Official Title:	**A Phase II Trial of Doxil, Carboplatin and Bevacizumab in Triple Negative Previously Untreated Metastatic Breast Cancer**
NCT number:	**NCT00608972**
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15.7 Data Monitoring and Source Document Verification

Each site participating in the accrual of patients to this protocol will be audited for protocol and regulatory compliance, data verification and source documentation.

The Cancer Institute of New Jersey staff will conduct remote monitoring on a continual basis of participating institutions with monitoring visits occurring as necessary. The monitoring visits will focus on verifying data with source documents. Adherence to the protocol(s), including the prompt reporting of serious adverse events, will be assessed. Findings of all monitoring visits are recorded on a Monitors Report, which is kept in the OHRS regulatory file.

15.8 Data and Center Audits

OHRS staff will conduct annual audits to each participating center in accordance with OHRS Standard Operating Procedures (SOPs). The audit guidelines are in accordance with the Data and Safety Monitoring Plan.

16. Statistical Considerations

The "Simon's two-stage minimax design", with a power =0.80 and alpha level of 0.05 will be used to rule out an uninteresting response rate of 35% (assumed with the single agent, Doxil) and to detect if the experimental triple combination has a higher response rate of 50%. That is, if the response rate for the triple combination is less than 35%, then it will not be further pursued for larger trials. If the triple combination's response rate is truly 50% or greater, then the design will have at least 80% power to detect it.

The design calls for accruing 31 patients during stage I. If 18 or more disease progression are observed within 1 year, the trial will be stopped early. Otherwise the trial will continue to accrue another 19 patients (i.e. total of 50 patients). The probability of stopping early at stage I is approximately 10% if the triple combination has 45% 1-year disease progression.

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. LVEF will be a primary endpoint as well. The primary LVEF evaluation will be based on an absolute decrease from baseline of >15% and /or 10% decline from baseline to below LLN at the time of evaluation. If two or more patients have such a decrease in LVEF the study will be stopped. If one patient has such a decrease, an additional three patients will be accrued to determine safety. If no further decreases in LVEF are noted, additional patients (total 31 during stage I) will be accrued. If more than 3 cases of CHF are observed with the combination, accrual to the study will be stopped. This is based on a true CHF rate of 3.5% being considered acceptable and a true CHF rate of 10% being unacceptably high. All patients with adequate cardiac function at baseline (normal LVEF and no history of clinically significant cardiovascular disease) who receive protocol treatment will be included in the primary analysis of CHF rates. (This is consistent with the cardiac analyses of ECOG 2104).

17. Ethical and Regulatory Considerations

17.1 Study Conduct

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

17.2 Institutional Review Board Approval

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

17.3 Informed Consent

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

17.4 Record Retention

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

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

17.5 Patient Confidentiality

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

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

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

17.6 Conflict of Interest

All Rutgers University faculty and other employees who, as investigators on behalf of the University, who apply for or receive funds through a grant, subgrant, contract, subcontract, or cooperative agreement for any research, educational or service purpose and investigators working as subgrantees, contractors or subcontractors to or collaborators with the University on projects funded or proposed for funding must disclose any real or apparent conflict of interest and abide by the Conflict of Interest Policy http://policies.rutgers.edu/ as it relates to conducting clinical research.

18. Human Subjects

18.1 Patient Population
Women with previously untreated metastatic breast cancer, ER/PR/HER2/*neu* negative.

18.2 Potential Risks
All care will be taken to minimize side effect, but they can be unpredictable in nature and severity. Risks are outlined in Section 12.

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

18.4 Potential Benefits
Potential benefits may be reduction in the size of tumor, improved tumor response, stability in size of tumor, a longer period of progression free survival and/or improvement in symptoms related to their disease.

18.5 Risk-Benefit Ratio
The potential benefit that may result from this study balances the potential risks to the patients. Results of previous trials suggests that these drugs are active against breast cancer. This protocol may or may not be helpful to a specific patient, but the results may help the Investigators learn about the administration and effectiveness of doxil or epirubicin, carboplatin and bevacizumab in breast cancer and may aid in the treatment of other patients. This research treatment is not curative, but may offer temporary control of the disease. Benefit can't be promised nor can the chance of benefit be accurately predicted. Literature presentations on recent studies using these drugs in breast cancer patients do not suggest an unacceptable risk-benefit ratio.

18.6 Gender and Minorities
[redacted]

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.

19. Economic/Financial Considerations

Patients and/or their insurance carriers will be expected to pay for all costs of therapy, monitoring, and follow-up. Bevacizumab will be provided free of charge by Genentech, Inc. respectively.

20. Publication of Research Findings

The policies and procedures of the [redacted] manner following the conclusion. The PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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Appendix A

Performance Status Criteria

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

Appendix B

New York Heart Association Criteria

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

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

Appendix C

Procedure for Obtaining a Urine Protein / Creatinine Ratio (UPC)

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio =
   protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports will need to be requested.