

**NSABP B-47 - A Randomized Phase III Trial of Adjuvant Therapy Comparing  
Chemotherapy Alone (Six Cycles of Docetaxel Plus Cyclophosphamide or Four Cycles of Doxorubicin Plus Cyclophosphamide  
Followed by Weekly Paclitaxel) to Chemotherapy Plus Trastuzumab in Women with Node-Positive or High-Risk Node-  
Negative HER2-Low Invasive Breast Cancer**

*Fast Facts*

CTC v.4; AJCC 7<sup>th</sup> ed.  
Herceptin provided

*Although the guidelines below are not inclusion/exclusion criteria, investigators should consider each of these factors when selecting patients for the trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.*

- Patients should have a life expectancy of at least 10 years, excluding their diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)
- Women of reproductive potential must agree to use an effective non-hormonal method of contraception (for example condoms, some intrauterine devices, diaphragms, tubal ligation, vasectomized partner, or abstinence) during therapy **and for at least 6 months after the last dose of study therapy (chemotherapy or trastuzumab).**
- **Submission of tumor samples from the breast surgery is required for all patients** (see Section 7.1). Therefore, the local pathology department policy regarding release of tumor samples must be considered in the screening process. Patients whose tumor samples are located in a pathology department that by policy will not submit any samples for research purposes should not be approached for participation in the B-47 trial.

**Patient eligibility**

1. The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.
2. The patient must be female.
3. The patient must be  $\geq 18$  years old.
4. The patient must have an 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 (using 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, one of the following criteria must be met:**

  - pT2 **and** ER negative **and** PgR negative; **or**
  - pT2 **and** ER positive (PgR status may be positive or negative) **and** either grade 3 histology or Oncotype DX® Recurrence Score of  $\geq 25$ ; **or**
  - pT3 regardless of hormone receptor status, histologic grade, and Oncotype DX®
7. HER2 status of the primary tumor must be evaluated prior to randomization; all testing performed must indicate that the tumor is **HER2-low** as defined below.
  - **IHC must be performed** and the IHC staining results must indicate a score of 1+ (in situ hybridization [ISH] testing is not required) or 2+ (ISH must also be performed and must indicate that the tumor is HER2-low as described below).
  - if ISH testing is performed, test results must be as follows **and** IHC must be 1+ or 2+: The ratio of HER2 to *CEP17* must be  $< 2.0$  or, if a ratio was not performed, the HER2 gene copy number must be  $< 4$  per nucleus.

**Note:** If the IHC staining intensity is reported as a range, e.g., 0 to 1+ or 1+ to 2+, the higher intensity score in the range should be used to determine eligibility. The patient must have undergone either a total mastectomy or breast-conserving surgery (lumpectomy). (Patients who have had a nipple-sparing mastectomy are eligible.)
8. 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 operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. (Patients with margins positive for LCIS are eligible without additional resection.)
9. For patients who undergo mastectomy, margins must be free of gross residual tumor. (Patients with microscopic positive margins are eligible as long as post-mastectomy RT of the chest wall will be administered.)
10. 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, 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.
11. The interval between the last surgery for breast cancer (treatment or staging) and randomization must be no more than 84 days.
  12. The patient must have ER analysis performed on the primary tumor prior to randomization. If ER analysis is negative, then PgR analysis must also be performed. (Either the core biopsy or surgical resection specimen can be used for ER/PgR testing.) Patients with a primary tumor that is hormone receptor-positive or receptor-negative are eligible.
  13. The most recent postoperative blood counts, performed within 6 weeks prior to randomization, must meet the following criteria:
    - ANC must be  $\geq 1200/\text{mm}^3$ ;
    - Platelet count must be  $\geq 100,000/\text{mm}^3$ ; and
    - Hemoglobin must be  $\geq 10 \text{ g/dL}$ .
  14. The following criteria for evidence of 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  $\leq \text{ULN}$  for the lab unless the patient has a bilirubin elevation  $> \text{ULN}$  to  $1.5 \times \text{ULN}$  due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
    - alkaline phosphatase must be  $\leq 2.5 \times \text{ULN}$  for the lab; *and*
    - AST must be  $\leq 1.5 \times \text{ULN}$  for the lab.
    - *Alkaline phosphatase and AST may not both be  $> \text{the ULN}$ .* For example, if the alkaline phosphatase is  $> \text{the ULN}$  but  $\leq 2.5 \times \text{ULN}$ , the AST must be  $\leq \text{the ULN}$ . If the AST is  $> \text{the ULN}$  but  $\leq 1.5 \times \text{ULN}$ , the alkaline phosphatase must be  $\leq \text{ULN}$ .

Note: If ALT is performed instead of AST (per institution's standard practice), the ALT value must be  $\leq 1.5 \times \text{ULN}$ ; if both were performed, the AST must be  $\leq 1.5 \times \text{ULN}$ .

