

## **B-44-I (BETH) – 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**

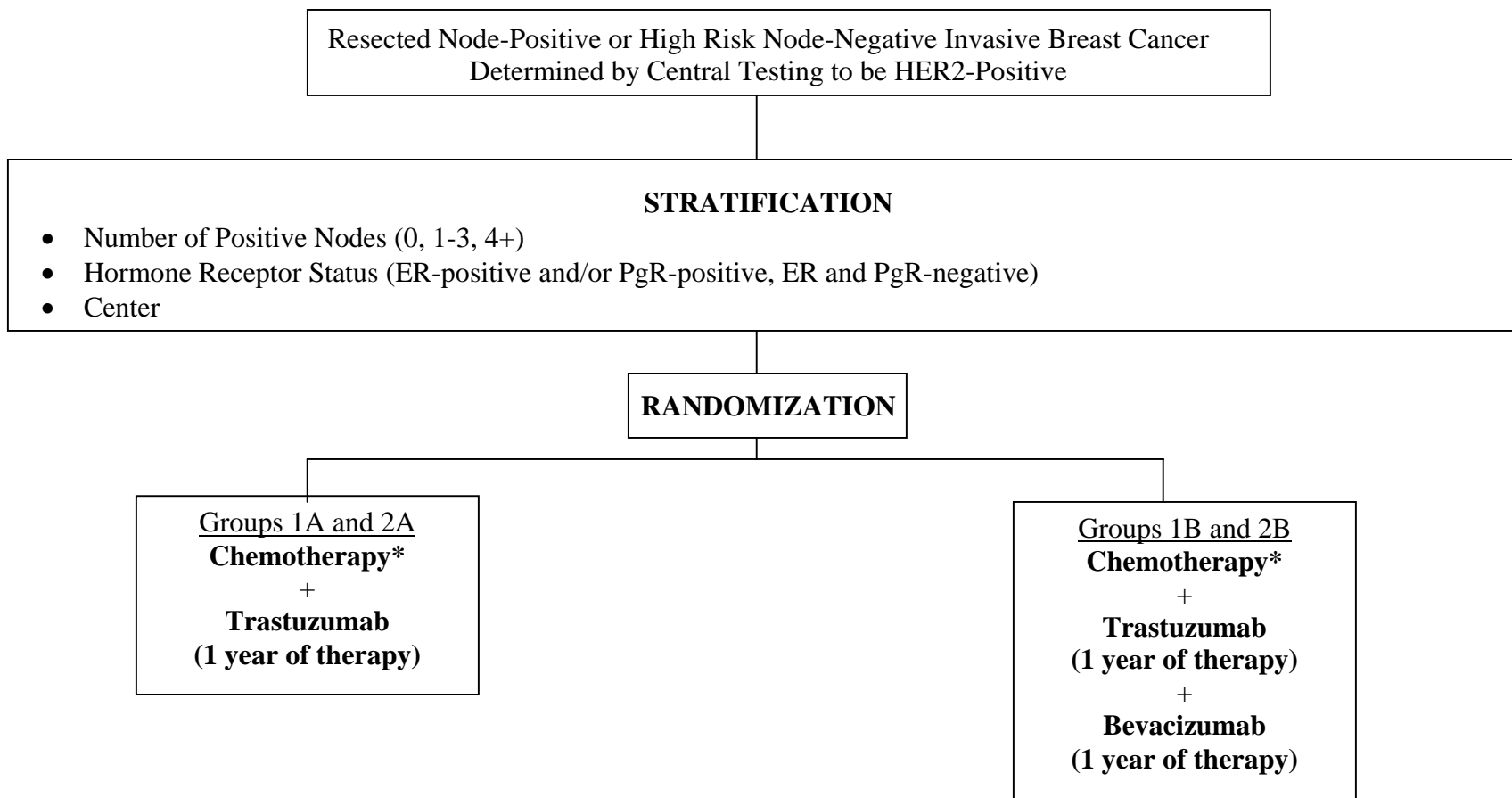
**Primary Objective:** To determine whether the addition of bevacizumab to the two designated regimens of chemotherapy + trastuzumab (TCHB→HB; THB→FEC→HB) improves invasive disease-free survival (IDFS) relative to the two designated regimens of chemotherapy + trastuzumab (TCH→H; TH→FEC→H).

