**IRB #: 264-12**

# A Phase II Study of Neoadjuvant Chemotherapy with and without Trastuzumab in Patients with Breast Cancer

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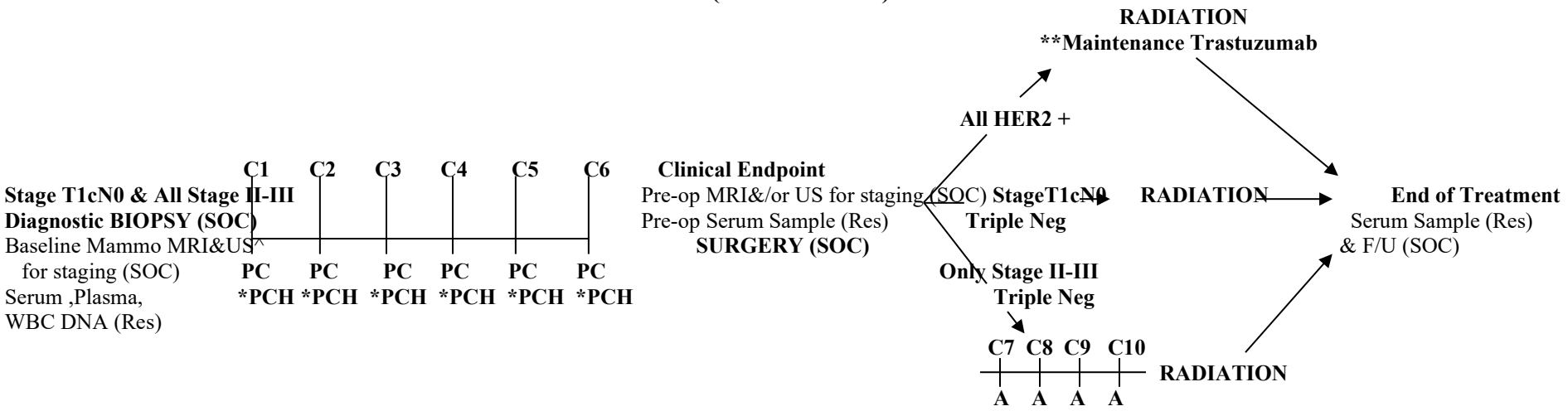
## NEO-ADJUVANT SCHEMA
## (Breast Cancer)




^Mammogram MRI&US of Breast and Axilla (pre-op MRIand/or US may be omitted in the case of planned mastectomy)

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**ALL PATIENTS = PC Paclitaxel** 175mg/m$^2$ in normal saline IV over 3 hrs **/ Cyclophosphamide** 600mg/m$^2$ in normal saline IV over 1 hr REPEAT Day 1 Q 2wks x 6 cycles (Cycles 1-6), **Pegfilgrastim** support 1-4 mg SQ after PC dose adjust down or hold for ANC >12,000 or bone pain (SOC), (Pegfilgrastim support is optional folloing cycle 6)

**PATIENTS WITH <u>HER-2 NEU POSITIVE</u> TUMOR = *PCH - Paclitaxel/Cyclophosphamide** REPEAT Day 1 Q 2wks x 6 cycles (Cycles 1-6), **Pegfilgrastim** SQ after PC **, H - Herceptin® (Trastuzumab)** loading dose 6mg/kg Day 1, Cycle 1THEN subsequent dosing 4mg/kg Day 1 Q2wks Cycles 2-6, (SOC) ****Maintenance Herceptin®** 6mg/kg Day 1 Q21 Days for a total of 52 weeks. (SOC)

**ALL PATIENTS = RADIATION Clinical Decision** per standard NCCN guidelines, following chemotherapyand surgery. (SOC)

**Only STAGE II-III, TRIPLE NEGATIVE PATIENTS (HER2 - ER- PR-) = Adriamycin** 60mg/m$^2$ in normal saline IV Q2wks x 4 cycles (Cycles 7-10), **Pegfilgrastim** support 1-6mg, (Pegfilgrastim support is optional following cycle 4)

**<u>PATIENTS WITH ER/PR + TUMOR</u> = HORMONAL THERAPY** Patients with **estrogen/progesterone receptor positive** tumors will also receive Hormonal Therapy to be determined by the medical oncologist as per standard NCCN guidelines. (SOC)

**<u>End of Treatment Follow-up (F/U)</u>** <u>(All subjects)</u>
Research Serum Samples collected at end of treatment (Res)
Patients will be monitored Q3 months until 2 years from date of treatment for safety. (SOC)
Patients will be followed annually for disease recurrence and overall survival to stop at 5 years from diagnosis.

## TABLE OF CONTENTS

## 1.0 OBJECTIVES

### 1.1 Primary Objective

**1.1.1** To evaluate the toxicities and tolerability of a neoadjuvant dose-dense regimen cyclophosphamide and paclitaxel with or without trastuzumab/radiation therapy (as clinically indicated) in patients with newly diagnosed stage T1cN0 and II-III breast cancer; followed by maintenance trastuzumab in HER2 positive OR adriamycin followed by RT in Stage II-III triple negative HER2 (-), ER (-), PR(-) Stage T1cN0 and II-III breast cancer patients.

**1.1.2** To determine the pathological complete response rate (pCR) of this treatment regimen.

**1.1.3** To identify possible gene expression profile signatures from whole genome array analysis that correlate with clinical response/resistance to chemotherapy as measured by pathologic complete response rate (pCR).

## 2.0 BACKGROUND

Breast cancer is the most common cancer diagnosed in American women and the second most common cause of cancer death. It is estimated that 226,870 women will be diagnosed with breast cancer while 39,920 women will die of their disease in 2012. (1) The mainstay of the treatment for early stage disease is surgical removal of the tumor followed by adjuvant systemic treatment (chemotherapy and/or hormonal therapy) with or without radiation therapy to reduce the recurrence. SEER Summary Stage 2000 indicates that 60% of patients with breast cancer were diagnosed in Stage I, while 33% were diagnosed as Stage II. The overall survival rates were 98.3% for localized Stage I and 83.5% for regional Stage II disease. (1) Adjuvant systemic therapy has been associated with increased disease-free and overall survival in breast cancer patients. Stage I and II breast cancer patients have an estimated 5%, and 11% risk of recurrence risk respectively even after adjuvant systemic therapy. (2)

In early stage breast cancer patients multiple combination chemotherapy regimens have been evaluated as adjuvant therapy. A meta-analysis of adjuvant chemotherapy regimens reported by the Early Breast Cancer Trialists' Collaborative Group showed that combination chemotherapy regimens containing anthracyclines (e.g. adriamycin) was associated with a small but significant decrease in recurrence and mortality compared to regimens that did not contain anthracyclines. (3) Based on this observation, the

National Institutes of Health Consensus Development Conference on Adjuvant Therapy for Breast Cancer recommended anthracycline-containing regimens for the adjuvant treatment of breast cancer. (4)

The development of taxanes and demonstration of their excellent clinical activity in metastatic breast cancer (5), lead to the clinical studies demonstrating improvement of recurrence free and overall survival with the addition of taxanes to adjuvant chemotherapy regimens in node positive breast cancer. Results of CALGB 9344 showed that the sequential addition of paclitaxel to 4 cycles of adriamycin and cyclophosphamide (AC) as adjuvant therapy was associated with improved disease free and overall survival in node positive breast cancer. (6)

Neoadjuvant chemotherapy has become one of the standards of care for both locally advanced breast cancer and for patients who desire breast-conserving therapy but are not candidates based on the initial size of the tumor in relation to the breast.(7) Neoadjuvant chemotherapy regimens that are considered "acceptable" include FAC(5FU, adriamycin, cyclophosphamide) ,CAF(cyclophosphamide, adriamycin, 5FU), CEF(cyclophopshamide, epirubicine, 5FU) and FEC(5FU, epirubicine, cyclophosphamide).(8) Taxanes have been compared to treatment with FAC as neo- adjuvant treatment in breast cancer. In one study breast cancer patients were randomized to receive either four cycles of FAC or paclitaxel as neoadjuvant treatment prior to surgery. As shown in Table I, there was no difference in the clinical response rates observed in breast cancer patients treated with paclitaxel alone compared to treatment with combination chemotherapy with FAC. (9)

Table I. FAC vs paclitaxel as neo adjuvant therapy in patients with operable breast cancer

| | FAC | Paclitaxel |
|---|---|---|
| Clinical CR | 24% | 27% |
| Clinical PR | 55% | 53% |
| Path CR | 18% | 6% |
| Path in situ | 5% | 8% |
| Path min. (<1cm) | 12% | 27% |

* Results not statistically significant. Buzdar et al. JCO 1999; 17:3412

Adriamycin containing chemotherapy regimens are effective as adjuvant therapy for early stage breast cancer but associated with increased cardiotoxicity. This has led to the evaluation of other effective but less toxic adjuvant chemotherapy regimens for breast cancer. In one recent study, Stage I – III breast cancer patients were randomized to receive four cycles of either Taxotere® (docetaxel) in combination with cyclophosphamide (TC) every 3 weeks or adriamycin and cyclophosphamide (AC) every three weeks. Both treatment groups were balanced with respect to major prognostic factors. At five years, patients treated with TC had a slightly better disease-free survival and less cardiac toxicity than patients treated with AC. (10)

Docetaxel has also been compared to Taxol® (paclitaxel) in a large randomized trial involving 4,950 women with early stage breast cancer. In this study, early stage breast cancer patients were treated with four cycles of AC every three weeks followed by treatment with either docetaxel or paclitaxel given either every week or every three weeks. This study demonstrated no difference in disease-free survival in patients treated with docetaxel or paclitaxel following treatment with four cycles of AC.

Based on the hypothesis that dose-dense schedules would limit the opportunity for re-growth of cancer cells following cytotoxic chemotherapy and improve anticancer efficacy, the effects of shortening the interval between treatment cycles from every three weeks (standard schedule) to every two weeks (dose-dense schedule) were evaluated. In a CALGB study, breast cancer patients were treated with four cycles of AC followed by four cycles of paclitaxel given either every three weeks (standard schedule) or every two weeks (dose-dense schedule). In this study, patients treated on the dose-dense schedule had improved disease free survival (risk ratio (RR) 0.74 p =.01) and overall survival (RR = 0.69, p = .013) compared to patients treated on the standard treatment schedule. (11) Dose-dense AC followed by paclitaxel is now one of the treatment options for node-positive women as defined by the National Comprehensive Cancer Network (NCCN). While the dose-dense schedule was associated with increased grade 3/4 neutropenia (11%), this was not associated with increased febrile episodes (<5%).

Since Her-2 neu targeted therapy has been shown to be effective in the treatment of metastatic cancer, its benefits have also been evaluated in early stage breast cancer. In two recent studies, patients with Her-2 neu positive tumors were treated with four cycles of AC followed by treatment with paclitaxel and they

were randomized to receive Herceptin® (trastuzumab) for a total of 52 weeks either starting concomitantly with paclitaxel or after chemotherapy. The results revealed an absolute difference in disease free survival of 12% at three years with a 33% reduction in risk of death ($p = .015$) in patients treated with trastuzumab. However, there was a 5% incidence of clinical cardiac failure in patients treated with trastuzumab following treatment with adriamycin (12). In another clinical trial (HERA trial) Her-2 neu positive breast cancer patients could be treated with any standard adjuvant chemotherapy regimen prior to treatment with trastuzumab. This study reported a 50% reduction in relapse free survival in patients receiving at least one year of trastuzumab. Clinical cardiac toxicity was also a major side effect in the HERA trial and was reported in 5% of patients (13).

