Official Title:	**A Phase II Trial of Doxil, Carboplatin and Bevacizumab in Triple Negative Previously Untreated Metastatic Breast Cancer**
NCT number:	**NCT00608972**
Document Type:	**Protocol #1**
Date of the Document:	**10/17/2013**

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A Phase II Trial of Doxil , Carboplatin and Bevacizumab in Triple Negative Previously Untreated Metastatic Breast Cancer

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Version Date: 10/17/13

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
BUN	Blood urea nitrogen
CBC	Complete blood count
[redacted]	[redacted]
CT	Computer Tomography
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PD	Progressive Disease
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
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
ULN	Upper limit of normal

1. Purpose/Specific Objectives

1.1 Primary Endpoint

The primary objective of this study is to determine the median progression free survival (PFS) and 1-year PFS after treatment with doxil, carboplatin and bevacizumab in patients with ER, PR, HER2*neu* negative metastatic breast cancer.

1.2 Secondary Endpoint(s)

1.2.1 To determine the response rate (as determined by RECIST criteria) to combination therapy with doxil, carboplatin and bevacizumab in patients with metastatic breast cancer.

1.2.2 To determine the toxicity of combination theapy with doxil, carboplatin, and bevacizumab.

1.2.3 To measure time to event efficacy variables including:

- time to progressive disease
- survival time

1.2.4 To perform molecular analyses of archived tumor tissue to identify potential markers of response or resistance to therapy.

2. Background and Significance

Approximately 215,000 new cases of breast cancer were diagnosed in the United States in 2004 and ~43,000 died from this disease. Single agent or combination chemotherapy produces response rates of 40-70% in the treatment of advanced breast cancer. Although numerous regimens are effective in palliating symptoms and inducing tumor regression, the complete response rate is less than 20%. Moreover, the median duration of response is nine months with a median survival of 12-24 months. Thus, most responses are of limited duration and nearly all patients with stage IV disease eventually die of disease progression (1). Therefore, the treatment of patients with metastatic and locally advanced breast cancer warrants investigation of novel therapeutic strategies including more rational design and sequencing of combination chemotherapy regimens.

The choice of cancer chemotherapy is usually empirical, based more on the histological appearance of the tumor than on an understanding of the molecular determinants of drug sensitivity. This may account for the suboptimal response rates in many treated patients. Recently, new molecularly-targeted, non-cytotoxic therapies have emerged as an option for treatment of a select set of malignancies, whereby inhibition of a pathologically-significant molecular target is thought to be responsible for disease regression. Given the comparatively non-toxic characteristics of these molecularly-targeted pharmacotherapies, a logical next step in the search for more effective chemotherapeutic regimens is their combination with standard cytotoxics.

One such biologic agent that has demonstrated significant activity in breast cancer, is the antiangiogenic agent, bevacizumab, a humanized monoclonal antibody directed to vascular endothelial growth factor. Compounds targeting angiogenesis are of particular interest as extensive laboratory data suggests that angiogenesis plays an essential role in breast cancer development, invasion and metastasis.

Hyperplastic murine breast papillomas (2) and histologically normal lobules adjacent to cancerous breast tissue (3) support angiogenesis in preclinical models suggesting that angiogenesis precedes transformation of mammary hyperplasia to malignancy. Transfection of tumor cells with angiogenic stimulatory peptides such as fibroblast growth factor-1 or -4 (4,5) , vascular endothelial growth factor (VEGF) (6,7), or progelatinase-B (matrix metalloproteinase-9, MMP-9) (8), increases tumor growth, invasiveness, microvasculature and metastasis (9). Conversely, transfection of tumor cells with inhibitors of angiogenesis, including thrombospondin-1 (10) or tissue inhibitor of metalloproteinase-4 (TIMP-4) (11) decreases growth and metastasis (12). Clinicopathologic correlations also confirm the central role of angiogenesis in breast cancer progression. Fibrocystic lesions with the highest vascular density were associated with a greater risk of breast cancer (13). Two distinct vascular patterns have been described in association with ductal carcinoma in situ: a diffuse increase in stromal vascularity between duct lesions and a dense rim of microvessels adjacent to the basement membrane of individual ducts (14,15). Microvessel density (MVD) was highest with histopathologically aggressive DCIS lesions and was associated with increased VEGF expression (16).

