A Phase II Study of Neoadjuvant Weekly Carboplatin/Paclitaxel followed by Dose-Dense Doxorubicin/Cyclophosphamide in Patients with Hormone Receptor Negative, HER2 Receptor Negative Breast Cancer

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PI: Kari B. Wisinski, MD
November 26, 2019

CLINICAL STUDY PROTOCOL

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Study PI: Kari B. Wisinski, MD
Study Chair: Yee Chung Cheng, MD

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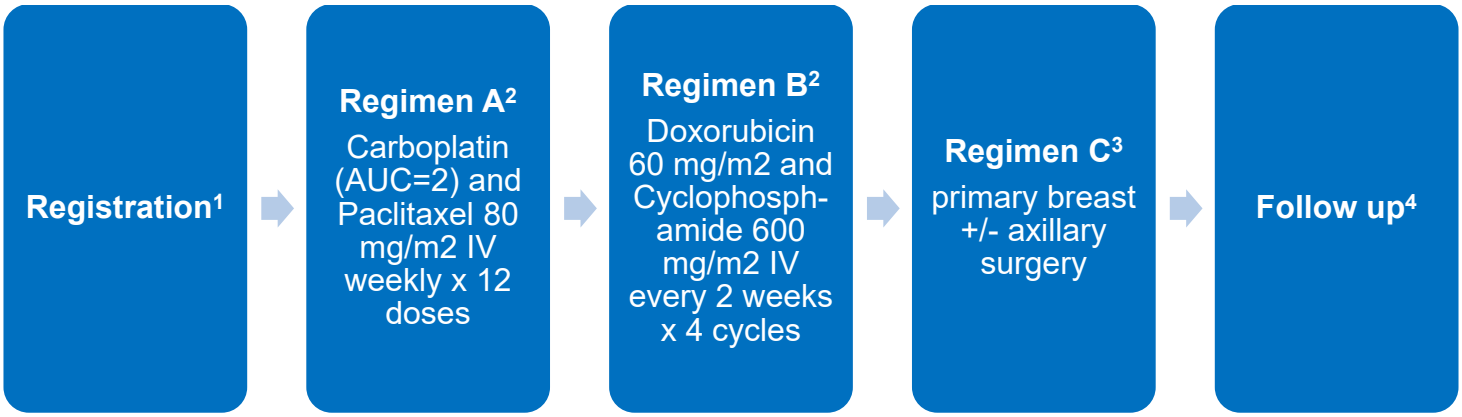
PROTOCOL SUMMARY

Title:	**A Phase II Study of Neoadjuvant Weekly Carboplatin/Paclitaxel followed by Dose-Dense Doxorubicin/Cyclophosphamide In Patients with Hormone Receptor Negative, HER2 Receptor Negative Breast Cancer**
Protocol Number:	UW16112
IND Sponsor:	*n/a*
Principal Investigator/ Study Chair:	Kari B. Wisinski, MD/ Yee Chung Cheng, MD
Study Sites:	UWCCC, MCW and Wisconsin Oncology Network
Clinical Trial Phase:	II
Study Disease:	Breast Cancer
Main Eligibility Criteria:	1. Biopsy proven invasive breast cancer that is cM0 and either a) at least T2 if node negative or b) any T if ipsilateral regional node positive 2. Candidate for neoadjuvant chemotherapy approach 3. ER- and PR-negative (Defined as <1%) 4. HER2-negative by either IHC or ISH. If ISH is used, ratio < 2 is considered negative. 5. LVEF ≥ institutional LLN 6. Adequate liver and renal function
Study Rationale:	CALGB40603 study showed that the addition of Carboplatin (AUC=6) every 3 weeks x 4 cycles to the standard weekly Paclitaxel followed by dose dense AC regimen in neoadjuvant setting of triple-negative breast cancer increased the pathologic complete response (pCR) rate from 34% to 55%. However, 36% of subjects had to skip at least 2 doses of weekly Paclitaxel due to the prolonged cytopenia from Carboplatin. We hypothesize the use of low dose weekly Carboplatin/Paclitaxel followed by dose-dense AC regimen will minimize the prolonged cytopenia, allow the regular treatment schedule and result in a similar pCR rate seen with the every 3 weeks Carboplatin schedule.
Primary Objective:	pCR rate
Secondary Objectives:	1. Number of cycles, doses and delays of chemotherapy administered 2. Treatment-related toxicity 3. 2-year Invasive disease-free survival 4. 2-year Overall survival

Primary Endpoint:	pCR rate
Study Design:	Phase II single arm prospective trial
Study Agent/ Intervention Description:	Carboplatin (AUC=2) and Paclitaxel 80 mg/m2 IV weekly x 12 doses (Regimen A), then Doxorubicin 60 mg/m2 and Cyclophosphamide 600 mg/m2 IV every 2 weeks with pegfilgrastim or filgrastim (or biosimilar) support x 4 cycles (Regimen B), then primary breast +/- axillary surgery (Regimen C).
Number of Subjects:	50
Subject Participation Duration:	6 months
Duration of Follow up	2 years after primary breast surgery
Estimated Time to Complete Enrollment:	24 months
Statistical Methodology:	A sample size of 48 achieves 80% power to detect a 20% difference using a one-sided binomial test at an alpha significance level of 0.025. These results assume that the population proportion under the null hypothesis is 0.34, which is the reported pCR rate with standard anthracyclines and taxane regimen in triple-negative breast cancer. Allowing for drop-out rate of 5%, a total of 50 subjects is planned.
Safety Assessments	Subjects will be followed every 2-3 weeks during chemotherapy for treatment related morbidities.
Efficacy Assessments	Tolerability of the chemotherapy is determined by the number of cycles, doses and delays subject receives. Efficacy of the chemotherapy is determined by pathology at the time of final breast/axillary surgery.
Unique Aspects of this Study	This is a multicenter prospective study to evaluate the addition of low dose weekly Carboplatin to standard anthracyclines/taxane regimen in subjects with triple-negative breast cancer who receive neoadjuvant chemotherapy.

SCHEMA



There are no stratification factors

Accrual = 50 subjects

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1. Subjects must meet the eligibility criteria outlined in Section 4 prior to registration
2. Subjects are expected to complete Regimens A and B within 6 months (allowing for potential dose delays)
3. It is recommended subjects undergo surgery 3-6 weeks after the last dose of chemotherapy
4. Subjects will be followed every 6 months (+/- 30 days) for 2 years after date of surgery or last date of study treatment

TABLE OF CONTENTS

1 BACKGROUND

Triple-Negative Breast Cancer

Breast cancer is the most common non-skin cancer in females and is estimated to have 246,660 new cases in 2016. It is also the second most common cancer-related mortality in females and is estimated to cause 40,450 deaths in 2016 [1]. Breast cancer is a heterogeneous group of diseases and is traditionally divided into different subtypes according to the receptor profile, namely the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Different subtypes of breast cancer present with different clinical behavior, response to standard treatment and prognosis.

The worst outcome is currently associated with the triple-negative group, which is defined as lack of expression of ER, PR and HER2. The lack of these specific targets makes the traditional cytotoxic chemotherapy as the only modality of systemic treatment in this subgroup. Triple-negative breast cancer (TNBC) only accounts for about 15-20% of all breast cancer cases. Patients with TNBC have a higher chance of harboring a breast cancer gene (BRCA) mutation. TNBC also more commonly occurs in premenopausal women or African Americans [2]. In 2012, a study reported the outcome of a total of 15,204 patients with breast cancer who presented to NCCN institutions between Jan 2000 to Dec 2006. The TNBC had the worst breast cancer specific survival (HR = 2.99) and overall survival (HR = 2.72) compared to other subtypes. It also had the highest risk of death within the 2 years of diagnosis [3].

Traditionally, treatment for early stage TNBC was upfront surgery followed by adjuvant chemotherapy. Studies showed that the use of adjuvant chemotherapy in TNBC significantly reduced the risk of recurrence and the risk of death which in turn improved the disease-free survival and overall survival [4]. For locally advanced cases, the use of neoadjuvant chemotherapy followed by surgery became the standard of care to improve surgical options. Both increased rates of breast conservation and reduced axillary surgery are feasible after neoadjuvant chemotherapy [5]. Thus, neoadjuvant chemotherapy has become a standard approach for the majority of patients with TNBC [6]. The standard chemotherapy used for TNBC contains both anthracyclines and taxanes. One of the commonly used regimens in the United States is the dose-dense Doxorubicin/Cyclophosphamide every 2 weeks with filgrastim or pegfilgrastim (or biosimilar) support for 4 cycles and weekly Paclitaxel for 12 doses. An additional study has shown that receiving a taxane before anthracycline is associated with improved pathologic complete response (pCR) compared with receiving an anthracycline first [7].