The cardiotoxicity associated with adjuvant therapy with trastuzumab and adriamycin emphasizes the need to evaluate non-anthracycline based regimens. In the BCIRG trial adjuvant chemotherapy with docetaxel, carboplatin and trastuzumab (TCH) given every three weeks for six cycles, was compared to treatment with four cycles of AC, followed by four cycles of paclitaxel given every three weeks, with trastuzumab (AC-TH) or without trastuzumab (AC-T). While the risk of recurrence was reduced by nearly 50% in both trastuzumab containing arms TCH and AC-TH, there was a lower risk of cardiotoxicity in the TCH arm compared to patients treated in the AC-TH arm, with fewer grade 3 or 4 changes in left ventricular ejection fraction (LVEF) and fewer patients with clinically symptomatic congestive heart failure ($p < 0.001$) in patients treated with TCH. (14,15)

A pilot study at UNMC/TNMC (IRB#371-09) is evaluating the toxicity of adjuvant therapy with six cycles of cyclophosphamide (600mg/m2) and Taxol® (paclitaxel) (175 mg/m2) given every two weeks (dose-dense schedule) in Her-2 neu positive and negative breast cancer. Thus far, 99 patients have been enrolled in the pilot study and 86 patients have completed all six cycles of chemotherapy with or without trastuzumab. Tables II and III reports the first interim analysis of the pilot study.

**Interim Analysis**
**Table II: Serious, Related Grade III or IV Adverse Events**
**n = 50**

| Event | Comment |
|---|---|
| Infection | |
| Febrile neutropenia | Hosp. salmonella gastroenteritis |
| | Urinary tract infection |
| Line associated sepsis | Hosp. port removed |
| Shingles | Treated as outpatient C. #3 delayed one week |
| Cellulitis, wound infection | Outpt. Surgery implant removed |
| Fever | Hosp. URI |
| Neuropathy | Cycle 6 dose reduced |
| | Cycle 2 removed from study |
| | Cycle 1 removed from study |
| | Cycle 4 & 5 dose reduced |
| Anaphylaxis | Off study C-2 treated outpatient |
| Perforated duodenum | Surgery off study 4 cycles |
| ↓ ejection fraction with CHF | Medical management, improvement. Stopped herceptin |
| Leukemia | Treatment associated 7 mos after last chemotherapy. See attachment A |
| Arm DVT | Associated with line sepsis |

**Table III: Serious, Related Grade III or IV Adverse Events**
**n = 50**

**OFF STUDY**
#2– neuropathy
#1 – perforated duodenum
#1 – withdrew after first cycle
#1 – withdrew before any treatment, screen failure

**CYCLE DELIVERY**
Expected cycles 49 pts = 294
Delivered cycles 279 (92%)
Dose reduced cycle or delayed 4
Full dose on time 275 (90%)

Based on these results, we plan to evaluate the overall clinical response rate and toxicities of neoadjuvant therapy offering six cycles of paclitaxel and cyclophosphamide (TC) given in a dose dense schedule in patients with clinical stage I-III breast cancer.

Treatment of breast cancer patients with neoadjuvant chemotherapy allows the assessment of *in vivo* response to systemic chemotherapy (16) as well as the long-term clinical outcomes (17-19) associated

with *in vivo* clinical and pathological responses. Neoadjuvant chemotherapy also affords the opportunity for some patients with locally advanced breast cancer (LABC) to undergo breast conservation therapy (BCT) as a result of therapeutic down staging of the tumor (20-22).

Patients with LABC receive neoadjuvant therapy followed by surgical treatment which usually consists of a modified radical mastectomy combined with radiation therapy. However, patients who are down staged by the neoadjuvant chemotherapy may be treated with BCT. Recent studies have demonstrated that patients with breast cancer that has metastasized to the regional axillae (T1-2) can also be treated with neoadjuvant chemotherapy prior to definitive surgery and can achieve a complete pathologic response in the breast and/or in the axillae (22-25). Sentinel node staging before treatment can optimize post treatment prognostic in clinically node negative patients (26).

As noted above, in an effort to avoid anthracycline use, recent work using a combination of paclitaxel and carboplatin has also demonstrated this combination to be "effective and well tolerated" (27). Additional efforts are underway such as the XeNA-trial (Xeloda in Neoadjuvant), in which non-anthracycline preoperative regimens are utilized in HER-2 neu positive breast cancer, as they offer less cardiotoxicity and thus can be used concomitantly with preoperative trastuzumab therapy (28).

**Microarray Genomic Testing in the Treatment of Breast Cancer**

While randomized clinical studies have demonstrated a benefit from adjuvant chemotherapy in early stage breast cancer, the toxicity associated with chemotherapy has encouraged studies that attempt to better define which breast cancer patients benefit most from chemotherapeutic strategies in the adjuvant setting. A variety of clinical and pathological features of breast cancer including stage and histologic grade have been associated with increased risk of relapse in the absence of adjuvant therapy, however standard clinical and pathological evaluation has limited utility in defining breast cancer patients that benefit form adjuvant therapy.

The development of microarray technology has allowed genomic data to be used to classify breast tumors along with standard clinical prognostic factors to help define which patients would benefit least or most from adjuvant chemotherapeutic treatment. Gene signatures have been developed and validated against

large retrospective databases and adopted by medical oncologists as a means to risk stratify patients and selectively recommend adjuvant treatments for breast cancer therapy. Another approach has used intrinsic subtyping and p53 mutations as a possible predictive test for response to therapy as in XeNA study (29).

**Development of new profiles for Neo-Adjuvant chemosensitivity**

One of the correlative objectives of the current study is to identify and/or cross validate a unique set of classifier genes that will accurately predict a complete Pathologic Response (pCR) to treatment with dose dense CT in the neoadjuvant setting. Studies to date have demonstrated a 25-27% complete pathologic response in both breast and axilla to a variety of neoadjuvant chemotherapy regimens. Furthermore, neoadjuvant trials have indicated that the achievement of a pathological complete response affords the patients a survival advantage of 80% in five years, which is double the expected survival of the remaining patients without complete pathologic response. (30-31) If the subset of patients with complete pathologic response could be identified by a genomic signature then the remaining patients would best be suited to treatment with an alternative regimen.

## 3.0 ELIGIBILITY CRITERIA

### 3.1 Inclusion Criteria

3.1.1 Women with histologically proven invasive breast cancer without distant metastases A clinical tumor classification of tumor size must be at least 1 cm with or without clinical pathologic evidence of positive nodes.

3.1.2 Age: Patients must be 19 years of age or older. (This is the age of consent in Nebraska. Breast cancer does not occur in the pediatric age group.)

3.1.3 ECOG performance status of 0 or 1. (Appendix A)

3.1.4 At least one lesion that can be accurately measured in two dimensions utilizing mammogram, ultrasound, or MRI images to define specific size and validate complete clinical and pathologic response.

3.1.5 Patients who received radiation therapy > 5 years ago for malignancies other than breast cancer and whose radiation therapy field is not overlapping with the 20% isodose line of current radiation field are eligible, provided that radiation therapy was completed > 5 years ago and that there is no evidence of the second malignancy at the time of study entry.

3.1.6 Patients must have adequate laboratory parameters within 30 days prior to enrollment defined as:

- Absolute neutrophil count greater than or equal to 1,500/mcl
- Platelet count equal to or greater than 150,000/mcl
- Alkaline phosphatase equal or less than 1.5 times the ULN
- Total bilirubin equal to or less than 1.5 times the ULN
- AST and ALT no greater than 1.5 times the ULN
- Creatinine less than 1.5 times the ULN

3.1.7 All included patients must have normal cardiac function as defined by an ejection fraction of ≥50% and no decrease in wall motion by echocardiogram.

3.1.8 The patient must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.

3.1.9 Women of reproductive potential must be non-pregnant and non-nursing and must agree to employ an effective barrier method of birth control throughout the study and for up to 6 months following treatment.

3.1.10 Women of child-bearing potential must have a negative pregnancy test within 7 days of initiating study. *(No childbearing potential is defined as age 55 years or older and no menses for two years or any age with surgical removal of the uterus and/or both ovaries).*

**3.2 Exclusion criteria**

3.2.1 Any patient with inflammatory breast cancer or Stage IV or confirmed metastatic disease.

3.2.2 Patients who have had any prior chemotherapy, or endocrine therapy for the treatment of breast cancer or any other cancer.

3.2.3 Patients who cannot undergo surgery.

3.2.4 Patients with a known or documented anaphylactic reaction or allergy to any of chemotherapy agents used in this protocol, or to antiemetic's appropriate for administration in conjunction with protocol-directed therapy.

3.2.5 Uncontrolled inter-current illness including, but not limited to ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, or serious, uncontrolled cardiac arrhythmia, that might jeopardize the ability of the patient to receive the therapy program outlined in this protocol with reasonable safety.

3.2.6 Patients with preexisting Grade II peripheral neuropathy.

3.2.7 Pregnant and nursing women are excluded from this study because the chemotherapy agents and radiation therapy all have the potential for teratogenic or abortifacient effects.

3.2.8 Patients with prior malignancy will be excluded **except** for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas.

3.2.9 Inability to cooperate with treatment protocol.

3.2.10 Patients with known HIV infection, infectious hepatitis, type A, B or C, active hepatitis, or hepatic insufficiency.

3.2.11 Patients may not be receiving or have received any other investigational agents during/or within 1 month prior.

3.2.12 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3.2.13 Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (Appendix B) Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.

**NOTE:** All questions regarding eligibility for potential subjects should be directed to the UNMC Coordinator at 402-559-5582 or 402-559-5286.

## 4.0 REGISTRATION PROCEDURES

All patients with breast cancer or suspicious breast masses referred to the Nebraska Medical Center (NMC) / UNMC or other IRB approved participating sites may be eligible for this trial.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of encounter. On initial presentation, a history and physical examination are performed, laboratory data obtained, and performance status is assessed. Imaging studies obtained may include a high-resolution multi-detector computed tomography (CT) of the chest, abdomen and pelvis to evaluate as indicated for metastatic disease. Further imaging studies will be obtained as clinically indicated that may include but are not limited to MRI, Mammogram and Ultrasound. At least 1 lesion must be accurately measured bi-dimensionally. Any pathologic specimens obtained at referring institutions are reviewed for accuracy except for IRB centers participating in the study. Patients with suspicious breast masses will require breast biopsy for confirmation of malignancy. Biopsy techniques available include percutaneous and CT/ultrasound guidance. The patient's primary oncologist will make the decision as to screened eligibility of the candidate based on the eligibility criteria listed above, prior to offering consent.