Recognition that angiogenesis is essential to the growth of solid tumors (17) has led to identification of angiogenic factors responsible for stimulating new blood vessel formation. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and is a crucial regulator of both normal and pathologic angiogenesis (18). VEGF expression is regulated by hypoxia via molecular pathways similar to those regulating erythropoietin gene expression. The biologic effects of VEGF are mediated through binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 (fms-like tyrosine kinase) and KDR (kinase domain region). Though multiple angiogenic factors are commonly expressed by invasive human breast cancers, the 121-amino acid isoform of VEGF predominates (19). Several studies have found an inverse correlation between VEGF expression and overall survival in both nodepositive and node-negative patients (20-22). Eppenberger confirmed the negative prognostic value of VEGF expression for both relapse and survival (23).

Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice including non–small cell lung cancer (Calu-6), colorectal cancer (LS174T, HM-7, LSLiM6), breast cancer (MCF-7, MDA-MB-435), prostate cancer (D-145), head and neck cancer (KB), and ovarian cancer (SK-OV-3) (18,24). In addition, the combination of anti-VEGF antibody and chemotherapy in nude mice injected with human cancer xenografts resulted in an increased antitumor effect compared with antibody or chemotherapy treatment alone (25). A recombinant humanized version of a murine anti–human VEGF monoclonal antibody, named bevacizumab (bevacizumab, Genentech, South San Francisco), has been created for clinical use (26).

Moreover, preclinical studies have demonstrated the combination of cytotoxics with bevacizumab to be synergistic (27).

The activity of single agent bevacizumab in the metastatic setting set the framework for the design and implementation of a phase III trial of weekly paclitaxel versus weekly paclitaxel plus bevacizumab as first line therapy for locally recurrent or metastatic breast cancer (E2100). The results of this study demonstrated a significantly improved 5 month progression free survival and a doubling of the response rate from 14% to 28% with the addition of bevacizumab to paclitaxel. The impressive results of this trial have established bevacizumab and weekly paclitaxel as the new standard to which future up front metatstatic regimens will be compared (28).

BEVACIZUMAB CLINICAL EXPERIENCE

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5 FU based chemotherapy for subjects with metastatic colorectal cancer.

2.1 Supporting Data and Rationale

The treatment paradigm in breast cancer, however, 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 biologics and chemotherpay.

Breast cancers are represented by a heterogenous group of tumors, characterized by a wide spectrum of clinical, pathologic and molecular features (29-31). This wide spectrum of factors accounts for variations in response to therapy and outcomes among women diagnosed with breast cancer (32-34). 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 (35-38). There have been numerous reports demonstrating that breast tumors will segregate into prognostic categories based on hierarchical cluster analysis of gene expression profiling

(29,32,37,39-42). These unique molecular patterns can help guide clinicians regarding both prognosis and response to therapies.

Recent attention has been devoted to a classification system which employs three commonly available molecular markers, estrogen receptor, progesterone receptor and HER2*neu* and classifies patients into subtypes (Luminal, HER2*neu* and Basal) (30,32,34,43). 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 (30,32,34). 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 (44).

Basal-like tumors lack both hormone receptor and HER2 expression, and despite having a poor prognosis, these tumors have been shown in neo-adjuvant studies to be responsive to chemotherapy (30). Basal type tumors have been shown to be more aggressive, are more commonly seen in African American women and are commonly seen in women who are BRCA1 carriers (30,32,40,45,46). 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, PR and HER2*neu* clinical assays make this system appealing and clinically useful. Accordingly, clinicians are utilizing the combination of ER, PR and HER2*neu* to classify patients into these subtypes and are increasingly utilizing "Triple Negative" (ER-, PR-, HER2-) in clinical decision making and protocol design. Recent 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 (29,36,40). 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 (45).

There are preclincial and clinical evidence demonstrating that loss of BRCA1 function predicts response to select chemotherapy agents (47). Indeed, a retrospective review of the literature examining the interaction of BRCA1 and response to chemotherapy suggests that the presence of a BRCA1 mutation confers increased sensitivity to DNA damaging agents including topoisomerase poisons and platinum-based compounds and resistance to the spindle poisons.

These data have lead to the design and implementation of several studies in the "triple negative population" utilizing platinum based regimens as well as targeted agents against EGFR. These preclinical and clinical data provide a strong rationale for piloting the combination of doxil, carboplatin and bevacizumab in patients with previously untreated ER, PR, and HER2*neu* negative breast cancer. The combination of doxil and carboplatin has

been shown to be a well tolerated and active regimen in patients with advanced ovarian cancer (48,49,50). Given the activity of both these agents in patients with breast cancer, we postulate this will be a very active regimen when combined with bevacizumab in the upfront metatstatic setting in the triple negative breast cancer population which currently has no definitive standard of care treatment regimen. Patients are treated with the usual breast cancer regimens. Doxil was selected as the preferred anthracyline given the increased cardiac toxicity observed in a small phase II study of doxorubicin and bevacizumab in patients with metastatic soft-tissue sarcomas (51) compared to doxil and bevacizumab in sarcomas (52) and the reduced cardiac toxicity and comparable efficacy of doxil versus doxorubicin reported in a phase III trial in women with metastatic breast cancer (53).

2.2 Availability of Doxil

When there is a shortage of Doxil at the [redacted], patients will be allowed to receive treatment with epirubicin, an alternative anthracycline. Treatment would then consist of epirubicin (60 mg/m^2), carboplatin (AUC 5) and bevacizumab (10 mg/kg) in patients with ER, PR, HER2*neu* negative metastatic breast cancer.

The patient will continue to follow all requirements per protocol guidelines.

3. Participating Institutions

[redacted]

4. Experimental Design and Methods

This is an open-label, multicenter, Phase II trial to determine the median progression free survival (PFS) and 1-year PFS after treatment with doxil, carboplatin and bevacizumab in patients with ER, PR, HER2*neu* negative metastatic breast cancer.

To assure cardiac safety of the combination, initially 6 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. Approximately 50 patients are expected to participate in this 2 year study.

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 metastatic breast cancer, ER/PR/HER2/*neu* negative. Prior treatment in the adjuvant setting is 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.
- 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 ≥ 12 weeks

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

- 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
    - In the presence of liver metastases, AST / ALT, and total bilirubin must be < 3 X ULN

5.1.8. Patients must have normal cardiac function, as evidenced by a left ventricular ejection fraction (LVEF) within institutional normal limits. Echocardiogram may be used if MUGA scan is not available, but the same test must be used throughout the study to evaluate LVEF.

5.1.9 Lesion Eligibility:

- Patients must have documented measurable disease as defined by RECIST criteria (see Section 9). or
- Bone-only disease

5.1.10 Patients may not receive concurrent treatment with other investigational or commercial agent(s) or have received any other investigational agents within 28 days of the first day of study drug dosing, other than a Genentech sponsored bevacizumab cancer study.

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. insitu carcinoma of the of the cervix, adequately treated non-melanomatous carcinoma of the skin) or other malignancy treated at least 5 years previously with no evidence of recurrence.

5.2.3 History of hypersensitivity reactions attributed to a conventional formulation of doxorubicin HCL or the components of DOXIL® or known hypersensitivity to any component of bevacizumab.

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

5.2.5 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, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities.

5.2.6 Prior anthracycline dose exceeding 360 mg/m^2 for doxorubicin (including DOXIL) or 720 mg/m^2 for epirubicin.
5.2.7 Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)
5.2.8 Any prior history of hypertensive crisis or hypertensive encephalopathy
5.2.9 Known CNS disease
5.2.10 Significant vascular disease (e.g., aortic aneurysm, aortic dissection)
5.2.11 Symptomatic peripheral vascular disease
5.2.12 Evidence of bleeding diathesis or coagulopathy
5.2.13 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment or anticipation of need for major surgical procedure during the course of the study
5.2.14 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to study enrollment
5.2.15 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment
5.2.16 Serious, non-healing wound, ulcer, or bone fracture
5.2.17 Proteinuria at screening as demonstrated by either:

- Urine protein: creatinine (UPC) ratio ≥ 1.0 at screening (see Appendix C) OR
- Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).

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 The Cancer Institute of New Jersey's clinical programs within the last year. African-Americans comprised 7%, Hispanics 8%, and Asians 3% of female patients, respectively. For all patients entering clinical trials, the percentages were 52% women, 6% African-American, 5% Hispanic, and 3% 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 [redacted].

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 Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients. The participating institution's consent form must be reviewed and approved by the OHRS and all documents must be received (i.e., IRB approved documentation, IRB approved consent form,).

[redacted]

If a patient is registered on-study but does not receive any protocol therapy, baseline data will be collected and submitted according to Section 13, Data Collection and Records to be Kept. 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 4 weeks (+/- 3 days) prior to therapy, unless otherwise indicated in one of the footnotes below the table.

Evaluations	Pre-Study	Weekly	Prior to Each Cycle[6]	End of Treatment[9]
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	X		X	
CBC, differential, platelets[8]	X[1]	X	X	X
Serum Chemistries[2]	X[1]		X	X
Urinalysis	X[10]		X[10]	
Liver Enzymes[3]	X[1]		X	X
EKG	X			
MUGA Scan[7]	X		X[7]	X[7]
CXR	X			
Bone Scan	X		X[12]	
Head CT	X			
Serum or Urine Pregnancy Test[4]	X			
Tumor measurements[5]	X		X	X
Survival [11]				X

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.
2. Includes: Electrolytes (sodium, potassium, chloride, carbon dioxide, calcium), BUN, Serum Creatinine, Glucose.
3. Includes: Total bilirubin, SGOT/SGPT, Alkaline Phosphatase, Albumin, Total Protein
4. Women of childbearing potential must have a negative pregnancy test verified by serum or urine BHCG within 1 week of enrollment.
5. Disease measurable by physical examination performed at baseline within 2 weeks (± 3 days) will be re-evaluated after each cycle of therapy. Radiographic assessments will be selected by the attending physician as clinically indicated for initial staging within 4 weeks and in accordance with the criteria for tumor measurement assessments using RECIST criteria. Disease measured by imaging procedures will be repeated after every 2 cycles if clinically indicated and upon apparent progression.
6. Within 72 hours of the start of the cycle beyond Cycle 1.
7. Performed at baseline, within 42 days prior to first dose, every 3 cycles and one month after the last Doxil or epirubicin , carboplatin, bevacizumab treatment (see Section 7.1.1.1). 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 Doxil or epirubicin, carboplatin, bevacizumab treatment.

10. Prior to each cycle monitor proteinuria by either urine protein: creatinine (UPC) ratio or dipstick (see Section 7.1.1.2 and Appendix C). Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible.
11. Patients will be followed for survival every 6 months. Time to progression will be followed using imaging scans/tumor evaluations every 6 months until disease progression is first documented. A telephone call may be made for survival follow-up.
12. For bone-only disease at baseline correlative imaging (plain film, CT or MRI) must be done to assess disease noted on bone scan. Documentation of non-target (bone lesion) is required. The same diagnostic method must be used throughout the study to evaluate the lesion. A bone scan will be performed after every even numbered cycle (Cycle 2, 4, 6 etc.).
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.

7. Treatment Plan

7.1 General Considerations

A cycle is defined as an interval of 28 days (delays due to holidays, weekends and bad 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. Study treatment will be administered until disease 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.

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) and bevacizumab (10 mg/kg) in patients with ER, PR, HER2*neu* negative metastatic breast cancer.

Epirubicin and carboplatin will be given on Day 1 of a 28 day cycle followed by bevacizumab on Day 1. Bevacizumab will also be given on Day 15 of the 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.

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

7.1.1.1 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 DOXIL 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%).

MUGA or ECHO (LVEF) Schedule for all patients:

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

LVEF assessment performed by MUGA scan every 3 cycles and one month after the last Doxil or epirubicin, carboplatin, bevacizumab treatment. Echocardiogram may be used if MUGA scan is not available, but the same test must be used throughout the study to evaluate LVEF.

7.1.1.2 Bevacizumab

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick prior to each cycle.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver