NRG BR003

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

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Treatment:

- **Arm I** (AC-->WP): Doxorubicin hydrochloride IV over 15 minutes & cyclophosphamide IV over 30 minutes on day 1. Treatment repeats every 2 weeks for 4 courses in the absence of disease progression or unacceptable toxicity. Patients then receive paclitaxel IV over 60 minutes on day 1. Treatment repeats weekly for 12 courses in the absence of disease progression or unacceptable toxicity.

- **Arm II** (Experimental) (AC-->WP + carboplatin): Doxorubicin hydrochloride & cyclophosphamide, then paclitaxel IV over 60 minutes on days 1, 8, and 15 & carboplatin IV over 30-60 minutes on day 1. Treatment repeats every 3 weeks for 4 courses in the absence of disease progression or unacceptable toxicity.

Inclusion Criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination
- All of the following staging criteria (according to the 7th edition of the American Joint Committee on Cancer [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, tumor must be > 3.0 cm
- The tumor must have been determined to be human epidermal growth factor receptor 2 (HER2)-negative as follows:
    - Immunohistochemistry (IHC) 0-1+; or IHC 2+ and in situ hybridization (ISH) non-amplified with a ratio of HER2 to centromere enumerator probe 17 (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
- The tumor must have been determined to be estrogen receptor (ER)-and progesterone receptor (PgR)-negative assessed by current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines; patients with < 1% ER and PgR staining by IHC are considered negative
- The patient must have undergone either a mastectomy (total, skin-sparing, or nipple-sparing) or lumpectomy
- For patients who undergo lumpectomy, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (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 lobular carcinoma in situ [LCIS] are eligible without additional resection)
- 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 radiation therapy [RT] of the chest wall will be administered)
- 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

  - 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
- The interval between the last surgery for breast cancer (including re-excision of margins) and randomization must be no more than 60 days
- ANC >= 1200/mm^3; Platelet >= 100,000/mm^3; Hemoglobin >= 10 g/dL; Total bilirubin =< 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; Alkaline phosphatase =< 2.5 x ULN; AST =< 1.5 x ULN
  Note: If alanine aminotransferase (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
- Patients with AST or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]-CT, or PET scan) performed within 90 days prior to randomization does not demonstrate metastatic disease and the requirements above are met
- 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
- 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
- Left ventricular ejection fraction (LVEF) assessment must be performed within 90 days prior to randomization; (LVEF assessment performed by 2-dimensional [D] echocardiogram is preferred; however, multi gated acquisition [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