

SCHEMA

TITLE: E5103, A Double Blind Phase III Trial of Doxorubicin and Cyclophosphamide Followed by Paclitaxel with Bevacizumab or Placebo in PHASE III Patients with Lymph Node Positive and High Risk Lymph Node Negative Breast Cancer

BREAST

ELIGIBILITIES:

1. Patients must have histologically confirmed adenocarcinoma of the breast at significant risk of distant recurrence based on at least one of the following criteria:
 - Involvement of at least one axillary lymph node on routine histologic examination. Patients with axillary node involvement only demonstrated by immunohistochemistry are not eligible unless they meet one of the other eligibility criteria below.
 - ER negative tumor ≥ 1 cm
 - ER+ tumor ≥ 5 cm regardless of recurrence score
 - ER+ tumor ≥ 1 cm but < 5 cm with a recurrence score ≥ 11 . (Patients enrolled in the TAILORx trial are eligible.)

NOTE: Pre-menopausal patients with ER+ tumor may participate in the IBCSG SOFT trial.

NOTE: Pre-menopausal patients with ER- tumor may participate in S0230.
2. Patients must have completed definitive breast surgery including total mastectomy and axillary dissection (modified radical mastectomy), total mastectomy and sentinel node biopsy, breast conservation surgery and axillary dissection or breast conservation surgery and sentinel node biopsy.

NOTE: Axillary dissection is strongly encouraged in patients with lymph node involvement identified on sentinel node biopsy.

NOTE: Breast conservation surgery includes lumpectomy, partial mastectomy, and excisional biopsy.
3. Margins of breast conservation surgery or mastectomy must be histologically free of invasive breast cancer and ductal carcinoma in situ (DCIS). Patients with resection margins positive for lobular carcinoma in situ (LCIS) are eligible
4. Interval between last surgery for breast cancer (breast conservation surgery, mastectomy, sentinel node biopsy, axillary dissection or re-excision of breast conservation surgery margins) and Day 1 of treatment must be > 28 days and ≤ 84 days.
5. ECOG performance status of 0-1
6. Patients must have adequate organ function within ≤ 8 weeks prior to randomization, as measure by: ANC ≥ 1000 ; Platelet count $\geq 100,000$; Total bilirubin ≤ 1.5 ; AST (SGOT) ≤ 2 ULN; Serum creatinine ≤ 1.5 ; Urine protein:creatinine (UPC) ratio < 1.0 (Please see Appendix V for instructions on how to obtain the urine protein:creatinine ratio); PTT ≤ 1.5 x normal X ULN; LVEF \geq institutional limits of normal by MUGA or ECHO
7. Patients who have undergone breast conservation surgery must receive radiation. Prior to randomization, the investigator must specify the planned radiation technique.
 - Whole breast radiation (WBRT) after chemotherapy
 - Accelerated partial breast radiation (APBI) after chemotherapy
 - Accelerated partial breast radiation (APBI) prior to chemotherapy

NOTE: If APBI was completed prior to study entry, day 1 of protocol therapy must be at least 4 weeks after the completion of APBI.

