels
Level 0: 75 mg/m^2
Level -1: 60 mg/m^2
Level -2: 45 mg/m^2

4.8.1 Hematologic Toxicities:

Toxicity[a]	Treatment Modifications
ANC[b] < 1 000/uL (day 1 of cycle)	Delay docetaxel and carboplatin until ANC ≥1,000/uL. If counts recover to ≥ 1,000/uL in ≤ 1 week, resume at current dose If docetaxel and carboplatin are delayed for 2 consecutive weeks for ANC < 1000/uL reduce docetaxel and carboplatin by one dose level for all subsequent cycles. If docetaxel and carboplatin are delayed for 3 consecutive weeks for ANC < 1000/uL discontinue docetaxel and carboplatin.

ANC <100/uL or febrile neutropenia[b] (at any time)	Reduce docetaxel and carboplatin by one dose level for all subsequent cycles.
Platelets < 50,000/uL (day 1 of cycle)	Hold docetaxel and carboplatin until platelets ≥ 75,000/uL then resume docetaxel and carboplatin with one dose level reduction for both drugs for all subsequent doses.
For platelets ≥ 50,000 and < 75,000 (day 1 of cycle)	Hold both docetaxel and carboplatin until platelets ≥75,000/ul and resume docetaxel at previous dose and carboplatin with one dose level reduction for all subsequent doses. If docetaxel and carboplatin are held for 3 consecutive weeks for platelets < 75,000/uL, discontinue treatment.

[a]There will be no dose modifications for grade 1 – 4 anemia.
[b]Febrile neutropenia: a single temperature ≥ 38.3°C or a sustained temperature of ≥ 38°C for more than an hour in presence of ANC < 1,000/uL)

4.8.2 Non-hematologic toxicities:

Peripheral neuropathy	• Grade 1: continue treatment • Grade 2: decrease the dose of docetaxel by one dose level for all subsequent doses. The dose of carboplatin is not reduced. • Grade 3: hold docetaxel and carboplatin. When neuropathy improves to ≤ grade 2, resume treatment with one dose level reduction of both docetaxel and carboplatin. • If grade 3 peripheral neuropathy does not improve within 3 weeks, discontinue docetaxel and carboplatin. • For grade 3 neuropathy that has recurred after recovery to ≤ grade 2, discontinue docetaxel and carboplatin. • Grade 4: discontinue docetaxel and carboplatin

Hypersensitivity reactions	see below for management
Fluid retention	There are no dose reductions for fluid retention (see below for management)
Hepatic dysfunction (day 1 LFTs)	See below for dose reductions chart. Patients with total bilirubin > 1.5 X IULN should not receive docetaxel. Patients with AST and/or ALT > 1.5 x IULN concomitant with alkaline phosphatase > 2.5 x IULN should not receive docetaxel.
Other non-hematologic toxicities	•For any other grade 3 or 4 toxicity (with the exception of fatigue, nausea or vomiting), delay docetaxel and carboplatin until toxicity improves to ≤ grade 2. When treatment is resumed, reduce the doses of docetaxel and carboplatin by one dose level. • If toxicity does not improve to ≤ grade 2 within 3 weeks, discontinue docetaxel and carboplatin and proceed to surgery when feasible

4.8.3 Hypersensitivity reactions

During docetaxel infusion

- Grade 1: Continue docetaxel infusion. Consider decreasing the rate of infusion Consider more intensive premedication prior to subsequent doses.
- Grade 2: Interrupt docetaxel infusion. Manage reaction according to institutional procedures. Resume docetaxel when reaction has completely resolved. Consider more intensive premedication prior to subsequent doses.
- Grade 3: Stop docetaxel infusion. Manage reaction according to institutional procedures. Do not resume docetaxel infusion that day and delay carboplatin dose that was to be administered that day. It is up to the treating physician to decide whether to attempt re-treatment with docetaxel the following cycle with more intensive premedication or to discontinue docetaxel.
- Grade 4: Stop docetaxel infusion. Manage reaction according to institutional procedures. Discontinue docetaxel. Carboplatin monotherapy can be continued per the discretion of the treating physician.

During carboplatin infusion

- Grade 1or 2: Stop carboplatin infusion. Manage reaction according to institutional procedures. Do not resume carboplatin infusion that day. It is up to the treating physician to decide whether to re-attempt carboplatin infusion with next cycle (with or without desensitization) or to discontinue carboplatin and continue treatment with docetaxel only.
- Grade 3 or 4: Stop carboplatin infusion. Manage reaction according to institutional procedures. Discontinue carboplatin. Docetaxel monotherapy can be continued per the discretion of the treating physician.

