

SCRI BRE 145: A Randomized Trial of Ixempra™ vs. Taxol in Adjuvant Therapy of Triple-Negative Breast Cancer (TITAN)

Fast Facts

Inclusion Criteria

1. Female patients ≥ 18 years of age.
2. Histologically confirmed invasive unilateral breast cancer (regardless of histology).
3. Early-stage breast cancer, defined as:
 - a. Node-positive disease: >0.2 -mm metastasis in at least one lymph node (pN1mi-pN2b) OR
 - b. Node-negative, with primary tumor >1.0 cm (T1c-T3)
4. Definitive loco-regional surgery must have been completed as specified below:
 - a. Patients must have undergone either breast conservation surgery (i.e., lumpectomy) or total mastectomy.
 - b. Surgical margins of the resected section must be histologically free of invasive adenocarcinoma and ductal carcinoma in situ.
 - c. Surgical margins involved with lobular carcinoma in situ (LCIS) will not be considered as a positive margin; therefore, such patients will be eligible for this study without additional resection.
 - d. Patients must have completed axillary lymph node sampling for the pathologic evaluation of axillary lymph nodes as specified below:
 - i. Sentinel node biopsy and/or either lymph node sampling procedure or axillary dissection.
5. Multicentric and multifocal invasive breast cancer is eligible if loco-regional surgery has been completed as described above.
6. Patients with synchronous bilateral cancers are eligible **only if**:
 - a. All cancers are of triple-negative phenotype, defined as ER-, PR-, and HER2
 - b. Eligibility is based on the highest stage grouping.
7. HER2 negative tumors. HER2 negativity must be confirmed by one of the following:
 - a. SISH testing that demonstrates HER2 negativity
 - b. FISH-negative (FISH ratio <2.2), or
 - c. IHC 0-1+, or
 - d. IHC 2-3+ AND FISH-negative (FISH ratio <2.2).
8. Estrogen receptor negative and progesterone receptor negative ($<10\%$ staining by IHC for estrogen receptor and progesterone receptor)
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
10. Patient must be ≤ 84 days from having completed definitive primary breast surgery (either lumpectomy or mastectomy).
11. MammoSite® brachytherapy radiation is acceptable if it is performed immediately following surgery and prior to chemotherapy. It is recommended that chemotherapy be started no earlier than 2 weeks following the removal of the MammoSite balloon catheter.
12. Adequate hematologic function, defined by:
 - a. Absolute neutrophil count (ANC) $>1500/\text{mm}^3$
 - b. Platelet count $\geq 100,000/\text{mm}^3$
 - c. Hemoglobin >9 g/dL
13. Adequate liver function, defined by:
 - a. AST and ALT ≤ 2.5 x the upper limit of normal (ULN)
 - b. Total bilirubin ≤ 1.5 x ULN (unless the patient has grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin).
14. Adequate renal function, defined by:
 - a. Serum creatinine ≤ 1.5 x ULN
15. Complete staging work-up ≤ 12 weeks prior to initiation of study treatment with computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or bone scan. **Note:** a PET/CT is acceptable for baseline imaging in lieu of CT examinations.
16. Adequate cardiac function, defined by left ventricular ejection fraction (LVEF) value $>50\%$ (or normal per institutional guidelines) by MUGA scan or echocardiogram (ECHO).

17. Adequate recovery from recent surgery. At least 1 week must have elapsed from the time of a minor surgery (i.e., sentinel node biopsy, port-a-cath placement); at least 3 weeks must have elapsed from the time of a major surgery (i.e., lumpectomy, partial or total mastectomy, axillary lymph node dissection, breast reconstruction procedure).
18. Patients with previous history of invasive cancers (including breast cancer) are eligible if definitive treatment was completed more than 5 years prior to initiating current study treatment, and there is no evidence of recurrent disease.
19. Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days prior to start of treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately.
20. Patient must be accessible for treatment and follow-up.
21. Women of childbearing potential must agree to use an acceptable method of birth control to avoid pregnancy for the duration of study treatment and for 3 months thereafter.
22. All patients must be able to understand the investigational nature of the study and give written informed consent prior to study entry.

Exclusion Criteria

1. Women who are pregnant or breastfeeding.
2. History of previous diagnosis of invasive breast cancer (unless treated >5 years previously with no recurrence). History of previously treated ductal carcinoma in situ (DCIS) is acceptable. Patients with previous cancer (with the exception of nonmelanoma skin cancer or cervical carcinoma in situ) in the past 5 years (including invasive contralateral breast cancer) are not allowed.
3. Any evidence or suspicion of metastatic disease other than ipsilateral axillary lymph nodes.
4. Any tumor \geq T4 (cutaneous invasion, deep adherence, inflammatory breast cancer).
5. Previous anthracycline chemotherapy.
6. Concurrent use of CYP3A4 inhibitors from 72 hours prior to initiation of study treatment until the end of treatment.
7. Previous treatment for this breast cancer (including neoadjuvant chemotherapy).
8. Peripheral neuropathy (motor or sensory) of > grade 1 per NCI CTCAE at study entry.
9. Cardiac disease, including: congestive heart failure (CHF) > Class II per New York Heart Association (NYHA) classification; unstable angina (anginal symptoms at rest) or new-onset angina (i.e., began within the last 3 months), or myocardial infarction within the past 6 months; symptomatic CHF, unstable angina pectoris, cardiac arrhythmia, or cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
10. History of hypersensitivity to Cremophor[®] EL (polyoxyethylated castor oil) or a drug formulated in Cremophor[®] EL, such as paclitaxel.
11. Use of any investigational agent within 30 days of administration of the first dose of study drug.
12. Patients may not receive any other investigational or anti-cancer treatments while participating in this study.
13. Concurrent severe, uncontrolled infection or intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.
14. Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study.
15. Inability to comply with study and/or follow-up procedures.

Patients must have the following assessments performed before receiving their first dose of study drug:

- Medical history
- Physical examination, including measurements of height, weight, and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature)
- Complete blood count (CBC), including differential and platelets
- Comprehensive metabolic profile (CMP) (see Section 5.6)
- ECOG PS
- CT scan of the chest (unless lymph node-negative; see below) (this test will be performed within 12 weeks of initiation of treatment)
- CT scan of the abdomen/pelvis (unless lymph node-negative; see below) (this test will be performed within 12 weeks of initiation of treatment)
- CT scan of the head or MRI of the brain, if symptomatic (unless lymph node-negative; see below) (this test will be performed within 12 weeks of initiation of treatment)
- Bone scan (unless lymph node-negative; see below) (this test will be performed within 12 weeks of initiation of treatment)
- PET scan (this test is optional; however, if a PET scan is done, it may be substituted for the bone scan) (this test will be performed within 12 weeks of initiation of treatment)
- Serum or urine pregnancy test (for women of childbearing potential only)E
- ECG
- Measurement of LVEF using MUGA scan or echocardiogram (ECHO)
- Bilateral mammography (this test may be performed any time within 1 year of beginning treatment in this study)
- Follicle-stimulating hormone (FSH) assessment (required for women <60 years of age without a uterus, and/or women with hormone replacement therapy [HRT])
- Paraffin-embedded tumor tissue blocks, or a minimum of 5 supercharged or silanized glass slides, each containing at least one unstained, 4-micron section (to be sent to a central location for beta-3 tubulin assay); refer to the Study Reference Manual for submission guidelines
- Concomitant medications

The physical examination, ECOG PS, complete blood counts, CMP, and pregnancy test should be done <7 days prior to initiation of treatment. Baseline CT scans should be performed ≤ 12 weeks prior to initiation of treatment. **Note:** a PET/CT is acceptable for baseline imaging in lieu of CT examinations.

For lymph node-negative patients only, a chest X-ray, bone scan, and hepatic ultrasound will be accepted in place of CT scans/PET scan/MRI.

Treatment

TREATMENT ARM 1:

Cycle	1			2			3			4			Cycle	5			6			7			8		
Week	1	2	3	4	5	6	7	8	9	10	11	12	Week	13	14	15	16	17	18	19	20	21	22	23	24