

CALGB 40502: A Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone Combined with Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Fast Facts

On-Study Guidelines

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV) or uncontrolled diabetes mellitus, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Inability to comply with study and/or follow-up procedures
- Ketoconazole, a potent inhibitor of CYP3A4 resulted in a 79% increase in ixabepilone AUC when the two drugs were administered concurrently. The use of potent CYP3A4 inhibitors should be avoided in patients getting ixabepilone (Arm C) on this trial. See Section 11.7 for examples of potent CYP3A4 inhibitors.

Patient Eligibility

1. Documentation of Disease: Histologic confirmation of invasive cancer of the breast.
2. Stage: Stage IV disease or Stage IIIC disease (using AJCC criteria, 6th edition) not amenable to local therapy.
3. Patients may not have a "currently active" second malignancy other than nonmelanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.
4. **HER2/neu status-** Patients with HER2 negative disease are eligible. Patients with HER2+ disease are eligible providing they have previously received trastuzumab or lapatinib. Documentation of progression on HER2 directed therapy is not required. Her2/neu status must be known at the time of protocol registration.
5. **Hormone receptor status-** ER and/ PgR status must be known at the time of registration. ER and/or PgR \geq 1% cells will be considered positive.
6. Age \geq 18 years of age.
7. **Prior treatment:**
 - a) May include adjuvant or neoadjuvant taxane, however, the interval between completion of adjuvant therapy and disease recurrence must be \geq 12 months.
 - b) No prior chemotherapy regimens for metastatic or locally advanced breast cancer.
 - c) Any number of prior hormonal therapies are allowed. The last dose should have been administered at least 7 days prior to the initiation of protocol therapy.
 - d) Prior radiotherapy must be completed at least 2 weeks prior to study entry.
 - e) Treatment with bisphosphonates is allowed and recommended as per ASCO guidelines.
 - f) Prior trastuzumab or lapatinib required for patients with HER2 overexpressing tumors.
 - g) Prior treatment with bevacizumab is allowed.
8. **Prior surgery:**
 - a) Patients must not have had a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study registration, and must have fully recovered from any such procedure. The following are NOT considered to be major procedures: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, and routine dental procedures.
 - b) Patients must not have anticipation of need for a major surgical procedure during the course of the study.
 - c) Patients must not have had a core biopsy or other minor surgical procedure, within 7 days prior to study registration. Placement of a vascular access device is allowed within 7 days of registration. Placement of a vascular access device after starting study therapy should be performed between day 15 and 28 of a treatment cycle (but not less than 48 hours before the next dose of bevacizumab) to allow for sufficient healing.

9. **Patients must have measurable disease (target lesions):** Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm with conventional techniques or as ≥ 1 cm with spiral CT scan.

Lesions that are considered non-measurable include the following:

- Bone lesions
- Leptomeningeal disease
- Ascites
- Pleural / pericardial effusion
- Inflammatory breast disease
- Lymphangitis cutis/pulmonitis
- Abdominal masses that are not confirmed and followed by imaging techniques
- Cystic lesions

10. Patients with pre-existing peripheral neuropathy \geq grade 2 are not eligible for this study.
11. Patients must have an ECOG (Zubrod) Performance Status of ≤ 1 to be eligible for this trial.
12. Pregnancy/Nursing Status: Women must not be pregnant or breast feeding. Premenopausal women must have a negative serum or urine β -Hcg.
13. Patients with a history of CTCAE grade ≥ 3 hypersensitivity to paclitaxel or Cremophor® EL are not eligible.
14. Patients with a history of abdominal fistula, or intra-abdominal abscess within 6 months prior to study registration are not eligible.
15. Patients with a history of GI perforation within 12 months prior to registration are not eligible.
16. Patients with a history of significant bleeding episodes (e.g., hemoptysis, upper or lower GI bleeding) within 6 months prior to registration are not eligible.

17. Cardiovascular status:

Patients must not have a history of clinically significant cardiovascular disease that includes the following:

- a) Uncontrolled hypertension defined as systolic blood pressure >150 and/or diastolic blood pressure >90 mmHg on antihypertensive medications or any prior history of hypertensive crisis or hypertensive encephalopathy.
 - b) History of myocardial infarction or unstable angina within past 6 months.
 - c) New York Heart Association (NYHA) congestive heart failure Grade 2 or greater (See Appendix IV).
 - d) Symptomatic peripheral vascular disease.
 - e) Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or arterial thrombotic events.
18. Patients on full dose anticoagulants must be on a stable dose of warfarin, or be on a stable dose of LMW heparin. Patients receiving anti-platelet or on daily prophylactic dose aspirin are eligible, as are patients receiving stable doses of anticoagulation for atrial fibrillation.
19. **CNS status:**
- a) Patients may not have a history of stroke or transient ischemic attack within 6 months prior to study registration.
 - b) Patients with a history of seizures must be well controlled with standard medication.
 - c) Patients must not have progressing or untreated CNS metastases or leptomeningeal disease. Patients with a history of resected brain metastases with stable MRI scans for 3 months including within 4 weeks of study start are eligible. Patients with a history of gamma knife radiosurgery or whole brain radiation with stable MRI scans for 3 months including within 4 weeks of study start are eligible.
20. No serious, non-healing wound, ulcer or bone fracture.
21. Life expectancy of ≥ 12 weeks.

22. Required Initial Laboratory Values:

- Granulocytes $\geq 1,500 / \mu\text{l}$
- Platelet count $\geq 100,000 / \mu\text{l}$
- Creatinine ≤ 2.0 mg/dL
- Bilirubin < 1.5 mg/dL (unless due to Gilbert's syndrome)
- Transaminases (AST, ALT) ≤ 2.5 X ULN
- Serum or urine β -Hcg Negative in premenopausal women of child-bearing potential
- Urine Protein $\leq 1 +$ protein* or UPC < 1

* Patients discovered to have $\geq 2+$ proteinuria at baseline must undergo a 24-hour urine collection that must demonstrate < 1 g of protein/24 hr or UPC ≤ 1 ratio to allow participation in the study.

Pre-study Parameters

1. History and physical including pulse, blood pressure, height, weight and performance status
2. CBC with differential, CMP, serum or urine β -Hcg (for women of child bearing potential), PT/INR, urinalysis
3. CT chest/abdomen/pelvis (or MRI, CT preferred), CXR (not required if CT of chest was obtained), bone scan with CT with bone windows

TreatmentArm A

Agent	Dose	Route	Frequency	Cycle
Paclitaxel	90 mg/m ²	IV	Days 1, 8, 15	28 days
Bevacizumab	10 mg/kg	IV	Days 1, 15	28 days

Arm B

Agent	Dose	Route	Frequency	Cycle
Nab-Paclitaxel	150 mg/m ²	IV	Days 1, 8, 15	28 days
Bevacizumab	10 mg/kg	IV	Days 1, 15	28 days

Arm C – see section 8.3.1 for Ixabepilone pre-meds

Agent	Dose	Route	Frequency	Cycle
Ixabepilone	16 mg/m ²	IV	Days 1, 8, 15	28 days
Bevacizumab	10 mg/kg	IV	Days 1, 15	28 days

Restage every two cycles.

Continue treatment until disease progression

Nab-paclitaxel, Ixabepilone and Bevacizumab are provided.