Patients with Stage T1cN0 and Stage II-III breast adenocarcinoma screened as potentially eligible, will then be offered the option to participate in the treatment portion of this trial. More subjects will participate in this pre-therapy evaluation phase than will ultimately be found to be suitable candidates for the chemotherapy/radiation therapy. An informed consent will be signed by the patient after thorough review of the study is completed by the physician and his/her designee.

Patients with localized or locally advanced breast cancer will traditionally receive surgical treatment following neoadjuvant therapy. This treatment usually consists of a modified radical mastectomy combined with radiation therapy while patients who are down staged by the treatment may be treated with breast conserving surgery.

Some insurance carrier's may decline to cover the costs of usual medical care if the patient is participating in a clinical trial. The patient will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The patient can then decide if they wish to participate.

### 4.1 Eligibility Verification/Registration

Before patients are enrolled into the study, an eligibility checklist (Appendix C) must be completed to verify the subject meets the eligibility criteria and may be used as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician. Study personnel from non-UNMC IRB approved sites will contact the UNMC Research Project Coordinator if a non-UNMC patient appears to meet the eligibility criteria. They will scan and email the completed eligibility checklist (Appendix C) along with de-identified relevant source documents to the UNMC Research Coordinator to verify the subject meets the eligibility criteria. If the UNMC Research Coordinator confirms that the non-UNMC patient meets criteria, and target accrual has not been met, approval for the non-UNMC patient will be given. A confirmation of registration will be forwarded by the UNMC Research Project Coordinator.

Enrollment: Date of enrollment is defined as the date of the start of study treatment / first protocol related intervention. All eligibility criteria do not need to be met until the date of the first study related treatment. The eligibility check list will be maintained in the study file.

Registration: Eligibility verification and notification of assigned subject number (by UNMC) to

Participating Sites will be known as the registration date.

UNMC:

Study personnel from UNMC will provide the UNMC Fred & Pamela Buffett Cancer Center PRMS office an electronic copy of the signed and dated consent form for each UNMC subject enrolled in the protocol within one (1) week that includes the following information:

- Protocol Number
- Patient Identification: Patient's name study subject number
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity
- Subject zip code/country (if not USA) and primary method of payment information

Participating Sites:

The UNMC Fred & Pamela Buffett Cancer Center Protocol Review & Monitoring System (PRMS) Office Audit Committee defines a *Participating Site* as: a hospital clinic, or other provider of medical services who has agreed to participate in a therapeutic trial that has been designed and developed by a University

of Nebraska Medical Center/Nebraska Medical Center (UNMC/NMC) investigator and is sponsored by UNMC.

Participating/Collaborating sites must have local *and* UNMC IRB approval, and have met all other criteria to enroll. Study personnel from non-UNMC IRB approved sites will provide the UNMC Multi-site Project Manager with the following information:

- Registration request with Demographics cover sheet (located in the Study site Manual)
- Copy of the signed and dated consent form (subject signature obliterated with signature line and subject initials visible)
- Signed Eligibility Checklist

## 5.0 TREATMENT PLAN

This is a Phase II study of neo-adjuvant therapy using a dose-dense regimen of cyclophosphamide and paclitaxel with or without trastuzumab in patients with newly diagnosed stage T1cN0 or stage II-III breast cancer. This will be a non-randomized study; all patients will receive the combination chemotherapy. All subjects will receive the same doses of the active compound. Dose modifications for adverse events are described in Tables 1-5.

### 5.1 Diagnostic Biopsy (SOC)

- Pathology review
- Determination of ER, PR, HER2 status

### 5.2 Pre-treatment Evaluations

*Standard of Care (SOC)* No tests or procedures are conducted solely for the purposes of research to determine subject eligibility.

- History and physical
- CBC, diff, plt, CMET,
- Serum pregnancy test
- Height and weight
- Vital signs, including blood pressure
- ECOG Performance status

- Neuropathy Assessment worksheet NOTE: Coordinator to complete the neuropathy worksheet **(Appendix E)** with the subject**.**
- Echocardiogram
- Mammogram/MRI/US radiologic evaluations for staging (SOC)

**Biospecimen Samples (Mandatory)** *Solely for the purposes of research*

- A baseline **Blood Draw** of 30 ml including two – 10ml purple top tubes and one – 10ml red top tube for WBC DNA to identify possible gene expression profile signatures from whole genome array analysis that correlate with clinical response/resistance to chemotherapy as measured by pathologic complete response rate (pCR) will be obtained pre-chemotherapy**.**

  **SEE APPENDIX D** for instructions. Blood Samples to be sent overnight at room temp Monday through Thursday only; do not send the day before a holiday.

### 5.3 Administration Schedule

**All Patients will receive:**

Premedication: All patients will receive premedication for nausea and vomiting with appropriate anti-emetic regimens (SOC). Patients will receive diphenhydramine, ranitidine and dexamethasone prior to paclitaxel (SOC). Pre and post medications as prescribed by the treating physician.

Systemic Therapy (Medicare Qualifying research related combination chemotherapy):

- Paclitaxel 175mg/$m^2$ in normal saline intravenously (IV) over 3 hours Day 1 cycled every 14 days (2 weeks) for 6 cycles
- Cyclophosphamide 600mg/$m^2$ in normal saline IV over 1 hour Day 1 cycled every 14 days (2 weeks) for 6 cycles
- All cycles are with pegfilgrastim support 1-4 mg (optional with cycle 6) given by subcutaneous injection after PC chemotherapy. Dose adjust down for ANC>12,000. (SOC)

**Patients with Her-2 neu positive tumor will also receive trastuzumab (SOC):**

Loading Dose trastuzumab 6mg/kg in normal saline IV over 30 minutes Day 1, Cycle 1

THEN for Subsequent Cycles (Cycles 2-6), trastuzumab 4mg/kg in normal saline IV over 30 minutes Day 1 every 14 days (2 weeks) Cycles 2-6.

**Clinical Endpoint/Restaging Assessments**

**A dedicated Breast MRI and/or Ultrasound restaging assessment will be done following 6 cycles of treatment with paclitaxel and cytoxan and prior to surgery if deemed appropriate.** Restaging imaging may be omitted if the patient is having a planned mastectomy.

Patients without metastasis will undergo definitive **surgery**.

If no contraindication for surgical resection is identified, surgery will be performed 4-8 weeks after completing PC/PCH. All surgery will be performed with curative intent with resection of all gross tumor (i.e. R0 [negative margins]. Standardized histopathologic analysis of resected specimens will be performed. Examination of regional lymphatics will be performed according to standard pathology techniques.

**Pre-op Biospecimen Samples (Mandatory)** *Solely for the purposes of research*

- A pre-op **Blood Draw** of 30 ml including two – 10ml purple top tubes and one – 10ml red top tube for WBC DNA to identify possible gene expression profile signatures from whole genome array analysis that correlate with clinical response/resistance to chemotherapy as measured by pathologic complete response rate (pCR)will be obtained anytime post chemotherapy but before surgery**. (San Ming Wang, MD)**

  **SEE APPENDIX D** for instructions. Blood Samples to be sent overnight at room temp Monday through Thursday only; do not send the day before a holiday.

**Post-Surgery / Systemic Therapy (Medicare Qualifying research related combination chemotherapy):**

**HER2 positive patients:**

Upon recovery from surgery HER-2 positive patients will receive Radiation Therapy given by the radiation oncologist and timing determined by the radiation and medical oncologist as per standard NCCN guidelines, following mastectomy or patients who are down staged by the treatment may be treated with breast conserving surgery. See attached NCCN guidelines. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Patients with Her-2 positive cancer will also receive maintenance therapy with trastuzumab 6mg/kg in

normal saline IV over 30 minutes Day 1 every 21 days (3 weeks) to complete a total of 52 weeks (Cycles 7- 19) timing determined by the radiation and medical oncologist as per standard NCCN guidelines, following mastectomy or breast conserving surgery.

**Hormone Therapy in ER/PR positive patients:**

Patients with estrogen/progesterone receptor (ER/PR) positive tumors will receive adjuvant hormonal or endocrine therapy as determined by the medical oncologist per standard NCCN guidelines. See attached NCCN guidelines. Patients with estrogen/progesterone receptor positive tumors will receive Hormonal Therapy following adjuvant chemotherapy. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

**Stage T1cN0 Triple negative patients (HER2-, ER-, PR-) patients:**

Patients with Stage T1 cN0 Triple negative patients (HER2-, ER-, PR-) will receive Radiation Therapy given by the radiation oncologist and timing determined by the radiation and medical oncologist as per standard NCCN guidelines, following mastectomy or patients who are down staged by the treatment may be treated with breast conserving surgery. See attached NCCN guidelines. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

**Stage II-III Triple negative (HER2-, ER-, PR-) patients:**

Upon recovery from surgery, only Stage II-III triple negative patients (HER2-, ER-, PR-) will receive four cycles of chemotherapy with adriamycin 60mg/$m^2$ in normal saline IVP over 15 minutes on Day 1 cycled every 14 days (2 weeks) for 4 cycles (cycles 7-10). All cycles are with pegfilgrastim support 1-6 mg (optional with cycle 4) given by subcutaneous injection Patients will also receive Radiation Therapy given by the radiation oncologist and timing determined by the radiation and medical oncologist as per standard NCCN guidelines; following mastectomy or patients who are down staged by the treatment may be treated with breast conserving surgery. See attached NCCN guidelines. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

**End of Treatment/Post-Trial Assessments all patients:**

**Biospecimen Samples (Mandatory)** *Solely for the purposes of research*

- A **Blood Draw** of 30 ml including two -10ml purple top tubes and one -10ml red top tube for WBC DNA to identify possible gene expression profile signatures from whole genome array analysis that correlate with clinical response/resistance to chemotherapy as measured by pathologic complete response rate (pCR)will be obtained**.**

  **SEE APPENDIX D** for instructions. Blood Samples to be sent overnight at room temp Monday through Thursday only; do not send the day before a holiday.

**Follow-up (SOC):** All patients will then be followed at three month intervals for two years for safety and annually thereafter for disease recurrence and overall survival to end at 5 years from diagnosis. During the first two years of follow up, physical exam and other tests may be done as requested by the physician.

Patients who go off study treatment at any time during the trial will be followed for 30 days after the last day of treatment or until other disease-related treatment begins. For all patients, drug-related SAEs and AEs will be followed until baseline or ≤ grade 1 levels.

### 5.4 Evaluations during therapy *(SOC)*:

- Patients will have standard hematological and cardiac evaluations.
- Patients will be clinically evaluated by an oncologist during chemotherapy every 2 weeks for toxicities, vital signs, performance status, and neuropathy assessment worksheet. *Her-2 neu positive patients* will be monitored at least every 12 weeks after completing chemotherapy until they complete 52 weeks of trastuzumab and then every 3 months for 2 years. *Her-2 neu negative patients* will be monitored every 3 months after completing chemotherapy for 2 years.
- *Her-2 neu positive patients* will have a repeat echocardiogram every 12 weeks to monitor their cardiac function. Normal cardiac function is defined by an ejection fraction of ≥50% and no decrease in wall motion by echocardiogram.
- *Her-2 neu negative patients* will have a repeat echocardiogram at the end of chemotherapy to evaluate their cardiac function. Normal cardiac function is defined by an ejection fraction of≥50% and no decrease in wall motion by echocardiogram.

