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NRG BR-003: A Randomized Phase III Trial of Adjuvant Therapy Comparing Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel with or without Carboplatin for Node-Positive or High-Risk Node-Negative Triple-Negative Invasive Breast Cancer

Fast Facts

Treatment Plan – Drugs all commercially available

ARM 1

- Doxorubicin (A) 60mg/m2 IV and Cyclophosphamide (C) 600mg/m2 IV Day 1 every 2 wks, Cycles 1-4
- Paclitaxel (WP) 80mg/m2 IV, weekly, 12 doses

ARM 2 - same as ARM 1 plus:

- Carboplatin AUC=5mg*min/mL IV, Day 1 every 21 days, Cycles 1-4

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial:

- Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of non-hormonal contraception during the therapy, and for at least 3 months after the last dose of study therapy.
- Submission of tumor tissue and blood is required for all patients. Investigators should check with their site Pathology department regarding release of tissue before approaching patients about participation in the trial. (See details of tumor tissue and blood sample submissions in Section 10.0.)
- *BRCA* mutation testing ***is not required*** for the BR003 study; however, *BRCA* mutation status (positive; negative, unknown) will be collected on Form Entry. If *BRCA* mutation testing is not done, record the *BRCA* mutation status as "Unknown."

Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

1. The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.
2. The trial is open to female and male patients.
3. Age ≥ 18 years.
4. ECOG Performance Status of 0 or 1 (see Appendix A).
5. The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.
6. All of the following staging criteria (according to the 7th edition of the AJCC Cancer Staging Manual) must be met:
   - By pathologic evaluation, primary tumor must be pT1-3;
   - By pathologic evaluation, ipsilateral nodes must be pN0, pN1 (pN1mi, pN1a, pN1b, pN1c), pN2a, pN2b, pN3a, or pN3b.

- If pN0, pathological tumor must be ≥ 3.0 cm.

7. The tumor must have been determined to be HER2-negative as follows:
   - Immunohistochemistry (IHC) 0-1+; ***or***
   - IHC 2+ and ISH non-amplified with a ratio of HER2 to CEP17 < 2.0, and if reported, average HER2 gene copy number < 4 signals/cells; ***or***
   - ISH non-amplified with a ratio of HER2 to CEP17 < 2.0, and if reported, average HER2 gene copy number < 4 signals/cells.
8. The tumor must have ER and PgR status assessed using current ASCO/CAP Guidelines. Patients are eligible if the tumor staining meets one of the following criteria:
   − ER-negative and PgR-negative by ASCO/CAP guidelines, OR
   − ER or PgR stains are positive in 1-9% of cells and neither is positive in ≥ 10% of cells.
9. The patient must have undergone either a mastectomy (total, skin-sparing, or nipple-sparing) or lumpectomy.
10. For patients who undergo lumpectomy, the margins of the resected specimen must be histologically free of invasive tumor and DCIS as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional excisions may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo mastectomy to be eligible. (Patients with margins positive for LCIS are eligible without additional resection.)
11. For patients who undergo mastectomy, the margins must be free of residual gross tumor. (Patients with microscopic positive margins are eligible as long as post-mastectomy RT of the chest wall will be administered.)
12. The patient must have completed ***one of the procedures*** for evaluation of pathologic nodal status listed below.
    - Sentinel lymphadenectomy alone:
      - If pathologic nodal staging based on sentinel lymphadenectomy is pN0 or pN1b;
      - If pathologic nodal staging based on sentinel lymphadenectomy is pN1mi or pN1a and the patient has undergone breast conserving surgery (with planned breast radiotherapy), the primary tumor must be T1 or T2 by pathologic evaluation and the nodal involvement must be limited to 1 or 2 positive nodes.
    - Sentinel lymphadenectomy followed by removal of additional non-sentinel lymph nodes if the sentinel node (SN) is positive; or
    - Axillary lymphadenectomy with or without SN isolation procedure.
13. The interval between the last surgery for breast cancer (including re-excision of margins) and randomization must be no more than 60 days.
14. Adequate hematologic function within 6 weeks prior to randomization defined as follows:
    - ANC must be ≥ 1200/mm3;
    - Platelet count must be ≥ 100,000/mm3; and
    - Hemoglobin must be ≥ 10 g/dL.
15. Adequate hepatic function must be met based on the results of the most recent postoperative tests performed within 6 weeks prior to randomization:
    - total bilirubin must be ≤ ULN for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
    - alkaline phosphatase must be ≤ 2.5 x ULN for the lab; *and*
    - AST must be ≤ 1.5 x ULN for the lab.

