

NSABP FB-6 - A Phase II Clinical Trial of Four Cycles of Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Given Concurrently with Pazopanib as Neoadjuvant Therapy Followed by Postoperative Pazopanib for Women with Locally Advanced Breast Cancer

Fast Facts

Pazopanib provided

Patient selection guidelines

- 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.)
- *In addition to the required block from the diagnostic biopsy*, submission of tumor samples from the definitive breast surgery, if gross residual disease ≥ 1.0 cm remains, is also required for all patients (see Section 7.1). *Therefore, the local pathology department policy regarding release of blocks must be considered when screening patients.*
- Patients who plan to have breast reconstruction utilizing tissue expanders must be in agreement with delaying surgery to replace the tissue expanders with permanent implants until 3 months following the last dose of pazopanib (see Section 8.6.3). Expansion of the tissue expanders during postoperative pazopanib therapy is at the investigator's discretion.
- Patients of reproductive potential must agree to use an effective non-hormonal method of contraception during therapy and for at least 3 months after the last dose of pazopanib.
- The investigator should assess the patient to determine if she has any psychiatric or addictive disorder or other condition that, in the opinion of the investigator, would preclude her from meeting the study requirements.

Patient eligibility criteria

1. The patient must have consented to participate and must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines *for the study treatment and submission of tumor and blood samples required* for the FB-6 correlative science studies (see Section 7.1). Prior to study entry, the local pathology department must have agreed to release the tumor block from the diagnostic biopsy sample. (*Note: The tumor block from the diagnostic biopsy sample must be submitted within 60 days after study entry.*)
2. Patients must be female.
3. Patients must be ≥ 18 years old.
4. The ECOG performance status must be 0 or 1 (see Appendix A).
5. Patients must have the ability to swallow oral medication.
6. The diagnosis of invasive adenocarcinoma of the breast must have been made by core needle biopsy or *limited incisional biopsy*.
7. 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. (Patients are eligible with either hormone receptor-positive or hormone receptor-negative tumors.)
8. Patients must have clinical stage IIIA, IIIB, or IIIC disease (see Appendix B) with a mass in the breast or axilla measuring ≥ 2.0 cm by physical exam, unless the patient has inflammatory breast cancer, in which case measurable disease by physical exam is not required. (*Clinical staging should be based on the assessment by physical exam.*)
9. At the time of study entry, blood counts must meet the following criteria:
 - ANC must be $\geq 1200/\text{mm}^3$
 - Platelet count must be $\geq 100,000/\text{mm}^3$
 - Hemoglobin must be ≥ 10 g/dl
10. PT/INR must be $<$ ULN for the lab.
11. The following criteria for evidence of adequate hepatic function must be met:
 - total bilirubin must be \leq 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 $\leq 1.5 \times$ ULN for the lab (see Sections 4.2.12 and 4.2.13); *and*
 - ALT must be \leq ULN for the lab; *and*
 - AST must be \leq ULN for the lab.

12. Patients with alkaline phosphatase $>$ ULN but $\leq 1.5 \times$ ULN are eligible for inclusion in the study if liver imaging (CT, MRI, or PET scan) does not demonstrate metastatic disease and the requirements in Section 4.2.11 are met.
13. Patients with either unexplained skeletal pain or alkaline phosphatase that is $>$ ULN but $\leq 1.5 \times$ ULN are eligible for inclusion in the study if a bone scan or PET scan does not demonstrate metastatic disease. Patients with suspicious findings on bone scan or PET scan are eligible if suspicious findings are confirmed to be benign by x-ray, MRI, or biopsy.
14. Serum creatinine \leq ULN for the lab.
15. A urine sample must be tested for proteinuria by the dipstick method (followed by determination of UPC ratio if needed) *or* by determination of the UPC ratio alone. Eligibility must be based on the most recent test result(s). (See Appendix D for UPC ratio instructions.) One of the following criteria must be met:
 - UPC ratio must be $<$ 1.0
 - Urine dipstick must indicate 0- 1 + protein. If dipstick reading is $\geq 2+$, a UPC ratio must be determined and must be $<$ 1.0.
16. The LVEF assessment by 2-D echocardiogram or MUGA scan performed within 3 months prior to study entry must be $\leq 50\%$ regardless of the facility's LLN. Note: Since the pre-entry LVEF serves as the baseline for comparing subsequent LVEF assessments to determine if pazopanib 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 $\geq 70\%$, the investigator is encouraged to have the accuracy of the initial LVEF result confirmed and to consider repeating the study if the accuracy is uncertain.*
17. ECG performed within 4 weeks before study entry must demonstrate a QTc interval that is ≤ 0.47 seconds.
18. The TSH level must be within normal limits for the laboratory. (Patients with TSH controlled by medication within normal range are eligible.

Patient ineligibility criteria

1. Tumor that has been determined to be HER2-positive by immunohistochemistry (3+) or by FISH or CISH (positive for gene amplification), *or* has been determined to be ER2-equivocal *and* the investigator plans to administer trastuzumab or other targeted therapy.
2. FNA alone to diagnose the primary breast cancer.
3. Excisional biopsy or lumpectomy performed prior to study entry.
4. Surgical axillary staging procedure prior to study entry. (Procedures that are permitted prior to study entry include: 1) FNA or core biopsy of an axillary node for any patient, and 2) although not recommended, a pre-neoadjuvant therapy SN biopsy for patients with *clinically negative axillary nodes*. See Section 8.6.4 for post-neoadjuvant therapy axillary staging requirements.
5. Definitive clinical or radiologic evidence of metastatic disease.
6. History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral DCIS treated with RT. (Patients with a history of LCIS are eligible.)
7. Contralateral invasive breast cancer at any time. (Patients with contralateral DCIS or LCIS are eligible.)
8. Non-breast malignancies unless the patient is considered to be disease-free for 5 or more years prior to study entry and is deemed by her physician to be at low risk for recurrence. Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.
9. Requirement for chronic use of any of the *prohibited* medications or substances specified in Appendix C. (Patients are eligible if these medications and/or substances can be discontinued prior to the first dose of pazopanib and will not need to be resumed until after the last dose of pazopanib.)
10. Previous therapy with anthracyclines, taxanes, or pazopanib for any malignancy.
11. Treatment including RT, chemotherapy, and/or targeted therapy, administered for the currently diagnosed breast cancer prior to study entry.
12. Continued therapy with any hormonal agent such as raloxifene, tamoxifen, or other SERM. (Patients are eligible if these medications are discontinued prior to study entry.)
13. Any sex hormonal therapy, e.g., birth control pills and ovarian hormone replacement therapy (see Section 8.10). These patients are eligible if this therapy is discontinued prior to study entry. (Women of reproductive potential must agree to use an effective non-hormonal method of contraception during study therapy and for at least 3 months after completion of pazopanib.)
14. History of hepatitis B or C.
15. Symptomatic pancreatitis or asymptomatic \geq grade 2 elevation of amylase or lipase as per NCI CTCAE v3.0.
16. History of documented pancreatitis.

17. Uncontrolled hypertension defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg, with or without anti-hypertensive medication. (Patients with hypertension that is well-controlled on medication are eligible.)
18. History of hypertensive crisis or hypertensive encephalopathy.
19. Cardiac disease that would preclude the use of any of the drugs included in the FB-6 treatment regimen. This includes but is not confined to:

Active cardiac disease:

- angina pectoris that requires the use of anti-anginal medication;
- ventricular arrhythmias except for benign premature ventricular contractions controlled by medication;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
- clinically significant valvular disease; and
- cardiac angioplasty or stenting

History of cardiac disease:

- myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
 - documented CHF; and
 - documented cardiomyopathy.
19. History of TIA or CVA.
 20. History of any arterial thrombotic event within 12 months prior to study entry.
 21. Pulmonary embolism or DVT within 6 months prior to study entry.
 22. Symptomatic peripheral vascular disease.
 23. Any significant bleeding within 6 months prior to study entry, exclusive of menorrhagia in premenopausal women.
 24. Known bleeding diathesis, coagulopathy, or requirement for therapeutic doses of coumadin.
 25. Serious or non-healing wound, skin ulcers, or bone fracture.
 26. Gastroduodenal ulcer(s) determined by endoscopy to be active.
 27. History of GI perforation, abdominal fistulae, or intra-abdominal abscess.
 28. Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease significantly affecting gastrointestinal function.
 29. Sensory/motor neuropathy \geq grade 2, as defined by the NCI's CTCAE v3.0.
 30. Conditions that would prohibit intermittent administration of corticosteroids for paclitaxel premedication.
 31. Anticipation of need for major surgical procedures (other than the required breast surgery) during the course of study therapy and for at least 3 months following the last dose of pazopanib.
 32. Pregnancy or lactation at the time of study entry. (*Note: Pregnancy testing should be performed according to institutional standards for women of childbearing potential.*)
 33. Other nonmalignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.
 34. Known immediate or delayed hypersensitivity reaction to doxorubicin, cyclophosphamide, paclitaxel, pazopanib, or drugs chemically related to pazopanib.
 35. Use of any investigational agent within 4 weeks prior to enrollment in the study.

Pre-Study Parameters

1. History and physical exam including **tumor assessment by physical exam with measurement**, performance status, height, weight, blood pressure, list of concomitant meds
2. HER-2 status
3. Labs including CBC with differential and platelets, CMP, magnesium, phosphorous, amylase, lipase, TSH, PT/INR, Urine dipstick or UPC ratio, pregnancy test for women of childbearing potential
4. ECG with QTc intervals, Echo or MUGA
5. PET-CT or all of the following liver imaging, bone nuclear imaging, CT chest (or CXR)
6. US of ipsilateral axilla (recommended), marking of primary tumor site (recommended)

See section 6.0 for details of pre-study requirements

Treatment

Institution must agree to release tumor block for diagnostic biopsy
Baseline tumor measurement by palpation required pre-study

