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TABLE OF CONTENTS

1. PURPOSE/SPECIFIC OBJECTIVES 6

1.1 PRIMARY OBJECTIVE 6
1.2 SECONDARY OBJECTIVES 6
1.3 SCHEMA 7
1.4 PRIMARY HYPOTHESIS 7
1.5 SECONDARY HYPOTHESES 7

2. BACKGROUND AND SIGNIFICANCE 8

2.1 BREAST CANCER STATISTICS 8
2.2 OUTCOMES FOR TRIPLE NEGATIVE BREAST CANCER 8
2.3 CHEMOTHERAPY FOR THE TREATMENT OF EARLY STAGE BREAST CANCER 8
2.4 RATIONALE FOR COMBINATORIAL THERAPY WITH ANTHRACYCLINES AND CARBOPLATIN 12
2.5 NEXT GENERATION SEQUENCING OF TUMORS FROM PATIENTS WITH TNBC 14
2.6 SUPPORTING DATA AND RATIONALE 15
2.7 AVAILABILITY OF DOXIL 16

3. PARTICIPATING INSTITUTIONS 17

4. EXPERIMENTAL DESIGN AND METHODS 17

5. PATIENT SELECTION CRITERIA 17

5.1 INCLUSION CRITERIA 17
5.2 EXCLUSION CRITERIA 18
5.3 INCLUSION OF WOMEN AND MINORITIES 19
5.4 PARTICIPATION OF CHILDREN 19
5.5 SOURCES OR METHODS OF RECRUITMENT 19
5.6 STUDY ENROLLMENT PROCEDURES 20

6. STUDY PARAMETERS 21

6.1 REQUIRED DATA COLLECTION 22
6.2 PATHOLOGY AND CORRELATIVE STUDIES 22
6.3 MUTATIONAL ANALYSIS/GENOMIC PROFILING 23
6.4 CORRELATIVE STUDIES 24
6.5 PATIENT-DERIVED XENOGRAFTS 24
6.5.1 RATIONALE 24
6.5.2 DESIGN 24

7. TREATMENT PLAN 26

7.1 GENERAL CONSIDERATIONS 26
7.2 DOSE CALCULATION 28
7.3 TREATMENT ADMINISTRATION 28
7.4 DOSE MODIFICATIONS 30
7.5 CONCOMITANT MEDICATIONS 37
7.6 SUPPORTIVE CARE GUIDELINES 37
7.7 ADHERENCE/COMPLIANCE 38

8. TOXICITY MONITORING AND ADVERSE EVENT REPORTING 38

8.1 ADVERSE EVENT REPORTING REQUIREMENTS 38
8.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAES) 39
8.3 DEFINITION OF RELATED 40
8.4 DEFINITION OF UNEXPECTED 40

9. TREATMENT EVALUATION/CRITERIA FOR [redacted]

[redacted]

10. REMOVAL OF PATIENTS FROM STUDY/OFF STUDY CRITERIA 45

11. LABORATORY EVALUATIONS 45

12. PHARMACEUTICAL INFORMATION 46

12.1 CARBOPLATIN 46
12.2 DOXIL® 46
12.3 PACLITAXEL 48
12.4 EPIRUBICIN HYDROCHLORIDE (ELLENCE™) 49

13. DATA COLLECTION AND RECORDS TO BE KEPT 50

13.1 CASE REPORT FORMS 50
13.2 DATA SUBMISSION TIMELINE AND FORMS 50
13.3 RESEARCH CHARTS 51
13.4 REPORTS 51

14. DATA AND SAFETY MONITORING 51

15. STATISTICAL CONSIDERATIONS 52

16. ETHICAL AND REGULATORY CONSIDERATIONS 54

16.1 STUDY CONDUCT 54
16.2 INSTITUTIONAL REVIEW BOARD APPROVAL 54
16.3 INFORMED CONSENT 54
16.4 RECORD RETENTION 54
16.5 PATIENT CONFIDENTIALITY 55
16.6 CONFLICT OF INTEREST 55

17. HUMAN SUBJECTS 56

17.1 PATIENT POPULATION 56
17.2 POTENTIAL RISKS 56
17.3 CONSENT PROCEDURES 56
17.4 POTENTIAL BENEFITS 56
17.5 RISK-BENEFIT RATIO 56
17.6 GENDER AND MINORITIES 57

18. ECONOMIC/FINANCIAL CONSIDERATIONS 57

19. PUBLICATION OF RESEARCH FINDINGS 57

REFERENCES 58

APPENDIX A - PERFORMANCE STATUS CRITERIA 69

APPENDIX B - NEW YORK HEART ASSOCIATION CRITERIA 70

APPENDIX C – FACT-B QUALITY OF LIFE SURVEY 71

APPENDIX D – PITTSBURGH SLEEP QUALITY INDEX 74

APPENDIX E – CLINICAL DISTRESS ASSESSMENT 78

APPENDIX F – HERTH HOPE INDEX 79

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LIST OF ABBREVIATIONS

AC	Adriamycin (doxorubicin) plus cyclophosphamide
AC→T	AC x 4 cycles followed by docetaxel x 4 cycles
AE	Adverse Event
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BRS	Biospecimen Repository Service
BUN	Blood urea nitrogen
CAR	Carboplatin
CBC	Complete blood count
CMF	Cyclophosphamide, methotrexate, and fluorouracil
CT	Computer Tomography
CT CAP	Computer Tomography chest, abdomen, pelvis
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Cyclophosphamide
DFS	Disease Free Survival
DOX	Liposomal doxorubicin
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
FAC	Fluorouracil, doxorubicin, and cyclophosphamide
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
GRD	Gross Residual Disease
G-CSF	Granulocyte Colony Stimulating Factor
HHS	Department of Health and Human Services
HR	Hormone receptor
IHC	Immunohistochemistry
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NIH	National Institutes of Health
NSM	Nonsense mutation
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
OS	Overall Survival
P	Paclitaxel
PPE	Palmar-Plantar Erythrodysesthesia Syndrome

[redacted]

PBMC	Peripheral blood mononuclear cells
pCR	Pathologic complete response
PD	Progressive Disease
PDX	Patient Derived Xenograft
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PI3K	Phosphatidylinositol 3-kinase
PR	Partial Response
PgR	Progesterone Receptor
PSQI	Pittsburgh Sleep Quality Index
RFS	Recurrence free survival
RTK	Receptor tyrosine kinase
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious Adverse Event
SD	Stable Disease
sCr	Serum creatinine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TAC	Docetaxel, doxorubicin, and cyclophosphamide
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
WP	Weekly paclitaxel

[redacted]

1. Purpose/Specific Objectives

1.1 Primary Objective

The primary objective of this study is to determine the rate of pathologic complete response with treatment of liposomal doxorubicin and carboplatin in patients with ER, PR, HER2 negative breast cancer (TNBC). Patients will be enrolled to receive the following treatment: four cycles of neoadjuvant carboplatin and liposomal doxorubicin administered every 28 days (carboplatin AUC 5, liposomal doxorubicin 30mg/m^2) then undergo definitive breast surgery followed by 12 weeks of adjuvant paclitaxel 80 mg/m^2 administered weekly.

1.2 Secondary Objectives and Endpoints

1.2.1 To determine the recurrence free survival (RFS), 2-year RFS, and overall survival (OS) after treatment with neoadjuvant liposomal doxorubicin and carboplatin followed by definitive breast surgery and then weekly paclitaxel in patients with ER, PgR, HER2 negative breast cancer.

Endpoint: RFS, 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. OS is defined as time from initiation of chemotherapy until death from any cause.

1.2.2 To describe the mutational spectrum of tumors found in primary, untreated ER, PgR, HER2 negative breast cancer and their association with pathologic complete response to neoadjuvant doxil and carboplatin.

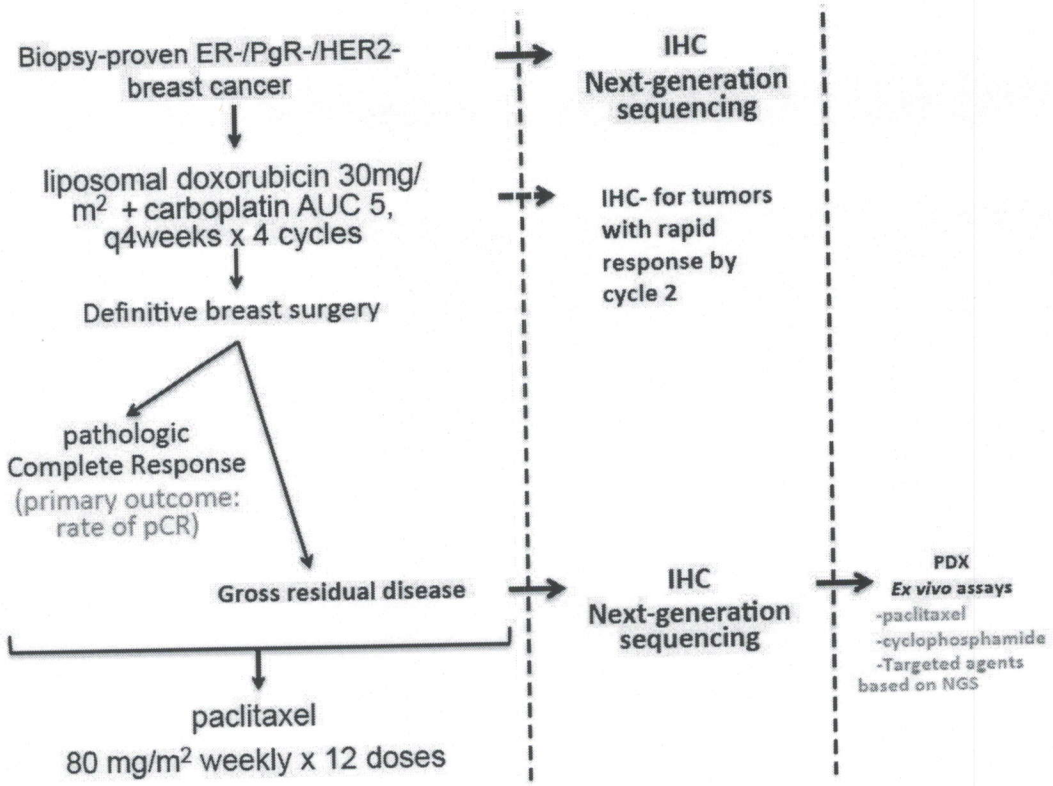
Endpoint: Tumor samples will be submitted for correlative science studies to evaluate predictors of study therapy benefit. Immunohistochemistry and/or FISH studies will used to confirm amplifications or translocations and determine the association between genomic alterations and altered protein expression and downstream effectors indicating activation of that pathway.

1.2.3 To determine functional significance of genomic landscape in predicting drug response using patient derived xenograft (PDX) and *ex vivo* models.

Endpoint: PDX and ex vivo assays will evaluate for sensitivity to paclitaxel or cyclophosphamide, targeted agents selected based on genomic profile, standard cytotoxins, or the combination of targeted agents with standard cytotoxins.

1.3 Treatment Schema

[redacted]



1.4 Primary Hypothesis

The combination of carboplatin and liposomal doxorubicin delivered neoadjuvantly will demonstrate clinical activity for the treatment of patients with triple negative breast cancer.

1.5 Secondary Hypotheses

1.5.1 The combination of carboplatin and liposomal doxorubicin delivered neoadjuvantly followed by definitive surgery and paclitaxel will have measurable benefit in recurrence free survival and overall survival when used for the treatment of patients with triple negative breast cancer.

1.5.2 The mutational spectrum of primary, untreated ER, PgR, HER2 negative breast cancer will demonstrate associations with pathologic complete response to neoadjuvant doxil and carboplatin.

1.5.3 Patient derived xenograft and *ex vivo* models will be useful for modeling triple negative breast cancer and for determining functional significance of genomic landscape in predicting drug response.

2. Background and Significance

2.1 *Breast Cancer Statistics.*

Breast cancer is the most common type of noncutaneous cancer among women in the United States, with approximately 232,340 new cases of invasive breast cancer expected in 2013 [1]. Moreover, breast cancer is second only to lung cancer as a cause of cancer deaths in women, with 39,620 expected deaths from breast cancer in 2013 [1]. Since 1990, the overall death rate for breast cancer has decreased by 2.2% per year. Improvements in breast cancer screening have resulted in more women [redacted]

stages of breast cancer, and the efficacy of treatments for early stage breast cancer has improved substantially. For instance, the 5-year survival rate for women with localized, node negative breast cancer has improved from 80% in the 1950s to 98.6% today [1]. Unfortunately, approximately 20% to 25% of patients still develop recurrence and ultimately succumb to their disease.