Note: If ALT is performed instead of AST (per institution's standard practice), the ALT value must be ≤ 1.5 x ULN; if both were performed, the AST must be ≤ 1.5 x ULN.

16. Patients with AST or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET-CT, or PET scan) performed within 90 days prior to randomization does not demonstrate metastatic disease and the requirements in Criterion 3.2.15 are met.
17. Patients with alkaline phosphatase that is > ULN but ≤ 2.5 x ULN or unexplained bone pain are eligible for inclusion in the study if a bone scan, PET-CT scan, or PET scan performed within 90 days prior to randomization does not demonstrate metastatic disease.
18. Adequate renal function determined within 6 weeks prior to randomization defined as the most recent serum creatinine ≤ ULN ***or*** measured or calculated creatinine clearance > 60 mL/min (see Section 5.3 for instructions regarding calculation of creatinine clearance).
19. LVEF assessment must be performed within 90 days prior to randomization. (LVEF assessment performed by 2-D echocardiogram is preferred; however, MUGA scan may be substituted based on institutional preferences.) ***The LVEF must be ≥ 50% regardless of the cardiac imaging facility's lower limit of normal.***

Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

1. T4 tumors including inflammatory breast cancer.
2. Definitive clinical or radiologic evidence of metastatic disease. Required imaging studies must have been performed within 90 days prior to randomization.
3. Synchronous or previous contralateral invasive breast cancer. (Patients with synchronous and/or previous contralateral DCIS or LCIS are eligible.)
4. Any previous history of ipsilateral invasive breast cancer or ipsilateral DCIS. (Patients with synchronous or previous ipsilateral LCIS are eligible.)
5. History of *non-breast* malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomization.
6. Previous therapy with anthracyclines or taxanes for any malignancy.
7. Chemotherapy administered for the currently diagnosed breast cancer prior to randomization.
8. Any continued use of sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy. Patients are eligible if these medications are discontinued prior to randomization (see Section 3.1).
9. Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens. This includes but is not confined to:

Active cardiac disease

- angina pectoris that requires the current use of anti-anginal medication;
- ventricular arrhythmias except for benign premature ventricular contractions;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
- valvular disease with documented compromise in cardiac function; or
- symptomatic pericarditis.

History of cardiac disease

- myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;

- history of documented CHF; or
- documented cardiomyopathy.

