



# Alliance A011106: Alternate Approaches for Clinical Stage II or III Estrogen Receptor Positive Breast Cancer Neoadjuvant Treatment (ALTERNATE) in Postmenopausal Women: A Phase III Study

Cynthia X. Ma, MD, PhD

Washington University School of Medicine

TAP TO RETURN TO KIOSK MENU

## Rationale

### Rationale

- Objective
- Study Schema
- Treatment Plan
- Key Eligibility Criteria
- Biopsy/Shipment Kit
- CLIA Ki67 Analysis
- Follow Up

Please use the headings above to navigate through the different sections of the poster

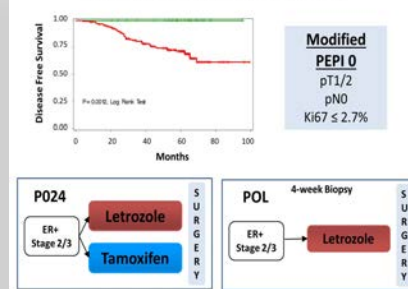
- Neoadjuvant endocrine therapy (ET) improves breast conservation rate, and importantly offers an opportunity for individualized assessment of tumor responsiveness to ET to guide subsequent treatment.
- Previous neoadjuvant ET trials demonstrated that pathologic tumor size (pT), axillary lymph node status (N), and tumor Ki67 value at surgery predicted risk of relapse (Ellis MJ, et al, JNCI 100: 1380-8).

- Preoperative endocrine prognostic index (PEPI) was therefore developed to assign risk scores based on these factors.
- Modified PEPI excludes ER

Preoperative Prognostic Index (PEPI)				
Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
<b>Tumor Size</b>				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
<b>Node status</b>				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
<b>Ki67 level</b>				
0–2.7%	—	0	—	0
>2.7–7.3%	1.3	1	1.4	1
>7.3–19.7%	1.7	1	2.0	2
>19.7–53.1%	2.2	2	2.7	3
>53.1%	2.9	3	3.8	3
<b>ER, Allred score</b>				
0–2	—	0	—	0
3–8	2.8	3	7.0	3

- Modified PEPI 0, defined by pT1-2, N0 Ki67 ≤ 2.7%, was associated with extremely low risk of recurrence without adjuvant chemotherapy (Fig 1).

Fig 1. Modified PEPI (Data from P024 and POL trial) median F/U 62.5 mons (Modified PEPI 0: n=29)



- P024: A randomized double-blind multicenter study of tamoxifen vs letrozole in postmenopausal women with ER and/or PR positive primary untreated breast cancer
- POL: PreOperative Letrozole trial: A multicenter phase II trial of letrozole in postmenopausal women with clinical stage II or III hormone receptor positive breast cancer
- In addition, high Ki67 post 2-4 weeks (wk) of neoadjuvant ET identified resistant tumors with poor outcome in previous neoadjuvant trials (Table 2).

4w Ki67	% PEPI 0	RFS (events) median F/U 5 years
>10%	1/19 (5%)	8/21 (38%)
≤10%	10/36 (28%)	3/45 (7%)
P Value	P=0.08 (Fisher)	P=0.003



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### Objective

#### Primary Objectives

- Compare neoadjuvant anastrozole and fulvestrant, alone or in combination, in achieving modified PEPI 0 (1<sup>st</sup> Phase)
- Validate the 5-year RFS rate in patients with a modified PEPI score of 0 is more than 90% (2nd Phase)

#### Secondary Objectives

- RFS in pts with PEPI 0
- RFS in pts with endocrine resistant tumors: Ki67 >10% (4 wk or 12 wk) or modified PEPI non-0
- Surgical outcome, clinical and radiological response, and safety profile
- pCR rate in the neoadjuvant chemotherapy in pts with 4-wk or 12-wk Ki67>10%

#### Correlative Science Objectives

- Compare the degree of Ki67 suppression at wk 4 among the three neoadjuvant endocrine therapy regimens
- Correlate degree of week 4 Ki67 suppression with modified PEPI 0 rate and RFS
- Examine the impact of post-neoadjuvant ER level on RFS

