Official Title:	**A Phase 2 Trial of Liposomal Doxorubicin and Carboplatin in Patients with ER, PR, HER2 Negative Breast Cancer (TNBC)**
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by cytology or pleural biopsy.

9.1.8 Skeletal

Acceptable documentation includes (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, (ii) biopsy proof of bone metastases, or (iii) bone scan or PET scan clearly positive for bone metastases. Note: If the diagnosis is equivocal by bone scan or radiologic evaluation or there are no other suspected sites of metastasis, a biopsy is strongly recommended for definitive diagnosis and for serial genomic analysis. A bone scan with uptake limited to joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

9.1.9 Liver

Acceptable documentation includes: (i) abdominal CT scan, liver scan, ultrasound, MRI, or PET scan consistent with liver metastases or (ii) liver biopsy confirmation of the metastatic disease. Note: If the radiologic findings are not definitive (especially with solitary liver nodules) or no other biopsy sites are available, a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

9.1.10 Central nervous system

Acceptable documentation includes: (i) positive CT scan or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology.

9.1.11 Second primary breast cancer

Defined as evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed by core, incisional or excisional biopsy. Cytology alone will not be adequate to document a second breast cancer primary.

9.1.12 Second primary cancer

Second primary cancer is defined as invasive or non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

9.1.13 Documentation requested following death

- Autopsy reports should be secured whenever possible.
- A copy of the death certificate should be forwarded to OHRS if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

9.2 Guidelines for Evaluation of Disease of the Breast and Axilla and Suspected Relapse

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

9.2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are palpable (e.g., breast mass and

[redacted]

palpable lymph nodes).

9.2.2 Digital Diagnostic Mammogram

All patients are required to have digital diagnostic mammography prior to treatment to document tumor size and other imaging characteristics. Ultrasound does not supplant the performance of a diagnostic mammogram.

9.2.3 Breast Ultrasound

Ultrasound will be used to confirm the complete disappearance of palpable lesions assessed by clinical examination. It may also be used for determining size of palpable breast or lymph node lesions, for biopsy guidance, and for clip placement.

9.2.4 Conventional CT and MRI

These techniques will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to suspected tumors of the chest, abdomen, and pelvis.

9.2.5 Whole Body Bone Scan

This scan should be performed for staging at initial diagnosis to identify potential metastatic foci and to restage at time of symptoms to rule out suspected distant bony metastasis.

9.2.6 Clip Placement

Patients should have clip placement at the time of breast biopsy to approximate location of disease at time of surgery. For patients in whom no clips were placed at the time of biopsy, clips should be placed by the treating surgeon prior to initiation of chemotherapy.

9.2.7 CT head

Patients with symptoms suggestive of potential central nervous system metastasis, may undergo CT head with contrast as initial study. However, if cerebellar signs are present, consideration of MRI brain with and without gadolinium should be considered.

9.3 Response Criteria

9.3.1 Gross Residual Disease

Breast tissue from the definitive breast surgery will be sent to the RWJUH pathology department for evaluation. Specimens with residual disease measuring 5mm or more in the breast or any residual disease in the lymph nodes will be identified as having gross residual disease. For synchronous disease, all foci will be measured.

9.3.2 Evaluation of Breast Lesions

Determination of best response in the breast will be determined at the time of pathologic analysis of tissue from the definitive breast surgery unless patient clinically progresses during neoadjuvant treatment. Evaluation will be made based on the Miller-Payne Criteria as outlined below. Grades 1–4 are categorized as partial pathological response (pPR) and grade 5 is a complete pathological response (pCR). Residual ductal carcinoma in situ only is classified as a complete response [83].

[redacted]

Miller-Payne Histological Grading System Following Neoadjuvant Chemotherapy for Patients with Breast Cancer	
Grade	Definition
1	No change or some alteration to individual malignant cells but no reduction in overall cellularity.
2	A minor loss of tumor cells but overall cellularity still high; up to 30% loss.
3	Between an estimated 30% and 90% reduction in tumor cells.
4	A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells.
5	No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains often containing macrophages. Ductal carcinoma in situ (DCIS) may be present.

9.3.3 Evaluation of Lymph Nodes

Determination of best response in the lymph nodes will be determined at the time of pathologic analysis of tissue from the definitive surgery unless patient clinically progresses during neoadjuvant treatment. Although there are three categories for best response in the axillary lymph nodes, any category other than complete response will be treated as residual disease.

Complete Response (CR):	Disappearance of all palpable nodes at the microscopic level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more lymph nodes
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing lymphadenopathy.

9.3.4 Evaluation of Best Overall Response-

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. For synchronous disease, the largest breast lesion at diagnosis will serve as the target lesion for calculation of overall response rate for this study. Response will be recorded on all synchronous lesions but not used in the calculation for overall response rate in this study.

[redacted]

Breast Target Lesion	Axillary Lymph Nodes	New Lesions	Overall Response
pCR	CR	No	pCR
pCR	Incomplete response/SD/PD	No	non-pCR
pPR	CR	No	non-pCR
pPR	Incomplete response/SD/PD	No	non-pCR
pPR	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort will be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination. The residual lesion will be investigated (fine needle aspirate/biopsy if possible) before confirming the complete response status.

9.4 Recurrence Free Survival and Overall Survival

Recurrence free survival (RFS) is defined as time to local recurrence following surgery, regional recurrence, distant recurrence, or death from any cause prior to recurrence or second primary cancer following initiation of chemotherapeutic treatment. Overall survival (OS) is defined as time from initiation of chemotherapy until death from any cause.

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Disease progression/relapse during active treatment,
b) Intercurrent illness that prevents further administration of treatment,
c) Unacceptable adverse event(s).
d) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment,
e) Patient decides to withdraw from the study,
f) Noncompliance with treatment plan or inability of the patient to comply with study requirements,

[redacted]

g) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
h) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator, or
i) Occurrence of the following events or conditions:
   - Grade 4 congestive heart failure

11. Laboratory Evaluations

Tumor tissue will be collected at the time of surgery by BRS. One small portion of the tissue (0.05 cm in one dimension) will be placed into neutral buffered formalin solution for histology (containers will be included in the sample collection kit). The remaining portion of the tissue will be placed in sample collection tubes containing optimized transport or preservative media and maintained at 4°C. After labeling and de-identification of the sample, the tissue collection kit will be shipped overnight to the CINJ BRS laboratories or used directly by staff at CINJ. In order to ensure timely processing of samples, the cut off for the collection of tumor tissue will be Friday 5.00 pm, each week with no weekend collections. For novel mutations found on FoundationOne targeted genomic sequencing or other sequencing platforms that have not been previously characterized, the mutations may be engineered for *in vitro* studies to evaluate protein function and/or activity, effect on cancer cell phenotype, and drug sensitivity using established, commercially-available cell lines. No clinical information or patient identifiers will be released to the laboratory performing these studies. Blood draws of 10ml, using a cell-free DNA BCT Streck blood collection tube for stabilization of cell-free plasma DNA, will be done at diagnosis, at surgery, and at 6 month intervals for total of 3 years then annually to complete 5 years will be performed, serum prepared, and serum cryopreserved for future analysis. Samples are stable for up to 10 days at room temperature before processing and storage. These specimens will be used to analyze cell free DNA as a method to determine patients at highest risk of recurrence. Circulating cell free DNA will undergo prospective genomic testing to evaluate for the presence of tumor-specific genomic alterations as an indicator of residual, occult TNBC. We predict that those patients in whom cell free DNA does not identify presence of tumor-specific genomic alterations will be those patients at lowest risk for recurrence of their TNBC.

12. Pharmaceutical Information

12.1 Carboplatin

- **How supplied**: Vials contain lyophilized, sterile white powder in single dose vials containing 450 mg (NDC 0015-3215-30). For this trial carboplatin will not be supplied free of charge, patients and their insurance carrier will pay for the product.
- **Preparation (how the dose is to be prepared)**: Immediately before use, the content of each vial is reconstituted with either sterile water for injection, USP, 5% Dextrose in Water, or 0.9% Sodium chloride injection, USP. The volume of diluent is 45 ml to produce a concentration of 10 mg/ml.
- **Storage**: Store unopened vials at 25 °C. Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.
- **Stability**: Unopened vials are stable for the life indicated when stored at 25 °C. When solutions prepared as directed, they are stable for 8 hours at room temperature.
- **Route of administration**: Intravenously. See Section 7.3 for detailed treatment plan.
- **Expected toxicities**: Bone marrow suppression, limited renal toxicity, nausea, vomiting, peripheral neurotoxicity, allergic reaction, liver enzyme abnormalities, electrolyte loss, asthenia, alopecia.

[redacted]

- **Drug Interactions**: Nephrotoxic and ototoxic potential is increased when used in combination with aminoglycosides. Renal effects of other nephrotoxic drugs may be potentiated with carboplatin.

12.2 Doxil®/Liposomal Doxorubicin

- **How supplied**: For this trial Doxil®/Liposomal Doxorubicin will not be supplied free of charge, patients and their insurance carrier will pay for the product.
- **Mode of Action:** Doxil®/Liposomal Doxorubicin (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH® liposomes for intravenous administration. The active ingredient of Doxil®/Liposomal Doxorubicin is doxorubicin HCl, a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.
  Doxil®/Liposomal Doxorubicin is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of Doxil®/Liposomal Doxorubicin are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.
- **Preparation (how the dose is to be prepared)**: The Doxil®/Liposomal Doxorubicin dose will be diluted in 250 ml of 5% dextrose in water (for doses of > 12 mg and < 90 mg) or 500 ml 5% dextrose in water (for doses > 90 mg) and should be infused via a peripheral or central vein.
  To minimize the risk of infusion-related reactions, the first infusion Doxil®/Liposomal Doxorubicin should be administered as detailed in section 7.3. If no infusion-related reactions are noted with the initial infusion, subsequent infusions will occur over 60 minutes.

  Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with Doxil®/Liposomal Doxorubicin. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. The majority of infusion-related events occurred during the first infusion. Serious and sometimes life-threatening or fatal allergic/anaphylactoid infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Infusion reactions if they occur, will be treated per each institutions standard procedure.
- **Storage and handling**: Refrigerate unopened vials of Doxil®/Liposomal Doxorubicin at 2°C to 8°C (36°F to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on Doxil®/Liposomal Doxorubicin.
  Caution should be exercised in the handling and preparation of Doxil®/Liposomal Doxorubicin. The use of gloves is required. If Doxil®/Liposomal Doxorubicin comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.
  Doxil®/Liposomal Doxorubicin should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil®/Liposomal Doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood

[redacted]

returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxil®/Liposomal Doxorubicin must not be given by the intramuscular or subcutaneous route. Doxil®/Liposomal Doxorubicin should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist.

- **Stability**: Diluted Doxil®/Liposomal Doxorubicin should be refrigerated at 2-8°C and administered with 24 hours.
- **Route of administration**: Intravenously. See Section 7.1 for detailed treatment plan.
- **Expected toxicities**: Leukopenia, anemia, thrombocytopenia; Infusion reactions: Acute reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in chest and throat, and/or hypotension have occurred in about 6.8% of patients. The rate of infusion reactions may actually be higher in patients with solid tumors who receive a higher dose. Doxil®/Liposomal Doxorubicin should be considered an irritant, and precautions should be taken to avoid extravasation; Palmar-plantar erythrodysesthesia, characterized by swelling, pain, erythema, and sometimes desquamation of the skin on the hands and feet. The reaction can be severe and debilitating in some patients. Generally seen after 6 or more weeks of treatment, but may occur earlier. Appreciable alopecia is rare. Acute left ventricular failure has occurred, particularly in those who have received a total dosage exceeding 550 mg/m^2. The limit appears to be lower (400 mg/m^2) in patients who receive radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents, such as cyclophosphamide; nausea and vomiting, usually mild-moderate, antiemetic therapy may be necessary; mucositis, stomatitis, less common, may be dose-limiting. Diarrhea and anorexia may also occur. Rarely, secondary malignancies may result.

12.3 Paclitaxel

- How Supplied: 30-300 mg/5 mL multidose vial individually packaged in a carton.
- Storage and Stability: The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
- Preparation: TAXOL (paclitaxel) Injection must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% 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.
- Route of Administration: Intravenously. TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as FVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP. The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of TAXOL since they can cause the stopper to collapse resulting in loss of sterile integrity of the TAXOL solution.
- Toxicities: neutropenia, thrombocytopenia, anemia, infection, bleeding, hypersensitivity reaction, bradycardia, hypotension or hypertension, abnormal EKG, peripheral neuropathy, myalgia/arthralgias, nausea/vomiting, diarrhea, mucositis, alopecia, hepatic function abnormalities, injection site reactions. *Hypersensitivity Reactions*: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (eg, cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. Minor symptoms such as flushing, skin reactions,

[redacted]

dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with TAXOL.

- Drug Interactions: In a Phase 1 trial using escalating doses of TAXOL (110-200mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (ie, TAXOL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when TAXOL was administered following cisplatin. The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3 A4. Caution should be exercised when TAXOL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when TAXOL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Potential interactions between TAXOL, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

12.4 Epirubicin hydrochloride (Ellence™)

- How Supplied: Manufactured by Pharmacia in polypropylene single-use vials containing 2 mg epirubicin hydrochloride per ml as a sterile preservative-free, ready-to-use solution in the following strengths: 50mg/25mL single-use vial and 200 mg/100ml single-use vial. It is commercially available.
- Storage and Stability: Store refrigerated (2°C to 8°C/36°F to 46°F), protected from light. Solution should be used within 24 hours of penetrating the rubber stopper.
- Preparation: Ellence is provided as a preservative-free, ready-to-use solution.
- Route of Administration: Intravenous push through the side arm of a running intravenous catheter line. Large vein should be used for injection whenever possible. Although rate of administration will depend on the size of the vein, the drug should not be administered in less than 5 minutes.
- Toxicities: The adverse effects associated with epirubicin are extravasation/vesicant irritation, lethargy, alopecia, amenorrhea, hot flashes, nausea, vomiting, mucositis, neutropenia, anemia, thrombocytopenia, injection site reactions, conjunctivitis, fever, rash, and anorexia. Cardiotoxicity, in the form of decreased LVEF, acute arrhythmias, or chronic congestive heart failure, may occur, especially in patients who previously received anthracycline therapy.
- Drug Interactions: No systematic evaluation of potential interactions with inhibitors or inducers of the cytochrome P-450 system have been evaluated. Cimetidine increases the AUC of epirubicin by 50%.

[redacted]

13. Data Collection and Records to be Kept

13.1 Case Report Forms

A subset of the NCI's CRFs, in electronic format, will be utilized to collect data required for study analysis. Completion of the e-CRFs will be done in accordance with the study-specific data collection plan and instructions provided by the NCI (http://theradex.com/capabilities/CTMS.htm). All e-CRFs will be submitted to OHRS via its secure web-based data management system. The e-CRFs are found in the study specific calendar that has been created in the data management system. The system will prompt the user to the forms that are required based upon the patient's enrollment and treatment dates.

The Principal Investigator (PI) at each institution will be responsible for assuring that all the required data is collected and entered onto the e-CRFs accurately and at the time intervals outlined in Section 13.2 and the data collection plan. The details of data submission will be coordinated with the OHRS and the participating institution(s) prior to enrollment of patients from the participating institution(s).

Periodically, monitoring visits will be conducted and the institution's PI will provide access to his/her original records to permit verification data submitted on e-CRFs.

13.2 Data Submission Timeline and Forms

Registration (Due Prior to Enrollment)
• Signed eligibility checklist • Signed copy of the informed consent form • Copy of the pathology report
Baseline (Due within 14 days after start of treatment)
• All baseline e-CRFs indicated by the data management system (e.g., concomitant medications, prior surgery, baseline symptoms, stage, etc.)
During Protocol Therapy (Due no later than 14 days after the end of each treatment cycle)
• All treatment segment e-CRFs indicated by the data management system (e.g., concomitant medications, adverse events, drug treatment, laboratory data, disease assessment as required, etc.)
End of Treatment (Due no later than 14 days after off-treatment)
• All off-treatment e-CRFs indicated by the data management system (e.g., concomitant medications, best response, etc.)
Follow-Up (Due no later than 14 days after each follow up period)
• All follow-up e-CRFs indicated by the data management system (e.g., survival, recurrence)

13.3 Research Charts

A research chart (*i.e.* shadow chart) is maintained at OHRS for each patient enrolled. Completed paper CRFs and copies of the most significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade

[redacted]

3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

13.4 Reports

Publications and annual reports for submission to the IRB will be written by the PI using the data captured on the CRFs.

14. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the [redacted] with the DSMP following enrollment of the first two (2) or three (3) patients. *The protocol states that "definitive breast surgery will be performed no sooner than four weeks from the last dose of liposomal doxorubicin". If any of the first three patients experience unexpected wound complications, the duration of time from last chemotherapy to definitive breast surgery will be extended to "no sooner than 6 weeks".* Subsequent audits will occur on an annual basis prior to annual IRB continuing review, if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary.

15. Statistical Considerations

15.1 Power Considerations

Table 2. Precision calculations (half-width of 95% CI).

	P				
N	0.15	0.20	0.25	0.30	0.40
40	0.09	0.11	0.12	0.13	0.14
50	0.08	0.10	0.11	0.12	0.13
60	0.08	0.09	0.10	0.11	0.12
100	0.06	0.07	0.08	0.08	0.09

The primary objective of this study is to determine the rate of pCR based on RECIST criteria with treatment of DOX plus CAR in patients with TNBC. The precision of the expected pCR rate was assessed by calculating half (1/2) of the width of 95% Confidence Intervals (CIs) based on binomial distributions (Table 2). Based on prior studies, an estimated pCR rate of 30% is expected [59]. The plan is to recruit n=60, which will yield a 95% confidence interval within the +/- 11% range. Secondary exploratory analysis will determine the two-year recurrence free survival (RFS) and overall survival (OS) in this study. RFS, defined as time to local recurrence following surgery, regional recurrence, distant recurrence, or death from any cause prior to recurrence following surgery. OS is defined as time from initiation of chemotherapy until death from any cause. To assess recurrence rate, the same 95% CI calculations were applied (Table 2) assuming each individual can be followed up until the end of study. With an expected 2-year risk of recurrence of 20% [59], this results in a 95% confidence interval within the +/- 9% range.

Table 3. Minimal detectable OR based on selected proportions of mutations and response rate P_0 in tumors without mutations, using the method of chi-square test with 80% power and α =0.05 (two-sided)

		P_0					
		0.15	0.20	0.25	0.30	0.35	0.40
Proportion of mutations of interest	0.2	6.77	6.33	6.20	6.30	6.58	7.11
	0.3	5.67	5.23	5.04	5.01	5.10	5.32
	0.4	5.27	4.83	4.61	4.54	4.57	4.98
	0.5	5.22	4.75	4.51	4.42	4.42	4.51
	0.6	5.44	4.92	4.66	4.54	4.53	4.62
	0.7	6.06	5.46	5.15	5.01	5.00	5.09
	0.8	7.57	6.77	*6.38*	6.22	6.23	6.39

To study the mutational spectrum of tumors (by number and type) and their association with pCR to neoadjuvant DOX and CAR, we used the method of chi-square test to estimate the minimal detectable association, in terms of an odds ratio (OR), with 80% power and two-sided alpha of 5% (Table 3). Preliminary data show the frequency of p53 mutations to be 80% in TNBC. Assuming a response rate for patients without p53 mutations is P_0=0.25 and with n=60, this study has 80% power (α=0.05, two-sided) to test a minimal OR of response associated with p53 mutations of 6.4. Due to moderate sample size (n=60), we do not expect to have sufficient power (e.g. 80%) to

[redacted]

test a small association between mutations and response, but aim to find the effect size for planning a future study. Mutations with more even distribution will be powered to detect smaller differences.

15.2 Statistical Methods.

To address the primary goal of this study, the pCR rate will first be determined as proportions and calculating its 95%CI. To study the association between pCR response (yes/no) and the presence of GRD, type and number of mutations, clinical lymph node status (positive/negative), tumor size (<2cm/≥2cm) based on p53, logistic regression analysis will be used, controlling for cancer treatment and disease stage and other covariates if numbers allow. To evaluate RFS and OS, survival functions will be computed using the Kaplan-Meier method, and compared between mutation status using the log-rank test. Adjustment for additional covariates, such as cancer treatment and disease stage, will be performed using Cox proportional hazards regression analysis if numbers allow [84]. We will use the Cox model analysis to study the association between cancer recurrence and the presence of specific mutations with IHC parameters, e.g. p53, Ki67, apoptotic markers (cleaved caspase 3), phosphorylated proteins in targeted pathways, gammaH2AX for DNA damage. All test procedures will be done at significance level 5%. All statistical analyses will be carried out using SAS Version 9.3 (SAS Institute, www.sas.com) and R Version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org) with support from the Biometrics division.

In the event the study closes early, e.g., due to slow accrual, all the statistical analyses will be performed as interim analyses. Specifically, the alpha level and the critical value will be adjusted according to the O'Brien-Fleming approach. The information time will be defined as the ratio of the number of patients actually recruited in the study vs. the originally planned sample size.

15.3 Statistical Analysis for Correlative Studies

It will be determined which tumors from patients with gross residual disease are sensitive to targeted agent, cytotoxins, or the combination as a function of mutational profile and will be tested for additive and synergistic effects. Dose response curves for treatments will be used to determine the IC_{50} for single agents with the GraphPad Prism software. Potential drug interactions will be calculated using the Combination Index-Isobologram Theorem. Mutations in key genes found in gross residual disease will be correlated to tumor responses.

15.3.1 Power considerations for PDX Studies.

We have 15 mice per treatment arm if we use one targeted agent and one cytotoxin. Based on the method of one-way ANOVA, our study has 80% power to test a medium effect size of Cohen's f^2 of 0.45 with α =0.05. To compare each treatment arm with the vehicle control, our study has 80% power to test a moderate effect size of Cohen's d=0.40 with α=0.017 (two-sided, Bonferroni correction).

15.3.2 Statistical Methods for PDX Studies.

The overall objective will be to demonstrate activity for our selected agents for a specific patient's tumor. Descriptive analysis (e.g., plots of tumor size vs. time since treatment, summary statistics and histograms) will be used to explore the distribution of data, identify outliers and inform any necessary transformations (e.g., logarithm) for subsequent statistical analysis. Mixed model analysis will be used to evaluate the treatment effect, represented by tumor inhibition ratio. Treatment, Time (of repeated measurements) and the interaction of Treatment and Time will be included as fixed effects. Intra-subject (intra-mouse) correlation between repeated measurements will modeled using random effects. Overall treatment effect will be evaluated by the interaction of Treatment and Time based on F test. Linear contrasts will be used to compare each treatment with the control. Bonferroni adjustment will be applied for multiple testing, as appropriate. The same methods will also be used to explore the treatment effect

[redacted]

for two drug combinations.

15.4 Quality of Life Measures and Related Statistics.

Based on the tolerability of the combination of carboplatin and doxil in the metastatic setting, quality of life will be assessed utilizing a quality of life survey instrument, e.g. FACT-B, Herth Hope Index, and PSQI, at several time points before, during, and after treatment with the combination of doxil and carboplatin and then with paclitaxel. Quality of life scores will be analyzed longitudinally for preservation of score within each segment of therapy and across the entire treatment regimen. Quality of life scores will also be compared to health care provider documented severity and presence of side effects. Quality of life scores will also be compared to outcome measures using pathologic complete response versus partial/stable response and survival data using logistic regression.

Up to 61% of breast cancer patients report clinically significant sleep disturbance [85]. We will examine the impact of the investigational treatment regimen on sleep disturbance, given the impact that sleep disturbance can have on vasomotor symptoms [86-90], immune function [91,92], and general quality of life [85, 86, 92, 93] among breast cancer patients. The Pittsburgh Sleep Quality Index (PSQI) is a valid and reliable measure of sleep quality and is widely used in studies of breast cancer patients. Scores ≥ 5 indicate clinically significant sleep disturbance. The PSQI will be administered before chemotherapy as well as after cycle 4 liposomal doxorubicin and carboplatin, and after week 12 of weekly paclitaxel. Analyses will determine whether sleep quality changed over time, whether the rate of sleep disturbance changed over time, and whether any observed changes in sleep quality meet the cutoff for the minimal clinically important difference.

Continuous scores will be analyzed longitudinally to determine whether participants report changes over time in sleep quality. PROC MIXED in SAS will be used to model change over time in sleep quality. If a significant change over time is observed for sleep quality, we will determine whether the change meets the cutoff for minimal clinically important difference ($\pm$ 0.5 standard deviation) [94]. Dichotomous scores (< 5 vs. ≥ 5) will also be analyzed longitudinally to determine whether the prevalence of clinically significant sleep disturbance changes over time. PROC GENMOD in SAS will be used to model change over time in the dichotomous sleep disturbance measure.

16. Ethical and Regulatory Considerations

16.1 Study Conduct

The PI takes full responsibility for the ethical conduct of the study with highest regard to protecting the rights and welfare of patients, including, but not limited to, adherence to the ethical principles laid out in the Belmont Report, Declaration of Helsinki and the Patient's Bill of Rights. This study is to be conducted according to local and international regulations, Good Clinical Practice guidelines and institutional policies and standard operating procedures. In order to ensure the safety and welfare of study participants and the scientific validity of the study, the approved protocol must be conducted as written. Should changes to the protocol or consent become necessary, protocol amendments will be submitted, in writing, to the PI and local IRB for approval prior to implementation, unless there is an urgent need to eliminate an immediate hazard to study participants. In that case, notification to the PI and the local IRB will be made as soon as possible.

16.2 Institutional Review Board Approval

Prior to initiating or making changes to the protocol, the PI must obtain written approval by an HHS/OHRP approved IRB.

16.3 Informed Consent

[redacted]

Current FDA, OHRP, NIH, state and institutional regulations concerning informed consent will be followed. A written consent document that embodies the elements of informed consent is required §46.116. The investigator shall give the patient adequate opportunity to read it before it is signed, explain all aspects for the study in lay language and answer all of the patient's questions regarding the study. If the patient decides to participate in the study, he/she will be asked to sign the Informed Consent Document. A copy of the signed Informed Consent Document will be given to the patient and this will be documented in the patient's medical record. Patients who decline to participate or withdraw from the study will be treated without prejudice.

16.4 Record Retention

The retention of accurately recorded and retrievable research data is necessary in order to ensure scientific integrity. Research records should include sufficient detail to permit examination for the purpose of replicating the research, responding to questions that may result from unintentional error or misinterpretation, establishing authenticity of the records, and confirming the validity of the conclusions.

All patients' medical records and shadow files/research records will be maintained in a secured location and retained until specified by the OHRS.

16.5 Patient Confidentiality

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

- The protected health information (PHI) that will be collected from patient.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (*i.e.* that the patient is alive) at the end of their scheduled study period. To ensure confidentiality is maintained at all times, CRFs will not identify any patient by name. A unique study identification number will be recorded on the CRF and all records will be secured in a locked location. No clinical information will be released without written permission of the patient, except as necessary for monitoring by the IRB, FDA, OHRP, and the [redacted]

16.6 Conflict of Interest

All [redacted] and other employees who, as investigators on behalf of the University, who apply for or receive funds through a grant, subgrant, contract, subcontract, or cooperative agreement for any research, educational or service purpose and investigators working as subgrantees, contractors or subcontractors to or collaborators with the University on projects funded or proposed for funding must disclose any real or apparent conflict of interest and abide by [redacted].

17. Human Subjects

[redacted]

17.1 Patient Population

Women with previously-untreated, stage II-III breast cancer, ER/PR/HER2 negative. High risk stage I TNBC with tumors at least 1.0 cm in size for which chemotherapy may be indicated per the NCCN guidelines may also be included.

17.2 Potential Risks

All care will be taken to minimize side effect, but they can be unpredictable in nature and severity. Risks are outlined in Section 7.

17.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the patient or representative. The informed consent document may not include any exculpatory language through which the patient or representative is made to waive any of the patient's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

Remote Consenting

Follow up will continue up to twenty years following completion of therapy. For IRB approvals that would involve re consenting due to a study change, the option to consent patients remotely can be done using the following process:

The patient will be called to inform him/her that a new version of the consent is available and will be mailed or faxed to them. If mailed, a stamped return envelope will be provided for them to return the signed consent.

After the consent is mailed or faxed, a call will be placed to the patient to review the consent, including the changes. Once the patient verbalizes an understanding of the consent and all of their questions have been answered, they will be instructed to sign and date the document and return it to [redacted] the stamped return envelope.

Upon receiving the signed consent, the consenting individual will sign the consent document and mail or fax a completed copy back to the patient.

The entire process will be documented in the patient's electronic medical record.

17.4 Potential Benefits

Potential benefits may be reduction in the size of tumor, improved tumor response, a longer period prior to recurrence, reduced risk of recurrence, improved overall survival, identification of potentially effective drugs that could be used if the disease recurs, and/or improvement in symptoms related to their disease.

17.5 Risk-Benefit Ratio

The potential benefit that may result from this study balances the potential risks to the patients. Results of previous trials suggest that these drugs are active against breast cancer. This protocol may or may not be helpful to a specific patient, but the results may help the Investigators learn about the administration and effectiveness of doxil/liposomal doxorubicin or epirubicin with carboplatin followed by paclitaxel in breast cancer and may aid in the treatment of other patients. This research treatment is a curative regimen, but may

[redacted]

not guarantee this outcome. Benefit can't be promised nor can the chance of benefit be accurately predicted. Literature presentations on recent studies using these drugs in breast cancer patients do not suggest an unacceptable risk-benefit ratio.

17.6 Gender and Minorities

Female patients accounted for 58% of cancer patients seen within [redacted] clinical programs within the last year. Of all female patients evaluated annually, African-Americans comprised 7.7%, American Indian/Alaska Native 0.2%, Native Hawaiian/Pacific Islander 0.3%, Asians 4.2%, multi-racial 4.3%, and 1.9% Hispanics. For all patients entering clinical trials, the percentages were 82% women, 14.7% African-American, 6.8% Hispanic, American Indian/Alaska Native 0.2%, Native Hawaiian/Pacific Islander 0.5%, multi-racial 0.2%, and 3.6% Asian.

No person shall, on the grounds of age, race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

18. Economic/Financial Considerations

Patients and/or their insurance carriers will be expected to pay for all costs of therapy, monitoring, and follow-up.

19. Publication of Research Findings

The policies and procedures of [redacted] legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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Appendix A

Performance Status Criteria

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

[redacted]

Appendix B

New York Heart Association Criteria

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, palpitation or anginal pain.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 9th ed. Boston, Little, Brown and Co, 1994:253-6.

[redacted]

Appendix C

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

[redacted]

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

[redacted]

[redacted]

[redacted] **circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

[redacted]

APPENDIX D - PITTSBURGH SLEEP QUALITY INDEX

[redacted]

[redacted]

Subject's Initials_____ ID#_____ Date_____ Time_____ AM PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

[redacted]

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Have pain

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

[redacted]

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

[redacted]

d) Episodes of disorientation or confusion during sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

APPENDIX E- CLINICAL DISTRESS ASSESSMENT

[redacted]

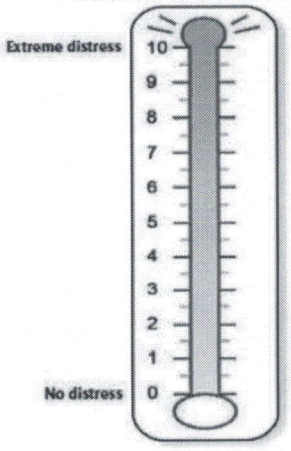
[redacted]

How Are You Doing?

Name_____
Date of Birth_____
Date Completed_____

1. Please indicate your level of distress on the thermometer.

During the past week, how distressed have you been?



2. Please circle the causes of your distress.

Practical Problems
- Child Care
- Housing
- Insurance/financial
- Transportation
- Work/School
- Treatment decisions

Family Problems
- Dealing with children
- Dealing with partner
- Ability to have children
- Family health issues

Spiritual/Religious Concerns

Emotional Problems
- Depression
- Fears
- Nervousness
- Sadness
- Worry
- Loss of interest in usual activities

Physical Problems
- Appearance
- Bathing/dressing
- Breathing
- Changes in urination
- Constipation
- Diarrhea
- Eating
- Fatigue
- Feeling Swollen
- Fevers
- Getting around
- Indigestion
- Memory/Concentration
- Mouth sores
- Nausea
- Nose dry/congested
- Pain
- Sexual
- Skin dry/itchy
- Sleep
- Substance Abuse
- Tingling in hands/feet

3. What do you do to cope or feel better?

_____

_____

4. What help are you already getting?

_____

_____

5. What else might help?

_____

[redacted]

Study No._____

HERTH HOPE INDEX

Listed below are a number of statements. Read each statement and place an [X] in the box that describes how much you agree with that statement right now.

	Strongly disagree	Disagree	Agree	Strongly Agree
1. I have a positive outlook toward life.				
2. I have short and/or long range goals.				
3. I feel all alone.				
4. I can see possibilities in the midst of difficulties.				
5. I have faith that gives me comfort.				
6. I feel scared about my future.				
7. I can recall happy/joyful times.				
8. I have deep inner strength.				
9. I am able to give and receive caring/love.				
10. I have a sense of direction.				
11. I believe that each day has potential.				
12. I feel my life has value and worth.				

1999 items 2 & 4 reworded

[redacted]