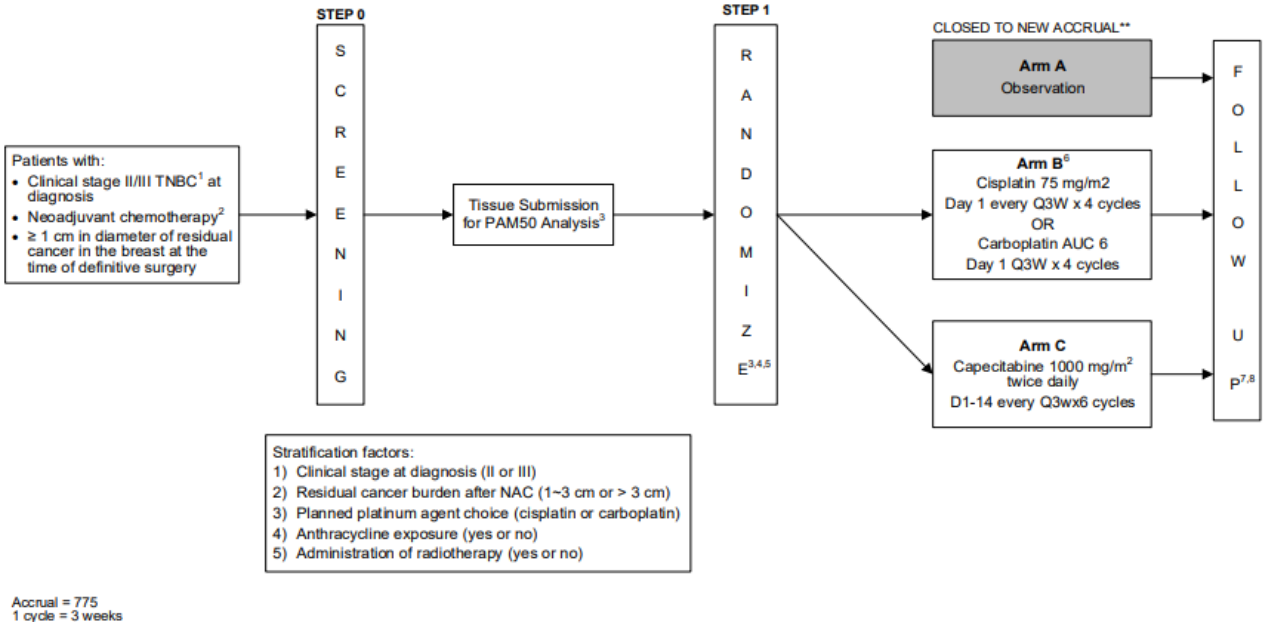
Fast Facts

EA1131: A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy vs Capecitabine in Patients with Residual Triple-Negative Breast Cancer following Neoadjuvant Chemotherapy

*Drugs are NOT provided

Schema



This study involves screening and randomization. **Tumor tissue specimen must be submitted for PAM50 analysis for stratification.**

Eligibility Criteria for Screening and Molecular Profiling (STEP 0)

1. Age ≥ 18 years.
2. ECOG Performance Status 0 or 1 within 2 weeks prior to screening.
3. Female and male patients must have histologically confirmed invasive breast cancer that meets the following criteria:
    a. Clinical stage II or III (AJCC 8th edition) at diagnosis, based on initial evaluation by clinical examination and/or breast imaging; no metastatic disease allowed
    b. ER- and PR- should meet one of the following criteria:
        i. 1 to ≤ 10% cells stain positive, with weak intensity score
        ii. ≤ 1% cells stain positive
    c. HER2 negative (not eligible for anti-HER2 therapy) will be defined as:
        i. IHC 0, 1+ without ISH HER2/neu chromosome 17 ratio OR

ii. IHC 2+ and ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells OR
iii. ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells without IHC)

NOTE: Patients that originally present with synchronous bilateral tumors are eligible provided both tumors are TNBC, and at least one of them fulfills the remainder eligibility criteria of the protocol. Multifocal or multicentric breast cancers are eligible as long as all tumors fulfill eligibility criteria.
NOTE: Patients that have a discrepancy in ER/PR/HER2 status between original diagnosis and surgical specimen (only applicable **if** ER/PR/HER2 status were repeated; repeating it is not mandatory) are eligible for study participation as long as the surgical specimens ER/PR/HER2 status fulfills eligibility criteria.

4. Patients must have received neoadjuvant taxane +/- anthracycline. Patients must NOT have received cisplatin or carboplatin or capecitabine as part of their neoadjuvant therapy regimen.
   NOTE: Patients who received preoperative therapy as part of a clinical trial may enroll.
   NOTE: Patients that were not able to complete their planned neoadjuvant chemotherapy for any reason (i.e. toxicities, etc.) are eligible to participate as long as no further systemic standard of care therapy is planned by the treating physician.
   NOTE: patients must have received a taxane for at least 1 cycle as part of their neoadjuvant therapy regimen.
5. Must have completed definitive resection of primary tumor.
   a. Negative margins for both invasive and ductal carcinoma in situ (DCIS) are desirable, however patients with positive margins may enroll if the treatment team believes no further surgery is possible and patient has received radiotherapy. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible.
   b. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable.
   c. Sentinel node biopsy either pre or post neoadjuvant chemotherapy (i.e. at the time of definitive surgery) are allowed. Axillary dissection is encouraged in patients with lymph node involvement, but is not mandatory.
6. Post neoadjuvant chemotherapy, patients must be found to have residual invasive cancer in the breast at the time of definitive surgery. Residual cancer is defined as a contiguous focus of residual invasive cancer, in the breast, measuring 1 cm in diameter, and with more than minimal cellularity, as per local pathologist determination. Please note that in patients that have multifocal or multicentric residual tumors these lesions cannot be added up; the biggest lesion has to measure 1 cm in diameter. This is required due to constraints in DNA extraction for PAM50 analysis.
   NOTE: The presence of ductal carcinoma in situ (DCIS) without invasion does not qualify as residual invasive disease in the breast.
   NOTE: Despite lymph node involvement if residual invasive cancer in the breast is < 1 cm in diameter patients are not eligible for participation.
7. Radiotherapy may be given before or after protocol treatment per standard of care guidelines. When radiotherapy is planned prior to protocol treatment administration, patients may be registered and screened while receiving radiation, and it has to be complete prior to randomization.

   Post-mastectomy radiotherapy is required for all patients with the following:

a. Primary tumor 5 cm or involvement of lymph nodes (prior to neoadjuvant chemotherapy [clinically] or at the time of definitive surgery) or involvement of lymph nodes at the time of definitive surgery.
b. For patients with primary tumors < 5 cm or without lymph node involvement prior to neoadjuvant chemotherapy and at the time of definitive surgery, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.

Radiation of regional nodal basins is at the discretion of the treating radiation oncologist.

NOTE: Breast radiotherapy (whole breast or partial) is required for patients who underwent breast-conserving therapy, including lumpectomy or partial mastectomy.

8. Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 8 weeks prior to screening for protocol therapy.
   a. Hemoglobin (Hgb) > 9.0 g/dL
   b. Platelets > 100,000 cells/mm3
   c. Absolute neutrophil count (ANC) > 1500 cells/mm3
   d. Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:
   e. Males: (140 – Age in years) × Actual Body Weight in kg 72 × Serum Creatinine (mg/dL)
   f. Females: Estimated creatinine clearance for females × 0.85
   g. Bilirubin ≤ 1.5 x ULN upper limit of normal (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)
   h. Aspartate aminotransferase (AST, SGOT) ≤ 2.5 x ULN
   i. Alanine aminotransferase (ALT, SGPT) ≤ 2.5 x ULN
9. No history of TNBC invasive breast cancer within 5 years of enrollment, no concurrent invasive malignancies except for synchronous bilateral tumors that are TNBC, skin, thyroid, or hematologic cancers with low metastic/death potential (i.e. squamous cell or basal cell skin cancers, DCIS, CLL, etc.).
10. No clinically significant infections as judged by the treating investigator.
11. Patients with active □ CTCAE v.4 grade 2 neuropathy are ineligible.
12. Adjuvant chemotherapy after surgery other than that specified in this protocol is not allowed. LHRH agonists and adjuvant bisphosphonate or denosumab use is allowed.
13. Patients must have archived formalin-fixed paraffin-embedded (FFPE) tumor tissue specimen from the residual disease on the definitive surgical specimen available for PAM50 analysis.
    a. Tumor tissue specimen from the definitive surgery has been collected and is ready to ship to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF) within 21 weeks post-surgery as indicated in Section 10.2.1.

       The EA CBPF will notify the ECOG-ACRIN Operations Office and submitting institution of receipt of the tumor tissue specimen.

       NOTE: Tumor tissue must and can be submitted any time during screening period, even if patient is getting radiation.

       NOTE: Every effort should be made to submit the tumor tissue specimen to the EA CBPF immediately.

       Date of surgery: _____

       Date tumor tissue sent to EA CBPF: _____

Eligibility Criteria for Randomization (Step 1):

Screened patients will remain on the study and be randomized if they meet the above and below following criteria. No specific timeframe between registration and randomization needs to be observed, as long as:

• After assignment of randomization patients must begin Cycle 1/ Day 1 (platinum based or capecitabine chemotherapy) within 6 weeks (30 working days) of the randomization date.
• Randomization occurs no more than 24 weeks from surgery date

1. Must have confirmation from EA CBPF of receipt of adequate quality formalin-fixed paraffin-embedded tumor tissue specimen (FFPE) of the residual disease in the breast resected at the time of definitive surgery.
2. ECOG Performance Status 0 or 1 within 2 weeks prior to randomization.
3. Radiotherapy, if applicable, may be given before or after protocol treatment. When radiotherapy is planned prior to protocol treatment administration, patients must have completed adjuvant radiotherapy ≥ 2 weeks prior to randomization for protocol therapy initiation (cycle 1/day 1).
4. Patients must have completed treatment with any investigational agent ≥ 30 days prior to randomization for protocol therapy, if applicable.
5. Patients must be randomized within 24 weeks from surgery
6. Women must not be pregnant or breast-feeding due to risk of teratogenicity/ toxicity with capecitabine or platinum based therapy. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.
    a. A female of childbearing potential is defined as any woman that has achieved menarche at some point, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
7. Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.
8. Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 2 weeks prior to randomization.
    a. Hemoglobin (Hgb) > 9.0 g/dL
    b. Platelets > 100,000 cells/mm3
    c. Absolute neutrophil count (ANC) > 1500 cells/mm3
    d. INR ≤ 3 (to be done/tested only for subjects on warfarin)
    e. Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:
    Males: (140 – Age in years) × Actual Body Weight in kg 72 × Serum Creatinine (mg/dL)
    Females: Estimated creatinine clearance for females × 0.85
    f. Bilirubin ≤ 1.5 x ULN (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)
    g. Aspartate aminotransferase (AST, SGOT) ≤ 2.5 x ULN
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Pre-Study Parameters

- History and Physical, Vital Signs and Weight, Height, ECOG Performance Status
- CBC with Differential, CMP
- Mandatory Tumor Tissue