4.8.4 Management of edema/fluid retention related to docetaxel

No dose reduction is required. Subjects developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. pound weight gain) can be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below.

- Hydrochlorothiazide/Triamterene one capsule 25/37.5 po up to three times per day per the discretion of the treating physician
- Furosemide 40 mg po daily if edema progresses despite hydrochlorothiazide/triamterene therapy. Potassium supplementation should be given as needed.
- If after a two week trial, furosemide 40 mg po daily is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the subject, the overall tumor response and the medical judgment of the investigator will determine if it is in the subject's best interest to continue or discontinue treatment.

4.8.5 Hepatic dysfunction (dose modifications based on day 1 liver function tests)

Liver Function Tests	**Dose Modification**
Total bilirubin > 1.5 x IULN concomitant with alkaline phosphatase > 2.5 x IULN	Do NOT administer docetaxel. If not resolved in one week, subject should be removed from protocol treatment.
AST/ALT >2.5 x IULN by $\leq$ 5 x IULN AND Alkaline phosphatase > IULN but $\leq$2.5 x IULN	Docetaxel dose reduced by 20%
AST/ALT >1.5 x IULN and $\leq$ 5 x IULN AND Alkaline phosphatase > 2.5 x IULN but $\leq$5 x IULN	Docetaxel dose reduced by 20%
AST/ALT > 5 x IULN AND/OR Alkaline phosphatase > 5 x IULN	Do NOT administer docetaxel. If not resolved in one week, subject should be removed from protocol treatment.

4.9 Concomitant Medications/Treatments

Permitted Concomitant Therapy: In general, the use of any concomitant medication or therapy deemed necessary for the care of the subject is permitted.

- Use of anti-emetics is allowed.
- Use of erythropoietin stimulating agents is not allowed
- Use of goserelin for fertility preservation is allowed.

Anticoagulants

Anticoagulants or other anti-aggregation agents may be administered under the discretion of the investigator. Subjects on anticoagulation with warfarin should be carefully monitored and have PT/INR checked every week.

Contraceptives
Hormonal contraceptives are not allowed for this study. Allowed contraceptive methods are barrier method of birth control or abstinence.
.
Highly effective contraception should be maintained throughout the study and for 90 days after study drug discontinuation.

Other investigational therapies must not be used while the subject is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy and surgery) other than the study treatments must not be given to subjects while the subject is on the study medication. If such agents are required for a subject, then the subject must be discontinued from the study

4.10 Duration of Therapy

In the absence of treatment delays due to adverse events, all subjects in Arm A will receive neoadjuvant chemotherapy with paclitaxel weekly for 12 weeks plus carboplatin given every 3 weeks x 4 cycles. The total duration of this treatment should not exceed 12 weeks. Missed doses (for any reason) of either paclitaxel or carboplatin should not be made up at the end of the 12 week treatment period.

This treatment will be followed by 4 cycles of doxorubicin and cyclophosphamide given every 14 days. Doxorubicin/cyclophosphamide should start 3 weeks (+7 days) after the last dose of carboplatin and/or one week (+7 days) after the last dose of paclitaxel.

All subjects in Arm B will receive 6 cycles of neoadjuvant chemotherapy with carboplatin and docetaxel given every 21 days.

4.11 Duration of Follow Up

The subjects will be followed for 6 months after completion of all local and systemic treatment for breast cancer (surgery +/- radiation).

4.12 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in section with title *Removal of Subjects from Study* apply.

Notify the Principal Investigator and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol. Subjects who are removed from protocol therapy due to disease progression will be counted as a treatment failure in the efficacy analysis and will continue to be followed per protocol.

4.13 Subject Replacement

Subjects who do not complete the study treatment due to toxicity or other reasons will not be replaced.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

Complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

5.1.3 Demographics

Demographic profile will include date of birth, gender, race, and zip code.

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

All prior medications taken by the subject within 4 weeks before starting the study are to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30 days after last study dose. If a reportable adverse event (see section with title *ADVERSE EVENTS*) occurs within 30 days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight and assessment of all major body systems

5.1.7 Performance status

Subject performance status based on ECOG criteria (Zubrod scale) will be evaluated prior to study entry and possibly during study. Specific criteria for assessing performance status can be found in **APPENDIX B**.

5.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See section with title *ADVERSE EVENTS f*or Adverse Event monitoring and reporting.

5.1.9 Hematology (to be performed no more than 14 days prior to treatment start date)

Hematology to include hemoglobin (Hgb), platelets, red blood cells, white blood cells and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)

5.1.10 Serum chemistries (to be performed no more than 14 days prior to treatment start date)

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin (direct must be collected only in case total bilirubin is elevated >ULN), total protein, BUN or urea.

5.1.11 Blood draw for correlative studies

See section with title *CORRELATIVES/SPECIAL STUDIES* for details.

5.1.12 Pregnancy test (for females of child bearing potential)

See section with title S*UBJECT ELIGIBILITY / Inclusion Criteria* for definition.

5.1.13 MUGA/ECHO

Subjects assigned to Arm A of the study must have a Left Ventricular Ejection Fraction (LVEF) of ≥ 50% as determined by MUGA scan or ECHO

5.1.14 Determination of eligibility for breast conservation

Breast conservation eligibility as Yes/No should be documented

5.1.15 Tumor assessment

All patients must have breast and axillary ultrasound and breast MRI (unless MRI is contraindicated, e.g. in presence of metal hardware in body) for accurate assessment of the breast and axillary disease. Subjects with radiologically abnormal axillary lymph node(s) should have had pathological documentation of the nodal involvement (FNA or core needle biopsy).

5.2 Procedures during Treatment

5.2.1 Prior to Each Treatment Cycle

- Vital signs
- Hematology
- Serum chemistries
- Arm A: Carboplatin plus paclitaxel followed by Doxorubicin plus cyclophosphamide: Physical exam including performance status and clinical assessment of tumor response these are only required at pre-study, Weeks 4, 7, 10, 13, 15, 17, 19
- Arm B: Carboplatin plus Docetaxel: Physical exam including performance status and clinical assessment of tumor response at pre-study and at the start of each cycle.

5.2.2 Chemotherapy

Arm A

Carboplatin plus paclitaxel: carboplatin administration on days 1 (week1), 22 (week 4), 42 (week 7), 63 (week 10) paclitaxel administration every week (+/- one day) starting from day 1 of cycle 1.

Doxorubicin plus cyclophosphamide (AC) to start 3 weeks (+7 days) after the last dose of carboplatin and/or one week (+7 days) after the last dose of paclitaxel. AC will be given every 14 days (+/- 1 day) x 4 cycles. During AC patients will receive pegfilgrastim on day 2.

Arm B

Carboplatin plus docetaxel every 21 days (+/-1 day) x 6 cycles

Pegfilgrastim on day 2 or each cycle

5.2.3 Radiological assessment during neoadjuvant chemotherapy (breast MRI).

Prior to first cycle of doxorubicin/cyclophosphamide (+/- 7 days) in Arm A and

fifth cycle of carboplatin/docetaxel (+/- 7 days) in Arm B. In subjects with contraindication/intolerance to breast MRI, breast plus axillary ultrasound can be used for the assessment of response

5.2.4 Patient travel time survey

All patients will complete a travel time survey at one time point during the study. This survey can be completed at any time after cycle one of chemotherapy (preferably at Cycle 2 or 3 of chemotherapy).

5.2.5 Breast Surgery

After completion of neoadjuvant therapy, subjects will proceed to either modified radical mastectomy or lumpectomy. Breast conservation eligibility should be documented prior to surgery. Surgery should take place between 3-6 weeks after the last chemotherapy cycle.

All subjects with pretreatment lymph node positive disease and positive sentinel lymph node will undergo complete axillary lymph node dissection and/or axillary radiation. Histopathological examination of the surgical specimen will be done to determine the extent of residual disease. The pCR will be defined as no evidence of disease in the breast and axilla at the time of pathology review except for DCIS.

5.3 Follow-up Procedures

All subjects will be followed for 6 months after completion of all local and systemic treatment for breast cancer (surgery, chemotherapy and radiation whichever comes last).

5.4 Schedule of Events

Regimen A: Carboplatin + Paclitaxel followed by AC																				
Required Studies	Pre-study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20
Physical																					
History +Physical[1]	X				X			X			X			X		X		X		X	
Weight + PS[1]	X				X			X			X			X		X		X		X	
Toxicity Notation[1]	X				X			X			X			X		X		X		X	
Labs																					
CBC/ANC[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
CMP[1]	X				X			X			X			X		X		X		X	
Pregnancy Test	X[2]																				
Radiology																					
Ultrasound breast/axilla	X																				
MRI breast[3]	X													X							
Echo/MUGA[4]	X																				
Treatment [5]																					
Carboplatin		X			X			X			X										
Paclitaxel		X	X	X	X	X	X	X	X	X	X	X	X								
Doxorubicin														X[6]		X		X		X	
Cyclophosphamide														X[6]		X		X		X	
Pegfilgrastim[7]														X		X		X		X	
Correlative blood specimen[8]																					
Travel time survey[9]																					

[1] Allowed window, can be done within 14 days of starting the study treatment.
[2]All pre- and peri-menopausal women should have a negative urine pregnancy test prior to study entry (should be done on the day study treatment starts)
[3] In patients with contraindication/intolerance to MRI, ultrasound of the breast and axilla can be obtained instead
[4]Either ECHO or MUGA
[5]A subject who requires a treatment break (not to exceed 7 days) for reasons other than toxicity should resume treatment without skipping or modifying treatment doses; the reason for the treatment delay (family emergency, vacation, etc.) should be reported
[6]Start 3 wks (+7 days) after the last dose of carboplatin and/or one week (+7 days) after the last dose of paclitaxel, unless the patient meets criteria for treatment delay.
[7]Pegfilgrastim 6mcg SC will be given on day 2 during the period of AC. During weekly paclitaxel +/- carboplatin, filgrastim may be used at the discretion of the treating physician. Pegfilgrastim may **not** be used during weekly paclitaxel +/- carboplatin.
[8]To be drawn 21 +/- 7 days after the last chemotherapy and prior to breast surgery
[9] All patients will fill a travel time survey at one time point during the study. This survey can be filled at any time after cycle one of chemotherapy (preferably at Cycle 2 or 3 of chemotherapy).

Regimen B: Carboplatin + Docetaxel																				
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
Required Studies	Pre-study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20
Physical																					
History +Physical[1]	X				X			X			X			X			X				
Weight + PS[1]	X				X			X			X			X			X				
Toxicity Notation[1]	X				X			X			X			X			X				
Labs																					
CBC/ANC[1]	X				X			X			X			X			X				
CMP[1]	X				X			X			X			X			X				
Pregnancy Test	X[2]																				
Radiology																					
Ultrasound breast/axilla	X																				
MRI breast[3]	X													X							
Treatment																					
Carboplatin		X			X			X			X			X			X				
Docetaxel		X			X			X			X			X			X				
Pegfilgrastim[4]		X			X			X			X			X			X				
Correlative blood specimen[5]																					
Travel time survey																					

[1]Allowed window can be done within 14 days of starting the study treatment
[2]All pre- and peri-menopausal women should have a negative urine pregnancy test prior to study entry. (should be done on the day study treatment starts)
[3]In subjects with contraindication/intolerance to MRI, ultrasound of the breast and axilla can be obtained instead
[4]Pegfilgrastim 6mcg SC will be given on day 2
[5]To be drawn 21 +/- 7 days after the last chemotherapy and prior to breast surgery
[6]All subjects will fill a travel time survey at one time point during the study. This survey can be filled at any time after cycle one of chemotherapy (preferably at Cycle 2 or 3 of chemotherapy).

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own requestor they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject withdraws consent (termination of treatment and follow-up)

5.5.2 Treating physician judges continuation on the study would not be in the subject's best interest

5.5.3 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)

5.5.4 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study

6.0 ADVERSE EVENTS

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies", issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The guidance may be retrieved from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery

6.1 Definitions

6.1.1 **Adverse Event** [21 CFR 312.32(a)]

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

This study will use the descriptions and grading scales from Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03) for hematologic and non-hematologic toxicities. Detailed information may be found on the Cancer Therapy Evaluation Program (CTEP) website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Information for adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRF as described in the following sections.

Adverse events experienced by subjects will be collected and reported from initiation of study treatment and throughout the study, and within 30 days of the last dose of study treatment. Subjects who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the principal investigator. Study subjects should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after initiation of study treatment. Adverse clinical events occurring before starting study treatment but after signing the informed consent form are to be recorded on the Medical History/Current Medical Conditions CRF. All cancer-related symptoms that have occurred in the last 30 days prior to start of study drug must also be recorded on the CRF.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis.

As far as possible, each adverse event will also be described by:
- its duration (start and end dates),
- grading of severity,
- its relationship to the study drug,
- the action(s) taken,
- outcome.

6.1.2 Suspected Adverse Reaction [21 CFR 312.32(a)]

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Factors to be considered in assessing the relationship of the adverse event to study treatment include:
- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subjects response after drug discontinuation (de-challenge) or

subjects response after study drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Unrelated - The AE is clearly **NOT** related to the study treatment.
- Unlikely - The AE is **doubtfully related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Probable – The AE is **likely related** to the study treatment.
- Definite – The AE is **clearly related** to the study treatment.

6.1.3 Unexpected [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application… "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the Particular drug under investigation.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure…as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the Particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.