15. Patients with AST or alkaline phosphatase  $> \text{ULN}$  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 are met.
16. Patients with alkaline phosphatase that is  $> \text{ULN}$  but  $\leq 2.5 \times \text{ULN}$  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.
17. The most recent postoperative serum creatinine performed within 6 weeks prior to randomization must be  $\leq \text{ULN}$  for the lab.
18. 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.
  - For patients who will receive the **TC chemotherapy regimen, the LVEF must be  $\geq 50\%$**  regardless of the cardiac imaging facility's lower limit of normal.
  - For patients who will receive the **AC $\rightarrow$ WP chemotherapy regimen, the LVEF must be  $\geq 55\%$**  regardless of the cardiac imaging facility's lower limit of normal.

Note: Since the pre-entry LVEF serves as the baseline for comparing subsequent LVEF assessments, it is critical that this baseline study be an accurate assessment. If the baseline LVEF is  $> 70\%$ , the investigator is encouraged to have the accuracy of the initial LVEF result confirmed and repeat the test if the accuracy is uncertain. (See Sections 5.2 and 5.3 for LVEF instructions.)

### Patient ineligibility

1. Primary tumor with *any* of the following HER2 testing results:
  - IHC staining intensity:
    - 0 on *all* evaluations of specimen
    - 3+ on evaluations of *any* specimen
  - ISH with a ratio of HER2 of *CEP17*  $\geq 2.0$  on evaluation of *any* specimen
  - ISH result indicating HER2 gene copy number  $\geq 4$  per nucleus on evaluation of *any* specimen
2. T4 tumors including inflammatory breast cancer.
3. Definitive clinical or radiologic evidence of metastatic disease. (Note: Chest imaging [mandatory for all patients] and other imaging [if required] must have been performed within 90 days prior to randomization.)
4. Synchronous or previous contralateral invasive breast cancer. (Patients with synchronous and/or previous contralateral DCIS or LCIS are eligible.)
5. Any previous history of ipsilateral invasive breast cancer or ipsilateral DCIS. (Patients with synchronous or previous ipsilateral LCIS are eligible.)
6. 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.
7. Previous therapy with anthracyclines, taxanes, or trastuzumab for any malignancy.
8. Chemotherapy or HER2-targeted therapy administered for the currently diagnosed breast cancer prior to randomization.

9. Whole breast RT prior to randomization or partial breast RT that cannot be completed on or before the date of randomization (see Sections 9.8 and 9.10.3).
10. Continued endocrine therapy such as raloxifene or tamoxifen (or other SERM) or an aromatase inhibitor. Patients are eligible if these medications are discontinued prior to randomization (see Section 9.9).
11. 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 4.1).
12. 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; and
- 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; and
- documented cardiomyopathy.

13. Hypertension defined according to the following ineligibility criteria:
  - For patients who will receive **TC** (regardless of the patient's age): 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.)
  - For patients < **50 years** old who will receive **AC**→**WP**: 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.
  - For patients ≥ **50 years** old who will receive **AC**→**WP**:
    - Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg *or* diastolic BP > 90 mmHg.
    - Controlled hypertension (systolic BP ≤ 150 mmHg and diastolic BP ≤ 90 mmHg), **if anti-hypertensive medication(s) are needed.**

Note: Patients who are not eligible based on the AC→WP regimen BP criteria but who meet the TC regimen BP criteria are eligible for B-47, if the intended chemotherapy regimen is changed to TC.

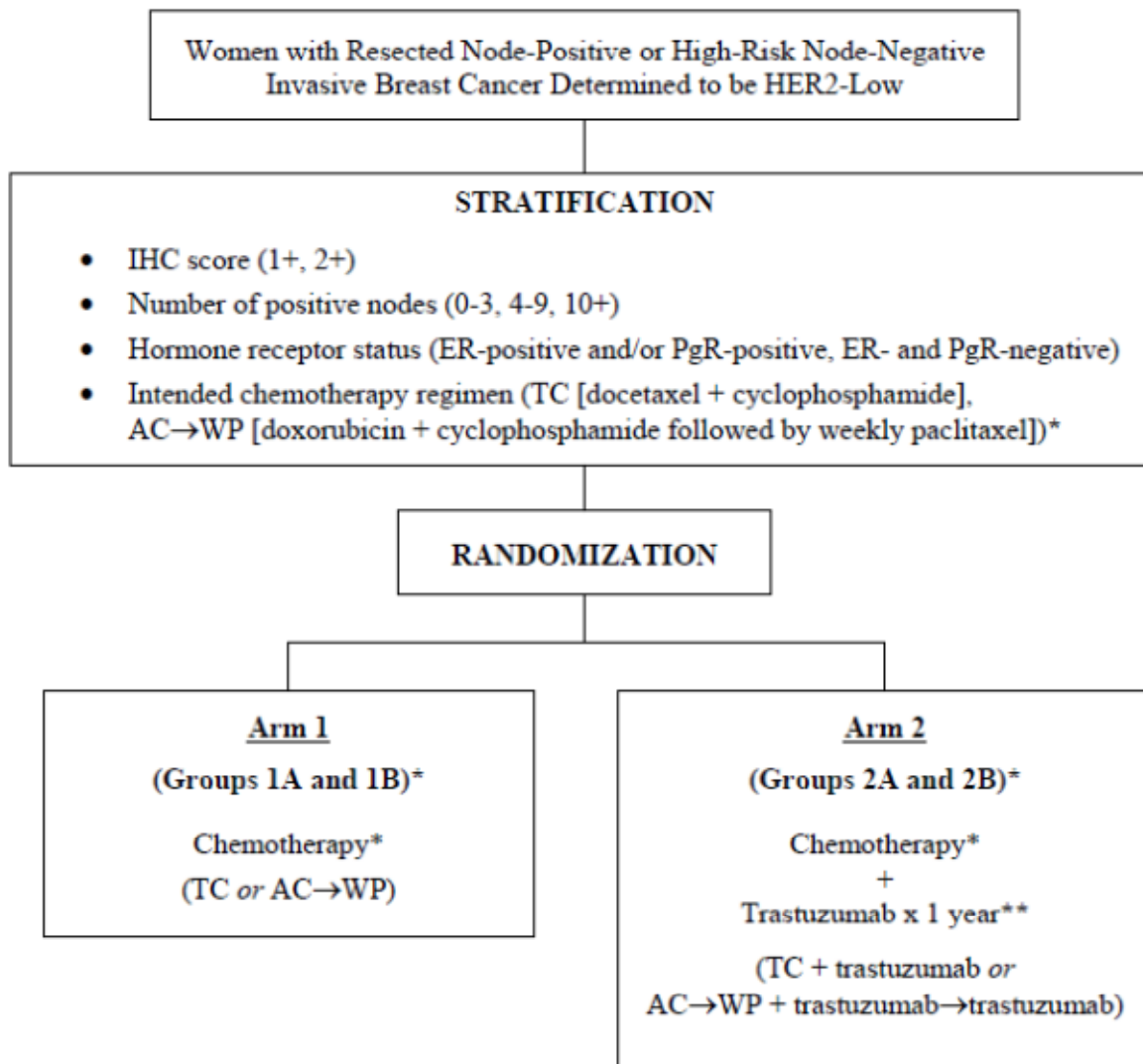
14. Active hepatitis B or hepatitis C with abnormal liver function tests.
15. Intrinsic lung disease resulting in dyspnea.
16. Poorly controlled diabetes mellitus.
17. Active infection or chronic infection requiring chronic suppressive antibiotics.
18. Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v4.0.
19. Conditions that would prohibit administration of corticosteroids.
20. Chronic daily treatment with corticosteroids with a dose of ≥ 10 mg/day methylprednisolone equivalent (excluding inhaled steroids).
21. Known hypersensitivity to any of the study drugs or excipients, e.g., polysorbate 80 and Cremophor® EL.
22. Pregnancy or lactation at the time of study entry. (**Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.**)
23. Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.
24. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
25. Use of any investigational product within 30 days prior to randomization.

**Pre-study Parameters**

1. History and physical including height, weight, performance status, menstrual history, menopausal status, BP, concomitant meds assessment including BP meds
2. CBC with differential, AST, Alk Phos, total bilirubin, serum creatinine, pregnancy test for women of child-bearing potential
3. Echo (preferred) or MUGA, ECG
4. Chest imaging (CT or x-ray) (PET or PET/CT may be substituted); Liver imaging if AST > ULN; Bone nuclear imaging if Alk Phos > ULN

5. Bilateral breast imaging (mammogram or MRI)

## NSABP B-47 SCHEMA



\* At the time of study entry, the investigator must designate which of the following two chemotherapy regimens will be administered:

– **Chemotherapy regimen A for Groups 1A and 2A**

TC: Docetaxel 75 mg/m<sup>2</sup> IV + cyclophosphamide 600 mg/m<sup>2</sup> IV every 3 weeks for 6 cycles.

– **Chemotherapy regimen B for Groups 1B and 2B**

AC→WP: Doxorubicin 60 mg/m<sup>2</sup> IV + cyclophosphamide 600 mg/m<sup>2</sup> IV every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m<sup>2</sup> IV weekly for 12 doses; at the investigator's discretion, doxorubicin/cyclophosphamide may be administered every 2 weeks for 4 cycles (dose-dense schedule).

\*\* Trastuzumab:

– Given with TC (Group 2A): 8 mg/kg loading dose on Day 1 of Cycle 1 of TC; then 6 mg/kg IV every 3 weeks for 11 doses.

– Given with AC → WP (Group 2B): 4 mg/kg loading dose beginning with the first dose of weekly paclitaxel; then 2 mg/kg weekly for a total of 12 weekly doses; after completion of WP, trastuzumab will continue with 6 mg/kg doses IV every 3 weeks for 12 doses.