

NSABP B-44-I, the BETH Trial
 (“Bevacizumab with Trastuzumab Adjuvant Therapy in HER2+ Breast Cancer”)

A Multicenter Phase III Randomized Trial of Adjuvant Therapy for Patients with HER2-Positive Node-Positive or High Risk Node-Negative Breast Cancer Comparing Chemotherapy Plus Trastuzumab with Chemotherapy Plus Trastuzumab Plus Bevacizumab

Fast Facts

Eligibility Criteria

1. The patient must have signed and dated IRBIEC-approved consent forms that conform to the guidelines of the local regulatory authority and of the institution. The consent forms will include a consent form for pre-entry central HER2 testing and a consent form for participation in the BETH Trial (see Section 14.1).
2. Patients must be female.
3. The patient must be ≥ 18 years old.
4. The patient must have an ECOG performance status of 0 or 1 (see Appendix D).
5. The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.
6. The breast cancer must be HER2-positive based on test results as follows:
 - a) **Local testing** should demonstrate that the tumor is IHC 2+ or 3+ *or* is considered to be HER2-positive for gene amplification by FISH, CISH, or other in situ hybridization (ISH) method. If local ISH test results are considered equivocal, the tumor can be submitted for central HER2 testing. (If local testing is not possible, the tumor can be submitted for central HER2 testing.)
 - b) **Central testing** (a requirement for ALL patients) must demonstrate that the tumor is HER2-positive which is defined as FISH-positive and/or IHC 3+. *Refer to Appendix C for an overview of the central HER2 testing, registration, and randomization process.*
7. All of the following staging criteria (according to the 6th edition of the AJCC Cancer Staging Manual) must be met:
 - a) By pathologic evaluation, primary tumor must be pT1-3;
 - b) By pathologic evaluation, ipsilateral nodes must be pN0, pN1 (pN1mi, pN1a, pN1b, pN1c) pN2a, pN3a, or pN3b
 - c) **If pN0**, at least one of the following criteria must be met:
 - i. Pathologic tumor size > 2.0 cm;
 - ii. ER negative *and* PgR negative;
 - iii. Histologic and/or nuclear grade 2 (intermediate) or 3 (high); or
 - iv. Age < 35 years
8. Patients must have undergone either a total mastectomy or breast conserving surgery (lumpectomy).
9. 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 operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after reexcision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ [LCIS] are eligible without additional resection.)
10. For patients who undergo mastectomy, margins must be free of gross residual tumor. Patients with microscopic positive margins are eligible (see Section 8.8 for radiation therapy requirements).
11. Patients must have completed one of the following procedures for evaluation of pathologic nodal status:
 - a. Sentinel lymphadenectomy followed by removal of additional non-sentinel lymph nodes if the sentinel node (SN) is positive;
 - b. Sentinel lymphadenectomy alone if pathologic nodal staging based on sentinel lymphadenectomy is pN0, pN1mi or pN1b; or
 - c. Axillary lymphadenectomy without SN isolation procedure.
12. The interval between the last surgery for breast cancer (treatment or staging) and randomization must be at least 28 days but no more than 84 days.
13. Patients must have ER analysis performed on the primary tumor prior to randomization. If ER analysis is negative, then PgR analysis must also be performed.
14. The most recent postoperative blood counts, performed within 6 weeks prior to randomization, must meet the following criteria:
 - a) ANC must be $\geq 1200/\text{mm}^3$ ($1.2 \times 10^9/\text{L}$);

- b) Platelet count must be $\geq 100,000/\text{mm}^3$ ($100.0 \times 10^9/\text{L}$); and
 - c) Hemoglobin must be ≥ 10 g/dL.
15. 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:
- a) total bilirubin must be \leq upper limit of normal (ULN) for the lab unless the patient has a bilirubin elevation $>$ ULN to $1.5 \times$ ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; and
 - b) alkaline phosphatase must be $\leq 2.5 \times$ ULN for the lab; and
 - c) AST must be $\leq 1.5 \times$ ULN for the lab.
 - d) ***Alkaline phosphatase and AST may not both be $>$ the ULN.*** For example, if the alkaline phosphatase is $>$ the ULN but $\leq 2.5 \times$ ULN, then the AST must be \leq the ULN. If the AST is $>$ the ULN but $\leq 1.5 \times$ ULN, then the alkaline phosphatase must be \leq ULN.
16. Patients with AST or alkaline phosphatase $>$ ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET scan or PET-CT performed within 3 months prior to randomization) does not demonstrate metastatic disease and the requirements in criterion 4.2.15 are met.
17. Patients with alkaline phosphatase that is $>$ ULN but $\leq 2.5 \times$ ULN are eligible for inclusion in the study if a bone scan, PET scan or PET-CT scan (performed within 3 months prior to randomization) does not demonstrate metastatic disease.
18. The following criteria for renal function must be met based on the results of the most recent postoperative tests performed within 6 weeks prior to randomization:
- a) Serum creatinine must be \leq ULN for the lab.
 - b) Measured or calculated creatinine clearance must be > 60 mL/min (see Section 8.5.1 for instructions regarding calculation of creatinine clearance).
19. A urine sample must be tested for protein by determination of the urine protein creatinine (UPC) ratio (see Appendix G) or by urine dipstick. (Eligibility must be based on postoperative test[s] performed within 6 weeks prior to randomization.)
- a) UPC ratio must be < 1.0 .
 - b) Urine dipstick must indicate 0-1+ protein. If dipstick reading is $\geq 2+$, determine the UPC ratio, which must be < 1.0 , *or* collect a 24-hour urine specimen, which must demonstrate < 1.0 g of protein per 24 hours.
- Note: If more than one test was performed, the patient is eligible if any of the test result
20. LVEF assessment must be performed within 3 months prior to randomization. It is preferred that LVEF assessment be performed by 2-D echocardiogram; however, MUGA scan may be substituted based on institutional preferences. ***The LVEF must be $\geq 55\%$ regardless of the cardiac imaging facility's lower limit of normal (LLN). (The same method should be used throughout the study; all assessments should be performed at the same cardiac imaging facility used at baseline.)***
- Note: Since the pre-entry LVEF serves as the baseline for comparing subsequent LVEF assessments to determine if trastuzumab and bevacizumab therapy can be administered, it is critical that this baseline study be an accurate assessment of the patient's LVEF. *If the baseline LVEF is $> 70\%$, the investigator is encouraged to have the accuracy of the initial LVEF result confirmed and to consider repeating the test if the accuracy is uncertain.*
21. The ECG (performed within 3 months prior to randomization) must not have demonstrated any of the following conditions:
- a) ventricular arrhythmias except for benign premature ventricular contractions;
 - b) supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication; and;
 - c) conduction abnormality requiring a pacemaker.

Ineligibility Criteria

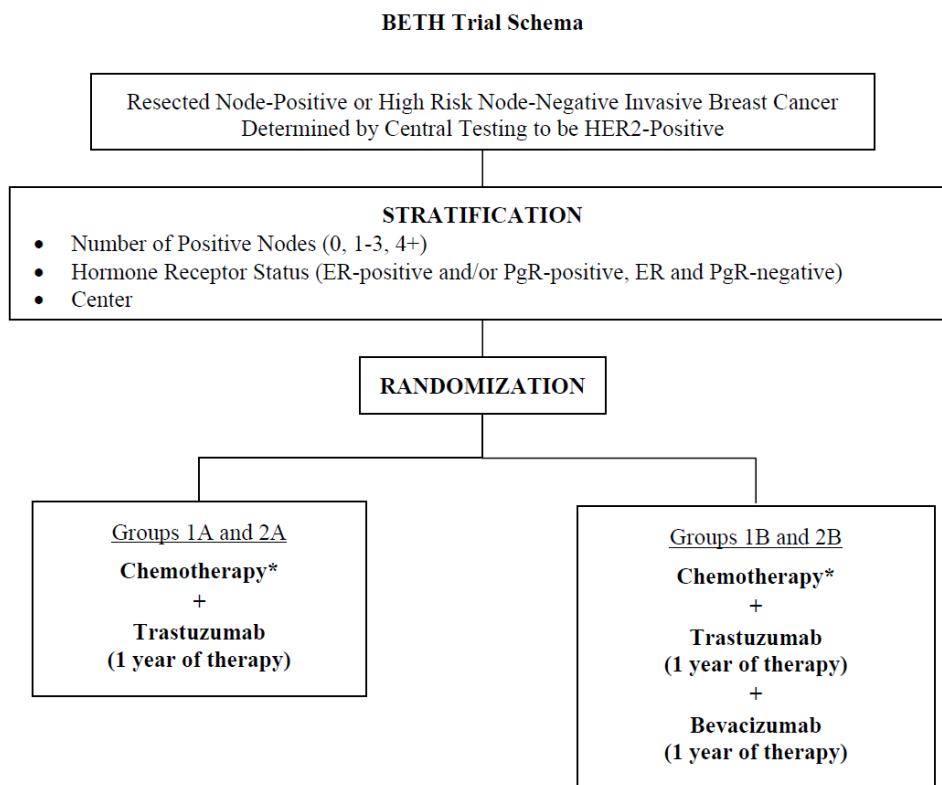
1. Inflammatory breast cancer.
2. Definitive clinical or radiologic evidence of metastatic disease. (Chest imaging [mandatory for all patients] and other imaging [if required] must have been performed within 3 months prior to randomization.)
3. Synchronous or previous contralateral invasive breast cancer (Patients with history of ipsilateral LCIS are eligible.)
4. History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral DCIS treated with excision and RT. (Patients with history of ipsilateral LCIS are eligible)

5. History of non-breast malignancies within the 5 years prior to study entry, except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ and basal cell and squamous cell carcinomas of the skin.
6. Previous therapy with anthracyclines, taxanes, carboplatin, trastuzumab, or bevacizumab for any malignancy.
7. RT, chemotherapy, and/or targeted therapy, administered for the currently diagnosed breast cancer prior to randomization.
8. Continued therapy with any hormonal agent such as raloxifene or tamoxifen (or other SERM) or an aromatase inhibitor. (Patients are eligible if these medications are discontinued prior to randomization.)
9. Any sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy, etc. as described in Section 8.10.4. Patients are eligible if these medications are discontinued prior to randomization.
10. 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:
 - a) *Active cardiac disease*
 - i. angina pectoris that requires the use of anti-anginal medication;
 - ii. ventricular arrhythmias except for benign premature ventricular contractions;
 - iii. supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
 - iv. conduction abnormality requiring a pacemaker;
 - v. valvular disease with documented compromise in cardiac function; and
 - vi. symptomatic pericarditis.
 - b) *History of cardiac disease*
 - i. myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
 - ii. history of documented CHF; and
 - iii. documented cardiomyopathy.
11. Uncontrolled hypertension defined as systolic blood pressure (BP) > 150 mmHg or diastolic BP > 90 mmHg, with or without anti-hypertensive medication. (BP must be assessed within 28 days prior to randomization.) Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria. (*See Appendix E for BP management requirements.*)
12. History of hypertensive crisis or hypertensive encephalopathy.
13. History of TIA or CVA.
14. History of any arterial thrombotic event within 12 months before randomization.
15. Symptomatic peripheral vascular disease.
16. Intrinsic lung disease resulting in dyspnea.
17. Unstable diabetes mellitus.
18. Active infection or chronic infection requiring chronic suppressive antibiotics.
19. Any significant bleeding within 6 months before randomization, exclusive of menorrhagia in premenopausal women.
20. Non-healing wound, skin ulcers, or incompletely healed bone fracture.
21. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to planned start of study therapy. (Note: Placement of a vascular access device is not considered a major surgical procedure. See Sections 8.2 and 8.4 for instructions regarding initiation of therapy after device placement.)
22. Anticipation of need for major surgical procedures during study therapy and for at least 3 months following completion of bevacizumab.
23. Gastroduodenal ulcer(s) documented by endoscopy to be active within 6 months before randomization.
24. History of GI perforation, abdominal fistulae, or intra-abdominal abscess.
25. Known bleeding diathesis or coagulopathy.
26. Requirement for therapeutic doses of coumadin or equivalent.
27. Sensory/motor neuropathy \geq grade 2, as defined by the NCI CTCAE v3.0.
28. Conditions that would prohibit administration of corticosteroids.
29. Chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
30. History of hypersensitivity reaction to drugs formulated with polysorbate 80.
31. Pregnancy or lactation at the time of study entry. (**Note: Pregnancy testing must be performed within 14 days prior to randomization according to institutional standards for women of child-bearing potential.**)
32. Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.

33. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
34. Use of any investigational product within 4 weeks prior to enrollment in the study.
35. All patients must be informed of the investigational nature of this study and give written informed consent according to institutional and federal guidelines.

Pre-Study Parameters

1. History and physical including performance status, BP, height, weight, concomitant meds, and menopausal status.
2. Labs: CBC with differential, CMP, calculated or measured creatinine clearance, urine dipstick for protein, pregnancy test (for women of child-bearing potential)
3. Imaging: CT chest or CXR, liver imaging if AST > ULN, bone nuclear imaging if alk phos > ULN. PET-CT alone can fulfill imaging requirement.
4. ECHO (or MUGA), ECG
5. Bilateral breast imaging (mammogram or MRI)



* CIRG and NSABP investigators will enroll patients in the TCH→H +/- bevacizumab cohort; based on institutional preference, Independent Investigators will enroll all patients in one of the two chemotherapy cohorts (either TCH→H +/- bevacizumab or TH→FEC→H +/- bevacizumab).

The chemotherapy/trastuzumab regimens are:

Groups 1A and 1B: TCH→H

docetaxel + carboplatin + trastuzumab (q3w x 6 cycles) → trastuzumab (q3w to complete 1 year of therapy)

Groups 2A and 2B: TH→FEC→H

docetaxel + trastuzumab (q3w x 3 cycles) → 5-FU, epirubicin, and cyclophosphamide (q3w x 3 cycles) → trastuzumab (q3w to complete a total of 1 year of therapy)