6.1.4 Serious [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.5 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

6.2 Reporting Requirements for Adverse Events -

6.2.1 Submitting Serious Adverse Events Reports to IRB

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

6.2.2 Study Investigator Notification of Adverse Events

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be reported to the study principal investigator within 24 hours of becoming aware of the event:

Priyanka Sharma, M.D.
University of Kansas Medical Center
3901 Rainbow Blvd, Mail Stop 3003
Kansas City, KS 66160-7233
[redacted]

6.2.3 DSMC Notification of SAEs

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be reported by phone or email to the KUCC DSMC within 24 hours of becoming aware of the event to:

KUCC DSMC
[redacted]

A follow-up written report in the form of MEDWATCH Form FDA 3500A is required within 5 days.

6.2.4 Recording Adverse Events and Documentation in VELOS

All **expected** and **unexpected** adverse events and serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be fully recorded in the subject's case record form.

All AEs and SAEs regardless of causality must be entered in the KU implementation of eVELOS, called the Comprehensive Research Information System (CRIS). All SAEs regardless of causality must be entered into CRIS within 24 hours. Unexpected and expected adverse events must be entered within 5 days and include: new unexpected adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not

present at baseline, and any event or findings that the Investigator feels is clinically significant.

Documentation must be supported by an entry in the subjects file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

6.2.5 Reporting of Unexpected, Related SAEs for Concomitant Medications

For concomitant medications, all unexpected, related serious adverse experiences will be forwarded to the product manufacturer by the investigator using the Voluntary MEDWATCH Form FDA 3500.

6.2.6 Summary of Expedited Serious Adverse Event Reporting

	Relationship to Study Drug	**KUCC DSMC**	**IRB**	**PI**	**Velos**
Unexpected SAE	Related	24 hrs	Follow local IRB reporting requirements*	24 hrs	24 hrs
Unexpected SAE	Not-related	24 hrs		24 hrs	24 hrs
Expected SAE	Related	24 hrs		24 hrs	24 hrs
Expected SAE	Not-related	24 hrs		24 hrs	24 hrs

7.0 DRUG INFORMATION

7.1 Chemotherapy Agents

Please refer to individual package inserts for more comprehensive information.

Agent 1: Carboplatin

- Other names: Paraplatin
- Classification: alkylating agent/platinum coordination compound
- Mode of action: covalently binds to DNA producing cross-links which leads to inhibition of DNA synthesis
- Storage and stability: Unopened vials of carboplatin injection, 10 mg/mL are stable to the date indicated on the package when stored at 25°C (77°F), excursions permitted from 15°C-30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Protect from light.
- Preparation: Carboplatin injection is a premixed aqueous solution of 10 mg/mL carboplatin. Carboplatin injection, 10 mg/mL can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection (NS), USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C).Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions are discarded 8 hours after dilution.
- Route of administration: IV
- Incompatibilities: amphotericin B cholesteryl sulfate complex
- Availability: commercially available
- Side effects:
  - Alopecia
  - Hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia
  - Nausea, vomiting, stomatitis
  - Myelosuppression (dose related and dose-limiting); thrombocytopenia (37% to 80%); leukopenia (27% to 38%)
  - Increase in alkaline phosphatase and AST (usually mild and reversible)
  - Hearing loss at high tones
  - BUN and/or creatinine increase
  - Peripheral neuropathy
- Nursing implications: Use appropriate precautions for handling and disposal (hazardous)

Agent 2: Paclitaxel

- Other name(s): Taxol
- Classification: antimicrotubule agent
- Mode of action: promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in formation of extremely stable and nonfunctional microtubules
- Storage and stability: Unopened vials are stored under refrigeration. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3-1.2 mg/mL in NS, 5% dextrose, 5% dextrose and NS, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.
- Preparation: The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 -1.2 mg/mL. Solutions exhibit a slight haze, common to all products

containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency. Solutions exhibiting excessive particulate formation should not be used.

- Route of administration: IV
- Incompatibilities: Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data.
- Availability: commercially available
- Side effects:
  - Myelosuppression
  - Hypersensitivity
  - Arrhythmias
  - Peripheral neuropathy
  - Alopecia
  - Nausea and vomiting
  - Diarrhea
  - Stomatitis
  - Elevated LFTs
  - Fatigue
  - Arthralgias
- Nursing implications: monitor CBC, pre-medicate with anti-emetics, monitor for abdominal cramping occurring after administration due to risk of ischemic and neutropenic colitis, advise about possible hair loss, monitor LFTs, advise of arthralgias and myalgias that may occur for several days after treatment, monitor for neuropathy, monitor for hypersensitivity reactions