- Data will be collected on dose delays/reductions, hospitalizations, treatment discontinuation, deaths, and hematologic and cardiac toxicity.

### 5.5 Criteria for holding and resuming treatment

Treatment should be held until any non-hematologic grade 3-4 toxicities resolve to less than a grade 1 with dose modifications as per instructions below.

### 5.6 Dose Modifications

5.6.1 General instructions for dose modifications and delays

• The Common Terminology Criteria for Adverse Events Version 4.0 (Appendix F) must be used to grade the severity of adverse events (AEs).

• All doses should be based on the AE requiring the greatest modification.

• Doses that have been reduced may not be escalated.

• Proceeding with study therapy after grade 4 events, other than neutropenia/granulocytopenia and thrombocytopenia, is at the discretion of the physician.

5.6.2 Dose modifications and delays for cyclophosphamide and paclitaxel

All dose modifications for cyclophosphamide are based on the dose level changes in Table1.

**TABLE 1. Dose level changes for cyclophosphamide**

| | **Dose Level-0 *Starting Dose* ($mg/m^2$)** | **Dose Level-1 ($mg/m^2$)** | **Dose Level-2 ($mg/m^2$)** | **Dose Level-3** |
|---|---|---|---|---|
| **cyclophosphamide** | 600 | 500 | 400 | Discontinue |

All dose modifications and delays for paclitaxel are based on the dose level changes in Table 2

**TABLE 2. Dose level changes for paclitaxel**

| | **Dose Level-0 Starting Dose ($mg/m^2$)** | **Dose Level-1 ($mg/m^2$)** | **DoseLevel-2 ($mg/m^2$)** | **Dose Level-3 ($mg/m^2$)** | **Dose Level-4 ($mg/m^2$)** |
|---|---|---|---|---|---|
| **paclitaxel** | 175 | 175 | 135 | 135 | 100 |

Table 3 revised to align more clearly 7/17/12
Instructions for all other toxicities are listed on Table 3.

**TABLE 3. Dose modifications and delays for <u>cyclophosphamide and paclitaxel</u>**
Note: Dose modifications must be based on AE requiring the greatest modification; AEs observed during the cycle; ***and*** AEs present on the scheduled Cycle Day 1.

| **NCI CTCAE v4.0 Category/Grade (Gd)** | **Modifications for AEs that occurred during a cycle but <u>DID NOT</u> REQUIRE TREATMENT DELAY a** | **Modifications for AEs that REQUIRED TREATMENT DELAY b** |
|---|---|---|
| **Blood/bone marrow:** | | |
| **Neutrophils/granulocytes**<br>Grades 3 or 4 | Gd 3/4 -Maintain dose | **ANC:** Hold until ≥ 1000/mm$^3$<br>If recovery takes:<br>1 week – maintain dose<br>2 to 3 weeks – ↓ one dose level<br>> 3 weeks – D/C study therapy |
| **Platelets**<br>Grades 2 or 3<br><br><br><br>Grade 4 | Gd 2/3 -Maintain dose<br><br><br><br>Gd 4 -↓ one dose level | **Platelets**: Hold until ≥ 75,000/mm$^3$<br>If Gd 2 or 3 recovery takes:<br>≤ 1 week – maintain dose<br>2 to 3 weeks - ↓ one dose level<br>> 3 weeks – D/C study therapy<br><br>If Gd 4: ↓ one dose level<br>If Gd 4 recovery takes:<br>> 3 weeks, D/C study therapy |
| **GI (if related to chemotherapy)** | | |
| **Diarrhea**<br>Grade 2<br>Grade 3<br>Grade 4 | <br>Gd 2 -Maintain dose<br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C | <br>Gd 2 -↓ one dose level<br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C |
| **Mucositis/stomatitis**<br>Grade 2<br>Grade 3<br>Grade 4 | <br>Gd 2 -Maintain dose<br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C | <br>Gd 2 -↓ one dose level<br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C |
| **Vomiting (*despite antiemetics*)**<br>Grade 2<br>Grades 3 or 4 | <br>Gd 2 -↓ one dose level (optional)<br>Gd 3/4 -↓ two dose levels or D/C | <br>Gd 2 -↓ one dose level (optional)<br>Gd3/4 -↓ two dose levels or D/C |
| **Hepatic function:** | | |
| **Bilirubin**<br>**AST**<br>**alk phos**<br>Grade 2<br>Grade 3 | <br><br><br>Gd 2 -↓ one dose level<br>Gd 3 -↓ two dose levels | Hold until bilirubin returns to the baseline grade and AST / alk phos have returned to ≤ Gd 1 then:<br>Gd 2 -↓ one dose level<br>Gd 3 -↓ two dose levels |

| | | |
|---|---|---|
| Grade 4 | Gd 4 -D/C | Gd 4 -D/C |
| **Infection:** | | |
| **Febrile neutropenia**<br>Grade 3<br>Grade 4 | <br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C | <br>Gd 3 -↓ one dose level<br>Gd4 -↓ two dose levels or D/C |
| **Infection with grade 3 or 4 ANC**<br>Grade 3<br>Grade 4 | <br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C | <br>Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C |
| **Infection with normal ANC**<br>Grade 3<br>Grade 4 | <br>Gd 3 -Maintain dose<br>Gd 4 -↓ two dose levels or D/C | <br>Gd 3 -Maintain dose<br>Gd 4 -↓ two dose levels or D/C |
| **Other clinically significant AEs c** | | |
| Grade 3<br>Grade 4 | Gd 3 -↓ one dose level<br>Gd4 -↓ two dose levels or D/C | Gd 3 -↓ one dose level<br>Gd 4 -↓ two dose levels or D/C |

**a** Treatment may not proceed until toxicity is ≤ grade 1, except for neutrophils/ granulocytes, which must be ≥ 1000/mm$^3$ and bilirubin, which must be at or below the baseline grade.
**b** Hold and check weekly. With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue chemotherapy.
**c** Determination of "clinically significant" AEs is at the discretion of the investigator.

5.6.3 Management of paclitaxel-related hypersensitivity reactions
Management of paclitaxel-related hypersensitivity reactions is at the investigator's discretion.

5.6.4 Management of paclitaxel-related Neurosensory Toxicity and Musculoskeletal pain
Dose modifications for paclitaxel related neurosensory toxicity are outlined on Table 4.
Dose modifications for paclitaxel related musculoskeletal pain are outlined on Table 5.

**TABLE 4. Dose modifications for neurosensory toxicity related to the paclitaxel**

| **Paresthesias/Dysesthesias** | **1-7 Day Duration** | **Persistent for > 7 Days *or* Caused the Next Cycle to be Delayed** |
|---|---|---|
| **Grade 1** Paresthesias/dysesthesias of short duration that resolve and do not interfere with function | Maintain dose | Maintain dose |
| **Grade 2** Paresthesias/dysesthesias interfering with function, but not activities of daily living | Maintain dose **a** | Decrease ***paclitaxel*** to next lower dose. **b,c** |
| **Grade 3** Paresthesias/dysesthesias with pain or with function impairment that also interfere with activities of daily living | **First episode:** Decrease ***paclitaxel*** to next lower dose **a,c**<br><br>**Second episode:** Stop ***paclitaxel*** | Stop ***paclitaxel*** |
| **Grade 4** Persistent paresthesias/dysesthesias | Stop ***paclitaxel*** | Stop ***paclitaxel*** |

| | | |
|---|---|---|
| that are disabling or life-threatening | | |

**a** Use of narcotics and NSAIDs is encouraged to maintain dose of paclitaxel if possible.
**b** Consider modifying G-CSF.
**c** Decrease the paclitaxel to the *next lower dose*, e.g., for paclitaxel, from 175 mg/m$^2$ to 135 mg/m$^2$ or from135 mg/m$^2$ to 100 mg/m$^2$. (Note that, the paclitaxel dose does not always decrease by one dose level; therefore, reducing the paclitaxel dose may mean adjusting by more than one dose level increment. Refer to Table 2.)

**TABLE 5. Dose modifications for musculoskeletal pain attributed to the paclitaxel and *not controlled by analgesics (*a)**

| **Musculoskeletal Pain** | **1-7 Day Duration** | **Persistent for > 7 Days *or* Caused Next Cycle to be Delayed** |
|---|---|---|
| **Grade 1** | Maintain dose | Maintain dose |
| **Grade 2** | Maintain dose | Maintain dose<br>OR<br>Decrease ***paclitaxel*** to next lower dose **b,c** |
| **Grade 3** | **First episode:**<br>Decrease the ***paclitaxel*** to next dose **b,c**<br><br>**Second episode:**<br>Stop the ***paclitaxel*** | **First episode:**<br>Decrease ***paclitaxel*** to next lower dose **b,c**<br>OR<br>Stop ***paclitaxel***<br><br>**Second episode:**<br>Stop ***paclitaxel*** |
| **Grade 4** | Stop the ***paclitaxel*** | Stop ***paclitaxel*** |

**a** Use of narcotics and NSAIDs is encouraged to maintain dose of paclitaxel if possible.
**b** Consider modifying G-CSF.
**c** Decrease the paclitaxel to the *next lower dose*, e.g., for paclitaxel, from 175 mg/m$^2$ to 135 mg/m$^2$ or from135 mg/m$^2$ to 100 mg/m$^2$. (Note that, the paclitaxel dose does not always decrease by one dose level; therefore, reducing the paclitaxel dose may mean adjusting by more than one dose level increment. Refer to Table 2.)

### 5.7 Criteria for Removal from Study

5.7.1 Progression of Disease

5.7.2 If at any time the constraints of this protocol are detrimental to the patient's wellbeing, or if the patient is unable to comply with the requirements of the protocol, the patient will be removed from protocol therapy. In this event, the reason(s) for withdrawal will be documented.

5.7.3 If the patient experiences an adverse reaction that, in the opinion of the investigator, necessitates the removal of the patient from the study, including any unresolved serious adverse event.

5.7.4 Any patient who suffers a serious systemic allergic response or severe degree of intolerance to the study medication will be withdrawn from further study treatment but will be followed up for a period of two years following treatment.

5.7.5 Development of intercurrent medical problems that would make continued protocol therapy detrimental to the patient's safety.

5.7.6 There is concurrent illness or other reasons that would, in the opinion of the investigator, affect assessment of clinical status or conduct of the study to a significant degree.

5.7.7 The patient completes study treatment as per study schedule.

5.7.8 The patient chooses to discontinue treatment or follow-up. In this event, the reason(s) for withdrawal will be documented.

### 5.8 Removal of subject from Study Therapy

The reason(s) for withdrawing the patient from the treatment portion of the study will be documented in the case report form. Where possible and feasible, patients who received at least one dose of study drugs should be subjected to the procedures scheduled at the end of the study and should be submitted to the follow up to assess disease progression. If available, the following information will be recorded in the case report form: date of disease relapse, date of death, cause of death, and autopsy report.

## 6.0 Measurement of Effect

### 6.1 Tumor Response

The primary endpoint is pathological complete response (pCR) which is defined as the absence of invasive carcinoma in both the breast and axilla at microscopic examination of the resection specimen, regardless of the presence of carcinoma in situ. Partial response is defined as decrease in longest tumor diameter or RCB1as defined using the online calculator at http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3., a secondary endpoint for neo-adjuvant chemotherapy patients.