8. Post-mastectomy RT is required for all patients with a primary tumor of ≥ 5 cm or involvement of 4 or more lymph nodes. Post-mastectomy RT may be administered at the investigator's discretion for all other mastectomy patients.
9. Patients with HER2 + (3+ by IHC or FISH +) breast cancer are not eligible.
10. Patients with synchronous bilateral breast cancer (diagnosed within one month) are eligible if the higher TNM stage tumor meets the eligibility criteria for this trial.
11. Patients must not have clinical evidence of inflammatory disease or fixed axillary nodes at diagnosis.
12. Patients must not have received prior cytotoxic chemotherapy or hormonal therapy for the breast cancer. Prior treatment with an anthracycline, anthracenedione or taxane for any condition is not allowed.
NOTE: Prior use of tamoxifen for chemoprevention is allowed but must be discontinued at study entry. Similarly, prior raloxifene use is allowed but must be discontinued at study entry.
13. Patients must not have had any major surgical procedure within 28 days of day 1 treatment.
NOTE: Non-operative biopsy or placement of a vascular access device is not considered a major surgery.
14. Patients may not have had placement of a vascular access device within 24 hours of planned Day 1 of treatment.
15. Patients must not have clinically significant cardiovascular or cerebrovascular disease, including:
Any history of •Cerebrovascular disease including TIA, stroke or subarachnoid hemorrhage •Ischemic bowel
Within the last 12 months •Myocardial infarction •Unstable angina •New York Heart Association (NYHA) class II or greater congestive heart failure
•Grade II or greater peripheral vascular disease
NOTE: See Appendix X for NYHA classification and peripheral vascular disease grading criteria
Active at study entry •Uncontrolled hypertension defined as SBP > 160 or DBP > 90 •Uncontrolled or clinically significant arrhythmia
NOTE: Patients with controlled atrial fibrillation are eligible.
16. Patients who require full dose anticoagulation may enroll provided they meet the following criteria: •the patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on stable dose of LMW heparin. •the patient must not have active bleeding or pathological conditions that carry high risk of bleeding (e.g. varices)
NOTE: Prophylactic use of anticoagulants to maintain patency of a vascular access device is permitted.
17. Patients must not have a bleeding diathesis, hereditary or acquired bleeding disorder or coagulopathy.
18. Patients must not have a non-healing wound or fracture. Patients with an abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization are not eligible.
19. Patients must not have a hypersensitivity to paclitaxel or drugs using the vehicle Cremophor, Chinese hamster ovary cell products or other recombinant human antibodies.
20. Male or female patients age ≥ 18 years of age are eligible.

21. Women must not be pregnant or breast-feeding due to the potential harmful effects of bevacizumab on the developing fetus. All females of childbearing potential must have a blood or urine test within 7 days prior to randomization to rule out pregnancy.
22. Women of childbearing potential and sexually active males must use an accepted and effective method of contraception.
23. Follow-up will continue for 15 years from randomization.

Step 2: Unblinding and Re-registration to Arm D (see Section 4.7) UNBLINDING PROCEDURES: (see Section 4.6)

All patients will be unblinded on Day 1 of Cycle 8. Patients on Arms A or B will complete protocol therapy with Cycle 8. Patients on Arm C should be registered to Arm D to continue maintenance bevacizumab treatment for Cycles 9-18. To unblind patients on Cycle 8 Day 1, follow the instructions outlined in Appendix XI.

TREATMENT: For classical and dose dense. Doses should be based upon actual body weight. If subject's weight changes by $\geq 10\%$ during the course of the study, the body surface area and drug dose should be recalculated.

ARM A: Doxorubicin + Cyclophosphamide + Placebo (cycles 1-4) » Paclitaxel + Placebo (cycles 5-8)

ARM B: Doxorubicin + Cyclophosphamide + Bevacizumab (cycles 1-4) » Paclitaxel + Bevacizumab (cycles 5-8)

ARM C: Doxorubicin + Cyclophosphamide + Bevacizumab (cycles 1-4) » Paclitaxel + Bevacizumab (cycles 5-8)

All Arms will be unblinded after cycle 8. Arms A & B completed their chemotherapy. Arm C will be Registered to Arm D and receive Bevacizumab for cycles 9-18.