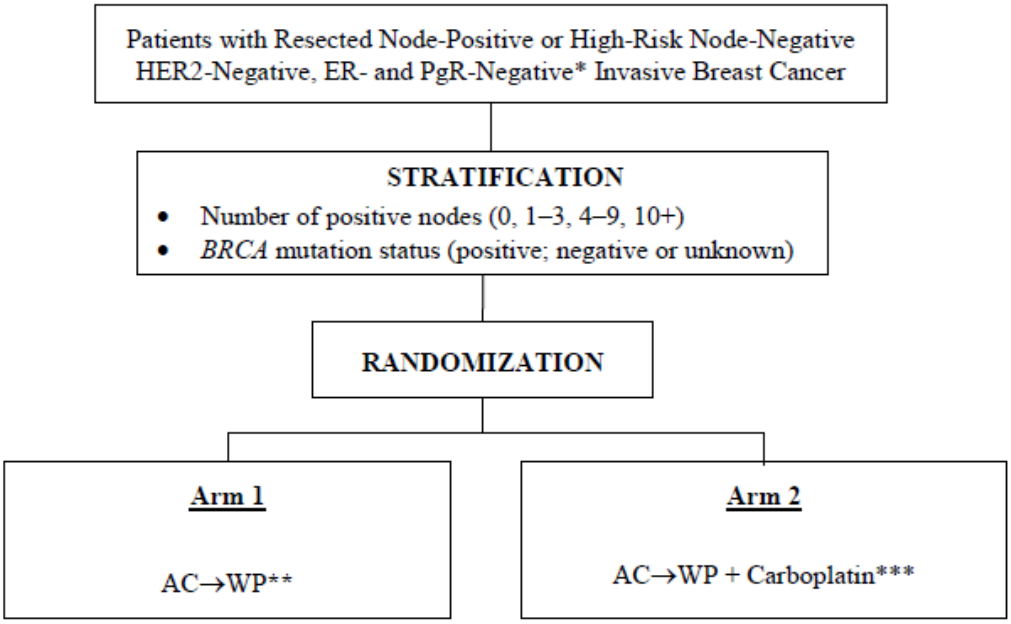
10. Uncontrolled hypertension defined as ***sustained*** systolic BP > 150 mmHg or diastolic BP > 90 mmHg. (Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.)
11. Active hepatitis B or hepatitis C with abnormal liver function tests.
12. Patients known to be HIV positive with a baseline CD4 count of < 250 cells/mm3 or have a history of AIDS indicator conditions.
13. Intrinsic lung disease resulting in dyspnea.
14. History of hospitalization in past 12 months for diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic nonketotic syndrome (HHNS).
15. Active infection or chronic infection requiring chronic suppressive antibiotics.
16. Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v4.0.
17. Conditions that would prohibit administration of corticosteroids.
18. Chronic daily treatment with corticosteroids with a dose of ≥ 10 mg/day methylprednisolone equivalent (excluding inhaled steroids).
19. Known hypersensitivity to any of the study drugs or excipients, e.g., polysorbate 80 and Cremophor® EL.
20. Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.
21. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
22. Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 2 weeks prior to randomization.)***
23. Use of any investigational product within 4 weeks prior to randomization.

Pre-study Parameters:

- Determination of HER2 status (Section 3.2.7)
- Determination of hormone receptor status (Section 3.2.8)
- History & physical exam
- Performance status (Appendix A)
- Height & weight
- Assessment of BP and BP meds
- CBC/differential/platelet count
- Total bilirubin/AST/Alkaline phosphatase
- Serum chemistries: glucose, BUN, sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, serum creatinine
- Magnesium
- Creatinine clearance (calculated or measured)
- Pregnancy test
- 2-D echocardiogram (or MUGA scan)
- Bilateral breast imaging
- Liver imaging

- Bone nuclear imaging
- Collection and submission of blood sample for ctDNA

Figure 1. NRG-BR003 SCHEMA



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- ER-negative and PgR-negative by ASCO/CAP guidelines, OR
- ER or PgR stains are positive in 1-9% of cells and neither is positive in ≥ 10% of cells.

** **Chemotherapy regimen for Arm 1**

AC→ Weekly Paclitaxel (WP): Doxorubicin (A) 60 mg/m^2 IV + cyclophosphamide (C) 600 mg/m^2 IV every 2 weeks for 4 cycles (dose-dense schedule) followed by paclitaxel 80 mg/m^2 IV weekly for 12 doses.

*** **Chemotherapy regimen for Arm 2**

AC→ Weekly Paclitaxel (WP) + Carboplatin: Doxorubicin (A) 60 mg/m^2 IV + cyclophosphamide (C) 600 mg/m^2 IV every 2 weeks for 4 cycles (dose-dense schedule) followed by paclitaxel 80 mg/m^2 IV weekly for 12 doses plus carboplatin AUC of 5 IV every 3 weeks for 4 cycles.