A Phase II Study of Breast Cancer Treatment Using Weekly Carboplatin+Nab-paclitaxel, plus Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting

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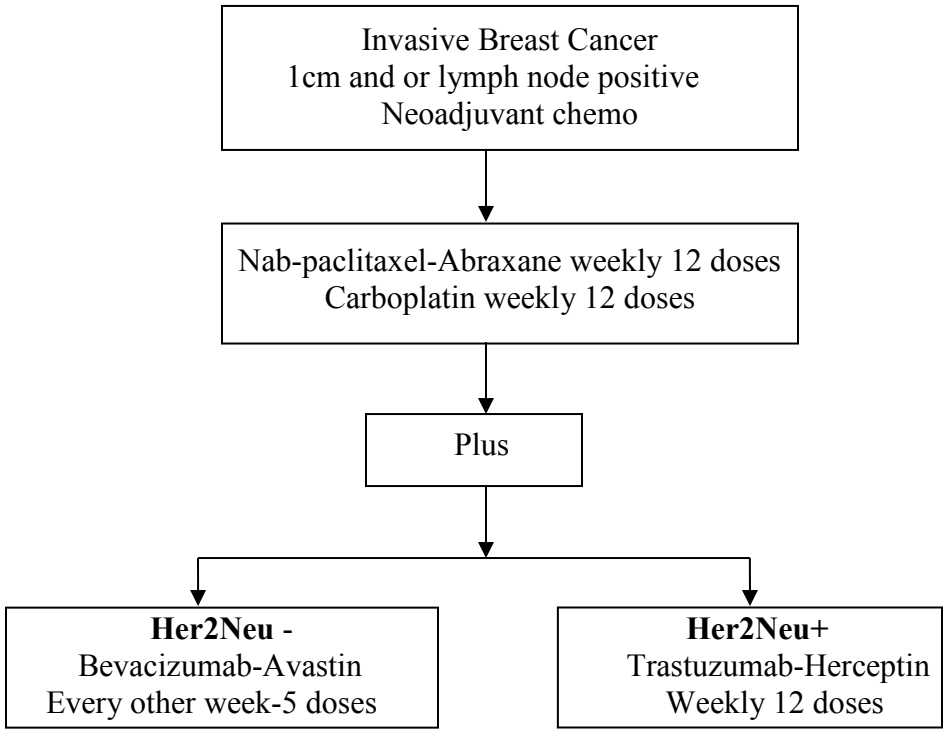
AGENTS:
Nab-paclitaxel (Abraxane®)(ABI 007)
Carboplatin (Paraplatin®) (NSC 241240)
Bevacizumab-Avastin
Trastuzumab-Herceptin

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

SCHEMA

UCI 07-61



1.0 OBJECTIVES

There are two study components, 1) to evaluate the treatment response and toxicity of the protocol, and 2) to investigate the role of Magnetic Resonance Imaging (MRI) to monitor and predict the final pathological response.

Objectives for treatment study component:

1.1 To estimate 2 year progression-free survival in patients with breast cancer more than 1 cm and/or lymph node positive breast cancer treated with weekly Carboplatin/Nab-Paclitaxel (with trastuzumab in patients with HER2+ disease, and with bevacizumab in HER2-).

1.2 To measure clinical response rates in patients treated in the neoadjuvant setting.

1.3 To measure the microscopic pathological response rate of this regimen in patients treated in the neoadjuvant setting.

1.4 To measure the toxicity and delivered dose intensity of this regimen.

1.5 To assess the association between microscopic pathologic complete response and clinical complete response at the primary tumor site in these patients.

1.6 To measure the outcome of patients treated with doxorubicin and cyclophosphamide with patients not treated with doxorubicin and cyclophosphamide.

Objectives for MRI response monitoring study component:

1.7 Develop quantitative analysis methods to obtain pre-treatment tumor characteristic morphological, enhancement kinetic, and Choline metabolic parameters in breast cancer. Select an optimal set of features using the logistic regression analysis and the Artificial Neural Network (ANN) to predict pathologic complete remission (pCR) in HER-2 positive and negative arm.

1.8 Investigate whether the early response patterns, analyzed using the percent tumor size changes, or changes in other lesion characteristic parameters, can be used to predict pathologic complete remission (pCR) in HER-2 positive and negative arm.

1.9 Investigate whether combining the pre-treatment tumor characteristic parameters, and the early response pattern during the treatment course, can achieve a higher AUC (area under the ROC curve) in prediction of pCR than those based on pre-treatment MRI characteristics or tumor response patterns alone.

2.0 BACKGROUND

The aim of neoadjuvant systemic therapy is to reduce the tumor volume in patients before surgical resection, thus reducing the surgical field. More recently, neoadjuvant therapy has been studied as a way of testing the relevance of biological markers in predicting disease outcome, monitoring treatment response, and thereby directing alternative effective therapy in patients with poor response the first line therapy.

The largest trial (1523 patients) run by the NSABP found no differences in disease-free and overall survival in patients treated with neoadjuvant versus adjuvant treatment (1). These trials were done in the era when the pathologic complete responses were typically in the range of 10-15% with non-targeted and non-biologic treatment putting majority of patients at risk of delaying one of the most effective therapy (surgery) needlessly.

But the use of neoadjuvant systemic treatment has been spurred by the use of ever increasing effective targeted systemic therapy with higher pathologic complete response, and accumulating knowledge of complete pathologic response as a surrogate marker of improved overall survival. Therefore, induction of clinical or pathologic Complete Response should be one of the primary goals of neoadjuvant therapy because patients with no evidence of tumor cells in breast and lymph nodes after treatment may have a longer disease-free and overall survival (1-3), and by extrapolation, patients with complete clinical response should similarly have a longer disease-free survival than patients not achieving this response.

Use of anthracycline has been standard in the treatment of breast cancer for over 40 years. Unfortunately, the use of anthracyclines is being questioned as the result of 2 trials (Slamon et al, Jones et al.) have shown diminished therapeutic rational for the use of anthracycline when compared to taxane based non anthracyline regimens. Therefore, while the use or non-use of anthracyline in breast cancer is being hotly contested, use of anthracycline is optional off study. However, the data will be analyzed for the whole group of patients enrolled, and subset analysis will be performed based on use or non-use of anthracycline.

Rationale for the use of Taxane/carboplatin:
Incorporation of taxanes on a 3 weekly schedule has resulted in statistically higher pathological CR (2, 3). Recently, weekly paclitaxel regimens have reported increased pathological responses compared to 3 weekly taxane regimens (4). Carboplatin has also emerged as an effective agent in the treatment of metastatic breast cancer (5). Moreover, the combination of carboplatin and paclitaxel has been found to be additive or synergistic both in three-weekly regimens and weekly regimens. Furthermore, the weekly regimens of these drugs have been found to have significantly improved tolerability over three weekly regimens (6). Albumin bound paclitaxel has been found to have a better therapeutic ratio compared to parent paclitaxel. We plan to administer nab-paclitaxel and carboplatin weekly for a total of 12 doses.

Rationale for the use of nab-paclitaxel:
Abraxane (ABI 007) was approved by the U.S. Food and Drug Administration (FDA) in 2004. Abraxane is a new formulation of paclitaxel that is bound with albumin and delivers high concentrations of this active ingredient to cancer cells with less toxicity. Gradishar et al reported on a large trial with metastatic breast cancer that was treated with either abraxane or paclitaxel. Some patients received prior chemotherapy regimens with progression of disease, while others received no previous chemotherapy. Patients who received abraxane demonstrated almost double the response rate compared to paclitaxel, as well as improvement in duration of survival of 65 weeks compared to 55 weeks in favor of abraxane. The subgroup of patients who received prior chemotherapy regimens had better response rates when treated with abraxane compared to paclitaxel with average survival time of 56 weeks compared to 46 weeks in favor of abraxane. It was concluded that the treatment of metastatic breast cancer with abraxane demonstrates improved therapeutic ratio compared to paclitaxel (7).

The rationale for use of Trastuzumab:

The use of trastuzumab which targets breast cancer with amplified HER2 has demonstrated improved pathologic response, disease-free and overall survival compared to patients not receiving trastuzumab with or without AC, with or without paclitaxel, with or without carboplatin (8-16).

At the San Antonio Breast Cancer Conference on December 8, 2004, we presented the sequential use of doxorubicin and cyclophosphamide (AC) followed by paclitaxel, carboplatin, and trastuzumab (TCH) in patients with Her-2 positive breast cancer. A pathological complete remission (pCR) was seen in 7 of 8 patients. All patients received 2-4 cycles of AC followed by 4 cycles of 3 weekly TCH regimens. Only 1 of 8 patients had a 3mm residual invasive carcinoma in the biopsy scan. Moreover, 7 of 7 patients with palpable lymph nodes demonstrated no residual cancer after this neoadjuvant regimen (17). A confirmatory phase II trial using TC [(+H in Her-2 positive, ± Bevacizumab (B)] in patients following in vivo response adjusted AC showed a high pathologic remission for the whole group of breast cancer patients with strikingly high rates in Her-2 positive breast cancer subset (18). As we found that TC± Bevacizumab, or strikingly TCH reverses anthracycline resistance, the patients may have improved therapeutic ratio without anthracyclines, as anthracyclines are historically associated with cardiac toxicity and leukemia risk. Therefore, we will compare the outcome of patients treated with nabTCH/nab-TCB with or without anthracyclines exposure, adjusted for various prognostic factors. Patients showing progression will be taken off the study.

The rationale for use of bevacizumab:
In metastatic breast cancer, the administration of bevacizumab to capecitabine has shown a significant increase in response rates. The combination arm of bevacizumab plus capecitabine demonstrated a response rate of 19.8% compared to 9.1% in the capecitabine arm alone (17). However, prolonged free survival or overall survival was comparable in both treatment arms. A randomized controlled, multicenter trial enrolled 878 patients who had not received previous chemotherapy for non-small cell lung cancer, and compared standard chemotherapy with paclitaxel and carboplatin with or without bevacizumab. The bevacizumab-based regimen was associated with improved survival compared to paclitaxel and carboplatin alone (18). A multi-center study enrolled 722 women with previously untreated metastatic breast cancer and randomized the patients to receive adjuvant paclitaxel with or without bevacizumab. The trial excluded women who had her-2/neu positive breast cancer unless they received trastuzumab previously or were unable to receive this medication. The analysis revealed a doubling of progression-free survival with the addition of bevacizumab to chemotherapy compared to chemotherapy alone. These findings were presented at ASCO 2006 (19).

3.0 DRUG INFORMATION

3.1 Albumin-stabilized nanoparticle formulation of paclitaxel. (Abraxane) (Nab-paclitaxel) (ABI 007)

a. DESCRIPTION
Abraxane is an albumin-bound nanoparticle of paclitaxel. It is solvent free and therefore does not contain cremophor or Tween 80. The active agent of abraxane is paclitaxel. Solvent-based taxanes affect optimal delivery of the drug to tumor. Abraxane is prepared by the homogenization of paclitaxel to albumin. Paclitaxel is a natural product derived from Taxus media demonstrating antitumor activity in many cancers that is bound to human serum albumin at a concentration of 3%-4% similar to albumin concentration in blood.

Molecular Weight: 853.9
Empiric Formula: $C_{47}H_{51}NO_{14}$
Description: White to yellow sterile, lyophilized powder
Mechanism of Action: A solvent-free taxane that is thought to accumulate in tumors and therefore have increased antitumor activity via albumin-mediated receptor transport. Nab-PC can cross the endothelial wall and then bind to albumin-mediated receptors, such as gp-60 receptors in tumor blood vessel walls. This will allow endocytosis of albumin-bound paclitaxel into the tumor cells by a process called receptor-mediated transcytosis via gb-60 receptors. This allows paclitaxel to penetrate tumor cells and inhibit tumor cell synthesis by binding to microtubules.

b. TOXICITY
The major toxicities include alopecia, which is often reversible, sensory neuropathy (dose-limited), and hematological toxicity (mild and not cumulative). Superficial keratopathy has been documented but this is a reversible and dose related/dependent phenomenon. Other toxicities include mucositis, arthralgias, myalgias, nausea, vomiting. Abraxane may cause bradycardia and hypotension during administration, but these side effects usually do not require treatment. No reported hypersensitivity reactions seen with this drug. Abraxane may cause irritation at the injection site. Reactions include: erythema, swelling, discomfort, or ulceration. These reactions are usually cause by extravasation of the drug into the surrounding tissue.

Pregnancy and Lactation: Abraxane may cause fetal harm when administered to a pregnant woman. Since the active agent of abraxane is paclitaxel and paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats, women should avoid becoming pregnant while on this medication. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased reabsorption and embryo-fetal deaths. Studies have also shown paclitaxel to be present in the breast milk of animals and therefore women should avoid breastfeeding when taking this medication. No information is available on the excretion of this drug in human milk.

c. PHARMACOLOGY
Formulation: Each mL of the reconstituted formulation will contain 5mg/mL paclitaxel. Each vial contains 100mg of abraxane in an individualized carton.
Solution Preparation: Abraxane is reconstituted by injecting 2mL of 0.9% Sodium Chloride Injection, USP over a minute onto the wall of the vial. Direct injection of 0.9% Sodium Chloride onto the solution will result in foaming. After the injection is complete, the vial must sit for a minimum of five minutes to allow the lyophilized power to wet and then must be swirled to allow for complete resolution of the powder. Each bag/bottle should be prepared immediately before administration.
Administration of Nab-paclitaxel: Nab-paclitaxel, at the appropriate dose, will be given as a continuous IV infusion over 30 minutes as specified in the protocol, diluted in 0.9% Sodium Chloride Injection, USP. Nothing else is to be infused through the line where paclitaxel is being administered. Premedication to prevent hypersensitivity reactions is not required prior to the administration of abraxane.
Storage and Stability: The intact vials of abraxane should be stored between 20-25°C. Unopened vials are stable until the expiration date and in the original bag to protect it from bright light. Reconstituted abraxane should be used immediately, but may be refrigerated at 2 degrees Celsius to 8 degrees Celsius for a maximum of eight hours.
Supplier: Commercially available

3.2 Carboplatin (Paraplatin®) (NSC 241240)

a. DESCRIPTION
Carboplatin (CBDCA) 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, hepatic toxicity, electrolyte imbalance, hypomagnesemia, hypocalcemia, 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 8hours 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.

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, and sinusitis. 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. Rash, nausea, vomiting, myelosuppression, and hypoprothrombinemia. 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.

3.4 Bevacizumab (Avastin)

a. DESCRIPTION

Bevacizumab is a recombinant human/murine monoclonal antibody to the vascular endothelial growth factor receptor.

b. TOXICOLOGY

Adverse effects include nausea, vomiting, diarrhea, anorexia, asthenia, abdominal pain, headache, deep vein thrombosis, hypertension, and constipation. Thrombocytopenia is commonly seen. Other side effects include proteinuria, nephritic syndrome, congestive heart failure, gastrointestinal perforations, dyspnea, epistaxis, severe hemorrhage, 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 was reported in 22/1032 patients who received avastin. CHF occurred in 6/44 patients who received avastin with concurrent anthracycline and 13/299 patients who received prior anthracyclines and/or left chest wall irradiation. The safety of continuation or resumption of avastin 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.

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 (22). 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: _____

____ 5.1 Patients must be women with a histologically confirmed diagnosis of breast cancer that is more than 1 cm and or lymph node positive.
Inflammatory breast cancer? (circle) Yes No

____ 5.2 Physical examination, and scans needed for tumor assessment must be performed within *90* days prior to registration.
Date of physical examination _____
Date of mammogram _____
Date of breast Ultrasound_____
Date of MRI breast_____

____ 5.3 Patients with the clinical diagnosis of congestive heart failure or angina pectoris are NOT eligible.

____ 5.4 Patients must have a serum creatinine and bilirubin within normal limits, and an SGOT or SGPT ≤ 2x the institutional upper limit of normal. These tests must have been performed within *90* days prior to registration.

Serum creatinine _____ IULN _____ Date Obtained _____

Bilirubin _____ IULN_____ Date Obtained _____

SGOT/SGPT (circle one) _____ IULN _____ Date _____

____ 5.5 Patients must have an ANC of ≥ 1,500/µl and a platelet count of ≥ 100,000/µl. These tests must have been performed within *90 d*ays prior to registration.

ANC_____ Platelets _____ Date Obtained _____

____ 5.6 Patients must have a performance status of 0-2 by Zubrod criteria (see section 10.2)

____ 5.7 Pregnant or nursing women may not participate due to the possibility of fetal harm or of harm to nursing infants from this treatment regimen. Women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.
Pregnancy test required for women of childbearing potential.

____ 5.8 In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a 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.

____ 5.9 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.

6.0 TREATMENT PLAN

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

6.1 Good Medical 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.

6.2 MRI Response Monitoring Study

If the subject also agrees to participate in the MRI response monitoring study, she will come to Center for Functional Onco-Imaging at Irvine campus for 4-5 MRI studies, one baseline before treatment, and 3-4 during the course of therapy before surgery. The study will be performed on the 3T scanner. After subject arrives at the center, she will fill out a medical questionnaire for the investigators to determine whether there are any contradictions for participating in this study. If not, the subject will be prepared for the study, including changing of clothes, and set-up of an IV line. Then the subject will be placed into the MRI scanner at a prone (facing down) position. The bilateral breasts will be positioned into a bra-shaped MR coil. After collecting some pre-contrast images, the MR contrast agent, Gadolinium (Omniscan® 287mg/ml Injections, 1 cc/10 lb body weight), will be injected

through the IV line. The imaging time for the entire protocol will last approximately one hour. The study time including preparation is approximately 1.5 hours.

The MRI schedule is summarized in the table below. The baseline study will be done before treatment. The first follow-up (F/U-1) is after week-4 chemo infusion. If the subject showing greater than 10% tumor size shrinkage, she will receive second follow-up (F/U-2) at week-12 after completing this protocol. If the tumor in F/U-1 is showing less than 10% reduction, the F/U-2 will be done after week-8 chemo infusion, and F/U-3 done at week-12 after completing this protocol. After completing the 12 weeks treatment the doctors may decide to give the subject additional chemotherapy using standard of care protocol, then she will receive another F/U after completing all treatment before surgery.

Week-4			Week-8	Week-12	if given more therapy
Baseline MRI	F/U-1 MRI	<10% size reduction	F/U-2	F/U-3	F/U-4
		>10% size reduction	→	F/U-2	F/U-3

6.3 Treatment: Weekly Carboplatin/Nab-Paclitaxel, (and Trastuzumab in HER2+ BC, Bevacizumab in HER2- BC).

Agent	Dose	Route	Days	Interval
Nab-paclitaxel***	90 mg/m^2	IV over 30 min.	1	weekly 12 doses
Carboplatin	AUC 2	IV over 60 min.	1	weekly 12 doses
Trastuzumab (for HER2+)	4mg/kg induction, followed by weekly 2mg/kg	IV-induction over 90 min., then weekly over 30-60 min.	1	weekly 12 doses
Bevacizumab (for HER2-)	10mg/Kg	IV over 90 or 60 or 30 min.	1	Every other week for 5 doses

*** Nab-paclitaxel must be administered prior to Carboplatin

1. Dosing of Carboplatin-The dose of Carboplatin will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft & Goult formula.

$$\text{GFR} + 0.85 \left[\frac{(140 - \text{age}) \times \text{Ideal Body Weight (Kg)}}{72 \times \text{Serum Creatinine}}\right]$$

Carboplatin Dose = Target AUC x (GFR + 25)
GFR will be capped at 125

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

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

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

6.4 Response Assessment

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

6.5 Surgery

Post-chemotherapy surgery for patients with a response or stable disease must take place no sooner than 21 days after last dose of Herceptin; and 40 days after last dose of bevacizumab to allow for normalization of blood counts.

Patients who progress will be removed from protocol treatment. Patients who have unresectable disease at the completion of chemotherapy will be taken off the study. 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. Delay of treatment for more than 3 weeks for hematologic toxicity or more than 2 weeks for other toxicity.
c. Unacceptable toxicity.
d. Completion of planned treatment.
e. The patient may withdraw from the study at any time for any reason.
f. Unresectability of the breast cancer

6.7 All patients will be followed for five years or until death, whichever occurs first.

7 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

7.1 This study will utilize the CTC (NCI Common Toxicity Criteria) Version 3.0 for toxicity and Adverse Event reporting. A copy of the CTC Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

7.2 Dose Modifications for Nab-paclitaxel/carboplatin – Chemo will be on hold if the following criteria are not met.

a. Hematologic: 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 Colon Stimulating Growth Factors).

b. Hepatic: Patients with Grade 4 hepatic toxicity will have nab- 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 (nab-paclitaxel only): Patients who experience ≥ Grade 3 peripheral neuropathy should have their nab-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 dose another week then resume with a reduction of 25% for this and subsequent cycles.

e. Proteinuria (Bevacizumab) Hold if Spot Urine Protein/Creatinine is greater than 3.5.

f. HTN (Bevacizumab): Patients will be treated with antihypertensive medicines at the physicians' discretion. Hold if BP> 150/90.

g. g . Other (for both carboplatin and nab-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. All held doses will be made up at the end of the treatment. Bevacizumab and Trastuzumab are given even if chemotherapy is held.

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/Nab-Paclitaxel, Plus 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/U9
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 (Avastin patients only. Week prior to scheduled Avastin)	X		X				X							
X-RAYS AND SCANS[8]														
Echocardiogram or MUGA [4]	X													X
Breast mammogram, breast ultrasound, for disease assessment	X						X							X
MRI breast	X				X[6]				X[6]					X
PET/CT	X[5]						X							X5
Bone scan	*X*[7]													
TREATMENT (See Section 6.0)														
Nab-paclitaxel-Abraxane		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/Herceptin (HER2+)		X	X	X	X	X	X	X	X	X	X	X	X	
Bevacizumab/Avastin (HER2-)		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, SGOT or SGPT.
[4] MUGA or echocardiogram is encouraged prestudy and at the completion of chemotherapy. MUGA or echocardiogram will be obtained prestudy for patients with hypertension or age > 60 years.
[5] These tests are encouraged prestudy, week 6, and post study.
6 See protocol section 6.2.
7 If clinically indicated.
8 Suggested week scheduling listed for x-rays and scans
9 Pre-surgery

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 findings of focal dermal lymphatic involvement on histology does not constitute inflammatory breast cancer.

b. **Microscopic path CR (pCR):** No evidence of microscopic invasive tumor at the primary tumor site in the surgical specimen.

c. **Clinical CR:** 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 Zubrod 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. Patient 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 with the nab-TCB/Nab-TCH regimen in the adjuvant setting. Secondary endpoints will be clinical complete response, pathologic complete response rates, and the toxicity of the combinations in HER2 positive and HER2 negative breast cancer will be secondary endpoints.

This is a non-randomized 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. Transformations will be considered for continuous variables that are not normally distributed. Progression-free survival and the proportion of patients with pathologic complete response (pCR) and clinical complete response will be determined. Two-year progression free survival will 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 between the two treatment arms, adjusted for clinical and demographic variables. The ninety-five percent confidence interval (CI) for each proportion will be computed. Let p_1=proportion of Her2- patients treated with Carboplatin+Nab-paclitaxel plus Bevacizumab who achieve pCr and let p_2=proportion Her2+ patients treated with Carboplatin+Nab-paclitaxel plus Trastuzumab 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 terms. Because different treatments are given to subgroups of Her2- and Her2+ patients, it will not be possible to estimate the independent effect of treatment on response outcomes. The frequency of toxicities will be recorded.

Patients will be invited to participate in an MRI study, funded by NCI CA 127927, entitled “Prediction of Neoadjuvant Chemo Pathological Response Using MRI Markers”. The objective is to investigate the role of MRI in monitoring and predicting the final pathological response. Three aims are proposed. The power analysis was performed for these aims.

Aim 1: Develop quantitative analysis methods to obtain pre-treatment tumor characteristic morphological, enhancement kinetic, and Choline metabolic parameters in breast cancer. Select an optimal set of features using the logistic regression analysis and the Artificial Neural Network (ANN) to predict pathologic complete remission (pCR) in HER-2 positive and negative arm.

Aim 2: Investigate whether the early response patterns, analyzed using the percent tumor size changes, or changes in other lesion characteristic parameters, can be used to predict pathologic complete remission (pCR) in HER-2 positive and negative arm.
Aim 3: Investigate whether combining the pre-treatment tumor characteristic parameters, and the early response pattern during the treatment course, can achieve a higher AUC (area under the ROC curve) in prediction of pCR than those based on pre-treatment MRI characteristics or tumor response patterns alone.

The role of MRI in monitoring and predicting the final pathological response will be investigated. In brief, artificial neural network (ANN) analysis will be applied to differentiate between pCR and non-pCR subjects with jackknife leave-one-out cross validation. After the selection, ANN models will be built to test the discriminative ability of morphologic/texture, kinetic, and combined features. Since patient age and tumor grade are likely confounding factors, they will be included in the input parameters. The receiver operating characteristic (ROC) curve of the classifier will be recorded. The area under the ROC curve (AUC) will used to evaluate classification performance. For comparison to results by ANN, statistical methods for variable reduction and logistic regression modeling also will be applied to avoid including correlated predictors and overfitting. Transformations will be considered for variables that exhibit departures from normality. The objective is to find parameters in pre-treatment biomarker data category to differentiate between pCR and non-pCR. A final set of parameters that can achieve the highest accuracy in differentiating between pCR and non-pCR within each treatment arm will be identified. The area under the ROC curve achieved by using each data category alone and combined will be compared to test the hypothesis that combining all 3 data categories can achieve a higher accuracy in prediction of pCR than using either set of data alone. Models selected by ANN and by logistic regression will be compared with regard to sensitivity, specificity, positive and negative predictive value, and AUC.

10.1 Sample Size Considerations

Eligible patients will be patients who do not have metastatic disease at presentation.

Many times patients sign consent before all studies are complete given we have to submit to insurance in parallel, so as not to prolong pretreatment time. This means some patients have metastatic disease found either by scans or later on biopsy. These patients are not eligible.

Eligible patients will be patients who received all protocol drugs and complete at least one cycle. Many patients sign consent, but the drugs get denied by insurance, these patients will not be eligible for study.

Some patients choose alternative Rx after signing consent these patients will not be eligible

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, we expect that we will be able to enroll 120 patients during 4.5 years, 48 positive HER-2 patients and 72 negative HER-2 patients.

Power analyses for evaluation of progression-free survival and pCr

The first study component is to evaluate progression-free survival and the response of patients receiving Carboplatin+Na-paclitaxel, plus Trastuzumab (HER2+) or Bevacizumab (HER2-) 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% progression-free survival on a similar patient population in the adjuvant setting has been reported with use of AC-based regimen. Empirically, a disease-free survival of approximately 78% would be unacceptable. As shown in the table, assuming an accrual of 48 months, a follow-up time of 36 month, the two-sided test of significance with an alternative survival probability of 0.85 has 95% power to detect a difference from the null survival rate of 0.76.

Null survival probability	Alternative survival probability	Power
0.76	0.85	0.95
0.77	0.85	0.91
0.78	0.85	0.82
0.79	0.85	0.71

Based on previous results, it is expected that 75% of patients in the positive HER-2 arm will achieve pCR (i.e. 36 pCR and 12 non-pCR), compared to 42% of patients in the negative HER-2 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- patients treated with Carboplatin+Nab-paclitaxel plus Bevacizumab who achieve pCr and let p_2=proportion Her2+ patients treated with Carboplatin+Nab-paclitaxel plus Trastuzumab 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.

The 2nd study component is to investigate the role of Magnetic Resonance Imaging (MRI) to monitor and predict the final pathological response.

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 UCIrvine Office of Research Human Research Protections Program (http://www.rgs.uci.edu/ora/rp/hrpp/adverseexperiences.htm).

Researcher Responsibility to Report Adverse Events/Unanticipated Problems Involving Risk to Participants or Others/Protocol Violations

Federal regulations require that UCI have written procedures for ensuring prompt reporting of unanticipated problems involving risk to subjects or others to the IRB, appropriate UCI officials, the funding agency or study sponsors, and federal department or agency heads including the Office of Human Research Protections (OHRP), the Food and Drug Administration (FDA), when applicable. Per UCI IRB policy the following events or problems must be reported to the UCI IRB within the specified timeframe via the electronic Adverse Events/Unanticipated Problems (AE/UP) reporting process.

The IRB will review the AE/UP report in a timely manner and determine whether the reported event is an unanticipated problem involving risk to participants or others (*hereinafter referred to as unanticipated problems*). Unanticipated problems will be reported to the appropriate entities per UCI IRB policy.

Reportable Events/Problems	
Report any event/problem listed below to the IRB within the specified timeframe	
1	Any unexpected, internal adverse events or external adverse events that occur anytime during the conduct of the research study or during the follow-up period after the research, which in the opinion of the UCI Investigator includes the following components: 1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents, such as the protocol and informed consent document; and (b) the characteristics of the subject population being studied; 2. Related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or problem may have been caused by the procedures involved in the research); and 3. Suggests that the research places subjects at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Report within 10 working days of the researcher becoming aware of the event.
2	Any internal, serious adverse event that is, 1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents, such as the protocol and informed consent document; 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 problem may have been caused by the procedures involved in the research). Report within 5 working days of the researcher becoming aware of the event.
3	Any external adverse event that occurs anytime during the conduct of the research study or during the follow-up period after the research, which in the

	opinion of the UCI Investigator: 1. changes the study's risk/benefit profile; ***and/or*** 2. necessitates submission of an e-MOD request to revise the IRB-approved consent document(s) and/or the IRB-approved protocol. Report within 10 working days of the researcher becoming aware of the event.
4	An event/problem that affects the safety and welfare of subjects and requires prompt reporting to the sponsor. Report within 10 working days of the researcher becoming aware of the event.
5	Any permanent or temporary hold on some or all research activities. Report within 10 working days of the researcher becoming aware of the event.
6	Early termination of the study due to a change in the risk/benefit profile. Report within 10 working days of the researcher becoming aware of the event.
7	Any change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in an IRB approved research study due to adverse events or unanticipated problems. Report within 10 working days of the researcher becoming aware of the event.
8	Protocol Violations Report within 5 working days of the researcher becoming aware of the event.
9	Any change to the IRB-approved protocol conducted without prior IRB approval to eliminate an apparent immediate hazard to a research subject. Report within 5 working days of the researcher becoming aware of the event.
10	Any publication in the literature, any safety monitoring reports, interim results, or other reports that indicates an unexpected change to the risk/benefit profile of the research. Report within 10 working days of the researcher becoming aware of the event.
11	Any breach in confidentiality that caused harm or places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm). Report within 10 working days of the researcher becoming aware of the event.
12	Any complaint by a subject that indicates an unexpected risk or which cannot be resolved by the UCI Investigator. Report within 10 working days of the researcher becoming aware of the event.
13	Other event/problem that involved subjects or others and which in the opinion

	of the UCI Investigator includes the following three components: 1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents, such as the protocol and informed consent document; and (b) the characteristics of the subject population being studied; 2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and 3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Report within 5 working days of the researcher becoming aware of the event.
The IRB will accept other reports when Investigators are unsure whether the event/problem should be reported.	

NOTE:

1. When changes to the IRB-approved documents (e.g., protocol narrative, informed consent form) are necessary, the Researcher must submit an electronic Modification (e-MOD) Request. **Please reference the e-AE/UP number when submitting the e-MOD request**.
2. Reasonable judgment must be used when determining what constitutes a reportable event, experience, or problem. Researchers must consider the psychological, emotional, economic and social harms, not merely physical harms. When in doubt, it is best to err on the side of reporting the event or contacting the HRP staff for guidance.
3. A follow-up report is required to be submitted via the e-AE/UP process if the AE is not resolved as expected or if the AE results in a chronic condition or death.

Adverse Events

Adverse events are untoward or undesirable experiences associated with research, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events may be the result of:

- the interventions and interactions used in the research,
- the collection of identifiable private information in the research,
- an underlying disease, disorder, or condition of the subject, and/or
- other circumstances unrelated to the research.

Most adverse events are not reportable to the IRB. The majority of adverse events that occur in the context of research are expected: (1) the known toxicities and side effects

of the research procedures; (2) the expected natural progression of the subjects' underlying diseases, disorders, and conditions; and (3) subjects' predisposing risk factor profiles for adverse events.

UNEXPECTED ADVERSE EVENT: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- **the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the IRB-approved documents (e.g., applicable investigator brochure, current protocol narrative, current informed consent document), and (b) other relevant sources of information, such as product labeling and package inserts; or**
- **the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.**

Unexpected adverse events as defined above are reportable to the IRB via the e-AE/UP process if in the opinion of the UCI Researcher, the event is *related* to the research procedures. That is, if the event could at least possibly be caused by the research activities, and suggests that the research places the subjects at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized. See the List of Reportable Events/Problems.

SERIOUS ADVERSE EVENT: is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- **results in death, #**
- **is life-threatening situation,**
- **requires inpatient hospitalization or prolongation of existing hospitalization,**
- **results in persistent or significant disability/incapacity,**
- **results in a congenital anomaly/birth defect,**
- **any *other adverse events* based upon the Researcher's medical judgment, that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.**

Serious adverse events as defined above are reportable to the IRB via the e-AE/UP process if in the opinion of the UCI Researcher, the event is "unexpected" and "related" to the research procedures. See the list of Reportable Events/Problems. Note the following exception:

Clinical Investigations exception: All internal, serious adverse events resulting in death that, in the judgment of the UCI Investigator, appear unrelated to the research procedures must still be reported to the IRB via the Internal Unrelated SAE Summary Log at the time of Continuing Review.

Protocol Violations

PROTOCOL VIOLATION: Accidental or unintentional change to, or non-compliance with the IRB approved protocol without prior sponsor and IRB approval. Violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data.

Protocol Violations are reportable events and must be submitted to the IRB via the e-AE/UP reporting process within *5 working days* of the researcher becoming aware of the event. See the list of Reportable Events/Problems.

Examples of protocol violations:

1. Failure to obtain valid informed consent (e.g., obtained verbal consent when IRB requires signed informed consent)
2. Loss of laptop computer that contained identifiable, private information about subjects
3. Accidental distribution of incorrect study medication

Protocol Deviations

PROTOCOL DEVIATION: Accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff.

A deviation may be due to the research subject's non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher. Examples of a deviation include:

1. A rescheduled study visit
2. Failure to collect an ancillary self-report questionnaire
3. Subject's refusal to complete scheduled research activities

Deviations are NOT reportable to the IRB. Investigators may report deviations to the Human Research Protections (HRP) staff by submitting the Tracking Log for Non-reportable Events. The HRP staff will confirm that the event does not qualify as a reportable event and send an acknowledgment to the researcher. If the event/problem is determined to be reportable, the Lead Researcher will be required to submit an e-AE/UP report.

It is the responsibility of the Lead Researcher to ensure that all research staff involved in the conduct of the research follows the IRB-approved research protocol. When modifications are necessary, an e-MOD request should be submitted to the IRB for review and approval prior to implementation of the changes.

Safety Reports/External Adverse Events

Safety Report (SR) alerts are issued by the FDA or the study sponsor to inform all researchers using the same pharmacological compound about serious adverse events or reactions that have occurred in patients/subjects. These events, considered external adverse events, may occur on the same clinical investigation being conducted by a UCI investigator, or more often these SR events occur on different clinical investigation using the same pharmacological compound as the UCI investigator.

It is the UCI Investigator's responsibility to ensure that each external adverse event is reviewed to determine whether the event is reportable to the IRB. External adverse events should be submitted to the IRB within the 10 working day timeframe if in the opinion of the UCI researcher the event is: [See 1 and 3 on the List of Reportable Events or Problems]

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved documents; and (b) the characteristics of the subject population being studied;
- At least possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or problem may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OR the event:

- changes the study's risk/benefit profile; and/or
- necessitates submission of an e-MOD request to revise the IRB-approved consent document(s) and/or the IRB-approved protocol.

Safety Reports that do not meet the 10 working day reporting timeframe are NOT reportable to the IRB. The researcher should initial and date the Safety Report and file with research documentation.

Reporting Methods and Timeframes

The following are types of events/problems require reporting to the IRB. If the event/problem does not fit the categories, the event is not reportable to the IRB; however may be reportable to the sponsor. Please notify the IRB within the specified reporting timeframe, followed by follow-up reports, as required.

Type of Event/Problem	Reporting Timeframe	Reporting Method
Any • internal, serious adverse event,	5 working days	e-AE/UP report

• protocol violation, • change to the protocol without prior IRB approval to eliminate an apparent immediate hazard to a research subject [see # 9] • other event/problem involving subjects or others tht is unexpected, related or possibly related to the research, and caused harm to others or places others at a greater risk of harm as a result of the research [see # 13]		
Any other event/problem described in the list of Reportable Events/ Problems	10 working days	e-AE/UP report
Any external adverse event described in the list of Reportable Events/ Problems (e.g., Safety Report)	1. 10 working days if event constitutes a reportable event [see # 1 and 3 on the list] 2. If not on list, reporting **NOT** required	1. e-AE/UP report 2. none
Any protocol deviation	1. Reporting **NOT** required 2. Researchers may report deviation to HRP staff	1. none 2. Tracking Log for Non-reportable Events
Any internal, unrelated death as determined by UCI Investigator *[REQUIRED FOR CLINICAL INVESTIGATIONS ONLY]*	At time of Continuing Review	Internal Unrelated SAE Summary Log

Important Notes when completing e-AE/UP report:

1. In order to maintain the subject's privacy, please **do not include any names and/or other personal identifiers** in the report and remember to remove all identifiable, private information from any supporting documentation you provide the IRB.
2. If the event/problem requires submission of an e-MOD request, please remember to submit a highlighted or underlined version of the revised document(s).

3. If an internal event/problem is unresolved at the time of initial reporting, a follow-up report is required to be submitted via the e-AE/UP process if the AE is not resolved as expected or if the AE results in a chronic condition or death.

Reporting DSMB Interim Reports to the IRB

The Lead Researcher is expected to review any Data and Safety Monitoring interim report and determine whether the report indicates a change in the risk/benefit profile. If the report indicates a change in the risk/benefit profile, an e-AE/UP report should be submitted [see #10 on the list of Reportable Events/Problems] to the IRB along with an e-MOD request. Be sure to reference the e-AE/UP number when submitting the e-MOD request. If there is no change in the risk/benefit profile, the DSMB report should be submitted along with the Summary Log, if applicable, at the time of continuing review.

IRB Actions Regarding Unanticipated Problems Involving Risk to Participants or Others

The IRB will review e-AE/UP reports in a timely manner and determine whether the reported event represents an unanticipated problem involving risk to participants or others. The IRB may take the following actions:

- Accept the report with no changes;
- Accept the report with changes to the risk/benefit ratio, the protocol, or the informed consent documents (submission of e-MOD Request required);
- Request re-consenting of participants or require notification to current and past participants of the changes (the changes must be reviewed by the IRB prior to notification);
- Request further information from the researcher or DSMB;
- Increase the frequency of continuing review;
- Impose additional monitoring requirements;
- Require additional training of the researcher and research team;
- Require notification of researchers at other sites; or
- Request "Administrative Hold" pending receipt of further information.

The IRB will report any unanticipated problems involving risk to participants or others to the Lead Researcher, appropriate UCI officials, the funding agency or study sponsor, if applicable, the Office of Human Research Protections, and other applicable regulatory authorities.

IRB Authority to Suspend or Terminate Approval

The IRB also has the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to participants. When an IRB Committee takes such action, it is required to provide a statement of reason for the action and to promptly report this action to the Lead Researcher, Department Chair or School Dean, and other UCI officials, the funding agency or study sponsor, if applicable, the Office of Human Research Protections, and possibly other regulatory authorities.

Serious Adverse Event Reporting Requirements for Human Gene Transfer Research

Lead Researchers of human gene transfer (a.k.a. "gene therapy") protocols have extra adverse event reporting responsibilities. In addition to submitting AE/UP reports to the UCI IRB, they also must complete and submit the NIH Office of Biotechnology Activities' (OBA) Serious Adverse Event report form when a subject on a gene transfer protocol experiences a hospitalization or a death. If the gene transfer study is supported by an external sponsor, this reporting should be coordinated with the sponsor.

Failure to report gene transfer SAEs to the federal oversight bodies (FDA, NIH-OBA) may result in sanctions for the individual researcher and for the institution. For more information regarding the additional AE reporting responsibilities for human gene transfer research, please contact a UCI biomedical IRB Administrator.

Serious Adverse Events or Unanticipated Problems Involving Risk to Participants or Others Related to a Humanitarian Use Device (HUD)

Whenever the physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that a HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA and the IRB as soon as possible, but no later than **5 working days** after the physician first learns of the event/problem. This reporting is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements in accordance with 21 CFR 803.30.

The physician or health care provider must promptly report any FDA action regarding the death or serious injury to the patient to the IRB.

11.2 Sponsorship: An NIH/NCI R01 CA127927 grant has been submitted for the data management of this trial. If funding is obtained, sponsors' adverse event report guidelines will also be followed.

11.3 Early Termination: Patients may be discontinued from participating in the study prior to completion of study requirement for any of the following reasons:

1. The patient has a clinically significant adverse event as determined by the Principal Investigator.
2. The patient requests to be withdrawn from the study.
3. The patient fails to comply with the requirements for study evaluations and visits.
4. Other conditions for which, in the investigator's opinion, it is in the patient's best interest to be withdrawn from the study. Patient did not meet the eligibility requirements.

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