UCI 14-67: A Phase II Study of Breast Cancer Treatment Using Weekly Carboplatin + Paclitaxel with Pertuzumab + Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting

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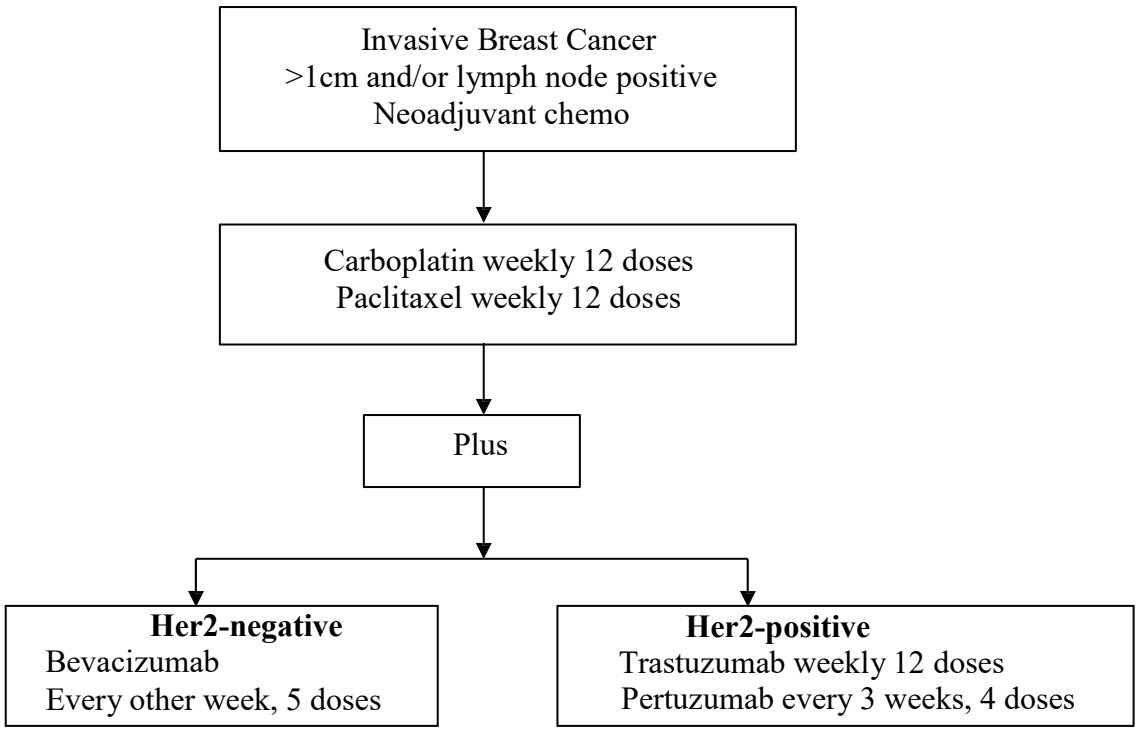
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Bevacizumab (Avastin®)
Carboplatin (Paraplatin®)
Paclitaxel (Taxol®)
Pertuzumab (Perjeta®) (L01XC13)
Trastuzumab (Herceptin®)

Please refer all questions regarding chemotherapy treatment or dose modifications to Dr. Rita Mehta at 714-456-2239, pager 714-506-6174.

SCHEMA

UCI 14-67



1.0 OBJECTIVES

The study component is to evaluate the treatment response and toxicity of theprotocol.

Objectives for treatment study component:

1.1 To estimate 2-year progression-free survival in patients with breast cancer with tumor more than 1 cm and/or with clinically detected lymph node treated with neoadjuvant weekly Carboplatin and Paclitaxel combined with Trastuzumab + Pertuzumab in HER2-positive disease or with Bevacizumab in HER2-negative disease.

1.2 To measure the microscopic complete pathological response (pCR) rates defined as ypT0 or ypTis tumors in patients treated with this regimen in the neoadjuvant setting.

1.3 To assess complete clinical response (cCR) rates after treatment by physical exam and imaging tests (ultrasonography, mammography, or magnetic resonance imaging) clinical objective response rate (by Response Evaluation Criteria In Solid Tumors [RECIST])

1.4 To determine the toxicity of this regimen.

1.5 To determine treatment adherence and delivered dose intensity of this regimen.

1.6 To assess the correlation between pCR and cCR.

1.7 To determine the rate of breast conservation following neoadjuvant therapy.

1.8 Determine treatment efficacy according to subgroups defined according to stage and receptor status.

2.0 BACKGROUND

Neoadjuvant chemotherapy (NAC) has been increasingly used in localized breast cancer since a large trial run by the NSABP found that traditional chemotherapy provides similar long-term outcomes whether given neoadjuvantly or adjuvantly,[1²3] but NAC offers many potential advantages. NAC can reduce local disease to allow more conservative surgery and may lead to better control of disease. Administration of NAC functions as an in vivo chemosensitivity test, which enables earlier modification of therapy and provides additional prognostic information. In addition, the neoadjuvant setting provides investigators the opportunity to identify biomarkers of response, assess serial tissue biopsies, and assess drug efficacy.

There is accumulating evidence that pathologic complete remission after NAC may predict better long-term outcomes with longer disease-free and overall survival[1,2,³,4]. Pathologic complete remission (pCR) is defined as the absence of invasive disease at the time of surgical resection (ypTis or ypT0 N0) and is often used in clinical research as a surrogate endpoint to detect treatment effect earlier in the clinical course and to power the study for smaller sample size. However, the relationship between pCR and long-term measures of outcome may vary according to breast cancer subtypes,[5,6] so subjects should be followed to primary endpoints like progression free survival (PFS) and overall survival (OS) to ensure the treatment provides meaningful clinical benefit.

Many studies have evaluated combination neoadjuvant chemotherapies, but no particular regimen has emerged as optimal therapy for all patients. The most well described chemotherapy regimens in breast cancer incorporate anthracyclines on the basis of the meta-analysis by the Early Breast Cancer Trialists' Group that showed superior efficacy of anthracycline-containing regimen.[7] However, retrospective evidence from meta-analysis of 5200 patients who participated in randomized adjuvant trials suggests that superiority of anthracycline-based chemotherapy is confined to HER2-positive tumors.[8] This has implications for both HER2-negative and HER2-positive treatments. Since HER2-negative tumors may not demonstrate the same superior benefit from anthracyclines, alternate regimen can be utilized to spare the toxicities of anthracycline, which include long-term risks of leukemia and congestive heart failure. For HER2-positive tumors, now that newer HER2 targeted therapies are available it is not clear which will be the most important, the anthracycline or the HER2 targeting therapies. Combinations of novel HER2 targeted therapies, like trastuzumab and pertuzumab, might overcome the superiority of an anthracycline-based regimen. Cardiac toxicity is a major safety issue that arose with the addition of trastuzumab to anthracycline⁹ and this has prompted the exploration of anthracycline-sparing combinations for comparative efficacy and safety.

This is a single-institution phase II neoadjuvant chemotherapy trial of weekly carboplatin and paclitaxel combined with either trastuzumab with pertuzumab for HER2-positive patients or bevacizumab for HER2-negative patients. This first component of this study will evaluate the treatment safety and efficacy using 2-year progression free survival and rate of pathologic complete response.

Rationale for the use of Weekly Paclitaxel:

Taxanes have been well established to improve efficacy in both adjuvant and neoadjuvant settings. Adjuvant dose dense chemotherapy using concurrent adriamycin and cyclophosphamide followed by paclitaxel with growth factor support showed improved disease free survival and overall survival with reduced toxicity when compared to other schedules of the same drugs.[10] The addition of neoadjuvant taxane after adriamycin with cyclophosphamide (AC) doubled the rate of pCR (13% to 26%) and reduced the incidence of local recurrence.[3]

There is evidence that weekly paclitaxel provides outcome advantages over docetaxel in both the adjuvant and neoadjuvant settings. The adjuvant ECOG E1199 study was a four-arm trial that randomized 4950 women to four treatment arms: AC followed by either paclitaxel or docetaxel given either every 3 weeks or weekly. The group treated with weekly paclitaxel showed superior 5-year OS 89.7% (OR 1.32, p=0.01) compared to 87.3% for every three weekly docetaxel.[11] When weekly paclitaxel was used in the neoadjuvant setting, this improved therate of pCR (28.2% v. 15.7%, p=0.02, n=258) when compared to every 3 weekly paclitaxel andadditionally showed improved rates of breast conservation surgery and decreased rates of adverse effects[12].

The phase 2 trials that support combining dual HER2 targeting with chemotherapy [13,14] used every 3-weekly docetaxel. Because of the efficacy data and side effect profile of weekly paclitaxel observed in the studies noted above, we hypothesize that that weekly paclitaxel can further improve the outcomes for this subset of patients.

Rationale for the use of Carboplatin with Paclitaxel and Trastuzumab:

In vitro data suggested synergy between trastuzumab and carboplatin as well as between paclitaxel and carboplatin. The addition of carboplatin to paclitaxel with trastuzumab was evaluated as first line therapy for metastatic HER2-positive breast cancer in a phase III trial and was shown to have improved progression free survival (10.7 v. 7.1months, p=0.03, n=196) with similar tolerability. This combination also has better tolerability compared to other non-anthracycline combinations and demonstrate a platelet-sparing phenomenon with lower rates of thrombocytopenia.[15]

In an adjuvant trial, an anthracycline-based chemotherapy was compared to non- anthracycline combination of carboplatin with docetaxel and trastuzumab. The risk-benefit ratio favored the non-anthracycline regimen because of similar disease free survival (DFS) and OS with lower rates of acute and chronic toxic effects include significantly lower rates of cardiac toxicity ($p<0.001$).[16] Similarly, neoadjuvant carboplatin combined with paclitaxel with or without trastuzumab has been found to be a tolerable and effective neoadjuvant, with pCR rates comparable to that seen with anthracycline plus taxane regimens.[17]

The rationale for use of Trastuzumab:

Human epidermal growth factor receptor (HER2) is overexpressed in 25-30% of breast cancers and is associated with aggressive disease[18]. Trastuzumab targets the HER2 receptor and has been well established to be effective in the metastatic and adjuvant setting. It was approved by the FDA for use with adjuvant chemotherapy because of improved progression free survival and overall survival[9]. The incorporation of trastuzumab into neoadjuvant chemotherapy is important in HER2-positive tumors because of evidence that it improves the rate of pCR and this correlates with survival benefit.

In the Neoadjuvant Herceptin (NOAH) trial, patients were assigned to neoadjuvant chemotherapy alone or in combination with trastuzumab. The addition of trastuzumab doubled the pCR rate (38% v. 19%, p=0.001) and showed sustained benefit with improvement of the 5-year PFS (58% v. 43%, p=0.016, n=235).[19,20] Another smaller trial was terminated early by the data monitoring committee because the addition of neoadjuvant trastuzumab showed superior rate of pCR (66.7% v. 25%, p=0.02, n=34). The 3-year PFS was prolonged in the trastuzumab arm (100% v. 85% p=0.041). [21,22]

One study evaluated the prognostic value of pCR by reviewing the outcomes of 229 women with HER2-positive breast cancer treated with neoadjuvant chemotherapy and Trastuzumab during the period from 2001 to 2008. The patients that achieved pCR had improved distant metastasis-free survival (96% v. 79%, p<0.001), 5-year relapse free survival (96% v. 79%, p<0.001) and overall survival (95% v. 84%, p=0.006). Failure to achieve pCR was the strongest predictor of recurrence (HR 4.09). Because of this data, pCR may be a surrogate of the long-term outcome in patients with HER2-positive disease treated with trastuzumab.[23]

The rationale for use of Pertuzumab:

Pertuzumab, like trastuzumab, targets breast cancer with overexpressed HER2, but has a complimentary mechanism of action to provide more complete inhibition when used in combination.

There is evidence that treatment with the combination of trastuzumab and pertuzumab (dual HER2 targeting) is effective in metastatic HER2-positive breast cancer. Pertuzumab showed initial promise in a phase II trial of 66 patients with HER2-positive metastatic breast cancer who had already had disease progression while on regimen containing trastuzumab. The patients were treated with pertuzumab and trastuzumab which resulted in clinical benefit for 50% of patients (7.6% CR, 16.7% PR, and 25.8% stable disease >6 months).[13] The CLEOPATRA phase III trial[24] enrolled patients with metastatic HER2-positive breast cancer and treated with first line trastuzumab with docetaxel with or without pertuzumab. They found that dual HER2 targeting showed improved outcomes including PFS (18.7 v. 12.4 months) and OS (median OS not yet reached v. 37.6 months, p <0.001) without an increased risk of cardiac dysfunction. The American Society of Clinical Oncology (ASCO 2014) panel strongly recommends this regimen as first line treatment in this the metastatic setting, but felt that the use of paclitaxel is also reasonable.

The favorable results from the phase II trial above prompted additional studies in the neoadjuvant setting. The NeoSphere phase II trial[25] investigated the combination of trastuzumab or pertuzumab, or both, with docetaxel every three weeks and found that the patients treated with neoadjuvant dual HER2 targeting plus docetaxel had the highest rate of pCR (45.8%) compared to the trastuzumab alone plus docetaxel (29.0%) without substantial differences in tolerability.

The TRYPHAENA phase II trial[14] was designed to evaluate the activity and cardiac toxicity of the combination of dual HER2 targeting plus either anthracycline-based or anthracycline-free chemotherapy. The highest rates of pCR were observed in the patients treated with docetaxel and carboplatin plus dual HER2 targeting (pCR 66.2%, ypT0N0 51.9%). Pertuzumab was granted FDA approval for combination use in metastatic breast cancer in 2012 and for neoadjuvant intent in 2013.

The rationale for use of bevacizumab:

In metastatic breast cancer previously treated with anthracycline and taxane, the addition of bevacizumab to capecitabine significantly increased the response rates (19.8% v. 9.1%, p=0.001), but PFS and OS were comparable in both treatment arms.[26] A subsequent study enrolled predominantly HER2-negative women with previously untreated metastatic breast cancer and showed the addition of bevacizumab to paclitaxel significantly prolonged PFS (11.3 v. 5.8 months, HR 0.60, p<0.001, n=722), but OS was similar.[27] It was because of this significantly prolonged PFS that the FDA granted accelerated approval for bevacizumab use in combination with paclitaxel for HER2-negative metastatic breast cancer in 2008. However in 2011 this indication was revoked because it ultimately failed to show improvement in OS despite the impact on PFS in landmark trials (E2100, AVADO, RIBBON-1 and RIBBON-2).[28–30,31]

Adding bevacizumab to NAC increased the rate of pCR in HER2-negative breast cancer. The GeparQuinto phase 3 study showed that the addition of bevacizumab to neoadjuvant chemotherapy (epirubicin+ cyclophosphamide followed by docetaxel +/-bevacizumab) showed significantly increased rate of pCR (18.4 v. 14.9%, OR 1.29, p=0.04, n=1948), but was associated with higher incidence of grade 3 or 4 toxicity.[32] The NASBP B-40 study also showed that the addition of bevacizumab to chemotherapy increased the rate of pCR (34.5% v. 28.2%, p=0.02, n=1166).[33]

3.0 DRUG INFORMATION

3.1 Carboplatin (Paraplatin®) (NSC 241240)

a. DESCRIPTION

Carboplatin is a platinum compound related to cisplatin. Carboplatin is formed by replacing the chloride leaving groups of cisplatin with 1, 1-cyclobutanedicarboxylato ligand, which increases the stability of the leaving groups. On a molar basis, carboplatin is 45 times less cytotoxic than cisplatin. Carboplatin has a more favorable adverse effect profile than cisplatin, which has led to the investigation of the replacement of cisplatin with carboplatin in many regimens.

b. TOXICOLOGY

Adverse effects include myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity (hearing loss), hepatic toxicity, electrolyte imbalance (which can be asymptomatic or result in muscle spasms, , hypomagnesemia (low level of magnesium), hypocalcemia (low level of calcium), and allergic reaction.

c. PHARMACOLOGY

Formulation: Paraplatin® is supplied as a sterile lyophilized powder available in single-dose vial containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule: Vial strength diluent volume (50 mg 5 ml/150 mg 15 ml/450mg 45 ml). These dilutions all produce a carboplatin concentration of 10mg/ml. When prepared as directed, Paraplatin® solutions are stable for 8 hours at room temperature, since no

antibacterial preservative is contained in the formulation it is recommended that Paraplatin® solutions be discarded 8 hours after dilution.

NOTE: Aluminum reacts with Paraplatin® causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Paraplatin®.

Storage: Unopened vials of Paraplatin® are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Supplier: Commercially available

Cost: 50 mg/5 mL (5 mL): $11.87, 150 mg/15 mL (15 mL): $28.98, 450 mg/45 mL (45 mL): $78.00, 600 mg/60 mL (60 mL): $118.75

3.2 Paclitaxel (Taxol®) (NSC 673089)

a. DESCRIPTION

Paclitaxel is an antimicrotubule agent that stabilizes microtubules resulting in inhibition of the normal reorganization of the microtubule network that is needed for mitotic cellular function.

b. TOXICOLOGY

Myelosuppression is common and can cause neutropenia, thrombocytopenia, anemia, bleeding and infection. Anaphylaxis and severe hypersensitivity were observed in 2-4% of patients receiving paclitaxel in clinical trials. Infusion related hypotension, bradycardia, or hypertension and injection site reactions may occur. Liver, renal, and cardiac toxicity as well as other important or life-threatening reactions may occur. Side effects also include peripheral neuropathy, arthralgia, weakness, alopecia, rash, nausea/vomiting, diarrhea, mucositis, flushing, edema, and cardiovascular events.

c. PHARMACOLOGY

Kinetics: Plasma drug concentrations decline in a biphasic manner because of an initial extravascular distribution into body fluids and tissues and a later phase because of the relatively slow efflux of Paclitaxel from the extravascular compartment. The half-life elimination depends on the dose and duration of infusion. The mean half-life for a 1- to 6-hour infusion is 6.4 hours

Formulation: Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Preparation: Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% 48 Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Storage and Stability: Store between 20 and 25 degrees Celsius and store in original package to protect from light. Unopened vials are stable until the expiration date indicated on the package. Upon refrigeration components in vial may precipitate, but will redissolve upon reaching room temperature. Refrigeration and Freezing do not adversely affect the stability of the product.

Solutions prepared for infusion are stable at room temperature for up to 27 hours. Taxol solutions should not contact plasticized PVC equipment because the plasticizer DEHP [di-(2-ethylhexyl) phthalate] may be leached from PVC infusion bags or sets.

Supplier: Commercially available.

Cost: 30 mg/5 mL (5 mL): $15.52, 100 mg/16.7 mL (16.7 mL): $51.96, 150 mg/25 mL (25 mL): $79.20, 300 mg/50 mL (50 mL): $155.16

3.3 Trastuzumab

a. DESCRIPTION

Trastuzumab is an anti-Her2/c-erbB2 monoclonal antibody.

b. TOXICOLOGY

Adverse effects include bronchospasm, dyspnea, pulmonary infiltrates, pleural effusions, cough, rhinitis, sinusitis, rash, nausea, vomiting, myelosuppression, and hypoprothrombinemia. Nephrotic syndrome has been reported in some patients. Hypersensitivity reactions have resulted after administration. Other infusion-related events include fever, chills, hypotension, headaches, and dizziness. Cardiac toxicity has been associated with administration including ventricular dysfunction, congestive heart failure, and peripheral edema. Other adverse effects include asthenia, insomnia, abdominal pain, and diarrhea.

c. PHARMACOLOGY

Kinetics: The half-life of trastuzumab is 6 days.

Formulation: Trastuzumab is available in 440mg vials in lipophilized powder. It is stored in 30mL vial in bacteriostatic water for injection of 1.1% benzyl alcohol.

Storage and Stability: Vials of Herceptin are stable at 2 to degrees Celsius. Reconstituted vials of Herceptin with bacteriostatic water for injection containing 1.1% benzyl alcohol as a preservative can be kept for 28 days stored at 2-8 degrees Celsius.

Administration: Trastuzumab, at the appropriate dose, will be administered intravenously with the loading dose over 90 minutes and monitored for 60 minutes post-administration. Maintenance doses will be administered over 30 minute infusions if the loading dose is tolerated.

Supplier: Commercially available.

Cost: 440 mg (1): $4330.38

3.4 Pertuzumab

a. DESCRIPTION

Pertuzumab is an anti-Her2/c-erbB2 monoclonal antibody that targets the extracellular dimerization domain.

b. TOXICOLOGY

Adverse effects of pertuzumab have been described when it is used in combination with trastuzumab and docetaxel. Cardiac toxicity can cause decline in left ventricular ejection fraction (LVEF) or systolic dysfunction and cardiac function should be monitored throughout treatment. Hematologic toxicity can cause neutropenia, anemia, thrombocytopenia and febrile neutropenia. Skin toxicities include alopecia, skin rash, puritis, hand-foot syndrome, mucositis, dry skin, and nail changes. Respiratory symptoms of dyspnea, cough, upper respiratory infection, nasopharyngitis, and epistaxis have been reported. Infusion reactions and hypersensitivity/anaphylaxis have occurred after administration. Other side effects include fatigue, insomnia, headache, dizziness, decreased appetite, dysgeusia, nausea, vomiting, diarrhea, abdominal pain, weakness, myalgia, arthralgia, peripheral neuropathy, peripheral edema, and increased lacrimation. This drug in combination can also cause increased serum ALT.

b. PHARMACOLOGY

Kinetics. The half-life of pertuzumab is 18 days.

Formulation: Pertuzumab is available in 440mg/14mL single use vial.

Storage and Stability: Stable in NS, but incompatible with D5W. Do not mix with other medications.

Administration: Pertuzumab, at the appropriate dose, can be diluted into a 250ml 0.9% sodium chloride. The loading dose can be administered intravenously over 60 minutes. Maintenance doses can be administered over 30 to 60 minutes.

Supplier: Commercially available

Cost: 420 mg/14 mL (14 mL): $4890.79

3.5 Bevacizumab (Avastin)

a. DESCRIPTION

Bevacizumab is a recombinant, humanized monoclonal antibody that binds to and inhibits the activity of vascular endothelial growth factor receptor (VEGF) leading to antiangiogenic effects.

b. TOXICOLOGY

Common adverse reactions include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder and dermatitis. Adverse effects include nausea, vomiting, diarrhea, anorexia, asthenia, abdominal pain, deep vein thrombosis, and constipation, thrombocytopenia. Other side effects include nephritic syndrome, congestive heart failure, gastrointestinal perforations, dyspnea, severe hemorrhage, and wound healing complications. Skin toxicities include exfoliative dermatitis, skin ulcers, dry skin, and nail changes. The effect of this drug on pregnancy and lactation remain largely unknown and therefore not recommended during pregnancy or breastfeeding.

Congestive heart failure (CHF) was reported in 22/1032 patients who received bevacizumab.

CHF occurred in 6/44 patients who received bevacizumab with concurrent anthracycline and 13/299 patients who received prior anthracyclines and/or left chest wall irradiation. The safety of continuation or resumption of bevacizumab in patients with cardiac dysfunction has not been studied.

c. PHARMACOLOGY:

Kinetics: The pharmacokinetics of bevacizumab are linear after doses of 0.3 mg/kg or greater (Anon, 2002). The estimated elimination half-life of bevacizumab was 20 days (range 11 to 50 days) in a pharmacokinetic population analysis of 491 patients receiving 1 to 20 mg/kg weekly, every 2 weeks, or every 3 weeks (Prod Info Avastin(TM), 2004).

Storage and Stability: Bevacizumab contains no preservatives and stored in vials protected by light. It must be kept under refrigeration conditions at 2 to 8 degrees Celsius. The product cannot be freeze or shaken. Diluted solutions of bevacizumab may be stored up to a maximum of eight hours under refrigeration conditions at 2 to 8 degrees Celsius.

Administration: The calculated dose of bevacizumab in 100mL of 0.9% sodium chloride Injection to be given over 60-90 minutes.

Supplier: Commercially available.

Cost: 100 mg/4 mL (4 mL): $796.50, 400 mg/16 mL (16 mL): $3186.00

4.0 STAGING:

This study will utilize the American Joint Committee on Cancer (AJCC) staging system which provides a strategy for grouping patients with respect to prognosis. The AJCC has designated staging by TNM classification.[34] The researchers will also review tumor size, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, menopausal status, and the general health of the patient.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility.

Patient Number: _____

Patient's Initials: _____

Inclusion Criteria:

5.1 Histologically proven unilateral or bilateral primary breast carcinoma. (In case of bilateral cancer, the investigator has to decide prospectively which side will be evaluated for the primary endpoint.)

5.2 Tumor size is clinically at least 1 cm in greatest diameter (palpable or by imaging) and/or with involved lymph node. In case of inflammatory disease, the extent of inflammation may be the measurable lesion.

5.3 Documentation of inflammatory breast cancer
Inflammatory breast cancer? (circle) Yes No

5.4 Woman age > or = 18

5.5 Performance status of 0-2 by ECOG criteria (see section 10.2)

5.6 Known HER2 status

5.7 Normal cardiac function must be documented within 90 days prior to registration either via an ECHO or MUGA or per physician's review of symptoms and medical history. If an ECHO is performed as standard of care, the ejection fraction must be above the normal limit of the institution.. If not available in the medical chart, the ECHOs or MUGAs are not required to be repeated for research purposes.
Date of Echo or MUGA (within 90 days) if performed _____

5.8 Staging work-up prior to registration
Date of physical examination (within 90 days) _____
Date of bilateral mammogram (within 90 days) _____
Date of breast ultrasound (within 90 days) _____
Date of MRI breast (within 90 days)_____
Chest X-ray or CT- Chest or CT/PET Scan that includes the Chest may be done at physician's discretion (within 90 days). If not available in the medical chart, the Chest X-ray or CT- Chest or CT/PET Scan that includes the Chest is not required to be repeated for research purposes. If performed, indicate date of procedure:
_____
Other tests as clinically indicated

5.9 Laboratory requirements:
Hematology
-Absolute Neutrophil Count (ANC) ≥ 1,500/µl
-Platelets ≥ 100,000/µl
Hepatic Function
-Total Bilirubin <1x ULN
-AST and ALT ≤ 2x ULN
Renal Function
-Creatinine <1.5x ULN
Proteinuria (For Bevacizumab patients only)
- Random urine total protein <100mg/dL. Urine Protein Creatinine (UPC) ratio <2g
Negative pregnancy test for women of childbearing potential within 14 days prior to registration.

5.10 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

Exclusion Criteria:

5.11 Evidence of distant metastasis. If radiographic suspicion of distant metastatic site, a negative biopsy must be available in the medical record. If not available in the medical record, the subject may be included and a confirmatory biopsy is not required to be performed for research purposes.

5.12Known or suspected congestive heart failure, angina pectoris requiring antianginal medication, or other clinically significant cardiac condition.

5.13Pregnant or nursing women may not participate due to the possibility of harm to fetus or nursing infants from this treatment regimen. Women of childbearing potential may not participate unless they have agreed to use an adequate contraceptive method throughout

study treatment and for one month after completion of treatment.

5.14 Male patients

5.15 Pre-existing peripheral neuropathy of severity grade ≥ 2 (limiting instrumental activities of daily living).

5.16 Incomplete wound healing.

5.17 Active and significant bleeding

5.18 Known allergy, hypersensitivity or prior infusion reaction to one or more of the therapies incorporated into this treatment protocol.

5.19 Bone marrow depression or hematologic parameters in the range that would increase the risk for severe bleeding

6.1 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Rita Mehta at 714-456-3800/2239 or pager 714-506-6174.

6.2 Good Clinical Practice

The pre-study tests should be obtained within 90 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician.

All patients will be followed in the clinic every month, where they routinely will be examined for clinical response and toxicity evaluations like swelling of extremities, shortness of breath. Routine lab work and procedures such as urinalysis, CBC and Comprehensive Metabolic Panel are outlined in the Study Calendar.

It is recommended that the following tests be done to evaluate for metastatic disease and test to evaluate heart function:

a. CT scan of abdomen and chest and/or CT/PET fusion.
b. Bone scan if indicated.
c. All patients preferably should have a MUGA or echocardiogram scan performed prior to registration.

6.3 Treatment: A Phase II Study of Breast Cancer Treatment Using Weekly Carboplatin + Paclitaxel with Pertuzumab + Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting

Agent	Dose	Route	Days	Interval
Paclitaxel	80 mg/m^2	IV over 1-3 hours	1	weekly 12 doses
Carboplatin	Area under the curve (AUC) 2*	IV over 60 min.	1	weekly 12 doses
Trastuzumab (for HER2-positive)	4mg/kg induction, followed by weekly 2mg/kg	IV-induction over 90 min., then weekly over 30-60 min.	1	weekly 12 doses

Pertuzumab (for HER2-positive)	840mg induction, followed by 420mg every 3 weeks	IV induction over 60 min., then every 3 weeks over 30-60 min.	1	Every 3 weeks for 4 doses
Bevacizumab (for HER2-negative)	10mg/kg	IV over 90 or 60 or 30 min.	1	Every other week for 5 doses

*AUC 2: From a pharmacokinetic (movement of drug into, through, and out of the body) standpoint, area under the curve (AUC) describes the drug concentration in blood plasma over time. The targeted AUC, along with weight and kidney function, are used to determine the carboplatin dose administered to the patient. AUC can range from 1 to 6 with 1 being the lowest dose and 6 being the highest dose. Based on previous trials targeting advanced breast cancers, an AUC of 2 was the ideal dose chosen for patients receiving weekly carboplatin.

1. Dosing of Carboplatin: The dose of carboplatin will be calculated using the standard of care Carboplatin pharmacy SOP for dose calculation.

2. BSA will be capped at 2.2 m2 for paclitaxel dosing.

3. Actual body weight will be used for Trastuzumab, Pertuzumab, and Bevacizumab dosing.

4. Suggested pre-medications:
   a. Antiemetic- Ondansetron 16 mg IV or PO
   b. Diphenhydramine 25mg PO or IV
   c. Acetaminophen 650mg PO prior to Trastuzumab
   d. Dexamethasone 10mg IVPB
   e. Ranitidine IV

6.4 **Response Assessment**

Patients will have the primary disease site evaluated at minimum with physical exam every 4 weeks and any clinically indicated x-rays and scans for tumor measurement every 4 weeks (see sections 8, Study Calendar).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 1. If test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

6.5 **Surgery**

Patients with responsive or stable disease:
Breast surgery should not be performed within 21 days of the last dose of Trastuzumab or within 28 days of the last dose of Bevacizumab or to allow for normalization of blood counts and reduce risk of wound dehiscence. A four-week interval between the last Bevacizumab and surgery appears to be sufficient to reduce risk of therapy-associated surgical outcomes.[32]

Patients with progressive disease or with unresectable disease at the completion of chemotherapy will be removed from protocol treatment. Further treatment (radiation or additional chemotherapy) is allowed and will be per the treating physician's discretion.

6.6 **Criteria for Removal from Protocol Treatment:**

a. Progression of disease (as defined in Section 10.3)
b. Subjective intolerability of toxicity
c. Medically unacceptable toxicity
b. Delay of treatment for more than 3 weeks for hematologic toxicity or more than 2 weeks for other toxicity.
d. Completion of planned treatment.
f. Unresectablility of breast cancer
g. The patient may withdraw from the study at any time for any reason.

6.7 **All patients will be followed for 15 years**

Patients will be followed for efficacy at surgery, long-term disease status, and toxicity as long as the patient does not withdraw her consent. This includes patients who are removed from protocol treatment.

7 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

7.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

7.2 Dose modifications for paclitaxel/carboplatin – Chemo will be on hold according to the following

a. Hematologic (Bone Marrow): If ANC < 1,000 or platelets < 75,000, therapy will be withheld until ANC ≥1,000 or platelets ≥75,000.
Remaining doses will be treated according to the physician judgment (i.e. dose reduction and/or use of Colony Stimulating Growth Factors).

b. Hepatic: Patients with Grade 4 hepatic toxicity (Liver damage) will have paclitaxel/carboplatin treatment held until toxicity recovers to ≤ Grade 2.

c. Stomatitis: If Grade 3 or 4 stomatitis occurs, hold carboplatin/paclitaxel until recover to Grade ≤ 1, and then resume at 25% dose reduction for this and subsequent cycles.

d. Peripheral neuropathy (paclitaxel only): Patients who experience ≥ Grade 3 peripheral neuropathy should have their paclitaxel dose held for one week. If the peripheral neuropathy has improved by the next week, resume at full dose. If the peripheral neuropathy is not improved, hold the dose another week then resume with a reduction of 25% for this and subsequent cycles.

e. Proteinuria (Bevacizumab) 24-hour urine collection can be obtained for urine dipstick of 2+. Hold Bevacizumab for protein >2,000mg per 24 hours.

f. Hypertension (Bevacizumab): Patients will be treated with antihypertensive

medicines at the physicians' discretion. Hold if BP> 150/90.

g. Other (for both carboplatin and paclitaxel): If toxicities are ≤ Grade 2, manage symptomatically, if possible, and treat without dose reduction. If toxicities are > Grade 2, treatment should be withheld (except for anemia) until recover to ≤ Grade 1 (or baseline, if baseline was > Grade 1).

h. If all drugs are held, the doses should be made up at the next visit (All treatment is deferred by a week). For HER 2+ patients, if only chemo is held, Pertuzumab and Trastuzumab are given and visits should continue per protocol schedule. For HER 2- patients, if only chemo is held, Bevaciuzmab is given and visits should continue per protocol schedule.
    - The missed chemotherapy dose(s) will be administered after the completion of week 12 (i.e. week 13, week 14, etc).

i. For treatment or dose modification related questions, please contact Dr. Rita Mehta at 714-456-2239 or pager 714-506-6174.

j. Unexpected or fatal toxicities (included suspected reactions) must be reported to the IRB. The procedure for reporting adverse reactions is outlined in Section 11.0.

8 STUDY CALENDAR "A Phase II Study of Breast Cancer Treatment Using Weekly Carboplatin + Paclitaxel with Pertuzumab + Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting".

REQUIRED STUDIES	Pre-Study [1]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	F/U[9]
	+/- 1 week													Within 2-12 weeks
PHYSICAL														
History & Physical Exam	X				X				X				X	
Performance Status	X													
Disease Assessment[2]	X				X				X				X	
Toxicity Notation					X				X				X	
LABORATORY														
CBC, platelets, differential	X		X		X		X		X		X		X	
Comprehensive Metabolic Panel [3]	X		X		X		X		X		X		X	
Spot Urine Protein, Spot urine Creatinine, for Bevacizumab patients only, 1 month prior to infusion	X	X		X		X		X		X				
Pregnancy test[10]	X													
X-RAYS AND SCANS[8]														
Echocardiogram or MUGA [4]	X													X[4]
Breast mammogram, breast ultrasound, for disease assessment	X						X							X
MRI breast	X													X
Chest X-Ray or CT- Chest or PET/CT Scan that includes the chest	X[5]						X[5]							X[5]
Bone scan	X[7]													
TREATMENT (See Section 6.0)														
Paclitaxel		X	X	X	X	X	X	X	X	X	X	X	X	
Carboplatin		X	X	X	X	X	X	X	X	X	X	X	X	
Trastuzumab (HER2-positive)		X	X	X	X	X	X	X	X	X	X	X	X	

Pertuzumab (HER2-positive)		X			X			X			X			
Bevacizumab (HER2-negative)		X		X		X		X		X				

[1] Pre-entry exams and procedures must be performed within 90 days prior to registration.
2 A detailed description of the primary tumor, including results of physical exam or results of imaging studies.
[3] Comprehensive Metabolic Panel to include: Serum Creatinine, Bilirubin, AST or ALT.
4 MUGA or echocardiogram may be done at prestudy and at the completion of chemotherapy at physician′s discretion. MUGA or echocardiogram is recommended to be done every 6 months following discontinuation for up to 24 months from the last dose of Pertuzumab. MUGA or echocardiogram will be encouraged prestudy for patients with hypertension or age > 60 years;however, may be performed at the physician′s discretion. MUGAs or ECHOs will not need to be repeated if not done.
5 These tests may be done at physician′s discretion prestudy, week 6, and post study. Chest X-Ray or CT- Chest or PET/CT Scan that includes the chest will not need to be repeated if not done.
6 If clinically indicated.
7 Suggested week scheduling listed for x-rays and scans
8 Pre-surgery
9 Mammogram, ultrasound, and MRI should be done within 2-12 weeks from the completion of treatment.

9 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1 Definitions

a. **Inflammatory Disease:** Erythema AND peau d'orange involving 1/3 or more of the breast with a histological diagnosis of breast cancer. The finding of focal dermal lymphatic involvement on histology does not constitute inflammatory breast cancer.

b. **Pathologic complete response (pCR):** No histologic evidence of microscopic invasive tumor at the primary tumor site in the surgical specimen (ypT0 or ypTis).

c. **Clinical complete response:** Normal breast on physical exam. No mass, no thickening, no erythema, no peau d'orange.

d. **Progression of disease:** A new lesion or a greater than or equal to 25% increase in the product of the largest perpendicular diameters of any one lesion on clinical exam or by U/S or MRI

e. **Performance Status**: Patients will be graded according to the Eastern Cooperative Oncology Group (ECOG) performance status scale.

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

9.2 **Time to Progression:** From date of registration to date of first documentation of progressive disease defined as: clear increase in disease sites present at registration, or development of new sites of disease.

9.3 **Survival**: From date of registration to date of death.

9.4 **Breast Cancer Specific Survival**: From date of registration to date of death from breast cancer. Patients who die of other causes will be censored at the time of last contact.

10 STATISTICAL CONSIDERATIONS

The primary endpoint will be the 2-year progression free survival in patients treated with weekly carboplatin and paclitaxel combined with either trastuzumab and pertuzumab for HER2-positive patients or bevacizumab for HER2-negative patients in the neoadjuvant setting. Secondary endpoints will be clinical complete response, pathologic complete response rates, and the toxicity of the regimens.

This is a non-randomized Phase II study with two treatment arms. Clinical and demographic characteristics of the patients in each treatment arm will be described including frequency counts for categorical variables and mean, median, and standard deviation for continuous variables. For continuous variables that are not normally distributed, data transformation will be considered. Progression-free survival (PFS) and the proportion of patients with pathologic complete response (pCR) and clinical complete response (cCR) will be determined. Two-year PFS will be analyzed using the Kaplan-Meier method for the full cohort of patients and for each treatment group. In addition, treatment groups will be compared with regard to the estimated censoring distribution due to early treatment termination using the Kaplan-Meier method. Cox proportional-hazards analysis will be used to derive the hazard ratio and 95% confidence interval (CI) and to adjust for clinical and demographic variables. Let p_1=proportion of Her2-negative patients treated with carboplatin + paclitaxel plus bevacizumab who achieve pCR and let p_2=proportion of Her2- positive patients treated with carboplatin + paclitaxel plus trastuzumab with pertuzumab who achieve pCR. The two-sample test of binomial proportions will be applied to the null hypothesis that $p_1 = p_2$. Exploratory analyses will include application of log-binomial regression to assess the rates of pathologic and clinical complete response for the two treatment groups, adjusted for clinical and demographic measures and interaction variables. Because different treatments are given to the subgroups of Her2-negative and Her2-positive patients, it will not be possible to estimate the independent effect of treatment on response outcomes. The frequency of toxicities will be recorded.

10.1 Sample Size Considerations

Since it is difficult to recruit patients who meet the criteria for neoadjuvant chemotherapy, the total subject number is limited. According to the previous recruitment rate (UCI 07-61), we expect that each year we will be able to enroll and consent 22 patients and expect ~18.5 patients will complete the study treatment. We expect one third with be HER2+ and two thirds will be HER2 negative. In about 6.5 years we expect approximately 120 patients to complete protocol treatment.

Power analyses for evaluation of progression-free survival and pCR

The first study component will evaluate progression-free survival and the response of patients receiving carboplatin+ paclitaxel with trastuzumab and pertuzumab (HER2-positive) or with bevacizumab (HER2-negative) in the neoadjuvant setting. Sample size calculations were performed to assess the power of a one-sample test for survival probability assuming an exponential distribution (Lawless, J. *Statistical Models and Methods for Lifetime Data*, John Wiley and Sons, 1982). The computer program provided by the Southwest Oncology Group for

one arm survival sample size was utilized (http://www.swogstat.org/stat/public/one_survival.htm).

An 85% 2-year progression-free survival in a similar patient population has been reported with AC-based chemotherapy given in the adjuvant setting[10], and similar outcomes have also been reported in the neoadjuvant setting[3,19,20,32]. This historical data will is the basis to assume an alternative survival probability of 85%. Empirically, a disease-free survival of approximately 76% would be unacceptable. As shown in the table below, assuming an accrual rate of 18.5 patients per year (not including loss to follow-up), the two-sided test of significance with an alternative 2-year survival probability of 0.85 has 95% power to detect a difference from the null survival rate of 0.76.

Null	Alternate	Power	Accrual time (months)	Sample size
0.76	0.85	0.95	76	117
0.77	0.85	0.95	85	135
0.78	0.85	0.95	104	160
0.76	0.85	0.9	64	102
0.77	0.85	0.9	76	117
0.78	0.85	0.9	90	138

Based on previous results[14,33,35,36], it is expected that 75% of patients in the HER-2 positive arm will achieve pCR (i.e. 36 pCR and 12 non-pCR), compared to 42% of patients in the HER-2 negative arm (30 pCR and 42 non-pCR). Response rates will be compared between the two treatment groups using a 2-sided test of proportions. Let p_1=proportion of Her2 negative patients treated with carboplatin+ paclitaxel plus bevacizumab who achieve pCR and let p_2=proportion Her2 positive patients treated with carboplatin + paclitaxel plus trastuzumab + pertuzumab who achieve pCR. We will test the null hypothesis that $p_1=p_2$ versus the alternative that $p_1 \neq p_2$. Based on previous results, we expect the ratio of Her2- to Her2+ to be 1.5, and that 75% of patients in the Her2+ arm will achieve pCR (i.e. 36 pCR and 12 non-pCR), compared to 42% of patients in the Her2- arm (30 pCR and 42 non-pCR). PASS was used for sample size calculations. Under these assumptions, at a 5% significance level there is 96% power to detect a difference of 0.33 between the proportions of patients in the two treatment groups achieving pCR.

Power analysis for Aim-1, predicting pCR using the pre-treatment lesion MRI characteristics

In a previous study we performed logistic regression modeling to find optimal parameters for predicting response to AC treatment based on pre-treatment MRI morphological and kinetics parameters. For analysis of data from 33 patients, 17 responders and 16 non-responders, the area under the ROC curve was 0.76 using one morphologic predictor, roughness, compared to 0.84 using one LAWS' texture feature. The AUC for the predictive model including both parameters was 0.91. To address AIM-1, power calculations were performed for comparison of an hypothesized area under a receiver operating characteristic (ROC) curve to a null value of 0.50. Calculations were based on a 1-sided asymptotic *z*-test with significance level of 0.05 using the macro ROCPOWER.SAS (SAS 9.1 SAS, Cary, NC). The table 1 gives the power to compare an alternative AUC of 0.75 for various proportions of patients achieving pathologic complete

remission, i.e. pCR is the "event". Based on our preliminary results, an alternative AUC of 0.75 is achievable with only one predictor in the model.

For example, with the expected enrollment of 48 positive HER-2 patients, of whom 36 of 48 achieve pathologic complete remission, the power for a 1-tailed test is 0.88 for comparing an AUC of 0.75 to the null of 0.50. Higher power is achieved as the proportion of patients achieving pCR approaches 50% of the total enrolled with positive HER-2. Similarly, the expected enrollment of 72 negative HER-2 patients, of whom 30 of 72 achieve pathologic complete remission, the power is 0.99 to compare an improved AUC of 0.75, to a null AUC of 0.50

Table 1: power analysis for comparison of an hypothesized area under ROC to a null value of 0.50

Patient Group	No. (%) pCR	Power
Positive HER-2 (n=48)	36 (75%)	0.88
	30 (62.5%)	0.93
	24 (50%)	0.94
Negative HER-2 (n=72)	36 (50%)	0.99
	30 (42%)	0.99
	25 (34.7%)	0.98

Power analysis for Aim-3, improved pCR prediction by adding tumor size response patterns to the pre-treatment lesion MRI characteristics:

To address aim 3, power calculations were performed for comparison of the area under paired ROC curves assuming an average correlation between the two AUCs of 0.80. Power calculations were based on asymptotic 1-tailed *z*-tests with significance level of 0.05 using the macro ROCPOWER.SAS (SAS 9.1 SAS, Cary, NC). The table 2 gives the power to compare the AUC for paired ROCs for various proportions of patients achieving pathologic complete remission. For example, with the expected enrollment of 48 positive HER-2 patients, of whom 36 of 48 achieve pathologic complete remission, the power for a 2-sided test is 0.83 to detect a significant difference in AUCs, assuming an AUC of 0.75 compared to that of 0.90. Similarly, the expected enrollment of 72 negative HER-2 patients, of whom 30 of 72 achieve pathologic complete remission, the power is 0.97 to detect a significant difference in AUCs assuming an AUC of 0.9 compared to an AUC of 0.75.

Table 2: power calculations for comparison of the area under paired ROC curves between two AUCs of 0.80

Patient Group	No. (%) pCR	AUC 1	AUC 2	Power for 1-sided test	Power for 2-sided test
Positive HER-2 (n=48)	36 (75%)	.75	.9	0.90	0.83
			.95	0.98	0.96
	30 (62.5%)	.75	.9	0.94	0.89
			.95	0.99	0.98
	24 (50%)	.75	.9	0.94	0.90
			.95	0.99	0.98
	36 (75%)	.80	.9	0.67	0.54
			.95	0.91	0.86
	30 (62.5%)	.80	.9	0.73	0.61
			.95	0.95	0.91
	24 (50%)	.80	.9	0.74	0.62
			.95	0.95	0.91
Negative HER-2 (n=72)	36 (50%)	.75	.90	0.99	0.98
			.95	1.00	0.999
	30 (42%)	.75	.90	0.99	0.97
		.	.95	0.99	0.998
	25 (34.7%)	.75	.90	0.98	0.96
			.95	0.999	0.996
	36 (50%)	.80	.90	0.88	0.80
			.95	0.99	0.98
	30 (42%)	.80	.90	0.86	0.77
		.	.95	0.99	0.97
	25 (34.7%)	.80	.90	0.82	0.72
			.95	0.98	0.96

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

a. Informed Consent. The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

b. Institutional Review This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection of Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

11.2 Adverse events will be reported according to the following guidelines from the UC Irvine Office of Research Human Research Protections Program (http://www.rgs.uci.edu/ora/rp/hrpp/adverseexperiences.htm).

DESCRIPTION OF DATA SAFETY MONITORING PLAN (DSMP)

This is a risk level 2 study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is a UCI investigator-initiated interventional trial for which IND/IDE is except by FDA.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to the tables below.

The CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit will conduct monitoring and auditing activities as per the UC Irvine CFCCC Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC DSMB in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site.

Risk Level

Risk Level	Definition	Monitoring
Level 2	**Medium Risk** - UCI investigator-initiated interventional trials for which IND/IDE is exempt by FDA. Example: Use of commercially available agents for an unapproved indication.	Six months after subject enrollment

Recording of Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore. Adverse events and serious adverse events will begin to be collected when the participant starts treatment until 30 days after the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the

investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as any expected or unexpected adverse event that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that meets all three of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; AND
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation- a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Reporting Requirements to the CFCCC DSMB

Unanticipated Problems

Event Type	Reporting Timeframe
Unanticipated Problems	5 business days from the date the PI is aware of the event

Adverse Event/Serious Adverse Events

Event Type	Reporting Timeframe
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*	

Deviations/Violations

Event Type	Reporting Timeframe
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points)	5 business days from the date the PI is aware of the event
Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review

Reporting Requirements to UCI IRB

Report adverse events, serious adverse events, violations, and deviations within 5 business days if the event/incident met the criteria for an unanticipated problem (UP). The current policy can found at the following link: UCI Office of Research

1. Frequency of the DSMB review

   The DSMB will review and evaluate the accumulated data for subject safety, conduct and progress every six months for all sites. In addition, the DSMB will review monthly accumulated adverse events for all sites.

2. DSMB recommendations

   The DSMB will make recommendations concerning continuation, modification or termination of the trial by way of a memorandum or via electronic notification. The Board may identify safety issues and the need for additional data from the site PI; provide advice on issues regarding discrepancies listed in their review findings, or request protocol modifications. In the event the Board has concerns/recommendations, the DSMB will provide rationale for the decision. The PI has 30 days to respond. The DSMB will send a warning notification with an additional 30 days to respond. If an adequate resolution is not achieved at the end of the 60 day period, the Board may forward a recommendation to the IRB for protocol closure due to lack of response. Any unresolved DSMB concerns may be escalated to the Cancer Center Director via the Senior Leadership Council for dispute resolution.

3. DSMB Unscheduled Review

   The DSMB can require the stopping and un-blinding of a study if applicable.Any protocol in the opinion of the DSMB that is generating significant adverse events, unanticipated problems or protocol violations will be audited at the discretion of the Board. This would include questions of frequency and severity. Any protocol for which serious concerns are generated by the DSMB will be referred to the Associated Director of Clinical Research for consideration of a "For Cause" audit.

4. Study team *and IRB* monitoring

   A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria and routine monitoring as follows.

   Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

   Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment. Women of childbearing potential should have a negative pregnancy test prior to starting study drugtherapy and should use adequate contraceptive methods during and for at least 1 week after study drug therapy. If a patient becomes

pregnant despite precautions, she should be apprised of the potential risk of fetal morbidity or loss.

5. Progress reporting

   In addition to the monthly adverse event reviews by the DSMB each sites PI will be required to submit a bi-annual report documenting subject's status and the study progress.

References:

1. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J. Clin. Oncol.* 1998;16(8):2672-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704717. Accessed August 27, 2014.

2. Mieog JSD, van der Hage JA, van de Velde CJH. Preoperative chemotherapy for women with operable breast cancer. *Cochrane database Syst. Rev.* 2007;(2):CD005002. doi:10.1002/14651858.CD005002.pub2.

3. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J. Clin. Oncol.* 2006;24(13):2019-27. doi:10.1200/JCO.2005.04.1665.

4. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J. Clin. Oncol.* 2008;26(5):778-85. doi:10.1200/JCO.2007.15.0235.

5. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J. Clin. Oncol.* 2008;26(8):1275-81. doi:10.1200/JCO.2007.14.4147.

6. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin. Cancer Res.* 2005;11(16):5678-85. doi:10.1158/1078-0432.CCR-04-2421.

7. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352(9132):930-942. doi:10.1016/S0140-6736(98)03301-7.

8. Gennari A, Sormani MP, Pronzato P, et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J. Natl. Cancer Inst.* 2008;100(1):14-20. doi:10.1093/jnci/djm252.

9. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 2001;344(11):783-92. doi:10.1056/NEJM200103153441101.

10. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of

Intergroup Trial C9741/Cancer and Leukemia. *J. Clin. Oncol.* 2003;21(8):1431-9. doi:10.1200/JCO.2003.09.081.

11. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N. Engl. J. Med.* 2008;358(16):1663-71. doi:10.1056/NEJMoa0707056.

12. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J. Clin. Oncol.* 2005;23(25):5983-92. doi:10.1200/JCO.2005.06.232.

13. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J. Clin. Oncol.* 2010;28(7):1138-44. doi:10.1200/JCO.2009.24.2024.

14. Schneeweiss a, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann. Oncol.* 2013;24(9):2278-84. doi:10.1093/annonc/mdt182.

15. Loesch D. Phase II Multicenter Trial of a Weekly Paclitaxel and Carboplatin Regimen in Patients With Advanced Breast Cancer. *J. Clin. Oncol.* 2002;20(18):3857-3864. doi:10.1200/JCO.2002.08.129.

16. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N. Engl. J. Med.* 2011;365(14):1273-83. doi:10.1056/NEJMoa0910383.

17. Sikov WM, Dizon DS, Strenger R, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. *J. Clin. Oncol.* 2009;27(28):4693-700. doi:10.1200/JCO.2008.21.4163.

18. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244(4905):707-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2470152. Accessed September 3, 2014.

19. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER. *Lancet* 2010;375(9712):377-84. doi:10.1016/S0140-6736(09)61964-4.

20. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a

randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol.* 2014;15(6):640-7. doi:10.1016/S1470-2045(14)70080-4.

21. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J. Clin. Oncol.* 2005;23(16):3676-85. doi:10.1200/JCO.2005.07.032.

22. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study. *Clin. Cancer Res.* 2007;13(1):228-33. doi:10.1158/1078-0432.CCR-06-1345.

23. Kim MM, Allen P, Gonzalez-Angulo AM, et al. Pathologic complete response to neoadjuvant chemotherapy with trastuzumab predicts for improved survival in women with HER2-overexpressing breast cancer. *Ann. Oncol.* 2013;24(8):1999-2004. doi:10.1093/annonc/mdt131.

24. Swain SM, Kim S-B, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2013;14(6):461-71. doi:10.1016/S1470-2045(13)70130-X.

25. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25-32. doi:10.1016/S1470-2045(11)70336-9.

26. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J. Clin. Oncol.* 2005;23(4):792-9. doi:10.1200/JCO.2005.05.098.

27. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N. Engl. J. Med.* 2007;357(26):2666-2676.

28. Gray R, Bhattacharya S, Bowden C, Miller K, Comis RL. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J. Clin. Oncol.* 2009;27(30):4966-72. doi:10.1200/JCO.2008.21.6630.

29. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J. Clin. Oncol.* 2011;29(10):1252-60. doi:10.1200/JCO.2010.28.0982.

30. Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast c. *J. Clin. Oncol.* 2011;29(32):4286-93. doi:10.1200/JCO.2010.34.1255.

31. Miles DW, Chan A, Dirix LY, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. *J. Clin. Oncol.* 2010;28(20):3239-3247. doi:10.1200/JCO.2008.21.6457.

32. Von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N. Engl. J. Med.* 2012;366(4):299-309. doi:10.1056/NEJMoa1111065.

33. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N. Engl. J. Med.* 2012;366(4):310-20. doi:10.1056/NEJMoa1111097.

34. Singletary SE, Allred C, Ashley P, et al. Staging system for breast cancer: revisions for the 6th edition of the AJCC Cancer Staging Manual. *Surg. Clin. North Am.* 2003;83(4):803-19. doi:10.1016/S0039-6109(03)00034-3.

35. Mehta RS, Shubbert T, Hsiang D, Kong K. Phase II study of neoadjuvant biweekly doxorubicin and cyclophosphamide (AC) with GM-CSF followed by weekly paclitaxel, carboplatin +/- trastuzumab (TC +/- H) in the treatment of breast cancer (BC). *ASCO Meet. Abstr.* 2005;23(16_suppl):826. Available at: http://hwmaint.meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/826. Accessed October 15, 2014.

36. Mehta RS. In vivo response-adapted dose-dense (dd) doxorubicin and cyclophosphamide (AC) -> weekly carboplatin and albumin- bound paclitaxel (nab-TC) plus trastuzumab (H) or bevacizumab (B) in patients with large and inflammatory breast cancer (BC): A phase II stud. *ASCO Meet. Abstr.* 2008;26(15_suppl):11569. Available at: http://hwmaint.meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/11569. Accessed September 4, 2014.