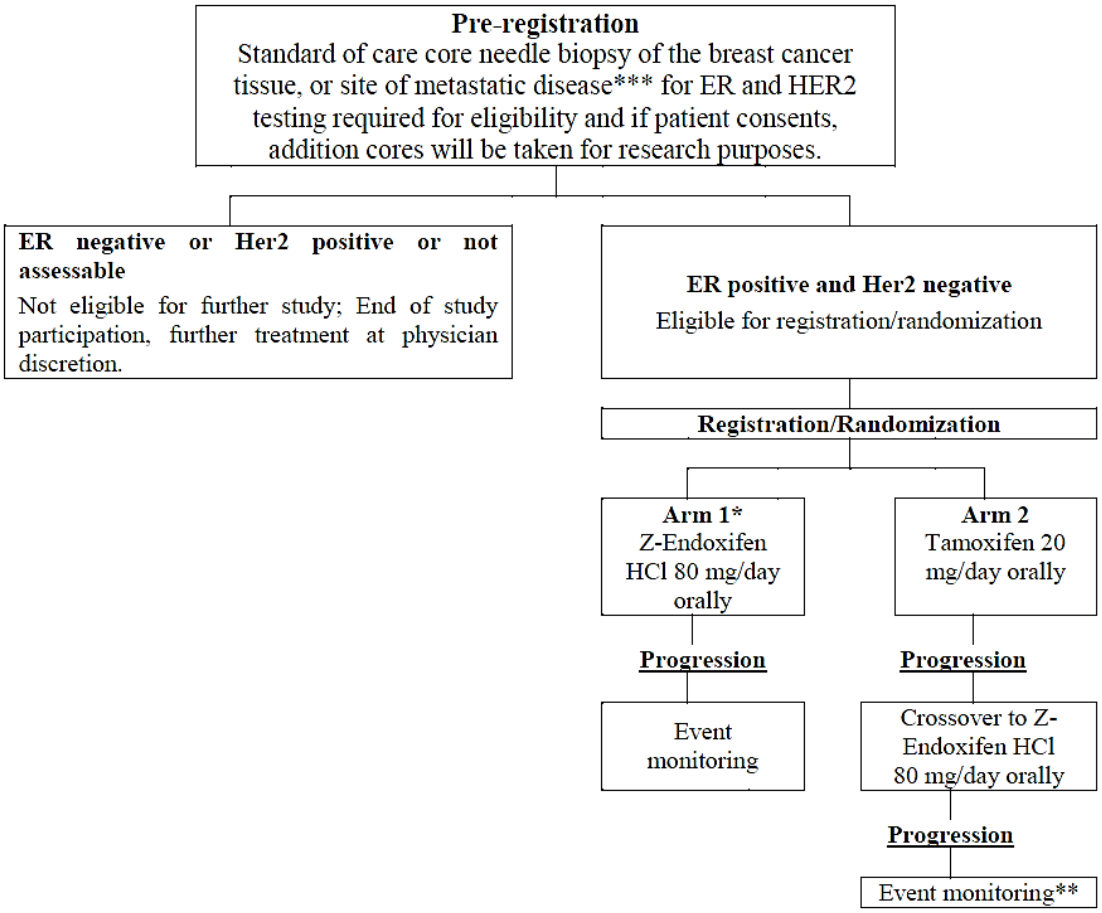
Fast Facts

Alliance A011203: A Randomized Phase II Trial of Tamoxifen vs Z-Endoxifen HCl in Postmenopausal Women with Metastatic, Estrogen Receptor Positive, HER2 Negative Breast Cancer

Schema

Treatment is to continue until disease progression or unacceptable adverse event. Patients will be followed until death, or a maximum of five years after randomization, whichever comes first.

1 Cycle = 21 days



Patient Selection

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

Pre-registration Eligibility Criteria

1. Women who agree to undergo a standard of care core biopsy of recurrent or metastatic breast cancer (see Section 6.2.2 for details of biopsy) to confirm that is ER+ (>10% nuclear staining) and HER2 negative (see Sections 3.3.5 and 3.3.6.)
2. Patient must have been previously treated with an aromatase inhibitor (either letrozole, anastrozole or exemestane) either in the adjuvant or metastatic setting, and have one of the following types of primary or secondary endocrine resistant disease.

   Primary Clinical Resistance is defined as one of the following:
   - Recurrence within the first 2 years of adjuvant endocrine therapy while on aromatase inhibitor therapy
   - Progression within first 6 months of initiating first-line endocrine therapy (either aromatase inhibitor or fulvestrant containing regimen) for the treatment of metastatic breast cancer.

   Secondary Clinical Resistance is defined as one of the following:
   - Recurrence after year 2 while receiving adjuvant aromatase inhibitor therapy, or within 12 months of completing adjuvant aromatase inhibitor therapy.
   - Progression occurring 6 or more months after initiating the first endocrine therapy for metastatic disease (either fulvestrant or aromatase inhibitor containing regimen).
3. Patients with a history of measurable disease as by the RECIST criteria (See Section 11.0) or bone only disease are eligible. Note: Those patients with non-measurable disease and bone metastases are eligible.
4. No history of tumors involving spinal cord or heart.
5. No history of visceral crisis or lymphangitic spread
6. No known brain metastases
7. Women age $\geq$ 18 years.
8. Women must be postmenopausal. Postmenopausal status is verified by:
   - Prior bilateral surgical oophorectomy, or
   - Age $\geq$ 60 years, or
   - Age < 60 with no menses for > 1 year with FSH and estradiol levels within post-menopausal range, according to institutional standard.
9. Prior treatment
   - No more than two prior chemotherapy regimens in the metastatic setting.
   - Prior treatment with an aromatase inhibitor (either anastrozole, letrozole or exemestane), either in the adjuvant or metastatic setting is required.
   - Unlimited prior endocrine regimens in the metastatic setting, which may have included everolimus or a CDK4/6 inhibitor (such as palbociclib, abemaciclib or ribociclib) containing regimens.
   - Prior tamoxifen treatment is allowed in the adjuvant setting, but patients must not have experienced relapse within 1 year of stopping tamoxifen.
   - No prior treatment with tamoxifen in the metastatic setting.
   - No prior treatment with endoxifen.
   - Patients who have not fully recovered from acute, reversible effects of prior therapy regardless of interval since last treatment are not eligible to participate in this study. EXCEPTION:

Neuropathies – if grade 2 neuropathies have been stable for at least 3 months since completion of prior treatment patient is eligible.
- Not receiving any medications or substances that are strong inhibitors of CYP2D6 (see Appendix II).

10. Not receiving any other investigational agents.
11. No uncontrolled intercurrent illness including, but not limited to:
    - ongoing or active infection
    - symptomatic congestive heart failure
    - unstable angina pectoris
    - uncontrolled symptomatic cardiac arrhythmia
    - Uncontrolled hypertension (defined as blood pressure > 160/90)
12. None of the following co-morbid conditions:
    - Cataracts of grade 2 or greater as per CTCAE Version 4.0
    - Retinopathy of grade 2 or greater as per CTCAE Version 4.0
    - Note: Patients that have cataracts that do not require surgery are eligible.
    - DVT/PE within the past 6 months

    Note: Patients that are on anticoagulant therapy for maintenance are eligible as long as the DVT and /or PE occurred > 6 months prior to enrollment, and there is no evidence for active thrombosis (either DVT or PE).
13. No other active second malignancy other than non-melanoma skin cancers within 3 years of pre-registration. A second malignancy is not considered active if all treatment for that malignancy is completed and the patient has been disease-free for at least 3 years prior to pre-registration.
14. ECOG Performance Status: 0-2
15. Able to swallow oral formulation of the study agent.
16. Required Initial Laboratory Values:
    - Hemoglobin > 9 g/dL
    - Platelet Count ≥ 75,000/mm3
    - Creatinine < 1.5 x upper limits of normal ULN
    - Total Bilirubin ≤ 1.5 x upper limits of normal (ULN)
    - AST ≤ 2.5 x upper limits of normal (ULN)
    - For patients with liver metastasis: < 5 x upper limits of normal (ULN)

Registration Eligibility Criteria

Registration must be completed within 28 days of Pre-registration

1. Patients with either measurable disease as defined by RECIST criteria (See Section 11.0) or bone only disease are eligible. Note: Those patients with both non-measurable disease and bone metastases are eligible.
    - Non-measurable bone only disease: Non-measurable bone only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft-tissue component, or mixed lytic-blastic bone lesions without a measurable soft-tissue component.
    - Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability previously described.
2. No tumors involving spinal cord or heart.

3. No visceral crisis, lymphangitic spread or known brain metastases: Visceral crisis is not the mere presence of visceral metastases, but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of disease.
4. Histologic confirmation, from the A011203 Pre-registration biopsy, by institutional/local pathologist of either locally advanced or metastatic breast cancer that is estrogen receptor positive and HER2 negative.
   Those patients with bone only disease with either no tumor or insufficient tumor for ER/PR and HER2 staining after the bone biopsy are still eligible to participate in this study.
5. Estrogen receptor positive disease is defined as > 10% nuclear staining.
6. HER2 Negative Disease as per 2013 ASCO/CAP guidelines, one of the following must apply:
   1) 0 or 1+ by IHC and not amplified by ISH
   2) 0 or 1+ by IHC and ISH not done
   3) 2+ by IHC and not amplified by ISH or
   4) IHC not done and not amplified by ISH
7. None of the following therapies are allowed prior to registration*:
   - Chemotherapy ≤ 2 weeks
   - Immunotherapy ≤ 2 weeks
   - Biologic therapy ≤ 2 weeks
   - Hormonal therapy ≤ 2weeks
   - Monoclonal antibodies ≤ 2 weeks
   - Radiation therapy ≤ 2 weeks
   - Anti-Her-2 or other "targeted" (e.g. mTOR) therapy ≤ 2 weeks
     Note: Any toxicities derived from these therapies must be < grade 2 prior to starting study therapy.

Pre-Study Parameters

- History and physical, PS, Weight, Height, Vitals
- Registration Fatigue/Uniscale assessment
- Standard of care breast tissue biopsy is required for determination of ER, PR and HER2 in metastatic disease specimen
- CBC/Diff/Platelets, CMP, Fasting lipid profile, Phosphorus,
- CT/MRI, Bone Scan