STEP 1 ALL TREATMENT GROUPS-Physician may choose classical or dose dense as described below

CLASSICAL: CYCLES 1-4, Cycle every 3 weeks (see Section 5.1.1)

Agent	Dose	Route	Day
Doxorubicin	60 mg/m ²	IV push through running IV of NS	1
Cyclophosphamide	600 mg/m ²	IV infusion in 250 mL NS over 20-30 min.	1
Bevacizumab/Placebo	15 mg/kg	IV infusion	1

OR

DOSE DENSE: CYLES 1-4. Cycle every 2 weeks. (see Section 5.2.1)

Agent	Dose	Route	Day
Doxorubicin	60 mg/m ²	IV push through running IV of NS	1
Cyclophosphamide	600 mg/m ²	IV infusion in 250 mL NS over 20-30 min.	1
Bevacizumab	10 mg/kg	IV infusion	1
Pegfilgrastim	6 mg (regardless of BSA)	SQ	2
OR Filgrastim	5 µg/kg rounded to the nearer of 300 or 480 µg		2-11

Followed by: Cycles 5-8

Agent	Dose	Route	Day
Dexamethasone	20 mg	IV or PO	30-60 min prior to paclitaxel. Every 7 days
Diphenhydramine	50 mg	IV or PO	
Cimetadine	300 mg	IV	
Paclitaxel	80 mg/m ²	IV infusion in 250 mL NS or D ₅ W over 1 hour	Every 7 days x 12 does
Bevacizumab/Placebo	15 mg/kg	IV infusion	Every 21 days x 4

Anaphylaxis Precautions should be observed and emergency cart available during Paclitaxel and/or the Cremophor vehicle

STEP 2: PATIENTS ON ARM C ONLY REGISTER TO ARM D – Classical, Every 3 weeks Bevacizumab Monotherapy

Agent	Dose	Route	Day
Bevacizumab	15 mg/kg	IV infusion	Day 1 every 21 days x 10

Radiation Therapy

For all patients receiving whole breast (WBR) or post-mastectomy radiation, the daily fraction size will be 1.8 or 2.0 Gy delivered daily Monday thru Friday. For patients undergoing definitive breast radiation after breast conserving surgery, the timing and method of delivering RT will be stratified at the time of patient entry into protocol. The options for definitive RT are : (a) standard (or conventional) WBR; (b) accelerated partial breast irradiation (APBI) delivered before protocol entry; or (c) APBI delivered after protocol chemotherapy. (see Section 5.1.4)

Hormonal Therapy

For patients in Arm D hormonal therapy will be administered concurrently with bevacizumab. Since it is possible Tamoxifen and bevacizumab may increase the risk of thrombosis, patients should be followed closely.

- Pre-menopausal women: Tamoxifen 20 mg daily for 5 years, should be used in women with ER + or PR + tumors. Tamoxifen should be initiated at the time of RT or within 6 weeks after the completion of chemotherapy for patients not receiving RT.
- Post-menopausal women: Patients with ER + or PR + tumors may receive tamoxifen 20 mg daily, aromatase inhibitors (anastrozole 1 mg daily, letrozole 2.5 mg daily or exemestane 25 mg daily, or tamoxifen followed by an aromatase inhibitor. The total duration of adjuvant anti-hormonal therapy should be no more than 10 years.

PRESUDIES: Baseline studies must be performed \leq 8 weeks prior to randomization: H&P, wt, Ht, ECOG PS; WBC, ANC, Hgb, Plts; Cr, T bili, AST, NA; PT/INR, PTT; Urinalysis with protein:creatinine ratio, see Appendix V for procedure to obtain ratio; Serum or Urine HCG required in women of child-bearing potential only, within 7 days prior to randomization; Chest x-ray, Chest Ct can be substituted; Bone scan if clinically indicated; ECG, MUGA or ECHO;

DRUGS SUPPLIED: Bevacizumab/Placebo No blinded started supplies will be available. Blinded, patient-specific supplies will be shipped from the PMB at the time of patient randomization and should arrive within 7-10 days. (see Section 8.1.)

ACCRUAL GOAL: 4950 participants

PATHOLOGY : OPTIONAL •Original diagnostic paraffin embedded tumor block •Paraffin embedded tumor positive lymph node block
• 2(5 ml) Lavender top tubes •serum from 1(6-10 ml) red top or SST tube

12/07 : le

03/08 : cc

06/08 : cc