In 2012, the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) working group reported the meta-analysis of 12 randomized neoadjuvant trials which included 12,993 patients [8]. It was found that patients who achieved a pathologic complete response (pCR) had significant improvements in event-free survival (HR = 0.48) and overall survival (HR = 0.36) compared with patients who did not. In the

subgroup analysis, TNBC had a pCR rate of 34% and those who achieved a pCR to neoadjuvant chemotherapy had improved event-free survival (HR = 0.24). Since chemotherapy is the only standard treatment modality for TNBC and majority of TNBC patients will receive chemotherapy as part of their treatment, one of the major investigative areas in TNBC is to improve the pathologic complete response rate to neoadjuvant therapy with the anticipation that this will result in improved overall survival.

Clinical Data of Additional Chemotherapy

Multiple chemotherapeutic agents have been studied to determine whether they could improve the pathologic response rate when added to the standard neoadjuvant anthracycline/taxane based regimens in breast cancer. A German study, the GeparQuattro trial, included 1421 patients who received 4 cycles of Epirubicin/Cyclophosphamide and then randomized to Docetaxel alone, concurrent Docetaxel/Capecitabine or sequential Docetaxel/Capecitabine. This trial demonstrated no difference in pCR rate [9]. Another study, the NSABP B-40 trial, included 1206 patients who were randomized to Docetaxel alone, Docetaxel/Gemcitabine or Docetaxel/Capecitabine, then followed by 4 cycles of Doxorubicin/Cyclophosphamide. This study also showed no difference in pCR rate [10]. Therefore, the addition of either Capecitabine or Gemcitabine did not improve the response rate to standard neoadjuvant chemotherapy in breast cancer.

However, 2 studies utilizing Carboplatin in addition to standard neoadjuvant chemotherapy showed an increase of pCR rate in TNBC. The GeparSixto trial included 315 patients with TNBC who received 18 doses of weekly combined liposomal Doxorubicin/Paclitaxel/Bevacizumab and then randomized to addition of weekly Carboplatin or not [11]. Those who received the addition of Carboplatin had a statistically significant higher pCR rate (53% vs 37%, OR = 1.97) but also higher treatment discontinuation rate (40% vs 36%). The CALGB 40603 trial included 443 patients with TNBC who received standard weekly Paclitaxel x 12 doses, followed by dose-dense Doxorubicin/Cyclophosphamide x 4 cycles and then randomized to addition of Carboplatin every 3 weeks x 4 cycles or not in combination with the Paclitaxel [12]. There was a second randomization for bevacizumab. Patient who receiving Carboplatin had a statistically significant higher pCR rate than those did not (54% vs 41%, OR = 1.71), but 36% of those received the addition of Carboplatin had to skip at least 2 doses of weekly Paclitaxel due to the prolonged cytopenia.

Known and Potential Risks and Benefits

Based on the clinical data of GeparSixto and CALGB 40603 trials, the addition of Carboplatin to standard anthracycline/taxane based regimen increased the pCR rate of TNBC in neoadjuvant approach. However, either the use of high dose Carboplatin (AUC=6) every 3 weeks or the use of low dose weekly Carboplatin (AUC=2) but combined with anthracycline and taxane concurrently had a significant side effect of prolonged cytopenia, which precluded patients from receiving chemotherapy as scheduled. GeparOla, a randomized study presented at ASCO 2019, included a

control arm of weekly paclitaxel with carboplatin at the same doses and number of cycles utilized in this study, which was then followed by 4 cycles epirubicin and cyclophosphamide. This study arm only included 27 patients with TNBC, but pCR rates in this subset was 59.3% (41.7-75.2%). Importantly, serious adverse events were reported in 19/37 (51.3%) patients treated with the carboplatin and paclitaxel regimen, primarily due to cytopenias.[19] Therefore, the benefit of improved response rate to chemotherapy carries the risk of delaying the treatment, prolonging the duration of treatment, or potential for increased complications such as infection or bleeding due to the cytopenia side effect.

Rationale of the Study

The effect of Carboplatin on the bone marrow causing clinical significant prolonged myelosuppression is dose dependent [13]. Another factor in prolonged myelosuppression is the concomitant use of other myelosuppressive chemotherapeutic agents. Therefore, the combination of low dose weekly Carboplatin and Paclitaxel for 12 doses followed by Doxorubicin/Cyclophosphamide separately may limit the severe myelosuppressive effect of the chemotherapy and allow patients to continue chemotherapy as scheduled. The low dose weekly Carboplatin regimen would be anticipated to have the same response rate as the high dose Carboplatin regimen given every 3 weeks. Furthermore, there is data that dose dense chemotherapy (defined as increasing dose frequency while the dose per cycle and overall dose remains the same) may result in better cancer outcomes [14, 15].

Hypothesis of the Study

The use of low dose weekly Carboplatin/Paclitaxel followed by dose-dense Doxorubicin/Cyclophosphamide in subjects with TNBC in neoadjuvant setting will result in less dose reductions or chemotherapy delays and similar pCR rate seen with the every 3 week carboplatin schedule.

Exploratory Study: Cytokines as the Biomarkers

Studies have showed that there is subpopulation of cells in breast cancer that display stem cell properties. These cancer stem cells are capable of self-renewal, as well as differentiation into non-self-renewing cells forming the tumor bulk. Therefore, the cancer stem cells play crucial roles in multiple aspects of cancer development including angiogenesis, growth, metastasis and even treatment resistance. According to a widely-accepted idea called soil (tumor microenvironment) and seed (cancer cells) hypothesis [16], all these cancer cells including the cancer stem cells are regulated by complex interactions with the tumor microenvironment through the cytokines and growth factors.

Cytokines are highly inducible secretory proteins that mediate intercellular communication in the immune system as well as the microenvironment. Certain cytokines such as IL-6, IL-8, CCL2 and TGF-beta are frequently elevated in breast

cancer. Preclinical data suggests that the growth of triple negative breast cancer is depended on IL-6 and IL-8 [17]. High circulating IL-6 levels are correlated with a poor prognosis in breast cancer [18]. Therefore, the cytokine profile could serve as a target for therapy and as a biomarker for treatment monitoring in breast cancer patients receiving systemic chemotherapy.

2 OBJECTIVES

2.1 Primary Objective

To determine the pathologic response rate to low dose weekly Carboplatin in combination with weekly Paclitaxel regimen **(Regimen A)** followed by dose dense AC **(Regimen B)** given in neoadjuvant setting for women with TNBC.

2.2 Secondary Objectives

2.2.1 To evaluate the number of cycles, doses and delays of low dose weekly Carboplatin/Paclitaxel regimen administered.

2.2.2 To describe any treatment-related toxicity from the low dose weekly Carboplatin/Paclitaxel regimen.

2.2.3 To evaluate two-year invasive disease-free survival after treatment with this neoadjuvant regimen.

2.2.4 To evaluate the two-year overall survival after treatment with this neoadjuvant regimen.

2.3 Exploratory Objectives

2.3.1 To store blood and tumor tissue for future studies to explore biomarkers of response to carboplatin and paclitaxel in TNBC.

3 STUDY DESIGN

3.1 General Description

This is a phase II single-arm, open-label, prospective study to evaluate the efficacy of the low dose weekly Carboplatin/Paclitaxel followed by dose-dense Doxorubicin/Cyclophosphamide in subjects with triple-negative breast cancer in neoadjuvant setting.

3.1.1 Number of Subjects

There will be 50 subjects enrolled. Subject accrual will be via the Wisconsin Oncology Network.

3.2 Primary Endpoint

Pathologic complete response (pCR) rate which is defined as no invasive disease in the breast and the ipsilateral regional lymph nodes.

3.3 Secondary Endpoint(s)

3.3.1 The number of cycles, doses and delays of chemotherapy administered.

3.3.2 Any treatment-related toxicity during chemotherapy.

3.3.3 2-year invasive disease-free survival defined as lack of any ipsilateral invasive breast cancer recurrence in the breast, regional nodes, chest wall or skin; any distant metastatic disease; any death; contralateral invasive breast cancer; or second primary invasive non-breast cancer.

3.3.4 2-year overall survival

3.4 Study Timeline

Once the neoadjuvant chemotherapy regimen is started, subject is expected to finish the treatment within 6 months (allowing for potential dose delays). Then 3-6 weeks after the last dose of chemotherapy, the subject will undergo primary breast +/- axillary surgery **(Regimen C)**. After surgery, subject will be followed according to the current standard of care for recurrence and survival up to 2 years.

3.5 Primary Completion

The study will reach primary completion 30 months from the time the study opens to accrual.

3.6 Study Completion

The study will reach study completion 54 months from the time the study opens to accrual.

4 PATIENT SELECTION

Use the below checklist to confirm a patient's eligibility. For each patient, this checklist must be completed and maintained in the subject's chart.

4.1 Eligibility Criteria

Subjects must have baseline evaluations performed prior to the first dose of chemotherapy and must meet all inclusion and exclusion criteria. In addition, the subject must be thoroughly informed about all study aspects, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the subject prior to enrollment. The following criteria apply to all subjects enrolled onto the study unless otherwise specified.

4.2 Inclusion Criteria

____ 1. Subjects must have histologically or cytologically confirmed invasive breast cancer which meets the following criteria:

a) Estrogen Receptor (ER) and Progesterone Receptor (PR)-negative as defined by local standard clinical immunohistochemistry (IHC) < 1%.

b) HER2-negative using local standard testing. Negative is defined as IHC 0 or 1+ (if 2+, must reflex to ISH method). If ISH method is used, ratio < 2 is considered negative.

c) Clinical tumor size of at least 2.1 cm (T2) by palpation or imaging, regardless of the ipsilateral regional lymph node status, or any tumor size but with ipsilateral regional lymph nodes involved by the tumor (any T if ipsilateral regional node positive). Subjects with inflammatory breast cancer are eligible. If bilateral breast cancer is present, the subject is eligible if the contralateral tumor is DCIS only (without any invasive disease on biopsy) or another invasive breast cancer of any size that is also ER, PR and HER2 negative.

d) Any radiographic abnormal ipsilateral regional lymph nodes or any clinically concerning ipsilateral regional lymph nodes with the exception of internal mammary nodes, should be sampled with a percutaneous biopsy, but no sentinel axillary lymph node mapping/biopsy is allowed before chemotherapy. If clinically node negative (cNO), pre-chemotherapy ipsilateral sentinel axillary lymph node mapping/biopsy is not allowed.

_____ 2. Candidate for neoadjuvant chemotherapy.

_____ 3. Age $\geq$ 18 years and < 75 years.

_____ 4. ECOG Performance Status $\leq$ 1.

_____ 5. Left ventricular ejection fraction (LVEF) ≥ LLN (per institutional normal) determined by echocardiogram or nuclear medicine scan, within 30 days of registration.

_____ 6. Adequate organ and marrow function as below:

Organ and Marrow Function Table	
Adequate bone marrow function:	
Hemoglobin	> 9.5 g/dL
Absolute neutrophil count	≥ institutional lower limit
Platelets	≥ institutional lower limit
Adequate hepatic function:	
Total bilirubin	≤ 1.25 x institutional upper limit
AST(SGOT)/ALT	≤ 2.5 times institutional upper limit
Adequate renal function:	
Serum creatinine or creatinine clearance	≤ institutional upper limit or ≥ 60 mL/min creatinine clearance for patients with serum creatinine > institutional upper limit

_____7. Non-Pregnant. Women of childbearing potential must have a negative pregnancy test (HCG serum or urine) within 30 days prior to study registration and to be repeated if not done within 7 days of starting chemotherapy.

It is not known what effects this treatment has on human pregnancy or development of the embryo or fetus. Therefore, female subjects participating in this study should avoid becoming pregnant, and male subjects should avoid impregnating a female partner. Non-sterilized female subjects of reproductive age and male subjects should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female subjects must meet one of the following:

- Natural postmenopausal before the screening visit defined as no menses at any time in the preceding 12 consecutive months, or
- Prior bilateral oophorectomy or bilateral tubal ligation, or
- If they are of childbearing potential, agree to practice two effective methods of contraception per discussion with the treating physicians from the time of signing of the informed consent form through three months after the last dose of study drug, or
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable contraception methods.)

Male subjects, even if surgically sterilized (i.e., status post vasectomy) must agree to one of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last study drug dose, or

- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)

_____ 8. Ability to understand a written informed consent document, and the willingness to sign it.

4.3 Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

_____ 1. Prior chemotherapy or radiation therapy for invasive breast cancer within 6 months before registration.

_____ 2. Prior investigational drugs or interventions for invasive breast cancer treatment within 6 months before registration are not allowed. Prior participation in window-of-opportunity trials without therapeutic intent is allowed if intervention is no more than 3 weeks in duration.

_____ 3. Stage IV metastatic breast cancer

_____ 4. History of allergic reactions attributed to compounds of similar chemical composition to chemotherapy to be used in this study.

_____ 5. Breastfeeding women. Cytotoxic chemotherapy is drug with the potential for teratogenic or abortifacient effects. Due to unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cytotoxic chemotherapy, breastfeeding should be discontinued.

_____ 6. Baseline peripheral neuropathy of severity > grade 1

_____ 7. Other invasive cancer diagnosis within the past 5 years other than non-melanoma skin cancer.

_____ 8. Prior axillary lymph node dissection that preclude patient from surgical evaluation of axillary lymph node status

_____ _____
Investigator Signature Date

_____ _____
Coordinator Signature Date

5. STUDY ENTRY AND WITHDRAWAL; STUDY PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Preregistration Screening Tests and Procedures

The study-specific assessments are detailed in this section and outlined in the Study Calendar (appendix 7). Screening assessments must be performed within 30 days prior to registration. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. All on-study visit procedures are allowed a window of 7 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All subjects who are consented will be registered in OnCore®, the UWCCC and WON Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

5.1.2 Registration Process

Each subject enrolled in the study is to be registered into the UWCCC OnCore Database prior to starting protocol treatment. Research personnel at WON sites who enter data into OnCore must have completed human subjects training and Health Insurance Portability and Accountability Act (HIPAA) training. WON site research personnel receive training from the UWCCC OnCore Support Team on how to enter subject data into OnCore.

At the time of registration, the following will be required and verified by (UWCCC):

- Subject eligibility
- Signed informed consent form
- Signed HIPAA

After registration, the subject must begin treatment within 14 days.

5.1.3 Pretreatment Period

Screening Assessments

The screening procedures and assessments must be completed within 30 days prior to registration. Once registered, the subject should start study treatment within 14 days.

- Physical examination
- Vital signs (weight, temperature, blood pressure, heart rate)
- Height (can be obtained at screening or Cycle 1 Day 1 of Chemotherapy)
- Complete medical history
- Documentation of disease assessment (disease-specific staging criteria)
- ECOG Performance Status
- Measurable disease (primary breast mass, axillary nodes, etc.)
- Result of tumor tissue biopsied, including ER, PR and HER2
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:

  Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate.
- If a woman of childbearing potential, must have a negative pregnancy prior to randomization.
- Serum or urine pregnancy test within 7 days prior to the start of first dose of chemotherapy for premenopausal subjects
- MRI or mammogram or ultrasound of breast for tumor/lesion assessment
- Cardiac assessment of LVEF (ECHO, MUGA, etc.)
- CT scan of body (i.e. chest, abdomen, pelvis) and Bone scan or PET/CT if clinically indicated.

All blood tests other than pregnancy test are accepted within 14 days prior to the Cycle 1 Day 1 of chemotherapy

5.2 Study Procedures during Treatment

- Subjects must meet eligibility criteria on Cycle 1 Day 1 to be started on treatment.
- Optional tumor tissue (archived from biopsy) and blood collection for research as per Appendix 2 and 3

5.2.1 Study Procedures Cycle 2, 3, 4 Day 1 (Regimen A)

- Physical examination
- Vital signs (weight, temperature, blood pressure, heart rate)
- ECOG Performance Status
- Clinical assessment of measurable disease sites

- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment, including:

  Alkaline phosphatase, ALT/AST, total bilirubin, calcium, BUN, creatinine, glucose, potassium, sodium, chloride, bicarbonate.

5.2.2 Study Procedures, Cycle 1, 2, 3, 4, Days 8, 15 (Regimen A)

- CBC with differential and platelet count (may do ANC rather than full differential per MD discretion)

5.2.3 Study Procedures Cycle 5, 6, 7, 8 Day 1 (Regimen B)

- Physical examination
- Vital signs (weight, temperature, blood pressure, heart rate)
- ECOG Performance Status
- Clinical assessment of measurable diseases
- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment, including:

  Alkaline phosphatase, ALT/AST, total bilirubin, calcium, BUN, creatinine, glucose, potassium, sodium, chloride, bicarbonate.
- MRI, Ultrasound, or Mammogram of breast for tumor/lesion assessment if clinically indicated within 45 days before the final breast surgery.

5.2.4 Surgery (Regimen C)

The surgical intervention for management of breast cancer (primary breast tumor and ipsilateral regional lymph nodes) including diagnosis will be determined by the surgical team; and the recommendation is for it to occur 3-6 weeks after the last dose of chemotherapy.Patients who cannot proceed to surgery will be deemed in-evaluable for the primary endpoint.

5.3 Post-treatment

5.3.1 Follow-Up Visit after Surgery

Subjects will be followed within 30 days after the final surgery. The following procedures will be performed at the Follow-up Visit:

- Review of the final pathologic result
- Physical examination
- Vital signs (weight, temperature, blood pressure, heart rate)
- ECOG Performance Status
- Evaluation of adverse events
- CBC with differential and platelet count, if clinically indicated
- Blood chemistry assessment, if clinically indicated:

  Alkaline phosphatase, ALT/AST, total bilirubin, calcium, BUN, creatinine, glucose, potassium, sodium, chloride, bicarbonate.
- Optional tumor tissue (archived from surgery) and blood collection for research as per Appendix 2 and 3

Any other clinical trials being considered before the final surgery will need the approval of study chair and/or study PI.

Patient is allowed to participate in other clinical trials after the final surgery, if eligible.

5.3.2 Subsequent Follow-Up Visits up to 2 years

Subjects will be followed according to the standard of care (SOC) recommended by NCCN guidelines.

To meet study objectives, each subject's disease status and overall survival status and any interval systemic anti-cancer treatment will be collected every 6 months (+/- 30 days) for 2 years after date of surgery or last date of study treatment. This includes all subjects who do not complete all cycles of the study treatment unless they are withdrawn from study. This information may be collected via record review or by contacting the subject.

5.4 Study Withdrawal Procedures

5.4.1 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for or until:

- Disease progression
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the investigator's judgment.

- Inter-current illness that prevents further treatment administration
- Subject decides to withdraw from the study
- Significant subject noncompliance with protocol
- Unacceptable adverse event(s)

5.4.2 Subject-Initiated Withdrawal: A subject may decide to withdraw from the study at any time by informing the study PI.

5.4.3 Investigator-Initiated Withdrawal: The Investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a subject's compliance with the prescribed treatment regimen.

Subjects withdrawn from study treatment will be asked to return for a 30 day follow up visit. These subjects will be followed every 6 months per the follow up schedule, which can be done via medical record review. If a subject is withdrawn from regimen A or B and receives non-protocol chemotherapy and/or radiotherapy prior to surgery, or never undergo breast surgery, they will be taken off study and no additional follow up will be conducted.**Withdrawal Documentation Procedure**: The reason for study withdrawal and the date the subject was removed from the study must be documented in the case report form.

6. TREATMENT PLAN

6.1 Chemotherapeutic Agents Administration

Treatment will be administered on an outpatient basis.

Regimen A (Cycles 1 – 4) Description*					
Study Drug	**Premedication; precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carboplatin	Same premedication as Paclitaxel. Paclitaxel is given before Carboplatin	AUC=2	Intravenous	Days 1, 8, 15 of cycle 1, 2, 3, 4	3 weeks (21 days)
Paclitaxel	Premedicate with steroids, H1 and H2 blocker per institutional SOC	80 mg/m^2	Intravenous	Days 1, 8, 15 of cycle 1, 2, 3, 4*	3 weeks (21 days)
Regimen B (Cycles 5 – 8) Description					
Doxorubicin[3]	Baseline LVEF before the start of 1st dose	60 mg/m2	Intravenous	Day 1 of cycle 5, 6, 7, 8	2 weeks (14 days)
Cyclophos-phamide[4]	Hydrate with normal saline before and after the infusion	600 mg/m2	Intravenous	Day 1 of cycle 5, 6, 7, 8	2 weeks (14 days)
Pegfilgrastim	Given approximately 24-48 hours after chemotherapy is completed. Filgrastim or biosimilar such as tbo-filgrastim given daily is allowed as substitute per institutional SOC.	6 mg	SC	Day 2-3 of cycle 5, 6, 7, 8	2 weeks (14 days)

1. Paclitaxel 80 mg/m2 per dose; administer intravenously in a volume of 0.9% sodium chloride injection (NS), or 5% dextrose injection (D5W) sufficient to produce a concentration within the range 0.3-1.2 mg/ml, over 60 minutes, or per institutional infusion time standard, for 3 doses, on day 1, 8, 15, every 3 weeks.

2. Carboplatin (calculated dose) AUC = 2; administer intravenously in 0.9% NS or 5% D5W 100-500 ml over 30-60 minutes, or per institutional infusion time standard, for 3 doses, on day 1, 8, 15 after completing Paclitaxel, every 3 weeks. For dose

calculation, it is preferred to determine creatinine clearance with Cockcroft Gault using adjusted body weight (see below). Rounding of all chemotherapy dosing per institutional standards is also permitted.

Adjusted Body Weight
Step 1: Estimate Ideal Body Weight (IBW) in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
Step 2: Determine Adjusted Body Weight (AdjBW)
AdjBW = IBW + 0.4(Actual Body Weight - IBW)
If a subject's actual body weight is less than the calculated ideal body weight, it is preferred that the actual body weight is used for calculating the creatinine clearance.

Determine Creatinine Clearance (Cockcroft Gault) using AdjBW

CCr={((140 –age) x AdjBW)/(72x SCr)}x 0.85 (if female)

***Minimum Serum Creatinine (SCr) = 0.6mg/dL

Determine Carboplatin dose (Calvert)

Carboplatin Dose (mg)*** = AUC (2) X (GFR + 25)

***Maximum Carboplatin Dose = 300mg

* **There is a one week break between the end of cycle 4 (Regimen A) and the beginning of cycle 5 (Regimen B).**

3. Doxorubicin 60 mg/m2; administer by intravenous injection over 3-5 minutes or per institutional standards on day 1, every 14 days. Of note, baseline LVEF is only required once for protocol eligibility and does not need to be repeated prior to starting AC, unless clinically indicated.

4. Cyclophosphamide 600 mg/m2; administer intravenously in 100-500 ml 0.9% NS or 5% D5W over 30-60 minutes or per institutional standards on day 1, every 14 days.

6.2 Concomitant Pre-Medication and Supportive Care Guidelines

6.2.1 Suggested Usage of Concomitant Pre-Medications for Paclitaxel

1. Dexamethasone
   - 20 mg administer intravenously over 10-15 minutes, 30-60 minutes before Paclitaxel on day 1, 8, and 15. May reduce to 10mg iv after cycle 1, day 1, or
   - Dexamethasone 20mg oral 12 and 6 hours prior to first dose of paclitaxel and then may reduce over time to 8mg doses, or

- Other institutional standard of care.

2. Diphenhydramine 25-50 mg; administer by intravenous injection 30-60 minutes before Paclitaxel on day 1, 8, and 15.

3. Famotidine
- 20 mg; administer intravenously over 10-15 minutes, 30-60 minutes before Paclitaxel on day 1, 8, and 15, or
- Ranitidine 50 mg; administer intravenously over 10-15 minutes, 30-60 minutes before Paclitaxel on day 1, 8, and 15.

6.2.2 Usage of Concomitant Antiemetics

- Ondansetron 16 mg; administer intravenously over 10-15 minutes, 30-60 minutes before Carboplatin on day 1, 8, and 15, or
- Granisetron 1 mg; administer intravenously over 10-15 minutes, 30-60 minutes before Carboplatin on day 1, 8, and 15, or
- Fosaprepitant 150 mg and Ondansetron 16 mg; administer intravenously over 10-15 minutes, 30-60 minutes before Doxorubicin/Cyclophosphamide on day 1, or
- Other institutional standard of care

6.2.3 Usage of Concomitant Supportive Care

1. Growth Factor Support:
    a. During Carboplatin/Paclitaxel:
        - Prophylactic filgrastim (or biosimilar such as tbo-filgrastim) is allowed during the weekly Carboplatin/Paclitaxel if clinically indicated.
        - Filgrastim (or biosimilar such as tbo-filgrastim) given during neutropenia period is also allowed as per treating physician's discretion.
        - Pegfilgrastim should not be used during these cycles

    b. During Doxorubicin/Cyclophosphamide:
        - Pegfilgrastim 6 mg/0.6 ml by subcutaneous injection for 1 dose begin 24- 48 hrs after chemotherapy of Doxorubicin/ Cyclophosphamide is completed, or
        - Filgrastim 5 mcg/kg per day rounded to 300 or 480mcg dose by subcutaneous injection for 7-10 days with dose to begin on day 3 after chemotherapy of Doxorubicin/Cyclophosphamide is completed. Biosimilar to filgrastim also allowed.

2. Post-treatment antiemetics to be given per institutional standard of care.During paclitaxel and carboplatin, treating physicians should try to limit additional steroid use.

3. Packed red blood cell or platelet transfusion is allowed for chemotherapy induced anemia or thrombocytopenia as clinically indicated per institutional guideline or individual physician discretion.

6.3 Follow-Up Period

After completion of chemotherapy, subjects will be seen within 30 days after the surgery for the primary endpoint determination. After that, subjects will be followed according to the standard of care recommended by NCCN guidelines up to 2 years.

AEs will be followed for 30 days after the last dose of chemotherapy. SAEs will be followed until resolution or until considered permanent by the treating physician. All subjects, including these, will be followed for two years post final study treatment (chemotherapy or surgery) per SOC..

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Monitoring and Toxicity Management

Each subject receiving cytotoxic chemotherapy will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, subjective symptoms and spontaneous reports of adverse events reported to the investigator by subjects.

Toxicity will be assessed according to the NCI CTCAE v5.0. Dose adjustments will be made according to the degree of toxicity. Treatment-related toxicities are those at least possibly related to the study therapy.

During the administration of chemotherapy, subjects will be evaluated on day 1 (+/- 1 day) of each cycle (except cycle 1 may be seen up to 3 days prior to C1D1).

Subjects will also be monitored for delayed or prolonged toxicities after completion of chemotherapy. This will be monitored by physician in charge of the subjects during the follow up according to standard of care.

If protocol therapy is discontinued during Regimen A due to toxicity, the subject may receive Regimen B per physician discretion. If no further chemotherapy is administered and subject proceeds next to breast surgery, then they should be entered in the follow up stage of the study. If protocol therapy is discontinued during Regimen B due to toxicity and the subject proceeds next to breast surgery, then they should be entered in the follow up stage of the study. If the treating physician decides that it is in the subject's best interest to receive non-protocol therapy prior to surgery, the subject should be withdrawn from the study and no further follow-up is required.

7.2 Toxicity Management Table

Toxicity	Management

Hematologic Toxicity on day of treatment (Regimen A: Cycle 1-4)* For Regimen B (Cycle 5-8), please refer to footnote c	
• Platelet count < 100 x 10^9/L and/or • ANC grade 3 (< 1.00 x 10^9/L)	• Hold Treatment, repeat CBC w/diff within 7 days. • If repeat platelet count is ≥ 100 x 10^9/L and ANC ≤ grade 2, then resume the delayed chemotherapy (both agents) as full dose. • If not recovered in 7 days, continue to hold and repeat CBC w/diff at least weekly until platelet count is ≥ 100 x 10^9/L and ANC ≤ grade 2. • If delayed ≤ 14 days, resume at full dose. • If delayed > 14 days up to 28 days, resume chemotherapy with 20% dose reduction. • If delayed > 28 days, discontinue regimen A protocol therapy and proceed to regimen B.
• Platelet count decreased < 25 x 10^9/L and/or • ANC grade 4 (<0.5 x 10^9/L)	• Hold Treatment, repeat CBC w/diff within 7 days. • If repeat platelet count is ≥ 100 x 10^9/L and ANC ≤ grade 2, then resume the delayed chemotherapy (both agents) with 20% reduction. • If not recovered in 7 days, continue to hold and repeat CBC w/diff at least weekly until platelet count is ≥ 100 x 10^9/L and ANC ≤ grade 2. • If delayed ≤ 14 days, resume with 20% dose reduction. • If delayed > 14 days, discontinue regimen A therapy and proceed to regimen B.
*There will be no dose modifications/delays for WBC or other components of the differential (i.e. lymphocytes, monocytes, eosinophils and basophils). Only hematology labs resulted on treatment days will be used to determine dose modifications.	
Anemia (Regimens A and B: Cycle 1-8)	
PRBC transfusions are recommended for symptomatic or clinically significant anemia.	
Cardiac Toxicity (Regimen B: Cycle 5-8)	
• Cardiomyopathy	• Discontinue doxorubicin. Cardiomyopathy to be managed per institutional standard of care.
Neuropathy (Regimen A: Cycle 1-4)	
• Grade 1[a]	• Consider symptomatic management (not required). • No dose modifications to carboplatin or paclitaxel.
• Grade 2	• Symptomatic management required. • Continue carboplatin at full dose. • Continue paclitaxel with 20% dose reduction for all subsequent doses as long as the neuropathy does not progress to grade 3 or 4.
• Grade 3 (first occurrence)	• Symptomatic management required. • Hold study drug. If recovers to ≤ grade 2 in less than 3 weeks, resume both carboplatin & paclitaxel with 20% dose reduction for all subsequent doses, as long as the neuropathy does not progress to grade 3 or 4. • If neuropathy does not recover to ≤ grade 2 within 3 weeks discontinue carboplatin & paclitaxel. Proceed to regimen B.

	• Skipped doses are made up.
• Grade 3 (recurrence)	• If grade 3 neuropathy recurs after previously recovering to ≤ grade 2, discontinue carboplatin & paclitaxel. Proceed to regimen B.
• Grade 4	• Discontinue carboplatin & paclitaxel. Proceed to regimen B.
All Other Non-Hematologic Toxicities (Cycle 1-4)[c]	
• Grade ≤ 2	• Continue study therapy at full dose. SOC management required.
• Grade 3[b]	• Hold until ≤ grade 2. SOC management is required. Resume at full dose if toxicity resolves to ≤ grade 2 in ≤ 14 days. If toxicity resolves to ≤ grade 2 in 14 to ≤ 28 days, resume therapy with 20% dose reduction. • If delayed > 28 days, discontinue regimen A therapy and proceed to regimen B.
• Grade 4	• Discontinue regimen A therapy, proceed to regimen B.

[a] This includes grade 1 paresthesia (mild symptoms)
[b]Exception will be for Grade 3 nausea, or any electrolyte abnormalities. These should be promptly maximally medically managed and only will result in treatment delay if grade 3 event is lasting longer than 24 hours despite maximal medical treatment.
[c]During AC chemotherapy (cycle 5-8), dose modifications or holds for hematologic or non-hematologic toxicity (except cardiomyopathy) should be per SOC and treating physician's discretion.

8. ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Adverse Event Attribution

Attribution is an assessment of the relationship between the AE and the medical intervention.

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

Relationship Assessment: In-Depth Definitions

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event

may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject’s clinical condition, other concomitant treatments).

Unrelated: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2 Known Adverse Events List

Refer to the potential side effects of each chemotherapeutic agent listed in section 10.

8.3 Time Period and Grade of Adverse Event Capture

Any AEs and the grade of the AEs will be captured from the beginning of the chemotherapy until it is completed.

8.4 Monitoring and Recording an Adverse Event

Definition. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

Reporting source. AEs may be spontaneously reported by the Subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

Prior to the trial. Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

Pretreatment events following signed informed consent. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Treatment events. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Not serious AEs. For non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management 30 days following the last dose of the study drug or treatment. SAEs will be followed until resolution or until considered permanent by the treating physician.

8.4.1 Procedure for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant, or suspects that she is pregnant, while participating in this study, she must inform the investigator immediately and permanently discontinue the study drug. The sponsor-investigator must notify the DSMC by email. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor-investigator must also immediately notify the DSMC by email. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

9. DATA AND SAFETY MONITORING PLAN (DSMP)

9.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

9.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

9.3 Review and Oversight Requirements

9.3.1 Serious Adverse Events – Reported Within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24-hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section 9.3.5 for detailed instructions on SAE reporting.

9.3.2 Serious Adverse Events – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section 9.3.5 for detailed instructions on SAE reporting.

9.3.3 Sponsor-Investigator Responsibilities for SAE Review

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1**) suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAE with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 7 calendar days.

Refer to Section 9.3.5.5 for UWCCC PI instructions for reporting to the FDA

9.3.4 Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, toxicities and

responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

9.4 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to the table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections 9.3.5.1 and 9.3.5.2 below if the SAE occurred at the UWCCC or sections 9.3.5.3 and 9.3.5.4 if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

Expedited Reporting Requirements for Adverse Events that occur on Studies within 30 Days of the Last Administration of the investigational Agent/Intervention

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)
NOTE: Investigators MUST immediately report to the *UWCCC* and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

<u>Expedited AE reporting timelines are defined as:</u>

- 24-Hour; 5 Calendar Days – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- 10 Calendar Days – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

9.4.1SAE Requiring [24] Hour Reporting Occurs at UWCCC

1. Report to the UWCCC:

   Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

   For this protocol, the following UWCCC entities are required to be notified:

   a) saenotify@uwcarbone.wisc.edu
   b) Kari Wisinski, MD: kbwisinski@medicine.wisc.edu
   c) Tamara Koehn: tmkoehn@medicine.wisc.edu
   d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. Report to the IRB:

   Consult the UW Health Sciences IRBs website for reporting guidelines.

9.4.2 SAE Reporting [10] Day Reporting Occurs at UWCCC:

1. Report to the UWCCC:

   Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [10] day reports.

   For this protocol, the following UWCCC entities are required to be notified:

   a) saenotify@uwcarbone.wisc.edu
   b) Kari Wisinski, MD: kbwisinski@medicine.wisc.edu
   c) Tamara Koehn: tmkoehn@medicine.wisc.edu
   d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. **Report to the IRB**:

   Consult the UW Health Sciences IRBs website for reporting guidelines.

9.4.3 SAE Requiring [24] Hour Reporting Occurs at 1 South Park (1SP), Johnson Creek (JC), or a WON Site:

1. **Report to the UWCCC:**

Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP, JC, and other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After 1SP, JC, or a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator or Study Chair is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, in accordance each entities' reporting requirements.**

2. **Report to the IRB:**

WON sites should follow their local IRB reporting guidelines for SAE submission. The UW PI/Study Chair is responsible for the submission of the SAE to the UW Health Sciences IRBs for any sites for which the UW serves as the IRB of record.

9.4.4 SAE Requiring [10] Day Reporting Occurs at 1 South Park (1SP), Johnson Creek (JC), or a WON site:

1. **Report to the UWCCC:**

Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP, JC, and other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [10] day reports.

Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After 1SP, JC, or a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator or Study Chair is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, and in accordance each entities' reporting requirements.**

2. **Report to the IRB:**

The UW PI/Study Chair is responsible for the submission of the SAE to the UW Health Sciences IRBs. WON sites should follow their local IRB reporting guidelines for SAE submission.

9.4.5 Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor/investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

10. PHARMACEUTICAL INFORMATION

10.1 Carboplatin

10.1.1 Product Description

Classification: Antineoplastic Agent, Alkylating Agent;
Antineoplastic Agent, Platinum Analog

Mechanism of Action: Carboplatin is a platinum compound alkylating agent which covalently binds to DNA; interferes with the function of DNA by producing interstrand DNA cross-links.

Metabolism: Carboplatin does not undergo significant metabolism. It undergoes aquation reaction in the presence of low concentrations of chloride. Carboplatin is extensively cleared by the kidneys, with about 60-70% of drug excreted in the urine within 4 hours.

Contraindications: History of severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, mannitol, or any component of the formulation; should not be used in subjects with severe bone marrow depression or significant bleeding

Side Effects: Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.
Common side effects include myelosuppression, nausea, vomiting, renal toxicity, peripheral neuropathy, elevation of liver enzymes, allergic reaction, amenorrhea, sterility and alopecia.

10.1.2 Solution Preparation

Carboplatin is available in solution of 50 mg/5 mL (5 mL); 150 mg/15 mL (15 mL); 450 mg/45 mL (45 mL); and 600 mg/60 mL (60 mL) for intravenous administration.

10.1.3 Storage Requirements

Store intact vials at room temperature at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

10.1.4 Stability

Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25°C) for 8 hours in NS or D5W. Stability has also been demonstrated for dilutions in D5W in PVC bags at room temperature for 9 days; however, the manufacturer recommends use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when stored at 25°C (77°F) following multiple needle entries.

10.1.5 Route of Administration

Intravenous.

10.1.6 Nursing Implications

Assess subject allergy history prior to therapy and note specific use cautions (e.g., bone marrow suppression and renal function). Assess other drugs subject may be taking for potential interactions (especially products that may be ototoxic or nephrotoxic and need for sequencing with taxane derivatives). Assess hematology, electrolytes, and renal and hepatic function tests prior to treatment and on a regular basis during therapy. Monitor for nausea and vomiting (pretreatment with antiemetic may be required), ototoxicity (audiometry may be advisable), bone marrow depression, anemia, bleeding, and peripheral neuropathy.

10.2 Cyclophosphamide

10.2.1 Product Description

Classification: Antineoplastic Agent, Alkylating Agent;

Mechanism of Action: Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

Metabolism: Extensively metabolized in the liver by the cytochrome P450 system to both active and inactive form. Parent drug and its metabolites are eliminated exclusively in urine. The elimination half-life ranges from 4 to 6 hours.

Contraindications: Hypersensitivity to cyclophosphamide or any component of the formulation; urinary outflow obstruction.

Side Effects: Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Common side effects include myelosuppression, bladder toxicity, nausea, vomiting, alopecia, amenorrhea with ovarian failure, sterility, cardiotoxicity in high dose, risk of second malignancies, immunosuppression with increased risk of infection, SIADH and hypersensitivity reaction.

10.2.2 Solution Preparation

Cyclophosphamide is available in reconstituted solution of 500 mg, 1 gm and 2 gm for intravenous administration. It also is available in 25 mg and 50 mg in capsule and tablet form for oral administration.

10.2.3 Storage Requirements

Injection powder for reconstitution: Store intact vials of powder at ≤25°C (77°F). Exposure to excessive temperatures during transport or storage may cause active ingredient to melt (vials with melting may have a clear to yellow viscous liquid which may appear as droplets); do not use vials with signs of melting. Solutions reconstituted in sterile water for injection should be further diluted immediately; do not inject SWFI reconstituted solution directly.

10.2.4 Stability

Reconstituted solutions in normal saline (NS) are stable for 24 hours at room temperature and for 6 days refrigerated at 2°C to 8°C (36°F to 46°F). Solutions diluted for infusion in 1/2NS or NS are stable for 24 hours at room temperature and for 6 days refrigerated; solutions diluted in D5W or D5NS are stable for 24 hours at room temperature and for 36 hours refrigerated.

10.2.5 Route of Administration

Intravenous or oral

10.2.6 Nursing Implications

Adjust dose for renal or hepatic dysfunction. Assess other drugs subject may be taking that may increase or prolong nephrotoxicity and cardiotoxicity. Note infusion specifics in administration. Adequate hydration is required for all uses, but protocol and method of administration may be indication-specific. Monitor IV site for signs of extravasation. Assess results of urinalysis, BUN, and serum creatinine to evaluate for nephrotoxicity. Monitor CBC with differential and platelet count to identify myelosuppression. Monitor for hemorrhagic cystitis and renal tubular necrosis, especially in high doses. Teach subject importance of adequate hydration, especially for subjects who are taking oral tablets. Teach subject the importance of follow-up to monitor for secondary malignancies.

10.3 Doxorubicin

10.3.1 Product Description

Classification: Antineoplastic Agent, Anthracycline; Antineoplastic Agent, Topoisomerase II Inhibitor

Mechanism of Action: Inhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and by steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes.

Metabolism: Metabolized extensively in the liver in the active hydroxylated metabolite, doxorubicinol. About 40-50% of drug is eliminated via biliary excretion in feces. Less than 10% of drug is cleared by the kidneys. Prolonged terminal half-life of 20-48 hours.

Contraindications: Hypersensitivity (including anaphylaxis) to doxorubicin, any component of the formulation, or to other anthracyclines or anthracenediones; recent MI (within past 4 to 6 weeks), severe myocardial insufficiency, severe arrhythmia; previous therapy with high cumulative doses of doxorubicin, daunorubicin, idarubicin, or other anthracycline and anthracenediones; severe persistent drug-induced myelosuppression or baseline neutrophil count <1500/mm^3; severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL)

Side Effects: Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Common side effects include myelosuppression, nausea, vomiting, mucositis, diarrhea, cardiotoxicity, hyperpigmentation of nails, alopecia, discoloration of urine, allergic reaction.

10.3.2 Solution Preparation

Doxorubicin is available in reconstituted solution of 10 mg; 20 mg; and 50 mg for intravenous administration.

10.3.3 Storage Requirements

Lyophilized powder: Store powder at 20°C to 25°C (68°F to 77°F). Protect from light. Retain in carton until time of use. Discard unused portion from single-dose vials.

Solution: Store refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Retain in carton until time of use. Discard unused portion. Storage of vials of solution under refrigeration may result in formation of a gelled product; if gelling occurs, place vials at room temperature for 2 to 4 hours to return the product to a slightly viscous, mobile solution.

10.3.4 Stability

Reconstituted doxorubicin is stable for 7 days at room temperature under normal room lighting and for 15 days when refrigerated at 2°C to 8°C (36°F to 46°F). Protect reconstituted solution from light.

10.3.5 Route of Administration

Intravenous.

10.3.6 Nursing Implications

Use with caution in subjects with history of heart failure, kidney or liver disease, prior treatment with same drug class, or past radiation to the chest. Assess cardiac function prior to beginning therapy with this drug and periodically during therapy. Initiate routine surveillance for risk of secondary malignancies. Subjects should not receive live vaccines while undergoing treatment. Antiemetics should be given to help prevent nausea and vomiting. Infusion site must be closely monitored; extravasation can cause sloughing or tissue necrosis (use dexrazoxane or DMSO).

10.4 Paclitaxel

10.4.1 Product Description

Classification: Antineoplastic Agent, Antimicrotubular;
Antineoplastic Agent, taxane derivative

Mechanism of Action: Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

Metabolism: Metabolized extensively by the hepatic P450 microsomal system. About 70-80% of drug is excreted via fecal elimination. Less than 10% is eliminated as the parent form with the majority being eliminated as metabolites. Renal clearance is relatively minor with less than 10% of drug cleared via the kidneys. Terminal elimination half-life ranges from 9 to 50 hours depending on the schedule of administration.

Contraindications: Hypersensitivity to paclitaxel, polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), or any component of the formulation; treatment of solid tumors in subjects with baseline neutrophil counts <1,500/mm^3; treatment of Kaposi sarcoma in subjects with baseline neutrophil counts <1,000/mm^3.

Side Effects: Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Common side effects include myelosuppression, hypersensitivity reaction, neurotoxicity, transient asymptomatic sinus bradycardia, alopecia, mucositis, diarrhea, transient elevation in liver enzymes, onycholysis.

10.4.2 Solution Preparation

Paclitaxel is available in concentrate of 100 mg/16.7 mL (16.7 mL); 30 mg/5 mL (5 mL); 150 mg/25 mL (25 mL); and 300 mg/50 mL (50 mL) for intravenous administration.

10.4.3 Storage Requirements

Store intact vials at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

10.4.4 Stability

Solutions diluted for infusion in D5W and NS are stable for up to 27 hours at ambient temperature (~25°C).

10.4.5 Route of Administration

Intravenous.

10.4.6 Nursing Implications

Paclitaxel (protein bound) is not interchangeable with paclitaxel (conventional). Assess subject carefully for cautious use indications and contraindications. Infusion site must be monitored closely to avoid extravasation. Monitor for hypersensitivity reaction, cardiovascular abnormalities, sensory neuropathy, myelosuppression, and GI irritation prior to, during, and between each infusion.

11. REPORTING AND DOCUMENTING RESULTS

11.1 Evaluation of Efficacy during Chemotherapy

This evaluation is recommended as SOC but not mandatory for the study. The evaluation is determined by the physician in charge of the subjects through the physical examination during the regular follow up visit while on chemotherapy (from cycle 2 to 8).

Objective radiographic response using MRI, ultrasound or mammogram if clinically indicated could also be obtained before the final surgery.

11.2 Evaluation of Final Objective Pathologic Response

Pathologic complete response (pCR)

This is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph

nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/T is ypN0 in the current AJCC staging system).

11.3 Evaluation of Survivals

Recurrence-free survival

Duration for which the subject is without evidence for local-regional or distant relapse, second primary, or death.

Overall survival

This is defined as the time from initiation of study until death from any cause.

11.4 Evaluation of Safety

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE v5.0 for reporting of nonhematologic adverse events and modified criteria for hematologic adverse events.

12 STATISTICAL CONSIDERATIONS

12.1 Study Endpoints

The primary endpoint is pathologic complete response rate (pCR) and the secondary endpoints are the number of cycles, doses and delays of chemotherapy administered, treatment-related toxicity, 2-year recurrence-free survival (RFS) and overall survival (OS).

12.2 Study Design

The hypothesis is that the use of low dose weekly Carboplatin/Paclitaxel followed by dose-dense Doxorubicin/Cyclophosphamide in subjects with TNBC in neoadjuvant setting will result in less dose reductions or delays and similar pCR rate seen with the every 3 week carboplatin schedule. This is a Phase II, open- label, single-arm, multicenter, prospective study. This is the first study to evaluate the addition of low dose weekly Carboplatin to standard anthracyclines/taxane regimen in subjects with triple-negative breast cancer.

12.3 Stratification Factors

None

12.4 Determination of Sample Size and Power Estimate

A sample size of 48 achieves 80% power to detect a 20% difference using a one-sided binomial test at an alpha significance level of 0.025. These results assume that the population proportion under the null hypothesis is 0.34, which is the reported pCR with anthracyclines and taxane regimens in TNBC. Allowing for drop-out rate of 5%, a total of 50 subjects is planned.

12.5 Accrual Estimates

Approximately 50 subjects are planned for accrual and it is estimated that enrollment will be completed in 24 months. On average, subjects will be on the study for 6 months.

12.6 Interim Analyses and Stopping Rules

No interim analyses are planned for this study

12.7 Analyses Plans

The analysis of the primary and secondary endpoints will be performed on all subjects according to the intention to treat (ITT) principle. All efficacy analyses will be performed on all subjects who receive at least 1 dose of study drug.

12.7.1 Primary Analysis (or Analysis of Primary Endpoints)

The primary endpoint of pCR will be assessed according to the RECIST 1.1 criteria by the investigator. The point estimate of the primary efficacy endpoint pCR and its exact 95% confidence intervals (CI) will be calculated. In evaluating pCR, subjects with missing data will be considered non-responders.

12.7.2 Secondary Analysis (or Analysis of Secondary Endpoints)

Simple descriptive statistics will be used to describe the number of cycles, doses and delays of chemotherapy administered. This would enhance the assessment of the chemotherapy regimen.

For the secondary endpoints of RFS and OS, the median RFS and OS will be obtained by the Kaplan-Meier technique. The 95% CI will be calculated. Also, estimates of the recurrence-free rate at fixed time point will be obtained using the Kaplan-Meier technique and 95% CI will be calculated using the Greenwood's formula for standard deviation. In addition, estimates of hazard ratios and their 95% CI will be obtained by Cox regression. All failure time variables would be measured by the time interval from the date of registration to the date of the first failure.

12.7.3 Demographic and Baseline Characteristics

Descriptive statistics will be provided to summarize demographics and baseline characteristics parameters. Categorical data will be summarized as frequency and its

corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters.

12.8 Evaluation of Safety

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the NCI CTCAE v5.0.

12.9 Study Results

The statistical analysis will be reported using summary tables, figures, and data listings. Continuous variables will be summarized by standard descriptive statistics in terms of means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the case report forms as well as any derived data will be included in data listings. Data analysis will be performed using SAS® version 9.4 or greater.

A formal statistical analysis plan (SAP) will be developed before the database lock. It will include detailed descriptions of summaries and mock-ups of tables, listings, and figures to be included in the clinical study report.

13 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

13.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

13.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

13.3 Prestudy Documentation

Prior to implementing this protocol, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UW Health Sciences IRB. Prior to implementing this protocol at the participating sites, approval for the UW Health Sciences IRB-approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UWCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UWCCC will formally contact the site and grant permission to proceed with enrollment.

13.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UW Health Sciences IRB. Prior to obtaining UWCCC approval, the protocol must be approved by the UWCCC Protocol Review and Monitoring Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

After the UW Health Sciences Institutional Review Board (HS-IRB) grants initial approval for a WON study, the Affiliate Coordinator provides the WON sites with the approved documents. Sites use the UW HS IRB-approved consent document as a template. WON sites may make minor changes to the consent form to reflect their institutional standards. No substantial changes, including changes to the risk language, are allowed (sites can always clarify existing risk information or add risk language if they wish to do so).

Each WON site must receive local IRB approval of both the UW-IRB approved protocol and informed consent/HIPAA documents (with minor revisions allowed). The local IRB approval notice and informed consent documents are forwarded to the Affiliate Coordinator at the address listed below. Once all of UWCCC administrative

requirements are completed and local IRB approval is verified, the Affiliate Coordinator issues an activation notice for the site. Study activities can begin at the local site only once this activation notice is issued.

Any site under the UW HS-IRB's purview must receive UW HS-IRB approval for their participation prior to study activation at the site. UWCCC-Johnson Creek uses the same UW HS-IRB approval process and consent form as the UW. Of note, member sites of the Wisconsin IRB Consortium (WIC), may be approved for participation through IRB deferral agreements made possible by the WIC mechanism. Both UWCC-Johnson Creek and WIC institutions must also be issued activation notices prior to enrolling subjects.

The Affiliate Coordinator is responsible for continued oversight of regulatory documentation for each WON site. The Affiliate Coordinator distributes all additional UW HS-IRB-approved amendments and consents to participating WON sites. The Affiliate Coordinator uses OnCore and additional spreadsheets to track local IRB approvals of all amendments and consents for participating WON sites. All local IRB approvals and informed consent documents should be forwarded to the Affiliate Coordinators at the UWCCC by email (affiliatecoordinators@uwcarbone.wisc.edu) or regular mail:

Affiliate Coordinators
University of Wisconsin Carbone Cancer Center
600 Highland Avenue, CSC, K4/6
Madison, WI 53792-6164

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/ products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Potential subjects will be told and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved UW Health Sciences IRB template language.

Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Subjects that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. Sites should follow their IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent for inclusion in the legal medical record.

All WON sites under the purview of their local IRBs follow recruitment and consent processes approved by the local IRB of record.

Documentation of both the informed consent process and that the process occurred prior to a subject's entry into a WON study is recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject, must be maintained in the investigator's study files at each site. All current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the principal investigator and all research staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator/study chair

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. Identifiable subject information will be maintained at the enrolling site. All source documentation will be maintained within the subject's research chart which will be accessible only to authorized study personnel. Subject research charts will be stored in a locked research office at each enrolling site.

Study data will be collected via the UWCCC Oncore database. Each enrolling site is responsible for entering data into study specific eCRFs. Subject data used for analysis will be coded. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the electronic Case Report Forms contains the study identifiers, subject initials, date of birth and date of service.

Personal identifiers such as name and medical record number will be removed from accompanying lab reports and test results. Any Data/PHI that is not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the Data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

The principal investigator/study chair will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator/study chair may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. Each clinical study site will permit access to such records.

13.6 Protection of Human Subjects

13.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

13.6.2 Protection of Privacy

As noted, subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be invited to sign informed consent documents. The original signed document will become part of the subject's medical records, and each subject will receive a copy of the signed documents.

13.7 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

WON sites will be audited in accordance with the WON auditing and monitoring plan.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14 DATA HANDLING AND RECORD KEEPING

14.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Data Management Responsibilities

14.2.1 Principal Investigator

The principal investigator oversees the management of subject records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) subject records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the Case Report Forms and the source documents**.** The Principal Investigator will have additional oversight responsibilities as applies to subjects enrolled trough Wisconsin Oncology Network affiliate sites:

- Verify that weekly summaries are obtained and verified.
- Review all SAE's submitted by WON sites.
- Verify remote or on-site auditing occurs at participating WON sites.

14.2.2 Research Coordinator

A research coordinator creates, collects and organizes Clinical Trial Documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

14.2.3 Research Nurse/Medical Staff

The research nurse and medical staff documents protocol required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

14.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

14.3 Handling and Documentation of Clinical Supplies

The Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of subjects to whom study drug has been dispensed by subject number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study subjects. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

14.4 Source Documents

Source documents for clinical information (subject history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the subject's clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

The source documents for this protocol are as follows:

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

14.5 Case Report Forms

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the study calendar, using single data entry with a secure access account.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the subject's medical records maintained by each site's personnel. All source documentation should be kept in separate research folders for each subject.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs.

All source documentation and data will be available for review/monitoring by the UWCCC DSMC and regulatory agencies.

14.6 Study Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the

investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

14.7 WON Site Oversight

The UWCCC Affiliate Office serves as the coordinating center for WON. Coordinating center responsibilities are shared between the Affiliate Coordinator and UWCCC Breast/Melanoma DOT. A detailed description of coordinating center responsibilities, as well as other WON processes and procedures, is provided in the WON Manual available on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=42878).

Regular communication between the UWCCC Affiliate Office and WON sites ensures that all participating parties are notified of protocol changes, informed consent document revisions, action letters, study status changes, reportable events/Serious Adverse Events (as necessary), and any other applicable information. This communication is accomplished through regular email updates and conference calls.

15 CORRELATIVE STUDIES

See Study Operations Manual for sample processing and shipping instructions. Testing will be completed to meet the exploratory endpoint of this study. Testing may be performed at UWCCC, MCW or an outside laboratory. Samples will be coded with subject number and date/time of acquisition. No subject health information will be provided with the samples. Results from the research testing will be provided to the investigators to be used for the purposes of this study. Samples will be stored until depleted or until subject withdraws consent for optional research testing.

Tissue samples will be stored at the UWCCC or MCW until the time of correlative research testing. Samples will be stored with study number, subject number, date and time of sample acquisition. Upon direction from the Principal Investigator, samples will be distributed by the staff at the designated laboratory to the facility performing the requested testing. Testing will be completed to meet the exploratory endpoint of this study. Testing may be performed at UWCCC, MCW or an outside laboratory. Samples will be coded with subject number and date/time of acquisition. No subject health

information will be provided with the samples. Results from the research testing will be provided to the investigators to be used for the purposes of this study. Samples will be kept indefinitely unless asked to be returned or subject withdraws consent for optional research testing.

All future projects using the banked data or samples from this study will be submitted to the Institutional Review Board (IRB) for review and approval or exemption. Distribution of the banked samples will be limited to researchers within UW-Madison or MCW. Request for samples would be directed to the study PI or the study chair who will determine if the banked samples would be suitable for use in that study. Prior to distribution, scientific and IRB approval of the research study would need to be provided to the PI and study chair. Additionally, the PI and study chair will be responsible for querying the data and tissue repositories and will manage the dispersion of data sets.

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APPENDIX 1. *PERFORMANCE STATUS CRITERIA*

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory 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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. *SPECIMEN COLLECTION*

Sampling and shipping information

- Research blood: two 10 ml EDTA tubes of blood will be collected at 2 time points (first sample prior to initiation of study chemotherapy; second sample between last chemotherapy treatment and prior to surgery). Samples can be frozen and stored at the research site for later batch shipping. If sites do not have room to store samples they may be shipped to MCW for storage. Please refer to the study operations manual for processing and shipping instructions.

- Tumor tissue

    - A formalin-fixed paraffin embedded tumor block (preferred) or 5-10 unstained slides from the biopsy of the primary tumor and the surgical specimen (if residual tumor identified) are requested if subject consents
    - Samples will be coded with the study ID and labeled as biopsy or surgical specimen.
    - At completion of analysis, all tumor blocks will be returned if requested by the originating institution and any remaining tumor blocks will be destroyed.
    - Please refer to the study operations manual for shipping instructions.

Sample shipment instructions

For all shipments, an inventory of the samples should accompany the shipment. This inventory should include the study ID, subject ID, sample number, visit number and time of collection.

A copy of the inventory will be retained at the site in the subject's binder along with any shipping documents.

All samples will be kept at the temperature specified up to and during the shipment and packed according to IATA shipping regulations.

If shipping samples off campus, shipment will be sent via overnight courier (i.e. Fedex) and shipped Monday through Thursday. Samples will not be shipped on Fridays.

APPENDIX 3. *STUDY CALENDAR*

Procedure	Screening	Regimen A: Cycle 1,2,3,4			Regimen B: Cycle 5[14],6,7,8		Follow up visit	Long term follow up
Study Day/Visit Day	**-30 to Registration**	**1 (+/- 1)**	**8 (+/- 1)**	**15 (+/- 1)**	**1 (+/- 1)**	**Regimen C: Surgery[6]**	**Within 30 days after surgery**	
Informed consent	X							
Treatment/Drug Administration								
Carboplatin		X	X	X				
Paclitaxel		X	X	X				
Doxorubicin					X			
Cyclophosphamide					X			
Clinical procedures								
Physical exam	X	X[12, 17]			X		X	
Vital signs (weight, temperature, blood pressure, heart rate)	X	X[17]			X		X	
Medical history	X							
Height	X[15]	X[15]						
Disease assessment [3]	X						X	
ECOG Performance status	X	X[12, 17]			X		X	
Measurable disease (clinical)	X	X[12]			X			
Breast biopsy (SOC)	X							
AE assessment	X	X[12]			X		X[18]	
Laboratory procedures								
CBC w/ Diff	X	X[9]	X[1]	X[1]	X		X[16]	
Blood chemistry [4]	X	X[9]			X		X[16]	
Pregnancy test (HCG)	X	X[7]						
Archived tumor tissue (optional)		X[11]					X	
Research blood (optional)		X[10]			X[10]	X[10]		
Imaging procedures								
Systemic Imaging (CT, bone scan, PET or MRI) [5]	X							
Cardiac Assessment (ECHO, MUGA)[13]	X							

Procedure	Screening	Regimen A: Cycle 1,2,3,4			Regimen B: Cycle 5[14],6,7,8		Follow up visit	Long term follow up
Study Day/Visit Day	**-30 to Registration**	**1 (+/- 1)**	**8 (+/- 1)**	**15 (+/- 1)**	**1 (+/- 1)**	**Regimen C: Surgery[6]**	**Within 30 days after surgery**	
MRI/ultrasound/ Mammogram[2]	X				X			
Long term follow up[8]								X

1. CBC, Plts and differential (ANC can also be done instead of full differential on these dates).
2. Disease assessment with MRI breast and/or ultrasound and/or mammogram is per standard of care for diagnosis, but at least one modality of imaging must be completed within 45 days of registration. Breast MRI, US or mammogram (if clinically indicated) within 45 days prior to surgery.
3. Disease specific staging (clinical staging and/ or pathologic staging)
4. Including alkaline phosphatase, ALT/AST, total bilirubin, calcium, (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate.
5. If clinically indicated (not required for study eligibility)
6. Surgical intervention for management of breast cancer diagnosis; procedure and timing as determined by surgical team
7. For women who are not postmenopausal. Serum or urine pregnancy test to be done at screening. To be repeated if not done within 7 days of starting chemotherapy (cycle 1 day 1).
8. Disease status, survival status and any interval systemic anti-cancer treatment will be collected every 6 months (+/- 30 days) for 2 years after date of surgery. Actual SOC follow up may be more frequent, data to be reported every 6 months. This includes all subjects who do not complete all cycles of the study treatment unless they are withdrawn from study.
9. Screening labs to be repeated if complete more than 14 days prior to C1D1 treatment.
10. Research sample to be drawn as follows: prior to starting chemotherapy on C1D1, prior to treatment on C8D1, and within 3 days prior to surgery. If the subject is taken off protocol therapy before C8D1, a blood sample should be drawn as close to the subject's last chemotherapy treatment as possible.
11. Cycle 1 Day 1 only (if subject agrees to archival tissue collection, it should be collected and submitted within 8 weeks of C1D1)
12. For Cycle 1 only; H&P, disease assessment, ECOG performance status and AE assessment do not need to be repeated if done up to 3 days prior to Cycle1 Day 1
13. ECHO or MUGA to be completed during screening period. During the study subjects should be monitored for changes to their left ventricular ejection fraction according to institutional standard of care.
14. There is one week break between the end of cycle 4 and the beginning of cycle 5.
15. Height can be obtained at screening or Cycle 1 Day
16. Perform if clinically indicated
17. For C2D1+; H&P, vitals and ECOG Performance Status do not need to be repeated if treatment is held for 7 days due to ANC and platelet counts per Table 7.2. If treatment is held for longer than 7 days, these procedures need to be repeated.
18. AEs will be followed for 30 days after the last dose of study drug or treatment. SAEs will be followed until resolution or until considered permanent by the treating physician.