- Examine pathologic tumor stage (T1 vs T2) on RFS in modified PEPI 0 group
- Correlate gene expression and mutation profiles with Ki67 response and RFS
- Assess the pCR/RCB-1 rate post neoadjuvant chemotherapy in endocrine resistant population
- Evaluate Cycle 1, day 2 tumor biopsy following the initiation of paclitaxel for early molecular markers of response
- Examine tumor, serum, and plasma specimens to understand endocrine and chemotherapy resistance mechanisms.
- Genomic analysis, including whole exome and RNA Sequencing, of tumors with 4-week Ki67>10% vs <10% to achieve the following aims:
  - Develop a mutation based classification of ER+ BC predictive of treatment responsiveness
  - Druggable genome analysis for the endocrine resistant population



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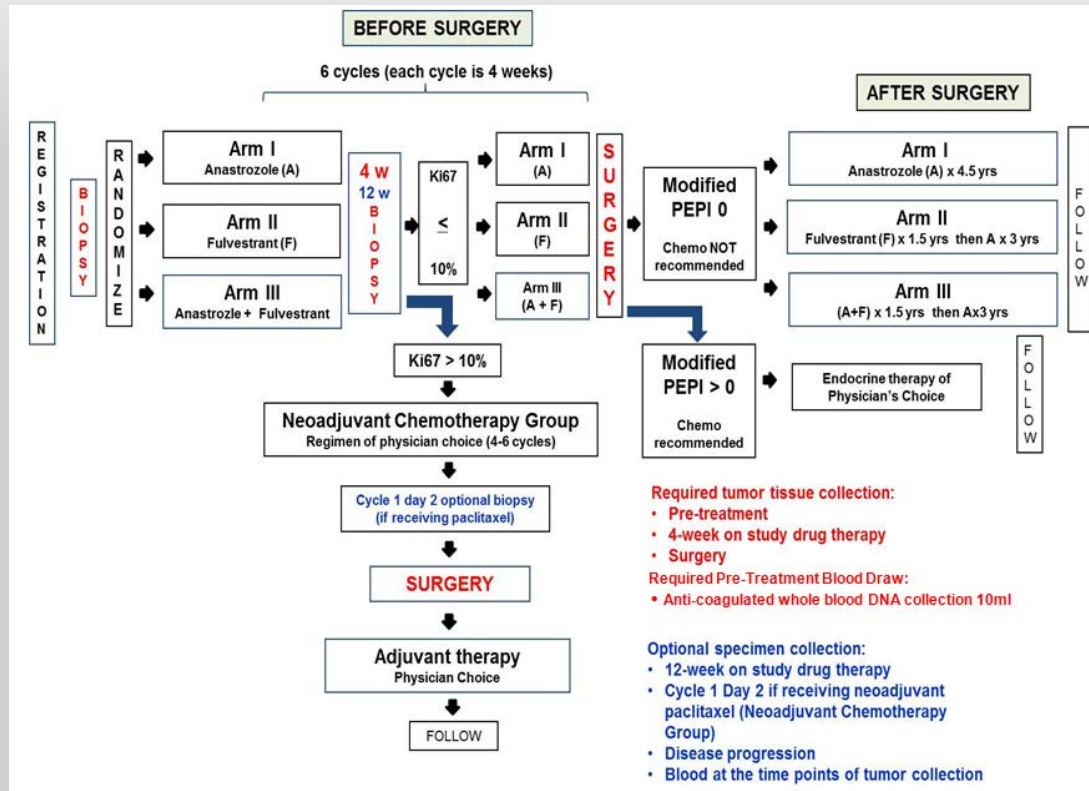
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### Sample Size and Statistics

**Sample size:** N = 1455, including 1275 (n=425 each arm) during the first phase enrollment plus an additional 180 patients to be enrolled to the anastrozole arm after first phase enrollment.

#### First Phase

- To determine whether the modified PEPI 0 rate in one or both of the fulvestrant containing arms exceeds that of anastrozole by at least 10%, assuming:
  - ✓ 0% modified PEPI 0 rate in the anastrozole arm
  - ✓ one sided alpha 0.025 chi-square test, power 84%

**Upon completion of the first phase enrollment, the anastrozole arm will continue to enroll an additional 180 patients while the fulvestrant containing arms will stop.**

#### Second Phase

- To validate the 5-year RFS is over 90% for pts with modified PEPI 0 in the anastrozole arm and to assess the point and interval estimate of the 5-year RFS in the patients treated with fulvestrant or fulvestrant plus anastrozole.
- A sample size of 150 (25%) to 210 (35%) pts with modified PEPI 0 are expected in the Anastrozole arm with:
  - ✓ one-sided alpha=0.025 nonparametric Brookmeyer-Crowley type one sample survival test and a power between (80.0% to 88.4%) to reject that the 5 year RFS rate is at most 90% in patients treated with anastrozole who have endocrine sensitive disease when the true 5 year RFS rate in this patient population is at least 95%.