### **Eligibility Criteria:**

- The patient must have signed and dated IRB/EC-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).
- Patients must be female.
- The patient must be  $\geq 18$  years old. (The minimum age for eligibility can be older than 18 years if required by local regulatory authority).
- The patient must have an ECOG performance status of 0 or 1 (see Appendix D).
- The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.
- The breast cancer must be HER2-positive based on test results as follows:
  - **Local testing** (if available) should demonstrate that the tumor is IHC 2+ or 3+ or is considered 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.)
  - **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+.
- All of the following staging criteria (according to the 6<sup>th</sup> edition of the AJCC Cancer Staging Manual) must be met:
  - By pathologic evaluation, primary tumor must be pT<sub>1-3</sub>;
  - By pathologic evaluation, ipsilateral nodes may be pN<sub>0</sub>, pN<sub>1</sub> (pN<sub>1mi</sub>, pN<sub>1a</sub>, pN<sub>1b</sub>, pN<sub>1c</sub>), pN<sub>2a</sub>, pN<sub>3a</sub>, or pN<sub>3b</sub>
  - **If pN<sub>0</sub>**, at least one of the following criteria must be met:
    - Pathologic tumor size > 2.0 cm;
    - ER negative and PgR negative;
    - Histologic and/or nuclear grade 2 (intermediate) or 3 (high); or
    - Age < 35 years
- Patients must have undergone either a total mastectomy or breast conserving surgery (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 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 lobular carcinoma in situ [LCIS] are eligible without additional resection.)
- 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 [RT] requirements).
- Patients must have completed one of the following procedures for evaluation of pathologic nodal status:
  - Sentinel lymphadenectomy followed by removal of additional non-sentinel lymph nodes if the sentinel node (SN) is positive;
  - Sentinel lymphadenectomy alone if pathologic nodal staging based on sentinel lymphadenectomy is pN<sub>0</sub>, pN<sub>1mi</sub> or pN<sub>1b</sub>; or
  - Axillary lymphadenectomy without SN isolation procedure
- 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.
- 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.
- The most recent postoperative blood counts, performed within 6 weeks prior to randomization, must meet the following criteria:
  - ANC must be  $\geq 1200/\text{mm}^3$  ( $1.2 \times 10^9/\text{L}$ );
  - Platelet count must be  $\geq 100,000/\text{mm}^3$  ( $100.0 \times 10^9/\text{L}$ ); and
  - Hemoglobin must be  $\geq 10\text{g/dL}$

- 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  $\leq$  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
  - Alkaline phosphatase must be  $\leq 2.5 \times$  ULN for the lab; and
  - AST must be  $\leq 1.5 \times$  ULN for the lab.
  - 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.
- Patients with AST or alkaline phosphatase  $>$  ULN are eligible for inclusion in the study if liver imaging (CT, MRI, or PET scan performed within 3 months prior to randomization) does not demonstrate metastatic disease and the requirements in criterion above are met.
- Patients with alkaline phosphatase that is  $>$  ULN but  $\leq 2.5 \times$  ULN are eligible for inclusion in the study if a bone scan or PET scan (performed within 3 months prior to randomization) does not demonstrate metastatic disease.
- 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:
  - Serum creatinine must be  $\leq$  ULN for the lab
  - Measured or calculated creatinine clearance must be  $> 60$  mL/min (see Section 8.5.1 for instructions regarding calculation of creatinine clearance).
- Urine dipstick indicating 0-1+ protein. If dipstick reading is  $\geq 2+$ , collect a 24-hour urine specimen, which must demonstrate  $< 1.0$  g of protein per 24 hours. (Eligibility must be based on the most recent postoperative test(s) performed within 6 weeks prior to randomization.)
- 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.
- The ECG (performed within 3 months prior to randomization) must not have demonstrated any of the following conditions:
  - Ventricular arrhythmias except for benign premature ventricular contractions;
  - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication; and
  - Conduction abnormality requiring a pacemaker.

**SCHEMA\*:**



\*CIRG and NSABP investigators will enroll patients in the TCH→H +/- bevacizumab cohort; Independent Investigators will enroll patients in either TCH→H +/- bevacizumab or TH→FEC→H +/- bevacizumab cohorts.

The chemotherapy/trastuzumab regimens are:

**Groups 1A and 1B: TCH→H**

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

**Groups 2A and 2B: TH→FEC→H**

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