### 6.2 Response criteria

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")

- If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross-sectional area of primary tumor bed were submitted in cassettes A5 - A9")

3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

- 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%
  - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
  - When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
  - Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.
  - e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

4. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:

- 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

5. The number of positive (metastatic) lymph nodes
6. The largest diameter (mm) of the largest nodal metastasis

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**Residual Cancer Burden Calculator**

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3:

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*Values must be entered into all fields for the calculation results to be accurate.

***(1) Primary Tumor Bed***

Primary Tumor Bed Area: _____ (mm) X ____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

***(2) Lymph Nodes***

Number of Positive Lymph Nodes: ____
Diameter of Largest Metastasis: ____ (mm)

Residual Cancer Burden: _____
Residual Cancer Burden Class: _____

### 6.3 Toxicity criteria

The NCI Common Toxicity Criteria Adverse Events Version 4.0 will be used to grade toxicity; it is available at the following internet site: http://ctep.cancer.gov/forms/CTCAEv4.pdf.

## 7.0 Study Parameters

| | Screening Staging **BASELINE** | Cycle1 | | Cycle2 | | Cycle3 | | Cycle4 | | Cycle5 | | Cycle6 | | CLINICAL ENDPOINT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnostic BIOPSY Pathology review | X | | | | | | | | | | | | | |
| ER/PR/HER2 status | X | | | | | | | | | | | | | |
| Staging Mammogram, MRI, US as necessary (may be omitted after chemo prior to surgery in the case of planned mastectomy) | X | | | | | | | | | | | X after chemo prior to surgery | | |
| **Chemotherapy Regimen** | | Day1 | | Day1 | | Day1 | | Day1 | | Day1 | | Day1 | | |
| ALL PATIENTS = PC Paclitaxel, Cyclophosphamide | | X | | X | | X | | X | | X | | X | | |
| Pegfilgrastim support (optional following cycle 6) | | | X | | X | | X | | X | | X | | X | |
| PATIENTS WITH HER-2 NEU POSITIVE TUMOR = *PCH, | | | | | | | | | | | | | | |
| H - Herceptin® (Trastuzumab) loading dose | | X | | | | | | | | | | | | |
| H - Herceptin® (Trastuzumab) maintenance | | | | X | | X | | X | | X | | X | | |
| **Blood Draw for Research(Res)** 2-10ml EDTA and 1-10ml Red | X prior to chemo | | | | | | | | | | | X after chemo prior to surgery | | |
| **Surgery** | | | | | | | | | | | | | | X |
| History | X | | | | | | | | | | | | | |
| Physical examination | X | Every 2 weeks | | | | | | | | | | | | |
| Vital signs, including BP | X | Every 2 weeks | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | |

| | | |
|---|---|---|
| Weight | X | Every 2 weeks |
| Performance status (ECOG) | X | Every 2 weeks |
| Neuropathy Assessment worksheet | X | Every 2 weeks |
| CBC, diff, Plt | X | Every 2 weeks |
| Comprehensive metabolic panel (including, alk phos) | X | Every 2 weeks |
| Echocardiogram | X | End of Chemotherapy Cycle 6 |

**ALL PATIENTS = PC Paclitaxel** 175mg/$m^2$ in normal saline IV over 3 hrs **/ Cyclophosphamide** 600mg/$m^2$ in normal saline IV over 1 hr REPEAT Day 1 Q 2wks x 6 cycles (Cycles 1-6), **Pegfilgrastim** support 1-4 mg (optional with cycle 6) SQ after PC dose adjust down or hold for ANC >12,000 or bone pain (SOC)

**PATIENTS WITH HER-2 NEU POSITIVE TUMOR = *PCH - Paclitaxel/Cyclophosphamide** REPEAT Day 1 Q 2wks x 6 cycles (Cycles 1-6), **Pegfilgrastim support 1-4mg (optional with cycle 6)** SQ after PC **, H - Herceptin® (Trastuzumab)** loading dose 6mg/kg Day 1, Cycle 1THEN subsequent dosing 4mg/kg Day 1 Q2wks Cycles 2-6, (SOC)

****Post-operative RECOVERY / ** Post-restaging:**

Start when the clinician's determine that the patient has recovered from surgery

| ****Post-operative RECOVERY/**Post-restaging** | SOC | Cycle7 | | Cycle8 | | Cycle9 | | Cycle10 | | | End of Treatment | Follow-Up Every 3 months for 2 years | Survival and disease recurrence Follow-up to 5 years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Triple NEG Stage II-III patients only** Chemotherapy Regimen Adriamycin | | Day1<br>X | | Day1<br>X | | Day1<br>X | | Day1<br>X | | | | | |
| Pegfilgrastim support (optional following cycle 4) | | | X | | X | | X | | X | | | | |
| **ALL PATIENTS WITH HER-2 NEU POSITIVE TUMOR** H - Herceptin® (Trastuzumab) maintenance every 21 days for a total of 52 weeks | X | | | | | | | | | | | | |
| **PATIENTS WITH ER/PR + TUMOR** = HORMONAL THERAPY | X | | | | | | | | | | | | |
| **ALL Patients** Radiotherapy (per clinical decision/NCCN guidelines) | X | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Blood Draw for Research(Res)** 2-10ml EDTA and 1-10ml Red | | | | | | | | | | | X | | |
| Physical examination | X | SOC | | | | | | | | | | X | |
| Weight | X | SOC | | | | | | | | | | X | |
| CBC, diff, Plt | X | SOC | | | | | | | | | | X | |
| Comprehensive metabolic panel (including, alk phos) | X | SOC | | | | | | | | | | X | |
| Echocardiogram | | HER2 positive echo every 12 weeks until complete 52 weeks of trastuzumab | | | | | | | | | | | |
| Mammogram, MRI, US as necessary | | SOC | | | | | | | | | | | |
| CT Chest/abdomen/pelvis with oral/IV contrast | | SOC | | | | | | | | | | | |
| Survival and disease status assessment | | | | | | | | | | | | | X |

**TRIPLE NEGATIVE PATIENTS (HER2 - ER- PR-) = Adriamycin** 60mg/$m^2$ in normal saline IV Q2wks x 4 cycles (Cycles 7-10) , **Pegfilgrastim** support 1-6 mg SQ (optionial with cycle 4)

**ALL PATIENTS WITH HER-2 NEU POSITIVE TUMOR** ****Maintenance Herceptin®** 6mg/kg Day 1 Q21 Days for a total of 52 weeks. (SOC)
**PATIENTS WITH ER/PR + TUMOR = HORMONAL THERAPY** Patients with **estrogen/progesterone receptor positive** tumors will also receive Hormonal Therapy to be determined by the medical oncologist as per standard NCCN guidelines. (SOC)
**RADIATION Clinical Decision** per standard NCCN guidelines, following chemotherapy. (SOC)
**End of Treatment Follow-up (F/U)** (All subjects)
Research Serum Samples collected at end of treatment (Res)
Patients will be followed Q3 months until 2 years from end date of study treatment. (SOC). After 2 years follow up, patients will be followed annually for disease recurrence and overall survival to end after 5 years from diagnosis.

## 8.0 Drug Formulation and Procurement

### 8.1 Trastuzumab (Herceptin)

8.1.1 Form: herceptin for injection

8.1.2 Preparation: Supplied as 440mg lyophilized Powder.

8.1.3 Dilution: Reconstitute with 20ml SWFI (sterile water for injection) or BWFI (bacteriostatic water for injection); dilute with NS to a concentration of 21mg/ml. DO NOT USE D5W.

8.1.4 Storage and Stability: Refrigerate vials, do not freeze.

8.1.5 Method of Administration: Loading dose: 6 mg/kg IV over 30 minutes. Subsequent dose: 4 mg/kg IV over 30 minutes. Maintenance dose: 2mg/kg IV over 30 minutes weekly.

8.1.6 Precautions: Benzyl alcohol hypersensitivity: use SWFI for reconstitution. Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction, congestive heart failure/ventricular dysfunction. Treatment discontinuation should be considered. Prior/concurrent AC or radiation to the chest may enhance the risk of cardiotoxicity.

8.1.7 Clinical Toxicities: Hypersensitivity reactions, including fatal anaphylaxis. Infusion reactions, including some with a fatal outcome. Trastuzumab may exacerbate chemotherapy induced neutropenia or anemia. May also cause diarrhea, cardiomyopathy, infusion associated symptoms, hypersensitivity reactions, changes in kidney function, pulmonary events such as ARDS, bronchospasm, pneumonitis. May cause "flu-like symptoms" with generalized aches and pains, headache, fever, chills, nausea, vomiting and diarrhea.

8.1.8 Commercial Availability: This drug is commercially available.

**8.2 Pegfilgrastim** (per Micromedex®) Other names: Neulasta

8.2.1Classification
Colony stimulating factor, hematopoietic

8.2.2 Mode of Action
Systemic: Pegfilgrastim is a Colony Stimulating Factor that acts on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

8.2.3 Storage and Stability
The manufacturer recommends storage of Neulasta(TM) syringes at 2 to 8 degrees C (36 to 46 degrees F), avoidance of freezing or shaking, and leaving syringes in the carton provided until time of use to protect from light (Prod Info Neulasta(TM), 2000).

Syringes of Neulasta(TM) can reach room temperature for up to 48 hours prior to use; during this time, they should be protected from light. Syringes left at room temperature for longer than 48 hours should be discarded (Prod Info Neulasta(TM), 2000).

If syringes are accidentally frozen, thawing under refrigeration is acceptable prior to use. However, syringes should be discarded if accidentally frozen a second time (Prod Info Neulasta(TM), 2000).

8.2.4 Known Clinical Toxicities

**COMMON** Gastrointestinal: Nausea and vomiting
Musculoskeletal: Bone pain
Other: Influenza-like illness

**SERIOUS** Hematologic: Hemoglobin SS disease with crisis
Respiratory: Acute respiratory distress syndrome
Other: Rupture of spleen (rare)

8.2.5 Supplier
AMGEN

8.2.6 Commercial Availability
This drug is commercially available

**8.3 Cyclophosphamide** per Micromedex®) Other names: Cytoxan, Cytoxan Lyophilized

8.3.1 Classification
Alkylating Agent, Antineoplastic Agent, Nitrogen Mustard

8.3.2 Mode of Action
Cyclophosphamide is classed as an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide, phosphoramide mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as to inhibition of protein synthesis. Cyclophosphamide is a potent immunosuppressant. It also causes marked and persistent inhibition of cholinesterase activity.

8.3.3 Storage and Stability
1) Intravenous Powder for Solution: 1 GM, 2 GM, 100 MG, 200 MG, 500 MG)

2) Reconstituted solutions of lyophilized cyclophosphamide are chemically and physically stable for 24 hours at room temperature or for 6 days in the refrigerator. Specific temperatures are not provided by the manufacturer (Prod Info Cytoxan(R), 2000a; Brooke et al, 1973).

3) The rate of dissolution is occasionally slow (10 to 15 minutes) due to various crystal forms. Warming the solution to 50 or 60 degrees Celsius for 15 minutes may improve dissolution with negligible decomposition. However, heating to 70 to 80 degrees Celsius for 15 minutes has resulted in 10% to 23% loss of potency. Lyophilized cyclophosphamide for injection has a rapid dissolution rate with no warming needed (Brooke et al, 1975).

4) Reconstitution of cyclophosphamide with bacteriostatic water containing benzyl alcohol preservative may result in decomposition (Brooke et al, 1973

8.3.4 Known Clinical Toxicities

**COMMON** Dermatologic: Alopecia Gastrointestinal: Nausea and vomiting Hematologic: Leukopenia Reproductive: Amenorrhea**SERIOUS** Cardiovascular: Cardiomyopathy Dermatologic: Stevens-Johnson syndrome, Toxic epidermal necrolysis (rare) Renal: Hemorrhagic cystitis Reproductive: Azoospermia, Oligozoospermia Respiratory: Interstitial pneumonia Other: Infectious disease

8.3.5 Supplier
Bristol-Myers Squibb

8.3.6 Commercial Availability
This drug is commercially available

**8.4 Paclitaxel** (per Micromedex®) Other names: Taxol, Onxol, Nov-Onxol, Paclitaxel Novaplus

8.4.1 Classification
Antineoplastic Agent, Mitotic Inhibitor

8.4.2 Mode of Action
Paclitaxel belongs to the class of medications known as antimicrotubule agents. It promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or 'bundles' of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. Paclitaxel enhances the cytotoxic effects of ionizing radiation in vitro.

8.4.3 Storage and Stability
1) Intravenous Solution: 6 MG/ML
2) Paclitaxel vials should be stored between 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit)) in the original containers protected from light. Refrigeration or freezing will not adversely affect the product. If a precipitate forms upon refrigeration, allow the vial to come to room temperature and the precipitate will dissolve with little or no agitation (Prod Info Taxol(R), 2000c).

3) Paclitaxel solutions prepared in 5% dextrose or 0.9% sodium chloride in concentrations of 1.2 mg/mL, leached diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags at 1, 2, 4, and 8 hours (DEHP range of 50 to 208 micrograms/mL). Leaching also occurred after simulated three-hour infusions. In all tested conditions, leaching was primarily due to the lipophilic vehicle. The highest amount of DEHP leached by the vehicle was 83 mcg/mL at 8 hours, with a 1.2 mg/mL 0.9% sodium chloride solution, stored at 20 to 22 degrees Celsius. Leaching of DEHP, a commonly used plasticizer in PVC bags, increased with time and was independent of the brand of PVC infusion materials. When compared to docetaxel, paclitaxel leached two to eight times more DEHP from the PVC infusion materials (Mazzo et al, 1997).

4) Extended-stability paclitaxel admixtures containing 1 mg/mL paclitaxel in 5% dextrose injection with the addition of sterile, dehydrated alcohol injection to yield a 20% or 25% ethanol concentration was found to be physically stable for at least 7 days as compared to conventional paclitaxel admixtures. Extended-stability paclitaxel 1 mg/mL containing 25% ethanol was also able to maintain a low concentration of bacteria, yeast and molds throughout the 28-day

antimicrobial preservatives effectiveness test period demonstrating its low potential for contamination during long-term continuous infusion (Trissel et al, 1997a).

5) Stability studies have demonstrated that paclitaxel, in concentrations of 0.3 to 1.2 milligrams/milliliter is stable for 24 hours at room temperature in Dextrose 5% in water or Sodium chloride 0.9% (Waugh et al, 1991).

8.4.4 **Black Box Warning**

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H(2) antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm(3). In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

8.4.5 Known Clinical Toxicities

**COMMON** Dermatologic: Alopecia
Gastrointestinal: Nausea and vomiting
Hepatic: Liver function tests abnormal
Musculoskeletal: Arthralgia, Myalgia
Neurologic: Peripheral neuropathy
**SERIOUS** Cardiovascular: Coronary artery stent thrombosis (late (> 1 year), 0.7%), Hypotension (12%) bradycardia
Hematologic: Myelosuppression, Neutropenic disorder
Immunologic: Anaphylaxis (2-4%), Immune hypersensitivity reaction

8.4.6 Supplier

Abbott Laboratories

8.4.7 Commercial Availability

This drug is commercially available

**8.5 Doxorubicin** (per Micromedex®) Other names: **Adriamycin**

8.5.1 Classification

Anthracycline , Antineoplastic Agent

8.5.2 Mode of Action

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic thought to act on malignant cells by intercalating the cell nucleotide base and binding the cell membrane lipid. Intercalation

blocks replication of nucleotide and action of DNA and RNA polymerases. It also interacts with topoisomerase II to form DNA-cleavable complexes, which is believed to be an important mechanism of its cytocidal activity .

8.5.3 Storage and Stability

1) Intravenous Powder for Solution: 10 MG, 20 MG, 50 MG, 100 MG, 150 MG , Intravenous Solution: 2 MG/ML

2) STABILITY IN ADMINISTRATION CONTAINERS

a) Doxorubicin 8 milligrams/500 milliliters glucose 5% was stable for 7 days when stored in PVC (polyvinyl chloride) bags at 4 degrees Celsius with light protection. There was also no loss of doxorubicin when infused via PVC infusion bags with PVC administration sets (Dine et al, 1992).

b) Doxorubicin 2 milligrams/milliliter was stable for up to 14 days at 3 or 23 degrees Celsius and for an additional 28 days at 30 degrees Celsius in portable pump reservoirs (Stiles & Allen, 1991).

c) Doxorubicin was stable (less than 10% loss of potency) for 24 days in 0.9% sodium chloride stored at 25 degrees Celsius in PVC (polyvinyl chloride) minibags and syringes at a pH of 6.47. Also, doxorubicin was stable for at least 43 days in 0.9% sodium chloride (pH, 6.47) and 5% dextrose (pH, 4.36) at 4 and -20 degrees Celsius (Wood et al, 1990).

8.5.4 **Black Box Warning**

Severe local tissue necrosis will occur if there is extravasation during administration. Doxorubicin must not be given by the intramuscular or subcutaneous route.

Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1% to 2% at a total cumulative dose of 300 mg/m(2) of doxorubicin, 3% to 5% at a dose of 400 mg/m(2), 5% to 8% at 450 mg/m(2) and 6% to 20% at 500 mg/m(2). The risk of developing congestive heart failure (CHF) increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m(2). Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.

Secondary acute myelogenous leukemia (AML) has been reported in patients treated with anthracyclines, including doxorubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging anti-neoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The rate of developing treatment-related leukemia was estimated in an analysis of 1474 breast cancer patients who received adjuvant treatment with doxorubicin-containing regimens (i.e., FAC) in clinical trials. The estimated risk of developing treatment-related leukemia at 10 years was 2.5% for the 810 patients receiving radiotherapy plus

chemotherapy and 0.5% for the 664 patients receiving chemotherapy alone. The overall risk was estimated at 1.5% at 10 years for the entire patient population. Pediatric patients are also at risk of developing secondary AML.

8.5.5 Known Clinical Toxicities

**COMMON**

- Dermatologic: Alopecia
- Gastrointestinal: Nausea, Vomiting
- Expect urine discoloration (red) for 1 to 2 days after therapy

**SERIOUS**

- Cardiovascular: Cardiac dysrhythmia, Congestive heart failure
- Hematologic: Myelosuppression

8.5.6 Supplier

Pharmacia & Upjohn

8.5.7 Commercial Availability

This drug is commercially available

## 9.0 Toxicity Reporting Guidelines

Reporting only for PC/PCH Adriamycin – Herceptin "study medication" until 30 days after last administration of study medication.

No surgery, hormonal or radiation related AE's will be recorded or reported.

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/ Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional IRB and FDA guidelines for the toxicity reporting.

All patients will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication.

Per NCI guidelines, adverse event (AE) and serious adverse events (SAEs) will be graded. Toxicity will be assessed using the NCI CTCAE Version 4.0 (Appendix F). AEs and SAEs will be followed until resolution, baseline or ≤ grade 1 levels.

Serious adverse events should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC.

### 9.1 Definitions

**Adverse Event**

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject

administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 5.0, Treatment Plan) and/or if the investigator considers them to be adverse events.

**Unexpected Adverse Event**

An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

**Serious Adverse Event**

A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- ☐ Results in death
- ☐ Is a serious threat to life, health, safety or welfare of subject [1]
- ☐ Requires inpatient hospitalization or prolongation of existing hospitalization
- ☐ Persistent or significant disability or incapacity[2]
- ☐ Is a congenital anomaly or birth defect
- ☐ Another serious important medical event[3]
- ☐ Any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- ☐ The rights, safety, or welfare of subjects is seriously jeopardized

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

## 9.2 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and FRED & PAMELA BUFFETT CANCER CENTER Data and Safety Monitoring Committee (DSMC)

### 9.2.1 IRB REPORTING

All internal adverse events (AE) will be reported to the local IRB promptly per institutional human research protection program policies.

### 9.2.2 Fred & Pamela Buffett Cancer Center DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

In its initial review, the DSMC will make a recommendation for the frequency of monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy. Reporting of the following will be done in accordance with DSMC guidelines:

- All serious adverse events (expected or unexpected, regardless of attribution) and toxicities will be reported to the DSMC
- All adverse events (AE) $\geq$ grade 3 will be reported to the DSMC.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

**Not related:** The subject was not exposed to the study treatment or another cause is obvious.

**Probably not related:** The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

**Possibly related:** Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

**Probably related:** Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

**Definitely related:** There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.0).

AEs will be collected from the time the subject signs the consent form and ending 30 days following the final chemotherapy. All AEs will be followed until resolution or a cause is identified. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final chemotherapy.

Surgical, hormonal, and radiation related Adverse Experiences (AE's) or Serious Adverse Experiences (SAE's) will NOT be collected. However, per the UNMC DSMC, any grade 4 and above non-hematologic toxicities (expected or unexpected, regardless of attribution) will be collected and reported to the UNMC DSMC.

All SAE and AE reporting will be completed using DSMC approved forms. Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

9.2.3 Food and Drug Administration (FDA) Reporting
It is the responsibility of the sponsor-investigator to submit to the FDA IND Safety Reports in accordance with 21 CFR 312.32. In addition the sponsor-investigator must notify the Ethics Review Committee/Institutional Review Board (EC/IRB) of a serious adverse event in writing in accordance with international and local laws and regulations. SAEs not meeting expedited criteria will be made available to FDA by the sponsor-investigator via the annual report. The Investigator will utilize the FDA MedWatch Form (Appendix G) for the reporting of adverse events and follow up information to those events. The form can be found at the following URL: http://www.fda.gov/medwatch

## 9.3 Auditing

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee will review this protocol on at least an annual basis.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

For participating site(s) that are NCI Cancer Centers, the protocol specific finding of the participating site's Audit Committee will be submitted to the UNMC Audit Committee for review on a schedule to be determined by the UNMC Audit Committee. For participating site(s) that are not NCI Cancer Centers, the audit process will be established by the UNMC Audit Committee on a site-by-site basis.

Adverse events will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC). The DSMC will also monitor the protocol on at least a quarterly basis and as per the DSMC request via the regularly scheduled DSMC review process.