Agent 3: Doxorubicin

- Other name(s): Adriamycin
- Classification: anthracycline
- Mode of action: Inhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II
- Storage and stability: intact vials (solution) refrigerate at 2ºC to 8ºC and protect from light. Intact vials (lyophilized powder) room temperature (15ºC to 30ºC). Reconstituted vials stable for 7 days at room temperature (25ºC) and 15 days under refrigeration (5ºC).
- Preparation: add 5, 10, 25, 50, 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vial to produce a solution containing 2 mg/mL
- Route of administration: IV
- Incompatibilities: Allopurinol, aminosyn II, amphotericin B cholesteryl sulfate complex, cefepime, freamine III, gallium nitrate, ganciclovir, lansoprazole, pemetrexed, piperacillin/tazobactam. Variable (consult detailed reference): Fluorouracil, furosemide, granisetron, heparin, methylprednisolone sodium succinate, propofol, sodium bicarbonate, TPN.
- Availability: commercially available
- Side effects:
  - Cardiovascular: Acute cardiotoxicity: Atrioventricular block, bradycardia, bundle

branch block, ECG abnormalities, extrasystoles (atrial or ventricular), sinus tachycardia, ST-T wave changes, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia
  - Delayed cardiotoxicity: LVEF decreased, CHF (manifestations include ascites, cardiomegaly, dyspnea, edema, gallop rhythm, hepatomegaly, oliguria, pleural effusion, pulmonary edema, tachycardia); myocarditis, pericarditis
  - Central nervous system: Malaise
  - Dermatologic: Alopecia, itching, photosensitivity, radiation recall, rash; discoloration of saliva, sweat, or tears
  - Endocrine & metabolic: Amenorrhea, dehydration, infertility (may be temporary), hyperuricemia
  - Gastrointestinal: Abdominal pain, anorexia, colon necrosis, diarrhea, GI ulceration, mucositis, nausea, vomiting
  - Genitourinary: Discoloration of urine
  - Hematologic: Leukopenia/neutropenia (75%; nadir: 10-14 days; recovery: by day 21); thrombocytopenia and anemia
  - Local: Skin “flare” at injection site, urticaria
  - Neuromuscular & skeletal: Weakness
- Nursing implications: vesicant – do not extravasate, refer to extravasation protocol if infiltration occurs, advise about alopecia, advise about red urine for 24 hours after drug administration, anti-emetics, monitor CBC, assess for stomatitis which typically occurs 7-10 days post injection, Adria-flare – most commonly consisting of erythematous streak up the vein, associated with urticarial and pruritus, monitor for signs of cardiotoxicity.

Agent 4: Cyclophosphamide
- Other name(s): Cytoxan (US), Procytox (Canada)
- Classification: alkylating agent
- Mode of action: prevents cell division by cross linking DNA strands and decreasing DNA synthesis
- Storage and stability: Tablets and injectable powder are stored at room temperature. Reconstituted cyclophosphamide is chemically and physically stable for 24 hours at room temperature or for six days under refrigeration.
- Preparation: add 0.9% sterile sodium chloride solution if injected directly
- Route of administration: IV
- Incompatibilities: barbiturates, phenytoin, and choral hydrate, allopurinol, imipramine, phenothiazines
- Availability: commercially available
- Side effects:
  - Alopecia
  - Amenorrhea
  - Gonadal suppression
  - Sterility
  - Abdominal pain
  - Anorexia
  - Diarrhea
  - Mucositis
  - Nausea and vomiting
  - Hemorrhagic cystitis
  - Myelosuppression

- Nursing implications: monitor CBC, assess hydration and fluid balance, premedicate with antiemetics, advise patient of metallic taste – hard candy may help

Agent 5: Docetaxel

- Other name(s):Taxotere
- Classification: an anti-microtubule agent
- Mode of action: induces apoptosis via bcl-2 phosphorylation, binds to tubulin and inhibits microtubule depolymerization, antiangiogenic properties
- Storage and stability: The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

  TAXOTERE® infusion solution, if stored between 2ºC and 25ºC (36ºF - 77ºF) is stable for 4 hours. Fully prepared TAXOTERE® infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour I.V. administration).
- Preparation of the initial diluted solution
  1. Gather the appropriate number of vials of TAXOTERE for Injection Concentrate and diluent (13% ethanol in water for injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
  2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of TAXOTERE for Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**
  3. Gently rotate the initial diluted solution for approximately 15 seconds to assure full mixture of the concentrate and diluent.
  4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution from the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.
     The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.
  5. Preparation of the final dilution for infusion

     Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
  6. Thoroughly mix the infusion by manual rotation.
  7. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE for injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.
- Route of administration: IV
- Incompatibilities: Amphotericin B, doxorubicin liposome, methylprednisolone sodium succinate, nalbuphine. Variable (consult detailed reference): Ceftriaxone.
- Availability: commercially available

- Side effects:
  - neutropenia is the dose-limiting hematologic toxicity
  - during organogenesis, docetaxel is embryotoxic and fetotoxic
  - fluid retention, possibly severe; requires appropriate steroid pre-medication
  - hypersensitivity reactions can occur within minutes following administration and subjects should be appropriately pre-medicated
  - neurotoxicity (paresthesias, dysethesias, pain)
  - alopecia
  - nausea/vomiting/diarrhea
  - transaminase or bilirubin elevation
- Nursing implications: anti-emetics, advise about alopecia, monitor for hypersensitivity reactions, evaluate LFTs, evaluate for sites of infiltration, peripheral neuropathy, monitor for fluid retention

7.1.1 Return and Retention of Study Drug

Study drug will be obtained from commercial supply and handled according to Institutional drug handling procedures.