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### Key Eligibility Criteria

#### Key Inclusion Criteria:

- Postmenopausal women, ECOG PS 0-2
- Clinical T2-T4c, any N, M0, invasive breast cancer
- ER positive (Allred score 6-8 or in at least 66% tumor cells), HER2 negative
- Must agree to required research samples at baseline, week 4 and surgery
- Primary tumor must be:
  - Palpable
  - It's largest diameter is > 2.0 cm by physical examination or by radiological assessment
  - Bi-dimensional measurement by tape, ruler or caliper technique must be provided

#### Key Exclusion Criteria:

- An excisional biopsy of this breast cancer
- Surgical axillary staging procedure prior to study entry except FNA or core biopsy of LN
- Treatment for this cancer, including surgery, radiation, chemotherapy, hormonal therapy or investigational agent prior to study entry
- History of invasive breast cancer or DCIS
- Contralateral DCIS

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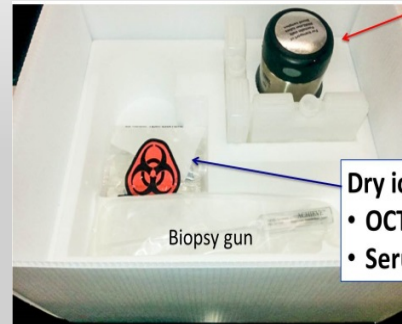
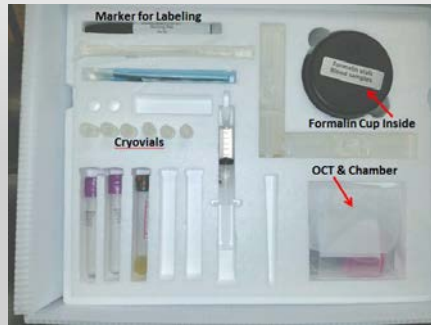
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### Biopsy/Shipment Kit



#### Room temperature shipping

- Formalin cup
- EDTA whole blood

#### Dry ice shipping for frozen samples

- OCT frozen tissue blocks
- Serum, plasma cryovials

The Biopsy/Shipment Kit allows shipping of both frozen and ambient kit requests should be done through BIOMS

### Education Activities

#### CTSU websites ([www.ctsu.org](http://www.ctsu.org))

- Patient Brochure and Investigator Education Material
  - Monthly Study Coordinator Teleconferences
- Dial-In: 1-800-501-8979 | Access Code: 2548435
- 1 pm CST the third Thursday of the month
- Monthly Newsletter



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### Central CLIA Ki67 Analysis

#### **Ki67 Immunohistochemistry**

- Centrally performed at the Washington University Anatomic and Molecular Pathology (AMP) Core Labs (CLIA number 26D2013203)
- Standard SOP for Ki67 staining
- FDA approved CONFIRM anti-Ki67 rabbit monoclonal antibody (clone 30-9) and reagents
- FDA approved Ventana Benchmark XT platform

#### **Ki67 Scoring**

- Pathologist guided image analysis using VIRTUOSO software
- FDA approved VENTANA Companion Algorithm Ki67 (30-9) image analysis and VENTANA iScan Coreo Au scanner running VIRTUOSO software
- Point counting in selected cases

#### **Ki67 Reporting**

- Ki67 results for 4w and 12w biopsies and surgery resection slides are reported real time for therapeutic decision makings on the trial.
- Ki67 reports are emailed or faxed to the study coordinator within 2 weeks after receiving the specimen.
- Contact Specimen Coordinator (e-mail: [alternatetrial@dom.wustl.edu](mailto:alternatetrial@dom.wustl.edu)) to track your samples.

#### **Ki67 Assay Validation**

- Sanati, S., et al, Validation of the Preoperative Endocrine Prognostic Index in ACOSOG (Alliance) Z1031 neoadjuvant aromatase inhibitor trial.
- SABCS 2014, Program number: P4-11-13, Poster: 1096; Dec 12, 7 am to 9 am



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