Detailed policy and procedures for this section may be reviewed at: http://www.unmc.edu/ccto.

### 9.4 Monitoring

9.3.1 Various methods will be implemented by the sponsor to exchange information with participating sites:

- Site Initiation/Orientation
- Regular Teleconferences including group wide progress within the agenda
- Investigator meetings as feasible (remote or TBA, possibly in conjunction with larger meetings)
- Email distributions/reports as needed

9.4.2 Ongoing safety monitoring for all the subjects in this study:

All participating sites are required to execute a data compliance policy agreement. UNMC will monitor the data of participating sites in adherence to applicable research regulations, the protocol, and the policy agreement. De-identified source documents which support data entered must be provided to the sponsor by mail, fax, or electronic means for centralized compliance monitoring.

## 10.0 STATISTICAL CONSIDERATIONS

Study Design: This is an open-label, single arm trial in subjects with histologically proven invasive breast cancer and a clinical tumor classification of T1cN0 or Stage II-III.

### 10.1 Primary End Point

The primary endpoint is pathological complete response (pCR) after the first six cycles of PC or PCH. Pathological complete response is determined form the surgical specimen and is defined as the absence of invasive carcinoma in both the breast and axilla at microscopic examination of the resection specimen, regardless of the presence of carcinoma in situ.

### 10.2 Safety Endpoints

Overall incidence and severity of toxicities.

**10.3 Secondary End Points**

- Failure –free survival
- Overall survival
- Research blood specimens, to identify possible gene expression profile signatures from whole genome array analysis that correlate with clinical response/resistance to chemotherapy as measured by pathologic complete response rate (pCR)

**10.4 Sample Size – 125 subjects**

The pathological complete response rate is expected to be 13%. Under the null hypothesis, the pCR rate is 13%. It is important to protect against the possibility that neoadjuvant chemotherapy with and without Trastuzumab will produce a pCR rate greater than 13%. A reduction in the pCR rate to 7% will be considered unacceptable. With accrual of 112 subjects, the study will have 90% power at the 0.20 level of significance (one-sided) to detect a decrease in the pCR rate to 7% using a one-sample Binomial test. Assuming a 10% withdrawal rate, the sample size will be increased to 125.

**10.5 Planned Analyses for Primary Endpoint**

The primary endpoint is the pCR rate after the first six cycles of PC or PCH. The pCR rates and exact one-sided 80% confidence intervals will be calculated. The primary analysis is based on the full analysis set (all treated patients). The pCR rates will be summarized overall and for HER+ and HER- subsets.

**10.6 Planned Analysis for Safety Endpoints**

Adverse events will be tallied for overall frequency (number and percentage of subjects), worst reported severity, and relationship to study drugs. Serious adverse events will be summarized similarly. Listings of deaths, SAEs and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided. Analyses will be reported overall and for HER+ and HER- subsets.

**10.7 Planned Analysis for Endpoints**

- Failure –free survival (FFS) will be defined as the date of administration of study drug to the date of first appearance of tumor lesions by imaging, or death. Patients who are lost to follow-up will be censored at the date they were last known to be alive. The analysis will be based on Kaplan-Meier estimates. FFS will be summarized overall and for HER+ and HER- subsets.
- Overall survival will be measured from the date of the date of administration of study drug to the date of death from any cause. Patients who are lost to follow-up will be censored at the date they were last known to be alive. The analysis will be based on Kaplan-Meier estimates. OAS will be summarized overall and for HER+ and HER- subsets.
- This study will carry out whole genome exome sequencing at depth to uncover mutations in the protein coding region in the genome, followed by rapid testing of the functional significance of genes using a unique human in vitro culture model. These studies are aimed to identify and/or cross validate a unique set of classifier genes that will accurately predict a complete Pathologic Response (pCR) to treatment with dose dense CT in the neoadjuvant setting. We hypothesize that if the subset of patients with complete pathologic response could

be identified by a genomic signature then the remaining patients would best be suited to treatment with an alternative regimen, allowing development of a new stratification methodology to guide therapeutic interventions.

Tests to be performed with HBM:

Exome sequencing through Illumina Genome Analyzer GAIIx as 2x 76-bp paired-end reads, following Illumina sequencing protocol.

DNA sequences will be aligned to the human reference genome sequences hg19 using Bowtie or MAQ. Potential single-nucleotide variants, deletions and insertions will be identified using BMA tool of MAQ or SAMtools. RNA will be used for validation for the mutated genes by using targeted, RT-PCR/Sanger sequencing methods.

The data of this study will be used for a NIH application for a validation study. There are no plans for disclosure of the marker results since this is a pilot/ discovery study.

Lymphocytes from the sample provides a source of DNA. This DNA will be extracted by the UNMC Dept. Genetics, Cell Biology & Anatomy laboratory personnel. The specimen is sent to the genetics laboratory without any personal identifying information such as name or date of birth; it is identified by an ID number assigned for the study. This ID number is linkable to personal identifying information and individual clinical findings. Summaries of this information, stripped of personal identifiers, are provided to the genetics laboratory.

The following clinical data will be collected:

- Patient demographics (age, sex,)
- Clinical and pathologic information
- Staging and other prognostic indicators
- Family history of cancers. Information about cancer family history is generally available in the patient's medical records and will be recorded as First Degree (father, mother, brothers, sisters, children) or Second Degree (aunts, uncles, grandfathers, grandmothers, grandchildren, nieces, nephews, half-brothers, half-sisters).

The proposed study is conducted to identify potential mutated genes. The number of the identified mutated genes, the frequency of each gene being validated by RT-PCR/Sanger sequencing method, and the functions of these identified genes will be descriptively summarized. Up to 125 subjects/samples will be enrolled/collected.

**10.8 Interim Analysis**

pCR: Two interim monitoring analyses for the pCR rate, using a one-sample Binomial test against a fixed null hypothesis of p=0.13, will be conducted after 42, and 84 patients have completed after the first six cycles of PC or PCH. The monitoring p-values to be used for the 2 interim analyses are p=.02644 and p=0.10871, with the final analyses at p=0.16592. These results assume that 3 sequential tests are made using the O'Brien-Fleming spending function truncated at 3 standard

deviations to determine the test boundaries. These p-values define the following interim stopping rules:

- After testing the regimen on 42 patients, the trial will be terminated if 1 or fewer achieve pCR. If 2 or more patients have achieved pCR, the trial will continue.
- After testing the regimen on 84 patients, the trial will be terminated if 7 or fewer achieve pCR. If 8 or more patients have achieved pCR, the trial will continue.
- At the final analysis, after testing the regimen on 125 patients, the regimen will be rejected if 12 or fewer patients have achieved pCR.

Neutropenic fever: Two interim analyses will be performed after 42, and 84 patients have patients have been off of their last cycle of chemotherapy for 2 weeks. It is important to protect against the possibility that neoadjuvant chemotherapy with and without Trastuzumab will produce a proportion with neutropenic fever greater than 11%. The proportion with neutropenic fever will be tested against a fixed null hypothesis of 11% at the one-sided 0.10 level of significance using a one-sample Binomial test. The monitoring p-values to be used for the 2 interim analyses are p=.00439 and p=0.04256, with the final analyses at p=0.08701. These results assume that 3 sequential tests are made using the O'Brien-Fleming spending function truncated at 3 standard deviations to determine the test boundaries. These p-values define the following interim stopping rules:

- After testing the regimen on 42 patients, the trial will be terminated if 10 or more patients experience neutropenic fever. If 9 or fewer patients experience neutropenic fever, the trial will continue.
- After testing the regimen on 84 patients, the trial will be terminated if 15 or more patients experience neutropenic fever. If 14 or fewer patients experience neutropenic fever, the trial will continue.
- At the final analysis, after testing the regimen on 125 patients, the regimen will be rejected if 19 or more patients experience neutropenic fever.

Neurotoxicity: Two interim analyses will be performed after 42, and 84 patients have patients have been off of their last cycle of chemotherapy for 2 weeks. It is important to protect against the possibility that neoadjuvant chemotherapy with and without Trastuzumab will produce a proportion with $\geq$ Grade III neurotoxicity greater than 11%. The proportion with neurotoxicity will be tested against a fixed null hypothesis of 11% at the one-sided 0.10 level of significance using a one-sample Binomial test. The monitoring p-values to be used for the 2 interim analyses are p=.00439 and p=0.04256, with the final analyses at p=0.08701. These results assume that 3 sequential tests are made using the O'Brien-Fleming spending function truncated at 3 standard deviations to determine the test boundaries. These p-values define the following interim stopping rules:

- After testing the regimen on 42 patients, the trial will be terminated if 10 or more patients experience $\geq$ Grade III neurotoxicity. If 9 or fewer patients experience neurotoxicity, the trial will continue.
- After testing the regimen on 84 patients, the trial will be terminated if 15 or more patients experience $\geq$ Grade III neurotoxicity. If 14 or fewer patients experience neurotoxicity, the trial will continue.
- At the final analysis, after testing the regimen on 125 patients, the regimen will be rejected if 19 or more patients experience $\geq$ Grade III neurotoxicity.

Cardiotoxicity: Two interim analyses will be performed after 42, and 84 patients have patients have been off of their last cycle of chemotherapy for 2 weeks. It is important to protect against the possibility that neoadjuvant chemotherapy with and without Trastuzumab will produce a proportion with a 10% reduction in ejection fraction from baseline and/or ≥ Grade III cardiotoxicity greater than 10%. The proportion with cardiotoxicity will be tested against a fixed null hypothesis of 10% at the one-sided 0.10 level of significance using a one-sample Binomial test. The monitoring p-values to be used for the 2 interim analyses are p=.00439 and p=0.04256, with the final analyses at p=0.08701. These results assume that 3 sequential tests are made using the O'Brien-Fleming spending function truncated at 3 standard deviations to determine the test boundaries. These p-values define the following interim stopping rules:

- After testing the regimen on 42 patients, the trial will be terminated if 10 or more patients experience a 10% reduction in ejection fraction from baseline and/or ≥ Grade III cardiotoxicity. If 9 or fewer patients experience cardiotoxicity, the trial will continue.
- After testing the regimen on 84 patients, the trial will be terminated if 14 or more patients experience a 10% reduction in ejection fraction from baseline and/or ≥ Grade III cardiotoxicity. If 13 or fewer patients experience cardiotoxicity, the trial will continue.
- At the final analysis, after testing the regimen on 125 patients, the regimen will be rejected if 18 or more patients experience a 10% reduction in ejection fraction from baseline and/or ≥ Grade III cardiotoxicity.

### 10.9 Definition of Analysis Sets

The analyses will be based on the full analysis set, consisting of all patients who received the study medication.

### 10.10 Missing Data

Only non-missing data will be analyzed, missing clinical data will not be replaced.

### 10.11 Stopping Rules for HBM

Subjects will be informed verbally and in the consent they sign, that they may withdrawal from the original study and/or revoke the authorization to use and share their HBM and all associated information at any time by contacting the principal investigator of the original study in writing.

Subjects may withdrawal from the original study and/or revoke the authorization to use and share their HBM and all associated information at any time. They will be informed in the consent of the original study that if they revoke this authorization, they may no longer participate in this research, that the use HBM and all associated information will be stopped immediately, and that the HBM and all associated information, which has already been collected, will be destroyed immediately.