7.1.2 Drug Accountability/Subject Compliance

Drug accountability will not be performed. All medications administered in this study are IV and will be administered by clinical staff.

8.0 CORRELATIVES/SPECIAL STUDIES

[redacted]

8.1 Specimen Banking

[redacted]

[redacted]

9.0 Measurement of Effect

9.1 Antitumor Effect

9.1.1 Response Criteria

Primary end point of the study is pathological response in the breast and axilla.

Pathologic complete response (pCR) in breast and axilla is defined as no evidence of disease in the breast and axillary lymph nodes at the time of pathology review, except for DCIS in the breast and isolated tumor cells in the axillary lymph nodes.

Secondary end point of the study is assessment of minimal residual disease (MRD) which is defined as residual cancer burden (RCB) score of 0/1. Residual cancer burden score will be calculated utilizing surgical pathology parameters by a study personnel by using a free online tool (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3)

9.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) for reporting non-hematologic adverse events and modified criteria for hematologic adverse events.

DATA AND SAFETY MONITORING

9.3 Oversight and Monitoring Plan

The DSMC of the KUCC is responsible for monitoring patient safety for this trial. The DSMC is responsible for:

- Review of all clinical trials conducted by the KUCC for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Submit recommendations for corrective action to the PI and the Deputy Director of the KUCC or designee.
- Notify external sites participating in multiple-institutional clinical trials coordinated by the KUCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.
- The University of Kansas Cancer Center Quality Assurance Unit will audit study activity and reported data on at least a quarterly basis for any collaborating sites.

9.4 Safety Review and Oversight Requirements

a) Serious Adverse Event
Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. Refer to section with title *ADVERSE EVENTS*. If determined to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

b) Review of Adverse Event Rates
Once per month, adverse event rates will be monitored by the DSMC Coordinator. If any study has had 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The DSMC Coordinator ensures that collaborating investigators and IRBs for all Participating sites are notified of any resulting action.

c) Study Safety and Progress – Quarterly Review
An overall assessment of toxicities as described in the protocol is reviewed at quarterly DSMC meetings. This review enables DSMC committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

[redacted]

[redacted]

10.0 REGULATORY CONSIDERATIONS

10.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

10.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. ICH Consolidated Good Clinical Practice: Guidelines (E6)
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

   http://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

With attention to the following specific regulations:

- Title 21 Part 11 – Electronic Records; Electronic Signatures
- Title 21 Part 50 – Protection of Human Patients Title 21 Part 54 – Financial Disclosure by Clinical Investigators
- Title 21 Part 56 – Institutional Review Boards
- Title 21 Part 312 – Investigational New Drug Application

3. State laws
4. Institutional research policies and procedures

[redacted]

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

11.0 REGISTRATION PROCEDURES

11.1 General Guidelines for KUCC and Other Participating Organization

[redacted]

11.2 Registration Process for KUCC and Other Participating Centers

[redacted]

12.0 STUDY MANAGEMENT

12.1 Investigator Files and Retention of Documents

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, subject diaries and pathology reports. All study related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

12.2 Case Report Forms

Electronic case report forms (eCRFs) will be completed for each subject enrolled and entered into CRIS. All eCRFs will be customized by the KU Biostatistics Department for this study, and will be complete and accurate. The medical chart and any other clinical worksheets, procedural reports, etc. are the source documentation of the data captured into the study database.

12.3 Study Monitoring

The study will be monitored at appropriate intervals to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design/Study Endpoints

This is a prospective, randomized, multi-centered study.
Study end points are:

- Primary end point: To estimate the rates of pathological complete response in breast and axilla (pCR) in the two treatment arms.
- Secondary end point: To estimate the rates of MRD in the two treatment arms

13.2 Sample Size and Accrual

Power justification and sample size calculation: Patients will be randomized 1:1, stratified on nodal status (positive/negative) to ensure balance, to either neoadjuvant carboplatin + docetaxel or carboplatin + paclitaxel followed by AC. The primary objective will be to estimate the pCR rates in both arms for the purposes of designing a larger randomized phase III comparative study. The estimated pCR rates in both the treatment arms is 50% with upper bound constraints for the standard errors at 7.5% and the upper bound constraint for the standard error of the difference between pCR rates of the two arms at 12%. The sample size required to satisfy these constraints is 45 patients per treatment arm (Mayo et. al. 2010). To ensure achieving 45 evaluable patients in each treatment arm, the overall maximum sample size will be inflated to 100 patients to account for patient drop outs. The pCR rates and MRD rates for each treatment arm will be estimated and 95% exact binomial confidence bounds will be calculated.

13.3 Data Analyses Plans

Baseline demographic and clinical characteristics will be summarized overall and by treatment assignment with means, standard deviations, medians, ranges, frequency counts and proportions. Two sample t-tests and chi-squared tests will be used to identify any differences in baseline demographics and clinical characteristics between treatment assignment groups. Safety data will be summarized and reported on all subjects who received at least one dose of a study drug.

Primary Objective Analysis: The pathological complete response rates will be estimated and 95% exact binomial confidence bounds will be calculated in both the carboplatin plus docetaxel treatment group, and the carboplatin plus paclitaxel and doxorubicin-cyclophosphamide treatment group.

Secondary Objective Analysis: The MRD rates (CbD and CbP→AC) will be estimated and 95% exact binomial confidence bounds will be calculated in both the carboplatin plus docetaxel treatment group, and the carboplatin plus paclitaxel and doxorubicin - cyclophosphamide treatment group.

Exploratory Objectives Analyses: Two-sided binomial tests for proportions will be used to compare pCR and MRD rates in patients with germline BRCA associated and BRCA wild type TNBC with the two neoadjuvant chemotherapy regimens.

Exploratory assessment of cost associated with the two chemotherapy regimens.

Cost Analysis [redacted] Our primary interest is to compare costs between Regimens A and B. The maintained hypothesis is that clinical outcomes from the Regimens should be similar, so we will conduct a cost minimization analysis (Drummond, Sculpher et al. 2005).

Costs will depend primarily on pharmaceutical costs, costs of administering pharmaceuticals, other medical costs related to the regimens, plus subject travel and time costs. To ensure that cost differences are due to differences in resource use (not variations in prices), medical costs will be based on the average amount paid for the drug or service (O'Keeffe-Rosetti, Hornbrook et al. 2013). Patient costs will be calculated using the local median wage rate.

[redacted]

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15.0 Appendices

Appendix A. Surgical Evaluation Form

[redacted]

Appendix B. Performance Status

Zubrod (ECOG) Performance Scale

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

Appendix C. Patient Travel Time Cost Analysis Survey

[redacted]

Appendix D. Suggested Chemotherapy Pre-Medication and Antiemetic's

ARM A

Carboplatin/Taxol

Day 1 Day of Treatment (Weeks 1, 4,7, 10) *
diphenhydrAMINE (BENADRYL) injection 50 mg
famotidine (PEPCID) injection 20 mg
dexamethasone (DECADRON) 20 mg in sodium chloride 0.9% (NS) 50 mL IVPB
palonosetron(+) (ALOXI) injection 0.25 mg
Take Home Medication
Decadron 4-8 mg PO BID Day 2,3 (week 1,4,7, 10)
Zofran 4 mg PO TID PRN
Compazine 10 mg PO TID PRN
Ativan 0.5 mg PO TID PRN

***Patients who have uncontrolled nausea after first cycle of carboplatin consider adding Emend (fosaprepitant dimeglumine) 150mg to chemotherapy premedication for remaining carboplatin doses.**

AC (Adriamycin and Cytoxan)

Day 1 Day of Treatment (Weeks 13, 15, 17, 19)
dexamethasone (DECADRON) tablet 12 mg
palonosetron(+) (ALOXI) injection 0.25 mg
fosaprepitant (EMEND) 150 mg in sodium chloride 0.9% (NS) 150 mL IVPB
Take Home Medication
Decadron 4-8 mg Day 1, 2, 3
Zofran 4 mg PO TID PRN
Compazine 10 mg PO TID PRN
Ativan 0.5 mg PO TID PRN

Arm B

Carboplatin/Taxotere

Day 1 Day of Treatment (Weeks 1, 4, 7, 10, 13, 16)
LORazepam (ATIVAN) tablet 0.5-1 mg
dexamethasone (DECADRON) 20 mg in sodium chloride 0.9% (NS) 50 mL IVPB
palonosetron(+) (ALOXI) injection 0.25 mg
Take Home Medication
Decadron 4-8mg PO BID Day -1, 1, 2
Zofran 4 mg PO TID PRN
Compazine 10 mg PO TID PRN
Ativan 0.5 mg PO TID PRN