2.2 *Outcomes For Triple Negative Breast Cancer.*

Although recent advances in detection and treatment have resulted in improved outcomes for patients with breast cancer overall, women with the triple negative breast cancer (TNBC) subtype continue to bear a disproportionate burden of morbidity and mortality associated with this disease. TNBC, *i.e.* estrogen receptor (ER) negative, progesterone receptor (PgR) negative, HER2 negative breast cancer, represents 10%–20% of invasive breast cancers with a propensity to affect younger women [2]. Moreover, stage I-III TNBC subtype: (i) is associated with an 8-fold greater risk of breast cancer death than receptor-positive tumors, (ii) has higher risk of death particularly in the first two years after diagnosis, and (iii) excess death is related to higher risk of distant disease affecting vital organs such as the lung and brain [2].

2.3 *Chemotherapy For The Treatment Of Early Stage Breast Cancer.*

The value of chemotherapy, both adjuvant and neoadjuvant, in substantially reducing the risk of breast cancer recurrence and death in early stage breast cancer has been consistently demonstrated from the data of individual randomized trials and affirmed in the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) 15-year meta-analyses combining data from the individual chemotherapy trials [3]. There are many chemotherapy regimens with established efficacy and safety data. However, the EBCTCG has shown that anthracycline-containing therapies, e.g. sequential doxorubicin and cyclophosphamide (AC) followed by taxanes, reduce the risk of recurrence by 11% and the risk of death by 16% compared with cyclophosphamide, methotrexate, and fluorouracil (CMF) combinations [4]. As such, regimens utilizing anthracycline in combination with cyclophosphamide have become the standard of care in the treatment of breast cancer.

2.3.1 *Anthracycline-Based Regimens Incorporating Taxanes.*

The role of taxanes as part of adjuvant therapy for treatment of patients with breast cancer was established with the clinical studies CALGB 9344 and NSABP B-28 [5;6]. Both the CALGB and NSABP B-28 studies demonstrated reduced risk recurrence and improved disease free survival, respectively, with the addition of paclitaxel to AC, though only CALGB showed improved overall survival [5;6]. The reduction in hazard for recurrence and death were 17% and 18%, respectively, with the addition of paclitaxel in CALGB. B-28 similarly showed improved disease free survival of 17% though overall survival was not different between arms with and without paclitaxel. Subsequent studies, e.g. ECOG 1199, employed comparisons between weekly and every 3-week schedule for paclitaxel or docetaxel following 4 cycles of AC women with node-positive or high-risk node-negative breast cancer [7;8]. There were no differences between the taxanes. As compared to every three-week paclitaxel, significantly improved overall survival was observed in the group receiving weekly paclitaxel (HR 1.32; p=0.01) that was not evident in the group receiving docetaxel every 3 weeks (HR 1.13; p>0.1) even though every 3-week docetaxel showed better DFS. Similarly, GEICAM which evaluated women with node-negative breast cancer and at least one high-risk factor for recurrence (tumor size > 2cm, negative hormone receptors, tumor histology grade 2 or 3, or < 35 years), demonstrated a significant improvement in disease free survival in the taxane-containing TAC arm (docetaxel, doxorubicin, and cyclophosphamide) over the FAC arm (fluorouracil, doxorubicin, and cyclophosphamide) with 87.8% and 81.8%, respectively (HR 0.68; 95% CI 0.49–0.93; p=0.01) though the difference in survival rates was not significant [9]. In studies comparing docetaxel administered

[redacted]

concurrently or sequentially with doxorubicin, there was a trend toward superiority of AC x 4 followed by docetaxel x 4 (AC→T) as compared to TAC x 4 in overall survival and AC→T was superior to TAC x 4 for disease free survival (p=0.006) [10]. However, BCIRG 005, a comparison between TAC x 6 to sequential AC x 4 followed by docetaxel x 4 in women with node-positive, HER2 negative breast cancer, showed no difference between the two regimens for DFS [11]. Overall, the majority of patients on all of these trials had the most common subtype of breast cancer: hormone receptor positive disease.

2.3.2 ***Rationale For Use Of Platinum-Based Chemotherapy For The Treatment Of Patients With TNBC.***
The treatment paradigm in breast cancer is evolving from an empiric approach to a more targeted one in which a particular breast cancer phenotype is identified that is more likely to respond to select combination regimens of targeted agents and chemotherapy.

Breast cancers are represented by a heterogenous group of tumors, characterized by a wide spectrum of clinical, pathologic and molecular features [12-14]. This wide spectrum of factors accounts for variations in response to therapy and outcomes among women diagnosed with breast cancer [15-17]. Routine clinical variables such as primary tumor size, nodal status, age, and hormonal receptor status have more recently been complemented by more extensive molecular profiling in an attempt to refine prognosis and response to therapy [18-21]. There have been numerous reports demonstrating that breast tumors will segregate into prognostic categories based on hierarchical cluster analysis of gene expression profiling [12;15;20-25]. These unique molecular patterns can help guide clinicians regarding both prognosis and response to therapies.

More recent attention has been devoted to a classification system which employs three commonly available molecular markers, estrogen receptor, progesterone receptor and HER2 and classifies patients into subtypes (Luminal, HER2 and Basal) [13;17;25;26]. Luminal subtypes make up the hormone receptor expressing tumors and carry a favorable prognosis. These tumors have gene expression patterns which are similar to the luminal epithelial component of the breast and genes associated with estrogen receptor activation. HER2 subtypes refers to the group of hormone receptor negative tumors with a specific gene expression pattern. Although not all tumors which are HER2 positive by clinical testing (immunohistochemistry and/or fluorescent in situ hybridization) strictly fall into this category, most HER2 positive tumors would fit this criteria [13;17;25]. While these tumors are generally receptor negative and carry a poorer prognosis than luminal types, the effectiveness of trastuzumab in HER2 positive patients can significantly impact on the outcomes of these patients [27].

Basal-like tumors lack both hormone receptor and HER2 expression, and despite having a poor prognosis, these tumors have been shown in neoadjuvant studies to be responsive to chemotherapy [13]. Basal type tumors have been shown to be more aggressive, are more commonly seen in African American women, in younger women, and are commonly seen in women who are BRCA1 carriers [13;15;23;28;29]. While this classification system is based on the more complex and extensive genetic profiling assays, the simplified method of classification based on the universally available and commonly employed ER, PgR and HER2 clinical assays make this system appealing and clinically useful. Accordingly, clinicians are utilizing the combination of ER, PgR and HER2 to classify patients into these subtypes and are increasingly utilizing "Triple Negative" (ER-, PgR-, HER2-) in clinical decision making and protocol design. Data using more extensive immunhistochemical staining and gene profiling studies have demonstrated that these "basal-like" cancers are more commonly positive for Her1 expression, basal cytokeratins and c-Kit [12;18;23].

[redacted]

These tumors also are characterized by low expression of BRCA1 and this phenotype is common among BRCA1 carriers and sporadic tumors that resemble tumors in BRCA1 carriers [28].

The TNBC designation arises from the lack of knowledge beyond conventional molecular features regarding specific aberrations giving rise to this breast cancer subtype and its biology. Cytotoxic agents are the mainstay for treatment of patients with TNBC given the absence of targeted therapies such as the hormonal manipulation and HER2-directed therapies used for hormone receptor or HER2 positive disease, respectively. Adjuvant anthracycline-based regimens plus taxanes substantially reduce the risk of breast cancer recurrence and death including those with at least one high risk factor for recurrence, e.g. tumor size > 2 cm, negative hormone receptors, high grade [3-9;30]. However, a paradox has emerged through clinical trial observations. While TNBC demonstrates higher pathologic complete response (pCR) with neoadjuvant chemotherapy as compared with non-TNBC [31], it still displays worse outcomes suggesting need for more effective therapy to eradicate tumor cells. The potential benefit of platinum salts for treatment of TNBC is emerging [31-33]. BRCA1-deficient breast cancer, a subset of TNBC, is known to be sensitive to double strand break-inducing agents, e.g. platinum salts. However, platinums are not used routinely in the treatment of patients with breast cancer. Links between the pathogenesis of both BRCA1-associated and nonBRCA1-associated TNBC subsets have renewed interest in the potential benefit of platinum-based therapy for TNBC.

Platinating agents have been under evaluation for use in the treatment of patients with early stage breast cancer as monotherapy but also in combination with other chemotherapeutic agents. These studies are summarized in Table 1. In a proof of concept neoadjuvant study, monotherapy with cisplatin at 75 mg/m^2 every 21 days for four cycles in patients with stage II-III TNBC demonstrated a 22% pCR rate and 64% clinical complete or partial response [32]. Benefits were similarly observed using cisplatin for BRCA1-associated tumors and with the combination of cisplatin and bevacizumab for TNBC [34;35]. GeparSixto evaluated addition of carboplatin (AUC 2) and bevacizumab to paclitaxel plus liposomal doxorubicin for TNBC [36]. Addition of carboplatin resulted in an additional 20% increase in pCR over that without. However, carboplatin was discontinued in nearly 50% due to its toxicity in the context of this multiple drug design. Promising results with platinum agents has led to the development of several studies for the treatment of patients with TNBC and/or BRCA1/2 mutation-associated tumors: neoadjuvant weekly paclitaxel plus anthracycline and cyclophosphamide, with or without carboplatin, and with or without bevacizumab (CALGB 40603); adjuvant cisplatin with or without the PARP inhibitor rucaparib for residual disease after standard neoadjuvant therapy (Hoosier Oncology); neoadjuvant anthracycline and cyclophosphamide followed by paclitaxel or gemcitabine plus carboplatin for tumors with a high homologous recombination deficiency score (ECOG 5112) [38]. However, the disadvantage of these study designs is that they either utilize a higher number of cytotoxic agents with greater risk of side effects and/or utilize a potentially less effective dose of platinum. These data support optimizing the use of platinum salts in the treatment of TNBC through rational design. However, the optimal incorporation of platinating agents into the treatment of patients with early stage triple negative breast cancer is not yet known.

[redacted]

Table 1. Neoadjuvant and adjuvant trials incorporating platinum salt for the treatment of patients with triple negative breast cancer.

Study Design	Population of TNBC	Results
Neo CDDP 75mg/m^2 q 21 days x 4 cycles [32]	Stage II-III	• pCR 22% • cCR or cPR 64%
Neo CDDP 75mg/m^2 q 21 days x 4 cycles [34]	BRCA1 tumors	• pCR 90%
Neo CDDP 75mg/m^2 q 21 days x 4 cycles + BEV 15 mg/kg q 3 weeks x 3 cycles [35]	TNBC (palpable/measurable)	• 26% cCR • 52% cPR • 11% SD • 2% PD
Geparsixto [36] CAR (AUC 2) + BEV + WP + lipoDOX	Stage II	• additional pCR of 20% with CAR but reduced CAR dose due to side effects
PrECOG 0105 Neo CAR (AUC 2) + GEM (1000mg/m^2) + IN (5.6 mg/kg) q21 days x 6 cycles	Stage I-III BRCA1/2 tumors	• pCR of 36% overall • 56% in those with BRCA1/2-TNBC

CALGB 40603 (ALLIANCE)
Neo WP (80mg/m^2) >> ANTHR + CTX ± CAR (AUC 6) ± BEV (10 mg/kg)
	Stage II-III	• Preliminary data: neutropenia, thrombocytopenia
		• Additive effects CAR + BEV:
		  • pCR (breast) 60%
		  • pCR (breast/axilla) in 50%

I-SPY 2 [37] Neo WP (80 mg/m^2) >> ANTHR + CTX q2-3weeks ± ABT-888+CAR	TNBC >2.5cm if palpable or >2cm by imaging BRCA1/2 tumors	• Combination superior to control • 52% (38-67%) vs 24% (9-43%)
Hoosier Oncology Adj CDDP ± RUCAPARIB	BRCA1/2 tumors Residual disease after standard neoadjuvant treatment	Pending
ECOG 5112 Neo ANTHR + CTX then P or GEM (1000mg/m^2) + CAR (AUC 2)	TNBC; BRCA1/2 tumors tumors with high homologous recombination deficiency score [38]	Pending

TNBC= triple negative breast cancer (ER-/PR-/HER2-), Neo=neoadjuvant, Adj= adjuvant, CDDP= cisplatin, CAR= carboplatin, GEM= gemcitabine, BEV= bevacizumab, DOX= liposomal doxorubicin, P=paclitaxel, WP= weekly paclitaxel, IN=iniparib, ANTHR=anthracycline, CTX=cyclophosphamide, pCR= pathologic complete response, cCR= complete clinical response, cPR= clinical partial response, AUC = area under the curve, (dose).

2.4 *Rationale For Combinatorial Therapy With Anthracycline And Carboplatin- Rutgers Cancer Institute of New Jersey Clinical Experience With The Combination Of Liposomal Doxorubicin And Carboplatin For The Treatment of Patients With Triple Negative Breast Cancer.*

Preclincial and clinical evidence demonstrate that loss of BRCA1 function, as occurs in BRCA1-associated breast cancers and in at least a subset of triple negative breast cancers, predicts response to select chemotherapy including platinum-based compounds [32;38]. Moreover, as prior preclinical studies suggested the combination of cytotoxics with bevacizumab to be synergistic, this led to the implementation of a phase III trial of weekly paclitaxel versus weekly paclitaxel plus bevacizumab as first line therapy for

[redacted]

locally recurrent or metastatic breast cancer (E2100 trial) [40;41]. As an improved 5 month progression free survival and response rate with the addition of bevacizumab to paclitaxel was observed, this provided a rationale for piloting the combination of doxil (DOX), carboplatin (CAR), and bevacizumab (BEV) in patients with previously untreated patients with metastatic ER, PgR, and HER2 negative breast cancer. We conducted a Phase I/II investigator-initiated trial at the Rutgers Cancer Institute of New Jersey in 31 patients with previously untreated TNBC [unpublished]. All patients had measurable disease and an ECOG PS ≤ 2, and adequate bone marrow, renal and hepatic function. Patients received DOX (30 mg/m^2), CAR (AUC 5) and BEV (15 mg/m^2) every 4 weeks. DOX was selected as the preferred anthracyline given the reduced cardiac toxicity and comparable efficacy of doxil versus doxorubicin reported in a phase III trial in women with metastatic breast cancer [42]. Grade 3 non-hematological toxicities included: hypertension, fatigue, and hand-foot skin reaction. Grade 4 hematological toxicity included thrombocytopenia. No significant change in cardiac function was observed among the first 6 patients enrolled in the phase I portion. Alopecia was not observed. Of 30 evaluable patients, 80% had complete, partial, or stable disease at 6 months with 11 responses lasting 6 months or longer. Median overall survival (OS) was 10 months where 15 patients were alive at 10 months or longer. Four were not evaluable for OS due to relocation. These results demonstrate that the combination of DOX, CAR, and BEV is an active and well-tolerated regimen in previously untreated TNBC. Bevacizumab contributed little to the activity of this regimen and was discontinued in a number of patients secondary to bevacizumab-related toxicities. Subsequent data suggest no benefit of bevacizumab in the treatment of patients with breast cancer including TNBC [43]. Collea *et al.* [44], the objective response rate for the combination of pegylated liposomal doxorubicin at 30 mg/m^2 and carboplatin, day 1 of each 28-day cycle, was 31% regardless of taxane pretreatment. Taxane-naïve (n=41; 12 were ER-/PR-) and taxane pretreated patients (n=42; 20 were ER-/PR-) had PFS of 8 and 5 months, respectively, with excellent tolerability.

2.4.1 *Use Of Liposomal Doxorubicin In The Neoadjuvant Setting For The Treatment Of Patients With Breast Cancer.*

Liposomal doxorubicin has been used in the treatment of breast cancer in the neoadjuvant setting. Selection of liposomal doxorubicin has gained favor due to the lower degree of toxicity, including cardiotoxicity, as compared to conventional doxorubicin while retaining similar efficacy [45-47]. Multiple studies demonstrate its safety and tolerability alone or in combination with other chemotherapeutic agents. Because skin toxicity of liposomal doxorubicin includes pruritus, maculopapular rash, palmar-plantar erythrodysesthesia and rarely Stevens-Johnson syndrome, its safety in the neoadjuvant setting has previously been raised. However, review of the literature has not revealed issues of poor wound healing after surgery. Pegylated liposomal doxorubicin at 20mg/m^2 was used in combination with cyclophosphamide as preoperative treatment for patients with locally advanced breast cancer where it was given every 2 weeks for eight doses [48]. In this study, definitive breast surgery was performed four weeks after the last dose of liposomal doxorubicin on all patients (13 breast-conserving surgery; 13 mastectomy, and included either sentinel lymph node biopsy in six or complete axillary lymph node dissection in the majority). Treatment was well tolerated, with no grade 4 toxicities, and had grade 3 skin toxicity in three patients and hand-foot syndrome in four patients. No documentation of delayed surgical healing was reported among the SAEs. The safety of the combination of neoadjuvant paclitaxel 175 mg/m^2 and pegylated liposomal doxorubicin 35 mg/m^2 every three weeks for six cycles was evaluated in 35 patients with locally advanced breast cancer [49]. While the primary toxicity was skin (grade 3 in 11% including palmar-plantar erythrodysesthesia in 9%). Although treatment was discontinued due to skin toxicity in four patients, it did not impede surgical healing after mastectomy. A similar study was undertaken for this neoadjuvant combination leading to breast conserving surgery in 55% of patients which showed the

[redacted]

combination was active in operable and locally advanced breast cancer with a manageable safety profile [50]. Only four of 27 patients experienced either grade 2 or grade 3 hand foot syndrome. To explore the activity of pegylated liposomal doxorubicin (PLD) as neoadjuvant therapy of breast cancer, it was combined with cisplatin and infusional fluorouracil (CCF) for 8 courses in patients with primary or recurrent T2-T4a-d N0-3 M0 breast cancer including ER+, ER- (n=1), and unknown ER status (n=9) [51]. No adverse events on wound healing reported and clinical response rate was 77.5%. However, as only one patient had TNBC and the majority of those with unknown ER status would be positive for expression of the receptor, the data cannot be extrapolated to the TNBC population for clinical response.

2.4.1 *Key Observations In The Use Of Platinum-Based Therapy For TNBC.*

Factors previously shown to be associated with good cisplatin response include low BRCA1 expression, BRCA1 promoter methylation, and p53 nonsense or frameshift mutations (NSM) [32]. A significant association of tumor p53 NSM with cisplatin response was noted though this did not exclude BRCA1-mutant tumors. Furthermore, mutational status of other genes was not evaluated [32;52]. P53 expression, as a surrogate for mutation status, as a predictor of chemotherapy outcome has produced variable results [53-58]. Tumor profiling of BRCA1 methylation status from patients treated with high dose platinum-based or conventional chemotherapy showed improved recurrence free and overall survival with platinum for patients with tumors characterized as BRCA1-like as compared with non-BRCA1-like tumors [33]. As only 25% of assessable tumors had BRCA1 mutation and 38% of the remaining assessable tumors had BRCA1 methylation, this identifies at least a subset of nonBRCA1-associated TNBC that is also platinum-sensitive.

Additionally, residual TNBC following neoadjuvant therapy represents a marker for high risk of distant relapse and poor outcome [reviewed in 59]. Up to 30% of patients have residual disease at the end of neoadjuvant chemotherapy [60]. Gene expression patterns, basal-like breast cancer status, apoptotic markers, and proliferation scores of this residual disease correlate with shorter recurrence free survival [60;61]. Understanding markers that would predict for residual disease would potentially lead to clinical trial design to improve clinical outcomes in TNBC. Current feasibility of tumor genomic sequencing offers a novel approach to identify genomic alterations that may not only predict for response but will inform the design of novel therapeutic or targeted approaches and drug development, potentially leading to improved outcomes for patients with TNBC.

2.5 *Next Generation Sequencing (NGS) Of Tumors From Patients With TNBC.*

Feasibility of next generation sequencing on tumor tissue has resulted in identification of tumor mutational landscapes in multiple tumor types. This primary identification has provided valuable insights into genomic alterations that impact on tumorigenesis specific to tissue types and cancer subtypes. The next generation of studies such as this study will aim to determine functional significance of specific mutations on prognosis, as predictive markers for response to conventional therapies, as predictive markers for response to targeted agents directed at actionable mutations, and as a guide for the development of future clinical trials combining targeted agents and/or cytotoxins.

Genomic profiling has catalogued mutational landscapes in tumors including breast cancer where the most common somatic mutations in TNBC are TP53 (54-86%) and PIK3CA (10-21%) with other frequent mutations variably observed in about 10% of TNBCs [62-64]. Although this has provided valuable insight into genomic alterations present in specific breast cancer subtypes, outcomes or response to specific chemotherapeutic agents have not been systematically evaluated. Whole genome sequencing in metastatic

[redacted]

TNBC has revealed potentially actionable molecular alterations [65]. Next generation sequencing of pre-treatment biopsies from patients with TNBC receiving neoadjuvant treatment with doxorubicin plus cyclophosphamide revealed a slightly higher somatic mutation rate per tumor and significantly higher frequency of mutations in the phosphatidylinositol signaling pathway in tumors from non-responders as compared to responders [66]. Furthermore, in patients with TNBC treated with neoadjuvant chemotherapy, amplifications were associated with enhanced gene expression and alterations in DNA repair also identified a subgroup with poor recurrence free survival and overall survival [60;61]. It is not known if the same mutations would be predictive of response to platinum. ***Therefore, the emerging technology of genomic profiling may identify genomic alterations predictive for drug response and inform the design of novel therapeutic or targeted approaches to actionable mutations to improve outcomes in TNBC.***

2.5.1 *Our Experience With Targeted Next Generation Sequencing Of TNBC.*

We have demonstrated our ability to procure and perform genomic sequencing of tumors through an IRB-approved protocol as part of the Rutgers Cancer Institute of New Jersey Precision Medicine Initiative (PI: Ganesan; Sub-investigator/Supporting Scientist: Hirshfield). We have successfully recruited 100 patients, have performed clinical grade NGS of tumors using the FoundationOne platform from Foundation Medicine to identify genomic alterations (mutations, copy number alterations, insertions, deletions, rearrangements) in roughly 240 cancer-related genes. We also hold weekly tumor boards to make recommendations for targeted therapies based on those profiles. Our genomic profiling of nine TNBCs reveals an average of 3.7 alterations per tumor including frequencies of the following gene alterations: p53 88% (3 nonsense, 1 splice site, 4 missense), PIK3CA 33%, NOTCH 33%, PTEN 22%, FGF/FGFR 22%, MYC 22% [unpublished]. Three of these TNBCs were from individuals on our DOX, CAR, BEV study. Of these, two had serial specimen NGS and revealed mutational gain in at least one gene over baseline.

2.6 Supporting Rationale

Hypothesis: Specific sets of ***genomic aberrations are associated with poor response of triple negative breast cancer to chemotherapeutics resulting in treatment failure and poor clinical outcomes***. Profiling residual TNBC after neoadjuvant chemotherapy will identify molecularly targetable lesions in the chemotherapy-resistant component of the tumor and provide testable hypotheses for drug targeting and therapeutic trial design for TNBC. A neoadjuvant regimen of liposomal doxorubicin (DOX) and carboplatin (CAR) followed by definitive surgery and weekly paclitaxel (WP) for stage II-III TNBC is being undertaken as the clinical setting in which to test these hypotheses. Higher risk stage I TNBC patients that may receive chemotherapy per NCCN guidelines may also be included.

Although the breast cancer death rate has decreased since 1990, nearly 40,000 US women are expected to die from it in 2013 [1]. Women with triple negative breast cancer (TNBC) still bear a disproportionate burden of the morbidity and mortality associated with this disease [2]. Given the known statistics, novel approaches are clearly needed to understand the basis for these observations and to improve outcomes for women with TNBC.

The TNBC designation arises from the lack of knowledge beyond conventional molecular features regarding specific aberrations giving rise to this breast cancer subtype and its biology. As these cancers lack expression of ER or amplification of HER2, there is no effective targeted therapy, and systemic therapy of TNBC currently relies on the use of cytotoxic chemotherapy. However, a paradox has emerged. Despite overall worse clinical outcomes, several studies demonstrate higher pathologic complete response (pCR) with neoadjuvant chemotherapy in TNBC as compared with non-TNBC. Those achieving pCR have excellent long-term outcome, while those with gross residual disease (GRD), particularly those with specific gene expression

[redacted]

patterns, apoptotic markers, and proliferation scores, have a very poor prognosis [reviewed in 59;60] This suggests that TNBC are heterogeneous and that a subset are sensitive to standard chemotherapy. In keeping with this, a subset of TNBC also appears to benefit from platinum-agents, with higher response rate being associated with p53 mutations [31-33]. This leads to two very important clinical challenges: 1) identifying which TNBC will respond well to standard chemotherapy and platinum, and 2) identifying novel therapeutic strategies for those cancers that do not respond well to these agents. Current genomic sequencing techniques make feasible a hypothesis-driven approach to both find predictors of response to neoadjuvant chemotherapy and identify potential targeted therapies for cancers that fail neoadjuvant therapy.

Standard neoadjuvant chemotherapy for patients with breast cancer consists of anthracycline plus cyclophosphamide (CTX) followed by taxane. However, pharmacokinetic properties of CTX are not ideal for TNBC as one of its main active metabolites is in equilibrium with its tautomer, aldophosphamide, which is oxidized by aldehyde dehydrogenase (ALDH). The increased ALDH1 expression observed in TNBC is correlated with resistance to CTX [67-70]. Furthermore, previous data have lead to the design and implementation of several studies in the "triple negative population" utilizing platinum based regimens. The trial designs, however, are based on addition of platinum agents to existing drug regimens which has previously resulted in increased toxicity and/or discontinuation of platinum agent. The combination of DOX and CAR has been shown to be a well tolerated and active regimen in patients with advanced ovarian cancer [71-76]. Therefore, we now propose to use carboplatin as an alternative to CTX in an anthracycline-based regimen that has demonstrated efficacy and excellent tolerability in the treatment of patients with other tumor types and in the setting of metastatic TNBC [44;71-76; unpublished]. We propose a neoadjuvant regimen of liposomal doxorubicin (DOX) and carboplatin (CAR) then definitive surgery followed by weekly paclitaxel (WP) for the treatment of early stage TNBC. Early stage breast cancer is defined as stage II-III for the purposes of this study. A weekly P schedule will be used as it improves disease-free and overall survival as compared to every 3week paclitaxel regardless of receptor status and has improved tolerability [77].

Our prospective clinical trial depicts a well-tolerated therapy incorporating carboplatin that could be moved into the adjuvant setting, and has little risk of hair loss, a profile that would be palatable to younger women with TNBC. It would be expected to be effective for BRCA1/2 associated tumors and for tumors with nonsense or missense mutations in p53. This trial seeks to substitute platinum for a standard agent, *i.e.* cyclophosphamide, which is predicted to be less effective for TNBC. We propose to utilize genomic profiling in the setting of the clinical trial to correlate profiles with response and to validate a therapeutic approach based on the genomic profile. Genomic analysis of TNBC may identify a mutational landscape that reflects tumor biology and/or identifies an actionable mutation for which targeted therapy could be applied. As individuals with gross residual disease following neoadjuvant chemotherapy have high risk of distant relapse, existing mutations may offer predictive value in those likely to relapse as well as what therapies may be effective. Patient-derived xenografts (PDX) from patients with gross residual disease will model each individual tumor, recapitulating the unique mutations found in their tumors and the genetic milieu. PDX and *ex vivo* assay response to specific therapies may inform future treatments likely to benefit to a particular patient at the time of their relapse. Therefore, this protocol could shed light on not only effective treatment of primary tumors but also that for recurrent disease or distant metastases.

2.7 Availability of Doxil

When there is a shortage of liposomal doxorubicin at the I[redacted] patients will be allowed to receive treatment with epirubicin, an alternative anthracycline. Neoadjuvant treatment would then consist of epirubicin (60 mg/m^2) and carboplatin (AUC 5) in patients with ER, PgR, HER2 negative

[redacted]

breast cancer. The patient will continue to follow all requirements per protocol guidelines. This protocol is to prioritize available liposomal doxorubicin to those patients for whom there is curative intent, lessening the possibility that epirubicin will need to be used for this cohort.

3. Participating Institutions

[redacted]

4. Experimental Design and Methods

This is an open-label, Phase II trial to determine the rate of pathologic complete response from the treatment of patients with stage II-III, ER, PgR, HER2 negative breast cancer with doxil and carboplatin. Higher risk stage I TNBC patients who may receive chemotherapy per NCCN guidelines are also included. Patients will be enrolled to receive the following treatment: 4 cycles of neoadjuvant carboplatin and liposomal doxorubicin administered every 28 days (carboplatin AUC 5, liposomal doxorubicin 30mg/m^2) followed by definitive breast surgery and then 12 weeks of weekly paclitaxel (80 mg/m^2). Definitive breast surgery will be performed no sooner than four weeks from the last dose of liposomal doxorubicin. Patients may also receive additional therapy, e.g. adjuvant radiation therapy, as clinically indicated at the discretion of the treating physician.

Secondary endpoints will be determined and include: recurrence free survival (RFS), 2-year RFS, and overall survival (OS), the mutational spectrum of tumors and their association with response, and *in vitro* and *ex vivo* components for functional prediction of drug response based on mutational landscape to inform future therapy at time of relapse.

To assure cardiac safety of the combination, initially six patients will be enrolled. Assessment of cardiac function will be made after 3 cycles. If one or more cases of CHF are observed, accrual to the study will be stopped. Sixty patients are expected to participate in this five year study. Clinical follow-up will continue up to twenty years following completion of therapy.

5. Patient Selection Criteria

5.1 Inclusion Criteria

A patient is eligible for enrollment if all of the following inclusion criteria are met.

5.1.1 Women with previously untreated, unilateral stage II-III breast cancer, ER/PgR/ HER2 negative (ER≤5%, PgR≤5%, HER2 0-1+ by IHC or FISH≤2.0 or ER≤5%, PgR≤20%, HER2 0-1+ by IHC or FISH≤2.0) confirmed by stereotactic biopsy, core biopsy or excisional biopsy (FNA inadequate). Stage I may be included if clinically negative lymph nodes and tumor size is a minimum of 1.0 cm, and tumor is identifiable under office-based ultrasound guidance. If ER and HER2 are negative, PgR<20% allowed.

5.1.2 Age ≥18. No upper limit.

5.1.3 Negative serum or urine β-hCG pregnancy test at screening for patients of child-bearing potential within 1 week prior to enrollment.

5.1.4 Patients with reproductive potential must use an adequate contraceptive method (e.g. abstinence, intrauterine device, oral contraceptives, barrier device with spermicide or surgical sterilization) during treatment and for three months after completing treatment.

5.1.5 Patients must have an ECOG performance status <2 (Appendix A).

5.1.6 Life expectancy ≥ 52 weeks excluding their diagnosis of breast cancer

5.1.7 Patients must have normal organ and marrow function as defined below:

[redacted]

- ANC ≥ 1,500 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin > 9.0 g/dL
- Creatinine < 2.5 mg/dL
- Total bilirubin < 1.5 X upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) < 2.5 X institutional ULN

5.1.8. Patients must have normal cardiac function, as evidenced by a left ventricular ejection fraction (LVEF) within institutional normal limits defined as LVEF greater than 50%. Echocardiogram or MUGA scan may be used, but the same test must be used throughout the study to evaluate LVEF.

5.1.9 CT CAP and bone scan performed within 30 days prior to study entry and does not demonstrate metastatic disease. PET-CT is allowed as an alternative modality to CT CAP and whole body bone scan at the discretion of the treating physician.

5.1.10 Patients may not receive concurrent treatment with other investigational or commercial agent(s) for treatment of their breast cancer.

5.1.11 The patient must have signed and dated an IRB-approved consent form that conforms to federal, state, and institutional guidelines.

5.1.12 Patients must be eligible to undergo surgery, either lumpectomy or mastectomy for local treatment of the breast cancer. Surgical margins at discretion of surgeon per NCCN guidelines. Axillary exploration at discretion of surgeon but all patients minimally have sentinel lymph node evaluation at time of surgery.

5.1.13 Imaging by mammogram and/or ultrasound must be performed within 6 months of study entry or MRI imaging of affected breast within 30 days of study entry.

5.1.14 Must not exhibit a non-healing wound or any skin breakdown such as from dental work.

5.1.15 Before administering liposomal doxorubicin, patients must wait 4-6 weeks after surgery as it can cause local reactions.

5.1.16 Synchronous ER/PgR/HER2 negative breast cancers (unilateral and/or bilateral) are allowed as long as at least one focus meets criteria 5.1.1 and no other exclusions exist. If bilateral breast cancer is present, then the patient must have confirmation of TNBC per 5.1.1 prior to treatment. ER/PgR/HER2 negative inflammatory breast cancer is allowed as long as no other exclusions exist.

5.1.17 ***Submission of tumor samples from the diagnostic biopsy and breast surgery is required for all patients***. If the patient had a diagnostic core biopsy that confirmed TNBC ***prior*** to the research biopsy, the patient does not need to wait for results of the research biopsy to begin protocol therapy. Prior FNA results only are insufficient to proceed to chemotherapy. If a patient is undergoing a diagnostic biopsy with prior FNA only or inadequate prior biopsy where ER, PR and/or HER2 status could not be reported, the patient must wait for the results of the diagnostic biopsy including confirmation of breast cancer, and ER, PR, and HER2 status before initiation of protocol therapy. Only results for diagnostic purposes (i.e. confirmation of breast cancer, ER/PR/HER2 status) will delay the start of study chemotherapy.

5.2 Exclusion Criteria

A patient will not be eligible for this study if any of the following exclusion criteria are met.

5.2.1 Women who are pregnant or breastfeeding.

5.2.2 Second primary malignancy except most situ carcinoma (e.g. in situ carcinoma of the cervix, adequately treated non-melanomatous carcinoma of the skin), other malignancy treated at least 5 years previously with no evidence of recurrence. A synchronous breast cancer is not considered an exclusion if criteria 5.1.16 is met.

[redacted]

5.2.3 Definitive clinical or radiologic evidence of metastatic disease. Imaging must have been performed no greater than 30 days (+/- 3 days) prior to initiation of chemotherapy.

5.2.4 History of hypersensitivity reactions attributed to a conventional formulation of doxorubicin HCL or the components of doxil, paclitaxel, or carboplatin.

5.2.5 Serious concomitant systemic disorders (including active infections or chronic infection requiring suppressive antibiotics) that would compromise the safety of the patient or compromise the patient's ability to complete the study, at the discretion of the investigator.

5.2.6 Myocardial infarct or unstable angina within 6 months before enrollment, New York Heart Association (NYHA) Class II or greater heart failure See Appendix B, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, valvular disease with documented compromise in cardiac function, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities.

5.2.7 Prior anthracycline, platinum salt, or taxane for any malignancy, within the previous 5 years.

5.2.8 Known or active hepatitis B or C with abnormal liver function tests.

5.2.9 Significant vascular disease (e.g., aortic aneurysm, aortic dissection).

5.2.10 Symptomatic peripheral vascular disease.

5.2.11 Evidence of bleeding diathesis or coagulopathy.

5.2.12 Intrinsic lung disease resulting in moderate to severe dyspnea.

5.2.13 History of a major organ allograft or condition requiring chronic immunosuppression, e.g., kidney, liver, lung, heart, bone marrow transplant, or autoimmune diseases. This includes treatment with corticosteroids within one month (dose of ≥10 mg/day methylprednisolone equivalent) (excluding inhaled steroids). Patients who have received corneal transplants, cadaver skin, or bone transplants are eligible.

5.2.14 Nervous system disorder (paresthesias, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v4.0.

5.2.15 Conditions that would prohibit administration of corticosteroids.

5.3 Inclusion of Women and Minorities

The National Institute of Health (NIH) and NCI have stressed the importance of gender and minority inclusion in clinical services and research. Female patients accounted for 58% of cancer patients seen within Rutgers Cancer Institute of New Jersey's 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.

5.4 Participation of Children

Patients under the age of 18 will be excluded from study participation.

5.5 Sources or Methods of Recruitment

Patients will be recruited through the [redacted] cancer clinics and through referrals from community clinicians or other academic clinicians including affiliate sites. Potential [redacted]

participants will be individuals who present to a medical or surgical oncologist for treatment of their breast cancer. Rutgers Cancer Institute oncologists are listed as study investigators. Clinicians will determine if the stage and molecular features of the individual's breast cancer, based on the pathology report, meet the inclusion criteria for study participation. Physicians will introduce the clinical trial to the individual. If the individual is interested in learning more about study participation, the study research nurse will review the study with the individual, review patient inclusion and exclusion criteria, discuss what is required of the individual during participation, and the consent form. No definite time frame from initial diagnosis is necessary so long as potential participants meet study inclusion criteria or have any exclusion criteria. There are no flyers, internet use, or physician letters for recruitment in this study.

The number of patients being sought for this study is 60. We anticipate that we will discuss potential participation with roughly 90 patients to achieve study number.

Potential participants will only be contacted once to participate in the study as commencement of any treatment for their breast cancer will result in ineligibility. Contact for participation will occur during the clinical visit at the time during which treatment options are discussed. A research nurse will meet with the patient at that the time of expressed study interest and may contact the patient by telephone following this meeting to determine if the individual wishes to participate or any further questions about study participation.

5.6 Study Enrollment Procedures

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the [redacted] before any participating institution may enter patients. The participating institution's consent form must be reviewed and approved by the OHRS Regulatory Affairs Manager and all documents must be received (*i.e.*, IRB approved documentation, IRB approved consent form).

To register eligible patients on this study, each site will contact the OHRS [redacted] **prior to registration.**

If a patient is registered on-study but does not receive any protocol therapy, baseline data will be collected and submitted according to Data Collection (Section 6.1) and Records to be Kept (Section 13). No further follow-up data will be collected. The reason for not starting protocol therapy will be documented.

6. Study Parameters

The following tests and evaluations will be performed according to the schedule below. Baseline (*i.e.*, pre-study) evaluations must be performed no longer than 30 days(+/- 3 days) prior to therapy, unless otherwise indicated in one of the footnotes below the table. For all cycles subsequent to cycle 1, there is a window of +/- 3 days allowed for completion of all protocol evaluations. Delays due to holidays, weekends, or inclement weather will not be considered deviations.

[redacted]

Evaluations	Pre-Study	Weekly	Prior to Each Cycle[6]	End of Treatment[9]	Other
Signed informed consent	X				
Initial History & Physical	X				
Interim History & Physical with Vital Signs			X	X	
Toxicity Assessment		X[13]	X[14]	X	
ECOG Performance Status	X		X	X	
Weight and Height	X		X		
CBC, differential, platelets[8]	X[1]	X[1]	X[1]	X	
Serum Chemistries[2]	X[1]		X[1]	X	
Urinalysis, 24hour creatinine clearance	X				
Liver Enzymes[3]	X[1]		X[1]	X	
EKG	X				
MUGA Scan[7]	X		X[7]	X[7]	
Bone scan, CT CAP with contrast	X[12]		X[12]	X[12]	
Serum or Urine Pregnancy Test[4]	X				
Tumor measurements[5]	X		X	X	
Recurrence[10]			X[10]	X[10]	
Survival [11]				X	
Mammogram and/or US, or MRI[15]	X			X[15]	
Breast tumor tissue[16]	X			X[16]	
Fresh tumor tissue for PDX[17]				X[17]	
Whole blood collection for research	X[18]				
Quality of life survey instruments	X		X[19]	X	X[19]
Tumor genomic testing	X			X[20]	X[20]
Venipuncture for blood[21]	X[21]				X[21]
Immunohistochemistry for ER, PR and FISH for HER2					X[22]

1. CBC, serum chemistries and liver enzymes will be repeated within 48 hours of starting treatment therapy to reconfirm eligibility if there appears to be any deterioration in the patient's status during the interval between registration and treatment. Baseline urinalysis and 24 hour urine creatinine for determination of creatinine clearance will be done only prior to first cycle. If either SGOT or SGPT are 1.5-2.5X the ULN, a hepatitis panel will be performed. CBC to be done weekly only during weekly paclitaxel and prior to each cycle of liposomal doxorubicin and carboplatin (and prior to each Docetaxel or Abraxane if receiving this in place of paclitaxel due to previous toxicity).
2. Includes: Electrolytes (sodium, potassium, chloride, carbon dioxide, calcium), BUN, serum creatinine, glucose.
3. Includes: Total bilirubin, SGOT/SGPT, alkaline phosphatase, albumin, total protein. If either SGOT or SGPT are 1.5-2.5X the ULN, a hepatitis panel will be performed.
4. Women of childbearing potential must have a negative pregnancy test verified by serum or urine BHCG within 1 week prior to enrollment.
5. Disease measurable by physical examination performed at baseline will be re-evaluated after each cycle of therapy using calipers. Surgical specimen is to give size of residual tumor.
6. Within 72 hours of the start of the cycle beyond Cycle 1. Cycles are defined as every 28 days (+/- 3 days) for both pre- and post-surgical therapies. Delays due to holidays, weekends, or holidays will not be considered a deviation..
7. Performed at baseline, within 30 days prior to first dose and within one month after cycle 4 dose of liposomal doxorubicin or epirubicin, carboplatin (see Section 7.1.1.1). The latter evaluation must be completed prior to surgery. Echocardiogram may be used if MUGA scan is not available, but the same test must be used throughout the study to evaluate LVEF.
8. For patients experiencing toxicity, counts will be repeated as outlined in Section 7.4 for individual toxicity assessments.
9. Completed 1 month after the last dose of liposomal doxorubicin or epirubicin (see footnote 7), carboplatin, paclitaxel (or docetaxel or abraxane) treatment.
10. Patients will be followed for recurrence every 6 months. Time to recurrence will be followed using imaging scans/tumor evaluation for symptom evaluation to document first documentation of relapse. Biopsy will be performed to document relapse .

[redacted]

11. Patients will be followed for survival every 6 months for the first 3 years than annually thereafter. A telephone call may be made for survival follow-up. Survival will be monitored for up to 20 years following completion of chemotherapy.
12. Imaging by mammogram and/or ultrasound must be performed within 6 months of study entry and/or breast MRI imaging within 30 days of study entry. PET-CT is allowed as an alternative staging study to CT CAP and whole body bone scan if deemed appropriate by treating physician. Additional imaging after cycle will be based on clinical suspicion and workup for metastatic disease.
13. The first 6 patients will need to be assessed for toxicity via telephone weekly for Cycle 1 only.
14. Performed when the patient comes in for their visit. The toxicity evaluation is optional in between visits and at the discretion of the Investigator. If an assessment is done, it may be done over the phone. Long term toxicity will be monitored during follow-up for survival.
15. Imaging with mammography and/or ultrasound, or breast MRI is to be performed prior to first cycle. Additional imaging to be performed as clinically indicated.
16. All patients will be required to undergo a new tumor biopsy prior to initiation of chemotherapy. If the diagnosis of triple negative breast cancer was made on FNA, confirmation of molecular status (ER-/PR-/HER2-) by core biopsy is required prior to study initiation. If patient has a core biopsy done prior to the research biopsy that confirms TNBC, they do not need to wait for the research biopsy result. FFPE tissue is to be sent for pathology consult with the breast pathologist at RWJUH, for genomic analysis by Foundation Medicine, and for IHC by the Histopathology and Imaging Core at CINJ. For synchronous disease, biopsy of each focus will be done and each focus will also be sent for testing with Foundation Medicine or other similar tumor genomic profiling platform.
17. Fresh tissue will be obtained at time of definitive breast surgery on identification of gross residual disease. Tissue will be preserved as per SOP.
18. Two purple top 4ml EDTA tubes will be collected at study entry, sent to the Biospecimen Repository Service, and stored for future studies.
19. Quality of life survey instruments (FACT-B, Appendix C; Pittsburgh Sleep Quality Index, Appendix D; A distress Assessessment, Appendix E; Hearth Hope Index, Appendix F) are optional and will be completed at baseline (prior to any chemotherapy), after cycle 4 liposomal doxorubicin/carboplatin, and after dose 12 paclitaxel. Hearth Hope Index (Appendix F) will also be done at the start of adjuvant paclitaxel. A Distress Assessment (Appendix E, equivalent at sites acceptable) will be administered (given by the medical health technician) and scores will be entered into the medical record. Social work will be notified of score results as per clinical protocols set forth by NCCN guidelines.
20. FFPE tissue to be sent to Foundation Medicine or for use with other available genomic platforms for genomic testing pretreatment and/or after surgery if gross residual disease identified. Initiation of treatment is not contingent upon obtaining results. It is recommended, but not mandatory, that genomic testing be performed at time of recurrence. Patients may opt against sending for FoundationOne CDx testing which may incur out of pocket cost and is ordered by the treating physician, but not research only genomic testing which is at no cost to the patient and is ordered by the study PI.
21. Optional at time point: Venipuncture for 10 ml of blood will be drawn (in Cell-Free DNA BCT Streck 10ml blood collection tube for stabilization of cell-free plasma DNA) at diagnosis, at cycle 4 liposomal doxorubicin, and at 6 month intervals for total of 3 years then annually to complete 5 years unless recurrence occurs sooner (at which time collection is discontinued). Plasma will be prepared and cryopreserved at -80°C for future analysis with tumor genomic profiling.
22. At the time of definitive surgery, immunohistochemistry for estrogen receptor (ER) and progesterone receptor (PR), and FISH for HER2 will be ordered on all specimens with gross residual disease at the discretion of the treating physician or study PI.

6.1 Required Data Collection

Required information for each patient will include the following: Patient characteristics/demographics, breast cancer pathologic and molecular features, AJCC TNM stage (clinical at diagnosis, pathologic at time of definitive surgery), Study treatment administered, Other treatment including radiation therapy, surgery, and other medical therapies, Adverse events as described in Section 7, Breast cancer events (local, regional, and distant recurrences), Second primary cancer events including second primary breast cancer, Survival.

6.2 Pathology and Correlative Studies

Up to six cores will be obtained during the pre-treatment research biopsy. One core will be sent to RWJUH Pathology to prepare a formalin-fixed, paraffin-embedded (FFPE) tissue block and then to undergo standard histologic review and molecular analysis (including ER, PR, HER2 analysis). FFPE tumor tissue from the

[redacted]

pathology specimen will be sent for testing by Foundation Medicine for genomic profiling. The requisition for genomic testing will be prepared by the Biospecimen Repository Service (BRS). The remaining five will be sent to BRS. BRS will generate FFPE on these pre-treatment cores with 2-3 cores per cassette. For inadequate biopsy tissue, additional biopsies may be performed and FFPE sent for genomic analysis. For patients with gross residual disease (GRD) at time of definitive surgery, defined as >5mm, tumor tissue will be sent for pathologic analysis (including histology and if indicated, analysis for ER, PR, and HER2). Correlative studies will be performed on tumor specimens obtained during the study: genomic profiling and IHC on pre-treatment biopsies and on GRD. For GRD >1cm in size, patient-derived xenografts (PDX) will be created as described below. Recurrent disease will be biopsied for confirmation (where clinically appropriate) and those specimens with adequate tissue will be sent for genomic analysis to determine development of serial somatic mutations. Blood specimens will be obtained at timed intervals in Streck cell-free DNA BCT tubes and sent to the Biospecimen Repository for the isolation of plasma as follows: Venipuncture for 10 ml of blood will be drawn (in Cell-Free DNA BCT Streck 10ml blood collection tube for stabilization of cell-free plasma DNA) at diagnosis, at cycle 4 liposomal doxorubicin, and at 6 month intervals for total of 3 years then annually to complete 5 years unless recurrence occurs sooner (at which point collection is stopped). Blood tube can be kept at room temperature until processed but must be immediately mixed by gentle inversion 8 to 10 times. Do NOT store in refrigerator or freezer. For separation, centrifuge whole blood at 300 x g for 20 minutes at room temperature. Remove the upper plasma layer and transfer to a new conical tube. Centrifuge the plasma at 5000 x g for 10 minutes. Plasma should be cryopreserved at -80°C for future to isolation of cell-free DNA for analysis with tumor genomic profiling.

6.3 Mutational Analysis/Genomic Profiling by Targeted Next Generation Sequencing

A tumor sample is required; a tumor block is strongly preferred. Tumor blocks will be submitted to Foundation Medicine or an alternative commercial laboratory for genomic profiling. Where adequate tissue remains, tumor tissue will be requested for immunohistochemical staining. If the pathology department will not agree to submit a block that can be kept for research purposes, the block should be submitted and Biospecimen Repository Service (BRS) will procure samples of the tumor and return the block to the pathology department that submitted it.

Formalin-fixed, paraffin embedded (FFPE) tumor of pre-treatment and gross residual disease may be sent to Foundation Medicine (Cambridge, MA) for targeted sequencing as ordered by the treating physician in the EMR. Other CLIA-certified, commercial pangenomic testing platforms may be used alternatively but ordered by the study PI. The CLIA-certified FoundationOne platform utilizes clinical grade next-generation sequencing (NGS) to identify genomic alterations (mutations, copy number alterations, insertions, deletions, rearrangements) in roughly 315 cancer-related genes. Foundation Medicine will perform DNA hybridization, library construction, hybrid capture, and then sequencing using the Illumina HiSeq 2000 (depth of coverage 500X-1000X). In cases where serial tumor specimens are available, e.g. serial biopsy at time of progression or recurrence, that tumor tissue will also be sequenced to identify additional mutations that develop. The mutational spectrum and number of mutations observed will be described as a function of patient and tumor characteristics. Secondary exploratory analysis will be to determine association with presence of specific gene mutations/pathway alterations with pathologic complete response (pCR), recurrence free survival (RFS), and overall survival (OS). Whole blood will be collected for isolation of genomic DNA. If cancer genes associated with familial predisposition are found in tumor samples raising the possibility of a germline mutation, a recommendation for assessment by a genetic counselor in the Hereditary Oncology Prevention and Evaluation program at the [redacted]r definitive genetic testing would be given by our Molecular Tumor Board. For patients whose tumors undergo genomic profiling, the Honest Broker will be

[redacted]

contacted to retrospectively enroll patients in the Precision Medicine Protocol ([redacted], barring study closure) and pending patient consent.

6.4 Correlative Studies

All specimens will be collected through the Biospecimen Repository Service in accordance with Honest Broker procedures to protect patient identity. FFPE blocks will be sent to Foundation Medicine or used in other commercial CLIA-certified sequencing platforms for targeted sequencing. Genomic results will be reviewed at the weekly Molecular Tumor Board, where all identifiers are removed to preserve patient privacy. Where tissue is available, immunohistochemistry (IHC) and/or FISH studies may be used to confirm amplifications or translocations and determine the association between genomic alterations and altered protein expression, e.g. measure concordance between p53 IHC with p53 mutation type, measure pAKT and pERK in tumors with receptor tyrosine kinase (RTK) mutations as downstream effectors indicating activation of that pathway. This will demonstrate that downstream targets may be an important therapeutic focus when specific RTK mutations are observed. IHC will be performed in the Histopathology and Imaging Core. For exploratory analysis, we will also evaluate and analyze routine H&E slides of tissue for presence of tumor infiltrating lymphocytes which will be correlated with patient outcomes. Although TNBC and HER2+ subtypes have the highest levels of tumor infiltrating lymphocytes (TILS) and a higher percentage of TILs has been associated with improved survival to both adjuvant and neoadjuvant therapy with anthracyclines [78-80], why varying levels of TILs are observed remains to be elucidated. Therefore, we will evaluate pre- and post-treatment GRD for TILs. Using routine H&E sections, our pathologist will evaluate each specimen for presence of stromal TILs in a blinded fashion and score for percentage of stroma containing lymphocytes [80,81]. We will use TILs as a binary variable (defined by others as $<50\%$ or $\geq 50\%$) and correlate, in an exploratory analysis, with pCR rate and other clinical outcomes. We will also assess presence of TILs for associations with spectrum of genomic alterations and with mutational burden.

6.5 Patient-Derived Xenografts and *Ex Vivo* Assays

6.5.1 PDX Rationale

Gross residual disease (GRD) in TNBC after neoadjuvant chemotherapy predicts for risk of relapse. Equally important to identifying markers that predict for GRD with the DOX/CAR then WP neoadjuvant regimen, would be to be able to identify potentially effective therapies that could be used at time of relapse. It is hypothesized that the mutational landscape of a breast tumor may: a) be representative of that found at relapse; b) predict for response to subsequent cytotoxic or targeted therapies. Patient-derived xenografts (PDX) will be utilized to validate therapeutic responses where each PDX will reflect an individual patient's TNBC. By utilizing this model, the most effective therapy will be identified *a priori* for a specific genomic profile corresponding to any specific patient. In addition, it will be used to identify who is likely to relapse after treatment with paclitaxel and which tumors would demonstrate resistance to cyclophosphamide as proof of principle.

6.5.2 Design

Table 1. Proposed agents for PDX and ex vivo assays

Target	Targeted Agent
P53	Wee1 or CHK1 inhibitors
PIK3CA	PI3K inh. or dual PI3K+mTOR inh.
NOTCH1	Gamma secretase inh.
FGF/FGFR	FGFR inh.
Cytotoxins	
Paclitaxel	er bulin
CTX	vinorelbine
capecitabine	

At the time of surgery, patients with GRD will have tumor sectioned for: a) pathology for clinical analysis, b) IHC, and c) fresh tissue (0.05cm in one dimension) preserved in fresh RPMI in a specimen container on ice for transport to the laboratory of [redacted].

[redacted]

Upon receipt by the research laboratory, one small portion of the tissue (0.05 cm in one dimension) will be placed into neutral buffered formalin solution for histology. The remaining portion of the tissue will be cut into near equal pieces for implantation into PDX model mice. The number of mice will be determined by the size of the tissue provided. CINJ has successfully established PDX models of TNBC with less than 3 passages. PDX will be created in NOD/SCID mice as a tumor cell incubator for each individual patient with GRD similar to other published protocols [82]. Tumor cells, number based on tumor weight, will be orthotopically injected into the mouse mammary fat pad (P0 generation), harvested at appropriate tumor size, and cells cryopreserved as a source for all subsequent experiments. Once prepared, PDX specimen will be deidentified and packaged according to OHSA packing requirements and shipped to the lab of Dr. Celeste Nelson in the department of Chemical and Biological Engineering at Princeton University.

At [redacted], explant (*ex vivo*) culture of cells will also be grown on the surface of biologically inert material without cancer cell dissociation, keeping stromal tissues intact. Drug response assays (Response3DX or similar assay) will be performed on explants. PDX will be frozen viable by and tested in Response3DX™ or similar drug screening platforms. Molecular characterization of samples from primary tumor material as compared to established PDX will provide valuable information on the predictive relevance of these models and our approach. A portion of the PDX tissue will be retained for custom analysis and characterization of the PDX model as well as generation of primary cell lines for in vitro drug testing. A portion of tumor and cryopreserved cells will be returned for sequencing and additional laboratory-based evaluation. Histology and IHC will be performed prior to pharmacology. *Ex vivo* pharmacology will be performed using either the first passage or if sufficient number of cells, non-propagated cells. Treatment of second generation mouse avatars with tumors will occur in parallel or subsequent to *ex vivo* assays. *Ex vivo* data may be used to guide drug selection. Studies to be performed on tumors include markers of apoptosis, proliferation, morphology. Preliminary data confirm that patient-specific histology, tumor architecture, molecular features, biomarkers are maintained over passage.

Drug response tests will proceed by: 1) *in vivo* testing of PDX in mice; 2) *ex vivo* pharmacologic assays. A minimum of 50,000 viable tumor cells from P1 or P2 (second or third passage in mice respectively) will be injected into 1-6 NOD/SCID mice (number to be based on total cells available), and grown until tumors reach an average size of $200mm^3$. Groups of 60 mice will be randomized to four treatment arms: 1) vehicle control, 2) targeted agent, 3) cytotoxin (eribulin, capecitabine, or vinorelbine), 4) cytotoxin and targeted agent (see Table 1 for examples of agents). It should be noted that 80 mice are typically inoculated to ensure 60 tumors with growth to the proper size. Drug-specific dosing over ~6-8 weeks will be based on established methods, with monitoring for body weight, tumor size, and clinical observations. At termination, tumor (where available) will be resected, measured, and FFPE made and tumor specimens stored for future molecular/genomic studies and resequencing. PDX tumors will also be evaluated for morphology, Ki67, p53, apoptotic markers, and phosphorylated proteins in relevant targeted pathways. *Ex vivo* Response3DX or similar drug assays will be performed on cells from first passage or non-propagated cells, at multiple concentrations to determine IC_{50} for any given tumor. Cells will be treated with various cytotoxins, targeted agents or combinations. Results from *ex vivo* assays may help direct treatment of PDX. Exact targeted agents and cytotoxins will be determined by genomic results. Histology and IHC will be performed prior to pharmacology.

As proof of concept for response to CTX and WP, each PDX will be treated with either agent, validate the relationship between ALDH1 expression and reduced sensitivity to CTX, and determine the predictive value in knowing which patients harbor tumors that may progress or relapse after WP due to intrinsic resistance.

[redacted]

NGS results from resistant PDX will be compared to genomic profile in tumors from patients recurring after WP. We would expect that PDX showing no reduction in tumor volume will correspond to tumors in patients for whom there will be a higher risk for future relapse or progression of disease during treatment with WP.

Drug selection for testing in PDX and *ex vivo* assays will be guided by each tumor's genomic alterations. Given the mutational frequencies observed in preliminary sequencing, we anticipate identification of p53, PIK3CA, NOTCH1, and FGF pathway alterations. Targeted agents are defined in Table 1. We will purchase clinical grade drugs from licensed suppliers of pharmaceutical company products and/or our research pharmacy, but we will also approach pharma to obtain approval to obtain clinical grade drug directly from the manufacturer. Cytotoxins will be purchased or obtained from our research pharmacy as available. For cytotoxin testing alone and in combination with targeted agent, we will prioritize drug selection from the right column as they appear in Table 1. Cyclophosphamide and paclitaxel will not be used for combinatorial testing. Results from PDX and *ex vivo* assays will not be used to direct treatment decisions for patients.

7. Treatment Plan

7.1 General Considerations

A cycle is defined as an interval of 28 days for DOX/CAR and as a weekly interval for WP (delays due to holidays, weekends and inclement weather will be permitted and will not be counted as a protocol violation). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy with this exception: peg-filgrastim can be given for the treatment of neutropenia, at the discretion of the treating physician, during treatment with liposomal doxorubicin and carboplatin. Study treatment will be administered until disease recurrence or progression, 2nd primary malignancy (except curatively treated nonmelanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawal of consent occurs. Patients may discontinue therapy at any time for any reason.

Schedule of Therapy				
Neoadjuvant DOX/CAR	**Drug**	**Dose**	**Dosing interval**	**Planned duration**
	Liposomal doxorubicin (DOX)	30mg/m^2 IV over 90 minutes for first infusion then 60 minutes subsequently	**Day 1 every 4 weeks**	**cycles 1-4** (one cycle = 4 weeks)
	Carboplatin (CAR)	AUC 5 IV over 30 – 60 minutes	**Day 1 every 4 weeks**	**cycles 1-4** (one cycle = 4 weeks)
Definitive breast surgery				
Adjuvant WP	**Drug[a,b,c]**	**Dose**	**Dosing interval**	**Planned duration**
	WP	80 mg/m^2 IV over 60 minutes[a]	**Weekly** (one cycle = 4 weeks)	**12 doses**

a All patients should receive premedications as follows before each paclitaxel dose: dexamethasone 10mg iv, famotidine 20mg, diphenhydramine 25mg. An equivalent dose of other steroid may be substituted for dexamethasone. Alternative IV H2 blocker may be given: cimetidine 300 mg, ranitidine 50 mg.

b Central venous access is at the investigator's discretion.

c Patients will be enrolled to receive the following treatment: 4 cycles of neoadjuvant carboplatin and liposomal doxorubicin administered every 28 days (carboplatin AUC 5, liposomal doxorubicin 30mg/m^2) followed by definitive breast surgery and then 12 weeks of weekly paclitaxel (80 mg/m^2). In the event that the patient has a reaction to paclitaxel, the patient may be treated with docetaxel or abraxane at standard dosing parameters at the treatment physician's discretion. Definitive breast surgery will

[redacted]

be performed no sooner than four weeks from the last dose of liposomal doxorubicin. Patients will also receive additional therapy, e.g. adjuvant radiation therapy, as clinically indicated at the treating physician's discretion.

7.1.1 Drug Specific Safety Monitoring Procedures

Note: When there is a shortage of doxil at the [redacted], patients will be allowed to receive treatment with epirubicin, a commercially available alternative anthracycline. Treatment would then consist of epirubicin (60 mg/m^2), carboplatin (AUC 5) in patients with ER, PgR, HER2 negative breast cancer.

Epirubicin and carboplatin will be given on Day 1 of a 28 day cycle. Epirubicin will be calculated using the patient's actual weight in the determination of body surface area. IV administration will be given over 15 to 20 minutes.

In the event that a patient has a reaction to paclitaxel, they will be allowed to switch to either docetaxel or abraxane per institutional guidelines at the treating physician's discretion. Additionally, if a patient has a reaction to doxil and the treating physician believes it is in the patient's best interest to treat the patient with epirubicin instead, this may be allowed. However, the physician must first consult with the PI for approval.

All treatment parameters, safety parameters and requirements will be followed as per protocol and outlined in the following sections.

7.1.2 Cardiac Safety Monitoring

Cardiac Safety Monitoring

Baseline left ventricular ejection fraction (LVEF) determinations will be performed on all patients prior to enrollment in the trial. Patients will not be enrolled if LVEF is below institutional normal limits.

Once on study, all patients will be monitored for a decrease in left ventricular ejection fraction (LVEF) based on the criteria below.

Treatment with liposomal doxorubicin or epirubicin should be discontinued if there is cardiac dysfunction as indicated by:

- symptomatic arrhythmia or congestive heart failure, **or**
- a decrease in LVEF to below the institutional lower limit of normal **and** at least an absolute 5 percentage points decrease from the patient's baseline LVEF value (e.g., 45% to 40%), **or**
- any absolute decrease of 15 percentage points or more from the patient's baseline value (e.g. 60% to 45%).

[redacted]

MUGA or ECHO (LVEF) Schedule for all patients:

- Prior anthracycline doses exceeding 360 mg/m^2 for doxorubicin (including liposomal doxorubicin) or 720 mg/m^2 for epirubicin are not allowed.

LVEF assessment performed by MUGA scan prior to cycle 1 and after cycle 4 of liposomal doxorubicin or epirubicin and carboplatin treatment. The latter evaluation must be completed prior to surgery. Echocardiogram may be used if MUGA scan is not available, but the same test must be used throughout the study to evaluate LVEF.

7.2 Dose Calculation

Doses of liposomal doxorubicin or epirubicin will be calculated using the patient's actual weight in the determination of body surface area. A variance of 5% of the calculated total dose will be allowed.

$$\text{BSA } (m^2) = \sqrt{\frac{height(in) x weight(lbs)}{3131}} \text{ or } \sqrt{\frac{height(cm) x weight(kg)}{3600}}$$

Doses of carboplatin will be calculated based on serum creatinine using the modified Calvert formula:

Total dose (mg) = Target AUC (mg/mL x min) x [Creatinine Clearance (mL/min) + 25]

Creatinine clearance can either be measured or estimated using the Cockroft-Gault formula, as follows:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

7.3 Treatment Administration

Carboplatin (AUC 5) and either liposomal doxorubicin 30 mg/m^2 or epirubicin 60 mg/m^2 will be administered on Day 1 of each 28-day cycle. After definitive surgery, paclitaxel 80 mg/m^2 IV will be administered on Day 1 of each week for total 12 doses.

General instructions:

- The CTCAE v4.0 must be used to grade the severity of adverse events (AEs).
- All doses must be based on the AE requiring the greatest modification.
- Chemotherapy doses that have been reduced may not be escalated.
- Chemotherapy should be held for at least 1 week until any AE requiring dose modification returns to ≤ grade 1 unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, chemotherapy must be discontinued.
- In the event of tumor recurrence, chemotherapy should be discontinued. Further therapy is at the investigator's discretion.
- Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) clinical practice guidelines.
- Management of anemia -Chemotherapy should not proceed with ≥ grade 3 anemia. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

[redacted]

7.3.1 Carboplatin

Carboplatin at target AUC = 5 mg/mL/min will be administered by IV infusion over 30 – 60 minutes.

7.3.2 Liposomal Doxorubicin

To minimize the risk of infusion-related reactions, the first infusion of liposomal doxorubicin should be administered over 90 minutes.
If no infusion-related reactions are noted with the initial infusion, subsequent infusions will occur over 60 minutes.

7.3.3 Epirubicin

In the event of a shortage of doxil/liposomal doxorubicin at the Rutgers Cancer Institute of New Jersey, patients will be allowed to receive epirubicin. Epirubicin will be given by IV administration over 15 to 20 minutes.

7.3.4 Paclitaxel

Paclitaxel will be given by IV administration over 60 minutes.

7.3.5 Docetaxel

In the event the patient has a reaction to paclitaxel, they will be allowed to switch to either docetaxel or abraxane. Docetaxel will be given by IV administration over 60 minutes per Institutional guidelines.

7.3.6 Abraxane

In the event the patient has a reaction to paclitaxel, they will be allowed to switch to either docetaxel or abraxane. Abraxane will be given by IV administration over 30 minutes per Institutional guidelines.

7.3.7 Additional Therapy

Breast surgery, mastectomy or breast conserving surgery, will be at the discretion of the treating physician. However, all procedures require lymph node evaluation with minimum of sentinel lymph node biopsy. Choice of radiation therapy, treatment fields, and treatment schedule will be at the discretion of the treating radiation oncologist. Whole breast radiation should begin within 6 weeks following the last dose of chemotherapy. Regional nodal basin irradiation is at the discretion of the treating radiation oncologist. Partial breast irradiation is not permitted. Post-mastectomy radiation therapy is at the discretion of the treating radiation oncologist. Therapy for progressive disease or recurrent disease is at the discretion of the treating medical oncologist. However, the Molecular Tumor Board may provide recommendations for therapy based on the genomic profile for that patient's tumor.

7.4 Dose Modifications

Chemotherapy dose will be adjusted according to the system showing the greatest degree of toxicity. Toxicities/adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events, Version 4.0. Patients are allowed a maximum of 2 dose reductions. If toxicity or adverse events cause one study drug to be held, all study drug doses will be held until criteria is met to resume dosing. Chemotherapy

[redacted]

will be held for a maximum of 3 weeks for toxicity or adverse events. If after 3 weeks no recovery is seen, study drugs will be permanently discontinued and the patient will be removed from the study.

Treatment with DOXIL/liposomal doxorubicin or epirubicin should be discontinued if there is cardiac dysfunction as indicated by:

- symptomatic arrhythmia or congestive heart failure, **or**
- a decrease in LVEF to below the institutional lower limit of normal **and** at least an absolute 5 percentage points decrease from the patient's baseline LVEF value (e.g., 45% to 40%), **or**
- any absolute decrease of 15 percentage points or more from the patient's baseline value (e.g. 60% to 45%).

Treatment with epirubicin is allowed if DOXIL/liposomal doxorubicin must be discontinued due to toxicity at the treating physician's discretion.

Dose reduction is planned in case of severe hematological and/or non-hematological toxicities as follows:

Carboplatin: from AUC 5 mg/mL/min to AUC of 4 mg/mL/min

Doxil/liposomal doxorubicin: from 30 mg/m^2 to 24 mg/m^2

Epirubicin if used in place of doxil/liposomal doxorubicin: will be reduced by 20% from 60 mg/m^2 to 48 mg/m^2. If epirubicin is given in place or a dose-reduced doxil, then the dose-reduced epirubicin is to be given.

Paclitaxel: If pre-treatment PMN <1000/m^3, do not re-treat until PMN >1000/m^3 and platelet count >100,000/m^3. If severe neutropenia occurs (PMN <500/m^3 for 7 days), reduce subsequent doses by 20% from 80 mg/m^2 to 64 mg/m^2. Filgrastim may be added to the treatment regimen per institutional guidelines at the discretion of the treating physician.

Docetaxel: If severe neutropenia occurs (PMN <500/m^3 for 7 days), moderate (grade 2) neurosensory, or severe/cumulative cutaneous reaction, reduce subsequent doses by 25% from 100 mg/m^2 to 75 mg/m^2. If AEs persist: Reduce further to 55 mg/m^2 or discontinue. Filgrastim should be given with this regimen per institutional guidelines. If patient has Grade 3 peripheral neuropathy: Discontinue. If patient has Grade 3/4 Stomatitis: Decrease to 75 mg/m^2. Do not administer if AST/ALT >5 times ULN or alkaline phosphatase >5 times ULN. Reduce dose by 20% if AST/ALT >2.5 - 5 times ULN and alkaline is 2.5 times ULN or lower; alternatively lower the dose by 20% if AST/ALT > 1.5-5 times ULN and alkaline phosphatase >2.5-5 times ULN.

Abraxane: Patients who experience severe neutropenia (neutrophils < 500 cells/mm3 for a week or longer) or severe sensory neuropathy during Abraxane therapy should have dosage reduced to 220 mg/m2 for subsequent courses of Abraxane. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of Abraxane. Filgrastim may be added to the treatment regimen per institutional guidelines at the discretion of the treating physician.

[redacted]

No additional dose reductions may be given except as indicated below for specific toxicities. If toxicity occurs that would indicate a further dose reduction is needed, the patient will be removed from the study. Doses, which have been reduced for toxicity, must not be re-escalated with the exception of liver function tests that improve within ranges given.

7.4.1 Carboplatin

Febrile Neutropenia

Febrile neutropenia shall be defined as oral or tympanic fever of $\geq$ 38.5°C or 101.3°F in the presence of neutropenia (where neutropenia is defined as ANC < 1000/mm^3). A therapeutic intervention should proceed immediately following the diagnosis of febrile neutropenia. Therapeutic interventions can be as per the institution's guidelines, or may include:

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery of ANC $\geq$ 1,000/mm^3 or oral temperature < 38.5°C. This must be documented in the specific adverse event section of the CRFs. For the first episode, resume treatment at full dose with peg-filgrastim (G-CSF) support. If despite peg-filgrastim support, a second episode occurs dose reduce carboplatin to 4 AUC and doxil/liposomal doxorubicin to 24 mg/m^2. If a third episode occurs the patient will be taken off-study. Peg-filgrastim support can be given at the discretion of the treating physician for grade 2 or higher neutropenia in the absence of fever or infection.

Infection With (or Without) Neutropenia

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy, with or without neutropenia, prophylactic G-CSF and prophylactic antibiotics will be added to all remaining cycles. Levofloxacin is recommended at 500 mg oral dose daily for 10 days starting on Day 5 of each cycle for remaining chemotherapy cycles. If levofloxacin is not available or not tolerated, another oral antibiotic must be used. The choice of antibiotic is at the discretion of the Investigator. G-CSF will be added to all subsequent chemotherapy cycles as per ASCO guidelines.

2nd Febrile Neutropenia and 2nd Infection Event

In the case of a second febrile neutropenia or infection event, patient will continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses will be reduced for all remaining cycles. In the case of a 3rd event, there will be no further dose reduction. The patient will stop carboplatin and be removed from the study.

Neutropenia in the Absence of Fever of Infection

In case of neutropenia in the absence of fever or infection, blood counts must be done every 2 days until recovery of ANC $\geq$ 1,000/mm^3. For the first episode, resume treatment at full dose with peg-filgrastim (G-CSF) support. If despite peg-filgrastim support, a second episode occurs dose reduce carboplatin to 4 AUC and doxil/liposomal doxorubicin to 24 mg/m^2. If a third episode occurs the patient will be taken off-study. Peg-filgrastim support can be given at the discretion of the treating physician for grade 2 or higher neutropenia in the absence of fever or infection.

[redacted]

Anemia
In case of Grade 2 decrease in hemoglobin, treatment with blood transfusion should be given. The use of prophylactic erythropoietin is discouraged. In case of Grade 3 or 4 decrease in hemoglobin, doses should be reduced as follows: carboplatin reduced from an AUC of 5 mg/mL/min to an AUC of 4 mg/mL/min. Maintain the doxil/liposomal doxorubicin or epirubicin dose.

Nausea and Vomiting
Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the Investigator. Acute episodes of nausea and vomiting should be controlled with adequate antiemetics. In case of Grade 4 vomiting that persists despite antiemetics, patient will discontinue carboplatin and be removed from the study.

Oral Mucositis
In case of Grade 4 oral mucositis (and/or esophagitis) the patient will discontinue carboplatin and be removed from the study.

Peripheral Neuropathy
If the patient experiences peripheral neuropathy of Grade 2, the following dose modifications should be performed: Delay carboplatin treatment by a maximum of two weeks. As soon as patient recovers, treatment should continue with the following dose recommendations:

- If patient recovers to Grade 1 toxicity, maintain the carboplatin and doxil/liposomal doxorubicin or epirubicin doses.
- If Grade 2 persists for > 2 weeks, patient will discontinue carboplatin and be removed from the study.

In case of a second episode, maintain the carboplatin dose. If the patient experiences another episode, no further dose reduction is planned and the patient will discontinue carboplatin and be removed from the study.

Patients who experience severe peripheral neuropathy while on weekly paclitaxel should have dosage reduced by 20% for subsequent courses.

Cutaneous Reactions

- For Grade 4: Patient will be taken off-study.

7.4.2 Doxil/Liposomal doxorubicin

Patients should be carefully monitored for toxicity. Adverse events, such as Palmar-Plantar Erythrodysesthesia Syndrome (PPE), hematologic toxicities, and mucositis may be managed by dose delays and adjustment. Following the first appearance of a Grade 2 or higher adverse event, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

[redacted]

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME(PPE)	
Toxicity Grade	**Dose Adjustment**
1 (Minimal skin changes or dermatitis (e.g., erythema,edema, or hyperkeratosis) without pain)	**No change in dose/schedule unless patient has experienced previous Grade 3 or 4 PPE.** If so, delay up to 2 weeks and decrease doxil dose by 20%.
2 (Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain;limiting instrumental ADL.)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, patient will be removed from the study. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 PPE, continue doxil treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 20% dose reduction of doxil.
3 (Severe skin changes (e.g.,peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease doxil dose by 20% and return to original dose interval. If after 2 weeks there is no resolution, doxil should be discontinued.

ORAL MUCOSITIS	
Toxicity Grade	**Dose Adjustment**
1 (Asymptomatic or mild symptoms; intervention not indicated)	**No change in dose/schedule unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease doxil dose by 20%. Maintain the Carboplatin dose.
2 (Moderate pain; not interfering with oral intake; modified diet indicated)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, patient will be removed from the study. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 mucositis, continue treatment at previous dose. If patient experience previous Grade 3-4 toxicity, continue treatment with a 20% doxil dose reduction. Maintain the Carboplatin dose.
3 (Severe pain; interfering with oral intake)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease doxil dose by 20%. Maintain the Carboplatin dose. If after 2 weeks there is no resolution, patient will be removed from the study.
4 (Life-threatening consequences; urgent intervention indicated)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose doxil by 20%. Maintain the Carboplatin dose. If after 2 weeks there is no resolution, patient will be removed from the study.

7.4.3 Paclitaxel

Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs at any time during the study, treatment with paclitaxel should be discontinued. Side effects requiring dose reduction should have dosage reduced by 20%. Side effects requiring dose reductions or delays are described below.

[redacted]

Neutropenia
Maintain dose if neutropenia occurs (grade 2-4) but recovers before the next treatment. Hold paclitaxel until $\geq 1000/mm^3$. If recovery takes: 1-3 weeks – maintain dose and add filgrastim. Only filgrastim on Days 2-6 may be used for weekly paclitaxel per treating physician discretion; pegfilgrastim is prohibited during weekly paclitaxel. If receiving filgrastim and recovery takes: 1 week – maintain dose; 2-3 weeks decrease one dose level.

Febrile Neutropenia
Febrile neutropenia shall be defined as oral or tympanic fever of $\geq 38.5°C$ or 101.3°F in the presence of neutropenia (where neutropenia is defined as ANC $< 1000/mm^3$). A therapeutic intervention should proceed immediately following the diagnosis of febrile neutropenia. Therapeutic interventions can be as per the institution's guidelines, or may include:

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery of ANC $\geq 1,000/mm^3$ or oral temperature $< 38.5°C$. This must be documented in the specific adverse event section of the CRFs.

With grade 2 infection, the dose should be maintained, but filgrastim prophylaxis added for subsequent chemotherapy if neutropenia was present. For grade 3 infection or febrile neutropenia, maintain dose and add filgrastim prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic filgrastim, reduce one dose level. For grade 4 infection or febrile neutropenia, maintain dose and add filgrastim prophylaxis with subsequent chemotherapy cycles. If receiving prophylactic filgrastim, reduce one dose level or discontinuation. Only filgrastim on Days 2-6 may be used for weekly paclitaxel per treating physician discretion; pegfilgrastim is prohibited during weekly paclitaxel.

Nausea and Vomiting
Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the Investigator. Acute episodes of nausea and vomiting should be controlled with adequate antiemetics. If vomiting is grade 2 despite antiemetics but recovers before next dose, maintain dose or reduce by one dose level. If vomiting is grade 2 despite antiemetics but does not recover before next dose, maintain dose or reduce by one dose level. If vomiting is grade 3 or 4 but recovers by the next dose, reduce dose by one level or discontinue. If vomiting is grade 3 or 4 but does not recover by the next dose, discontinue paclitaxel.

Diarrhea
For grade 2 diarrhea that resolves prior to next cycle, maintain dose. However, for grade 3 that resolves by next cycle, reduce by one dose level. For grade 4 toxicity that recovers by next dose, reduce dose by one level or discontinue. For grade 2 toxicity that does not recover by next dose, either maintain dose or reduce by one dose level. For grade 3 toxicity that does not recover by next dose, reduce dose by one level. For grade 4 toxicity that does not recover by next dose, discontinue paclitaxel.

Mucositis
In case of Grade 2 mucositis that recovers by next dose, maintain dose. If it is grade 2 but does not recover by the next dose, either maintain dose or reduce dose by one dose level. For grade 3 mucositis that either recovers or does not recover by the next dose, reduce dose by one dose level. For grade 4 mucositis that

[redacted]

recovers by the next dose, reduce dose by one level or discontinue paclitaxel. If a grade mucositis does not recover by the next dose, discontinue paclitaxel.

Thrombcytopenia
If platelet count is reduced (grade 2-3), maintain dose. Hold until ≥ 75,000/mm^3. If recovery takes: 1 week maintain dose; 2 to 3 weeks decrease one dose level. If toxicity is grade 4, hold until ≥ 75,000/mm3 and decrease one dose level.

Hepatic Dysfunction
Hepatic dysfunction is defined as elevated bilirubin, AST or alkaline phosphatase. For grade 2 toxicity that recovers by next dose, reduce dose by one level. For grade 2 toxicity that does not recover by the next dose, hold paclitaxel until bilirubin returns to the baseline grade and AST and alkaline phosphatase have returned to ≤ grade 1 and then reduce one dose level. For grade 3 toxicity that recovers by next dose, either reduce dose one level or discontinue. For grade 3 toxicity that does not recover by the next dose, hold until bilirubin returns to the baseline grade and AST and alkaline phosphatase have returned to ≤ grade 1 and then reduce one dose level or discontinue. For grade 4 toxicity, regardless of recovery, discontinue paclitaxel.

Peripheral Neuropathy (paresthesias or peripheral sensory neuropathy)
If the patient experiences peripheral neuropathy, the following dose recommendations should be followed: Grade 1 neuropathy that is less than 7 days duration, maintain paclitaxel dose. If grade 2, current dose may be maintained if improves to grade 1 by day of treatment. However, for a grade 2 that persists > 7 days or delays next treatment, decrease dose by one level. Only two dose reductions are allowed. If peripheral neuropathy worsens or persists despite two dose reductions, paclitaxel should be discontinued. The first episode of grade 3 neuropathy that resolves prior to next dose warrants one level dose reduction. For the second episode of grade 3 that resolves or first episode that persists > 7 days or would delay treatment or any grade 4 neuropathy, paclitaxel should be discontinued.

Musculoskeletal pain not controlled by analgesics (myalgia or arthralgia)
For grade 1 or 2 side effects that resolve days 1-7, maintain paclitaxel dose. For grade 2 that persists > 7 days, maintain dose or decrease paclitaxel dose by one dose. For the first episode of grade 3 neuropathy that resolves in 7 days or less, decrease paclitaxel by one dose. For the second episode of grade 3 that resolves in 7 days, discontinue paclitaxel. For grade 3 neuropathy that does not resolve by 7 days, for first episode either decrease dose one level or discontinue. For second episode, discontinue paclitaxel. Hold paclitaxel for ***persistent*** grade 2 or 3 musculoskeletal pain. When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue paclitaxel.

Other Clinically-Significant Adverse Events
For grade 2 that resolves prior to the next treatment, maintain dose or reduce by one level. For grade 3 that resolves prior to the next treatment, reduce by one dose. For grade 4 that resolves prior to the next treatment, reduce by one dose or discontinue. For grade 3 that requires delay of therapy, reduce by one dose or discontinue. For grade 4 that would require dose delay, discontinue paclitaxel.

7.4.3.1 Infusion Reaction

Infusion of paclitaxel should be interrupted for patients who develop dyspnea or clinically significant hypotension. Patients who experience a NCI CTCAE v4.0 Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from paclitaxel treatment.

[redacted]

The infusion should be slowed to 50% or less or interrupted for patients who experience any infusion-associated symptoms not specified above. When the patient's symptoms have completely resolved, the infusion may be continued at no more than 50% of the currently being received rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

7.4.4 Epirubicin

In the event that there is a shortage of doxil/liposomal doxorubicin, patients will be allowed to receive treatment with epirubicin. Treatment with epirubicin is allowed if DOXIL/liposomal doxorubicin must be discontinued due to toxicity at the treating physician's discretion.

Diarrhea and Mucositis

Antidiarrheal medication may be used at the discretion of the Investigator. Diarrhea and mucositis must return to ≤ Grade 1 before administration of the next cycle. If, after a 2 week delay, diarrhea and/or mucositis have not resolved, therapy must be discontinued.

Grade 1 and Grade 2: No dose reductions.

Grade 3: After the first episode of Grade 3 diarrhea and/or mucositis, decrease the epirubicin dose to 48 mg/m^2. Maintain the carboplatin dose.

Grade 4: If the patient experiences Grade 4 diarrhea and/or mucositis, therapy must be discontinued.

Hepatic Dysfunction

Therapy must be held for a ≥ Grade 2 increase in bilirubin (>1.5 x ULN) or Grade 2 increase in SGOT (> 2.5 x ULN). If the increase is not due to metastatic disease, therapy may be resumed at full dose if the following criteria are met:

- SGOT must return to < grade 2 (≤ 2.5 x ULN) within 2 weeks; and
- Bilirubin must return to normal range for the lab within 2 weeks.

7.5 Concomitant Medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. All concomitant medications must be documented in the patient's medical records.

7.6 Supportive Care Guidelines

All supportive measures consistent with optimal patient safety will be utilized, including but not limited to antiemetic medication, hydration, transfusion support and antibiotics. Peg-filgrastim may be given as support with liposomal doxorubicin and carboplatin while filgrastim may be given as support with weekly paclitaxel at the discretion of the treating physician. No other chemotherapy, immunotherapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are participating in this study.

Use of G-CSF or equivalent is to be used in accordance with ASCO Guidelines and as indicated above.

[redacted]

7.7 Adherence/Compliance

Patients who fail to present for treatment appointments may be removed from the study. Patients that are routinely non-compliant to protocol requirements may be removed at the discretion of the Investigator.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician or their designee will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Toxicities (including laboratory abnormalities) will be reported as outlined in the data capture plan.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1 Adverse Event Reporting Requirements

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

All "unexpected" and/or "serious" adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the OHRS at (732) 235-7577 or (732) 235-8675. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

Reporting SAEs using commercially available drugs:

In addition, any unexpected (*not listed in the package insert*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of doxil/liposomal doxorubicin and carboplatin or paclitaxel must be reported to the FDA within 7 working days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

Expedited reporting requirement for adverse events experienced by patients treated with commercial agents only					
Attribution	Grade 4		Grade 5[a]		**Protocol Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely					
Possible, Probable, Definite	REPORT		REPORT		

[redacted]

FDA MedWatch form 3500: Indicates that an expedited report is to be submitted to the FDA within 7 working days
a: This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Hospitalization that do not meet this criteria are:

- reasons described in the protocol, e.g. drug administration, protocol-required testing
- social reason in the absence of an AE
- surgery or procedure planned prior to entry into the study

8.3 Definition of Related

There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

8.4 Definition of Unexpected

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

9. Treatment Evaluation/Criteria for Response

9.1 DOCUMENTATION OF BREAST CANCER RECURRENCE AND SECOND MALIGNANCIES

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. Suspicious findings do not provide adequate documentation of a breast cancer recurrence and should not be an indication to alter protocol therapy.

[redacted]