## 11.0 RECORDS TO BE KEPT

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms. De-identified source documents which support data entered must be provided to the sponsor by mail, fax, or electronic means

for centralized compliance monitoring. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form.

### 11.1 Quality assurance

Complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., lab, report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate)

### 11.2 Forte Electronic Data Capturing (EDC) System

Data will be stored electronically for this study in the Forte EDC system contained on the Forte secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Forte logo.

Forte EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Forte through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

## 12.0 PATIENT CONSENT

### 12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical research included in this application will have approval by the institutional review board.

### 12.2 Study Population

Patients are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

### 12.3 Sources of Material

Pathology material must be reviewed, and the diagnosis confirmed by University Nebraska Medical Center pathology department as outlined in the protocol.

### 12.4 Recruitment and Informed Consent

Patients with an initial diagnosis of locally advanced breast carcinoma will be available for

recruitment. These patients will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine - http://clinicaltrials.gov (NCT01336933)
National Cancer Institute - http://www.cancer.gov (NCI-2011-00254)

### 12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

### 12.6 Process of Informed Consent

If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

### 12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

### 12.8 Information Purposely Withheld

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

### 12.9 Potential Benefits of the Proposed Research to the Subjects

It is anticipated that the use of neoadjuvant therapy in this patient population would result in greater tumor response and possibly prolong survival.

### 12.10 Potential Benefits to Society

Information obtained from this study may help other patients by contributing to the knowledge of the biology of breast cancer, and whether this treatment offers potential advantages over other treatments currently available.

### 12.11 Potential Risks

The use of cytototoxic chemotherapy, external beam radiotherapy, and surgical resection are associated with numerous potential risks. Combined chemotherapy/radiation is considered a valid treatment option for patients with breast cancer. Adjuvant therapy following surgical resection for breast cancer is considered a valid treatment option. It is believed the treatment option outlined in

the study will not pose significant additional risks compared to conventional treatment.

### 12.12 Therapeutic Alternatives

If patients choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include surgery, chemotherapy, or radiation, or a combination of these approaches. The treatment recommendations may or may not be similar to treatment as described in this protocol (pre-operative chemotherapy, followed by external beam radiotherapy), followed by tumor resection and additional chemotherapy).

### 12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy, radiotherapy in combination with surgical resection, we anticipate that patients who receive the treatment phase of the protocol will do no worse than expected with standard therapy, and may experience an improved outcome. The risk is considered to be acceptable in the setting of cancer.

### 12.14 Consent Form Documents

No information will be purposely withheld from the patients. The consent document used in this study will include the adult consent document. See attached consent form

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## 14.0 DATA FORMS Attached

**APPENDIX A**
**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 B

NYHA Classification

Excerpted from Oxford Textbook of Medicine. Vol 2, p.2228. Oxford Press.1997.

| Class | Description |
|---|---|
| I | Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. |
| II | Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. |
| III | Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain. |
| IV | Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased. |

## APPENDIX C

Eligibility Criteria Checklist CRF

| Date Completed: (dy/mth/yr) | Protocol #: | Institution: | Patient ID: |
|---|---|---|---|
| Checklist #:2.3 | Effective Date (dy/mth/yr) | | Waiver #: |

| Eligibility Checklist | | Yes | No | N/A | |
|---|---|---|---|---|---|
| 1 | Women with histologically proven invasive breast cancer without distant metastases<br>A clinical tumor classification of tumor size must be at least 1 cm with or without clinical pathologic evidence of positive nodes. | [ ] | [ ] | [ ] | 1. |
| 2 | Age: Patients must be 19 years of age or older. (This is the age of consent in Nebraska. Breast cancer does not occur in the pediatric age group.) | [ ] | [ ] | [ ] | 2. |
| 3 | ECOG performance status of 0 or 1. (Appendix A) | [ ] | [ ] | [ ] | 3. |
| 4 | At least one lesion that can be accurately measured in two dimensions utilizing mammogram, ultrasound, or MRI images to define specific size and validate complete clinical and pathologic response. | [ ] | [ ] | [ ] | 4. |
| 5 | Patients who received radiation therapy > 5 years ago for malignancies other than breast cancer and whose radiation therapy field is not overlapping with the 20% isodose line of current radiation field are eligible, provided that radiation therapy was completed > 5 years ago and that there is no evidence of the second malignancy at the time of study entry. | [ ] | [ ] | [ ] | 5. |
| 6 | Patients must have adequate laboratory parameters within 30 days prior to enrollment defined as:<br>• Absolute neutrophil count greater than or equal to 1,500/mcl<br>• Platelet count equal to or greater than 150,000/mcl<br>• Alkaline phosphatase equal or less than 1.5 times the ULN<br>• Total bilirubin equal to or less than 1.5 times the ULN<br>• AST and ALT no greater than 1.5 times the ULN<br>• Creatinine less than 1.5 times the ULN | [ ] | [ ] | [ ] | 6. |
| 7 | All included patients must have normal cardiac function as defined by an ejection fraction of ≥50% and no decrease in wall motion by echocardiogram. | [ ] | [ ] | [ ] | 7. |

| | | |
|---|---|---|
| 8 | The patient must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. | [ ] [ ] [ ]8. |
| 9 | Women of reproductive potential must be non-pregnant and non-nursing and must agree to employ an effective barrier method of birth control throughout the study and for up to 6 months following treatment. | [ ] [ ] [ ]9. |
| 10 | Women of child-bearing potential must have a negative pregnancy test within 7 days of initiating study. *(No childbearing potential is defined as age 55 years or older and no menses for two years or any age with surgical removal of the uterus and/or both ovaries).* | [ ] [ ] [ ]10. |
| *All of the above must be **yes** to be eligible.* | | |
| 1 | Any patient with inflammatory breast cancer or Stage IV or confirmed metastatic disease. | [ ] [ ] [ ]11. |
| 2 | Patients who have had any prior chemotherapy, or endocrine therapy for the treatment of breast cancer or any other cancer. | [ ] [ ] [ ]1. |
| 3 | Patients who cannot undergo surgery. | [ ] [ ] [ ]2. |
| 4 | Patients with a known or documented anaphylactic reaction or allergy to any of chemotherapy agents used in this protocol, or to antiemetic's appropriate for administration in conjunction with protocol-directed therapy. | [ ] [ ] [ ]3. |
| 5 | Uncontrolled inter-current illness including, but not limited to ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, or serious, uncontrolled cardiac arrhythmia, that might jeopardize the ability of the patient to receive the therapy program outlined in this protocol with reasonable safety. | [ ] [ ] [ ]4. |
| 6 | Patients with preexisting Grade II peripheral neuropathy. | |
| 7 | Pregnant and nursing women are excluded from this study because the chemotherapy agents and radiation therapy all have the potential for teratogenic or abortifacient effects. | [ ] [ ] [ ]5. |
| 8 | Patients with prior malignancy will be excluded **except** for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas. | [ ] [ ] [ ]6. |
| 9 | Inability to cooperate with treatment protocol. | [ ] [ ] [ ]7. |

| | | |
|---|---|---|
| 10 | Patients with known HIV infection, infectious hepatitis, type A, B or C, active hepatitis, or hepatic insufficiency. | [ ] [ ] [ ]8. |
| 11 | Patients may not be receiving or have received any other investigational agents during/or within 1 month prior. | [ ] [ ] [ ]9. |
| 12 | Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form. | [ ] [ ] [ ]10. |
| 13 | Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (Appendix B) Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant. | [ ] [ ] [ ]11.<br>[ ] [ ] [ ]12. |
| | *All of the above must be **no** to be eligible.*<br>**NOTE:** All questions regarding eligibility for potential subjects should be directed to the UNMC Coordinator at 402-559-5582 or 402-559-5286. | [ ] [ ] [ ]13. |

Eligibility: [ ] Patient satisfies all criteria.
[ ] Patient not formally eligible, but admitted to study because (state reason);

_____

_____

**Patient Initials: _____MR #_____DOB _____**

**ELIGIBILITY reviewed and confirmed**
**Site Investigator Signature _____Date_____**

## APPENDIX D
## HBM Sample Processing and Shipping (for research purposes only)

**Sample Collection:** Source and human biologic material (HBM) to be used: We will use two 10 ml EDTA (lavender top tubes) and one- 10ml red top tube blood sample from the patient for DNA sequencing.

Tests performed with HBM:

DNA sequencing through Illumina Genome Analyzer GAIIx as 2x 76-bp paired-end reads, following Illumina sequencing protocol.

DNA sequences of high quality will be aligned to the human reference genome sequences (hg19). Potential single-nucleotide variants, deletions and insertions will be identified.

| **Facility** | **Sample** | **Contact Person(s) and Shipping Address** | **Date and Time Points** |
|---|---|---|---|
| Laboratory of San Ming Wang<br><br>UNMC Dept. of Genetics, Cell Biology and Anatomy | Blood: (30 ml total) two-10*ml EDTA (lavender top) and one- 10ml red top* blood collection deliver or ship same day at room temperature | David L. Kelly PhD<br>Tel: (402) 559-9157<br>Cell: (402) 699-1132<br>Fax: (402) 559-4651<br>dkelly@unmc.edu<br><br>Amy Wells<br>Tel: (402) 559-6015<br>awells@unmc.edu<br><br>Shipping Address:<br>University of Nebraska Medical Center<br>601 S. Saddle Creek Rd.<br>Amy Wells, MS,<br>Fred & Pamela Buffett Cancer Center, Room # BCC 5.12.429<br>Omaha, Nebraska 68106 | Baseline date:<br>___/___/____<br>Pre-Chemo |
| | Blood: (30 ml total) two-10*ml EDTA (lavender top) and one- 10ml red top* blood collection deliver or ship same day at room temperature | **Same as above** | Sample Date:<br>___/___/____<br>Post-Chemo/ Pre-Surgery |
| | Blood: (30 ml total) two-10*ml EDTA (lavender top) and one- 10ml red top* blood collection deliver or ship same day at room temperature | **Same as above.** | Sample Date:<br>___/___/____<br>End of treatment Post-Chemo, Radiation |

## APPENDIX E
**Neuropathy Assessment Worksheet**
(1 page See Attached)

## APPENDIX F

**NCI Common Toxicity Criteria Version 4.0 (CTCAE)**
**Active Date: May 29, 2009**

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (**http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm**).
All appropriate treatment areas have access to a copy of the CTC Version 4.0.

**Minor editorial updates have been made to CTCAE v4.0, which are represented in v4.03. These edits do not change the meaning of v4.0 content and all previous versions (CTCAE v4.0, v4.01, v4.02) are still valid and referred to as CTCAE v4.0. V4.03 includes clarifications for a select few grading scales and adverse event term definitions. Most of the revisions are associated with grading scales that include a quantitative component. A list of changes is located at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.**

**An updated version (4.03) is now in use as of June 14, 2010.**

## APPENDIX G

**FDA MEDWATCH form**

Available on-line at http://www.fda.gov/medwatch/SAFETY/3500.pdf

NOTE: Attached NCCN guidelines. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf