ALTernate approaches for clinical stage II or III **E**strogen **R**eceptor positive breast cancer **N**eo**A**djuvant Tr**E**atment (**ALTERNATE**) in postmenopausal women: A Phase III Study (A011106)

Protocol version Update #2

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ALTERNATE Schema

Eligibility

Post-menopausal
Clinical Stage II or III
ER+ (Allred 6-8) HER2-

REGISTRATION

BIOPSY

RANDOMIZE

BEFORE SURGERY

6 cycles (each cycle is 4 weeks)

- Arm I
- Arm II
- Arm III

4w
12 w
BIOPSY

Ki67 ≤10%

- Arm I
- Arm II
- Arm III

Ki67>10%

Neoadjuvant Chemotherapy Group
Chemotherapy (4-6 cycles)

Cycle 1 day 2 optional biopsy
(if receiving paclitaxel)

SURGERY

AFTER SURGERY
Therapy of Physician Choice

FOLLOW

SURGERY

AFTER SURGERY

Modified PEPI 0
Chemo NOT recommended

- **Arm I** A x 4.5 yrs
- **Arm II** F x 1.5 yrs then A x 3 yrs
- **Arm III** (A+F) x 1.5 yrs then Ax3 yrs

FOLLOW

Modified PEPI > 0
Chemo recommended

- Endocrine therapy of Physician's Choice

FOLLOW

Arm I: Anastrozole (A)
Arm II: Fulvestrant (F)
Arm III: Anastrozole + Fulvestrant

Red: required tissue collection
Blue: optional tissue collection

Primary Endpoints:
1st Phase: Modified PEPI 0 rate
2nd Phase: RFS in Modified PEPI 0

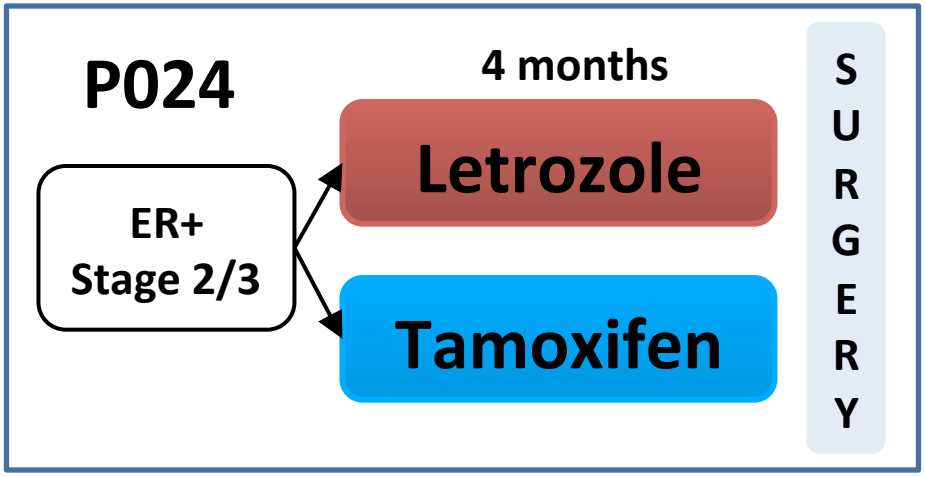
Sample size: n=2820
1st phase: n=400 each arm
2nd phase: n=540 each arm

Background

- Preoperative Prognostic Index (PEPI)
- Use of Ki67 as an early marker of endocrine therapy resistance
- Rationale to test fulvestrant with or without anastrozole

Predictors of Long-term Outcome in P024 Trial

Multivariable analysis of post-neoadjuvant surgical specimens on RFS and BCSS in P024 trial				
Post-therapy factors	RFS		Breast Cancer Specific Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor stage (T1/2 vs T3/4)	2.8 (1.4 to 5.4)	.003	4.4 (1.7 to 11.2)	.002
Node status (pos vs neg)	3.2 (1.5 to 6.9)	.004	3.9 (1.1 to 13.7)	.04
Ki67 level per 2.7-fold increase	1.3 (1.1 to 1.6)	.003	1.4 (1.07 to 1.9)	.01
ER, Allred score (0,2 vs 3-8)	2.8 (1.2 to 6.4)	.02	7.0 (2.4 to 20.9)	<.001



Ellis MJ, Tao Y, Luo J, et al: Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 100:1380-8, 2008

PEPI Score

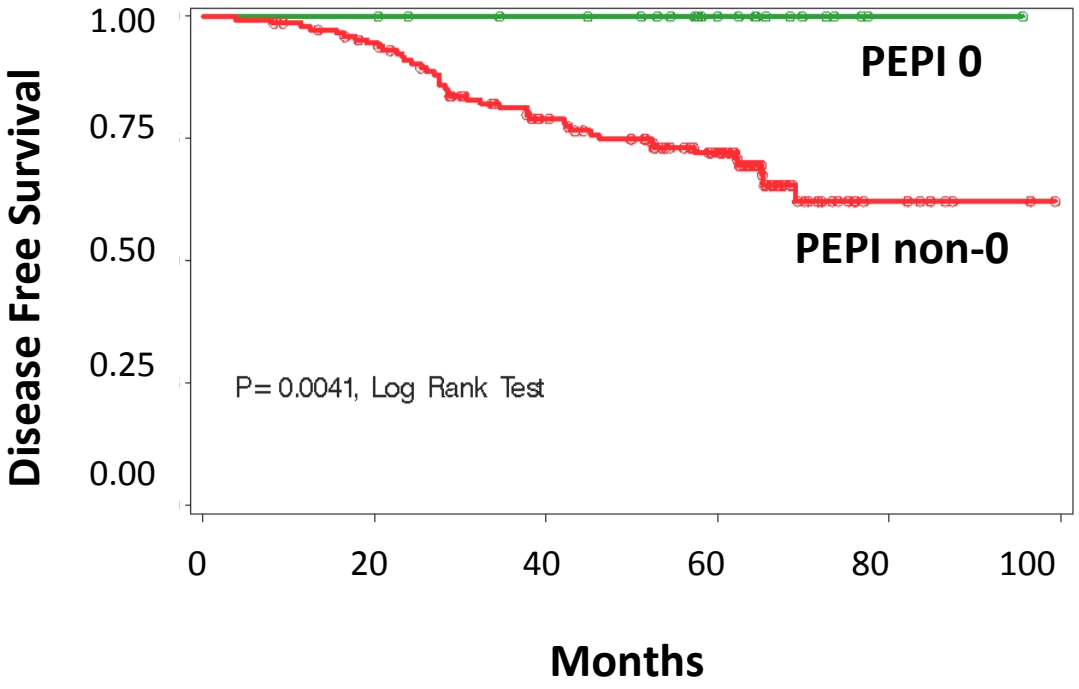
Preoperative Prognostic Index (PEPI)				
Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Tumor Size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0–2.7%	—	0	—	0
>2.7–7.3%	1.3	1	1.4	1
>7.3–19.7%	1.7	1	2.0	2
>19.7–53.1%	2.2	2	2.7	3
>53.1%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

Modified PEPI excludes ER

PEPI score was developed using results of PO24 trial to assess the risk of relapse based on pathologic tumor size, lymph node status, Ki67 level, and ER status of surgery specimen post neoadjuvant endocrine therapy.

Ellis MJ, et al, J Natl Cancer Inst 100:1380-8, 2008

PEPI 0 Predicts Disease Free Survival



In the combined analysis of P024 and POL, no relapses were observed during a median F/U of 5 years in patients with PEPI 0 after neoadjuvant endocrine treatment.
(unpublished data from Matthew Ellis)

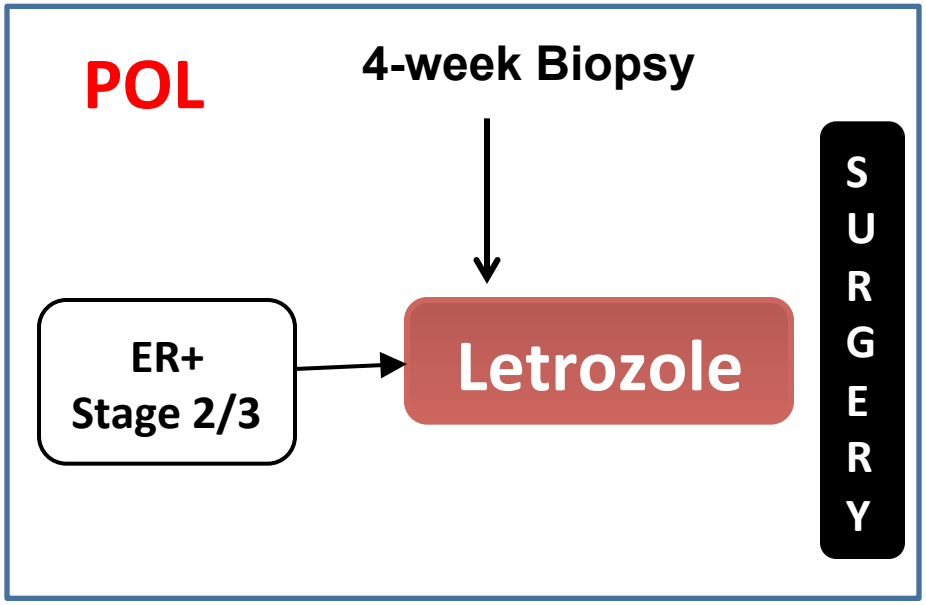
P024 trial: A randomized phase IIb-III double blind trial of neoadjuvant letrozole vs tamoxifen in postmenopausal women with clinical stage II or III ER+ breast cancer *Eiermann, et al, Ann Oncol 2001, 12(11):1527-1532.*

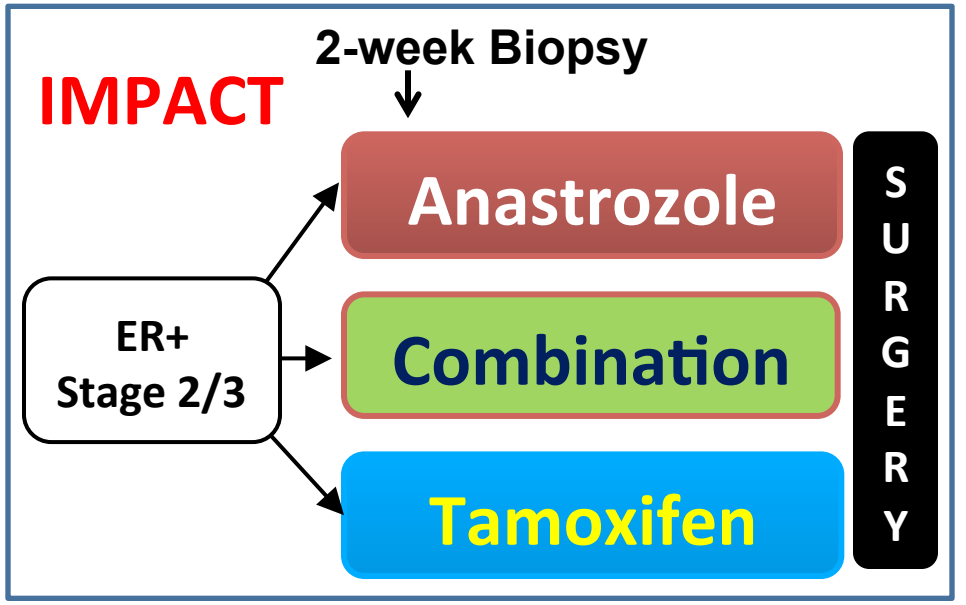
POL: A single arm phase II trial of neoadjuvant letrozole in postmenopausal women with clinical stage II or III ER+ breast cancer *Olson JA, et al J Am Coll Surg 2009,* ***208****(5):906-914; discussion 915-906.*

2-4 Wk Ki67 10% Cutpoint Predicted RFS in IMPACT and POL

POL 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

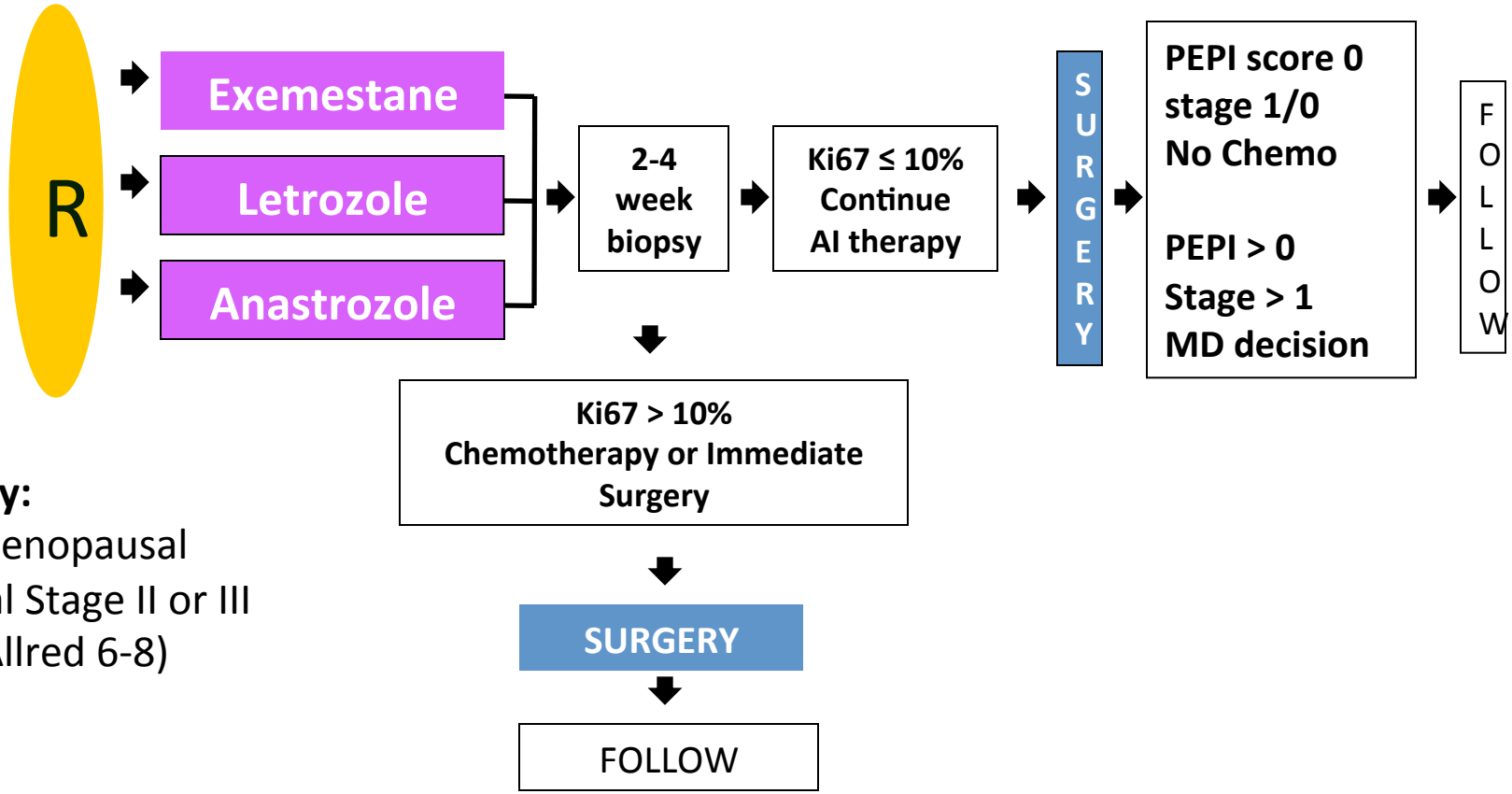
IMPACT 2W Ki67	% PEPI 0	RFS (events), median F/U 37 months
>10%	0/32 (0%)	9/35 (26%)
≤10%	21/101 (21%)	13/118 (11%)
P Value	P=0.004 (Fisher)	P=0.008 (log rank)





Data from Matthew Ellis

ACOSOG Z1031 Cohort B

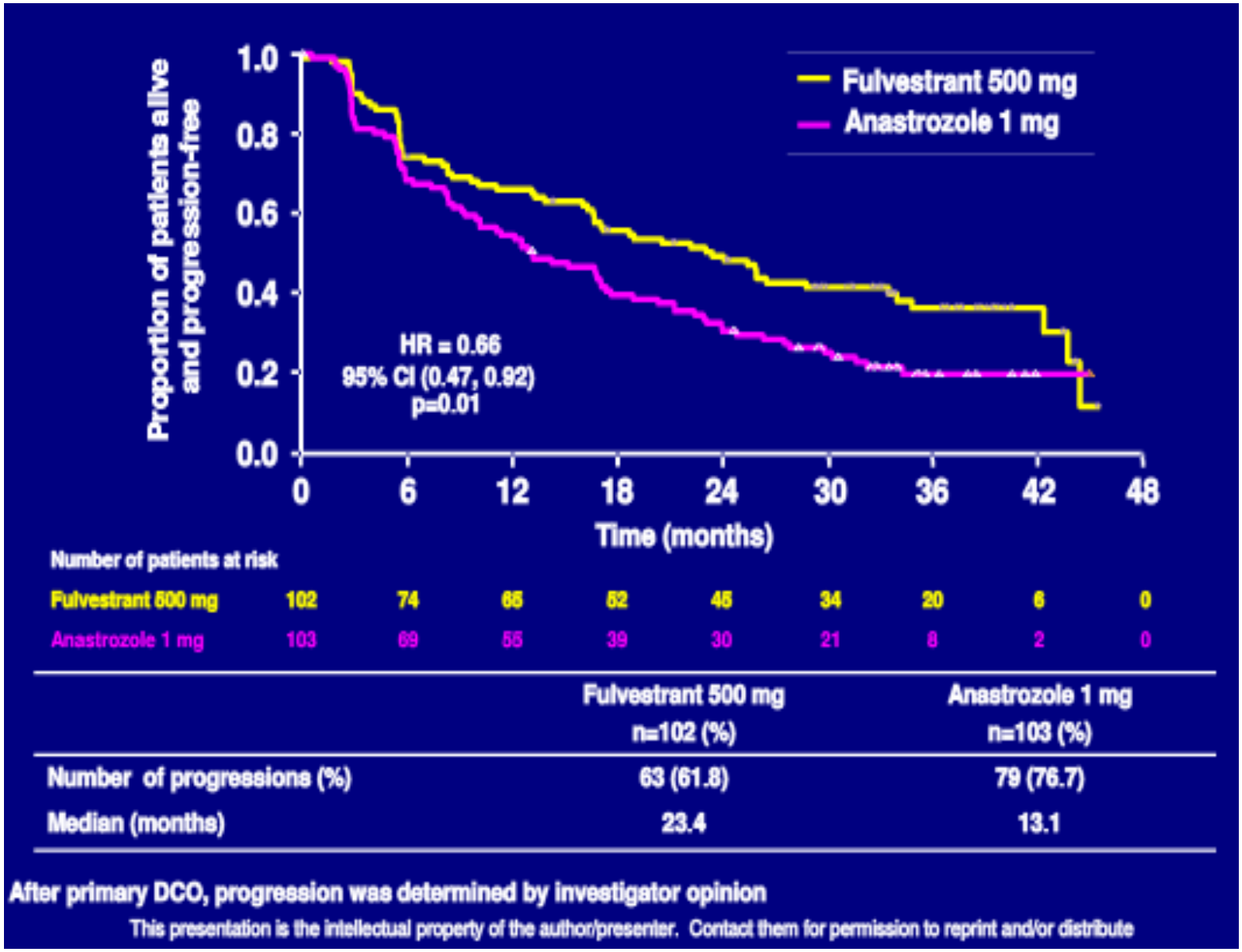


Eligibility:

- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-

This trial demonstrated the feasibility of using 2-4 week Ki67 and PEPI sore at surgery to tailor subsequent treatment.

Rationale to Study Fulvestrant



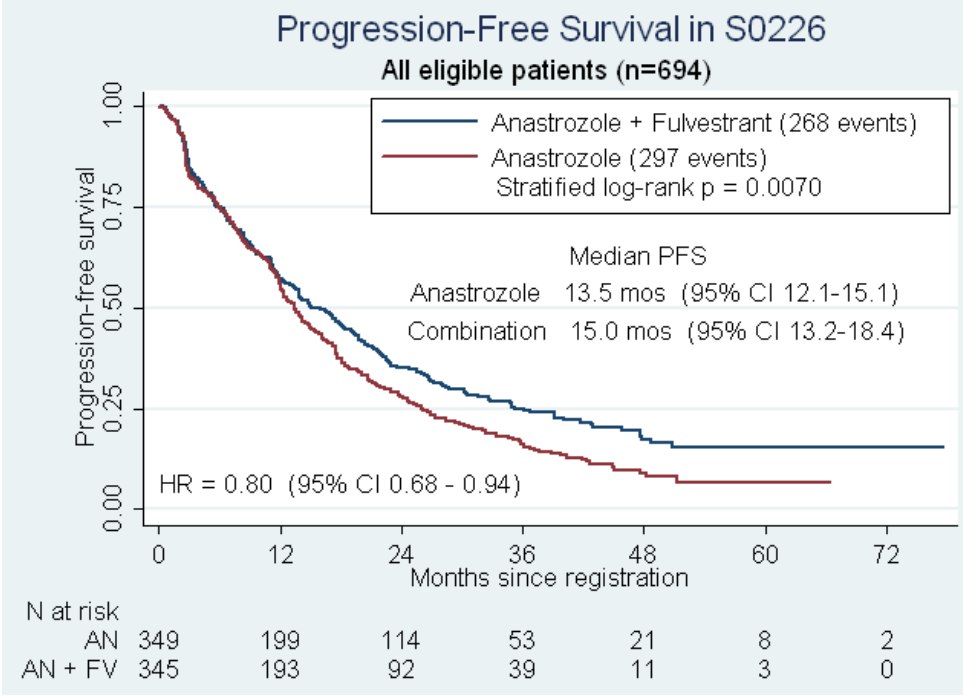
	Fulvestrant 500 mg n=102 (%)	Anastrozole 1 mg n=103 (%)
Number of progressions (%)	63 (61.8)	79 (76.7)
Median (months)	23.4	13.1

After primary DCO, progression was determined by investigator opinion

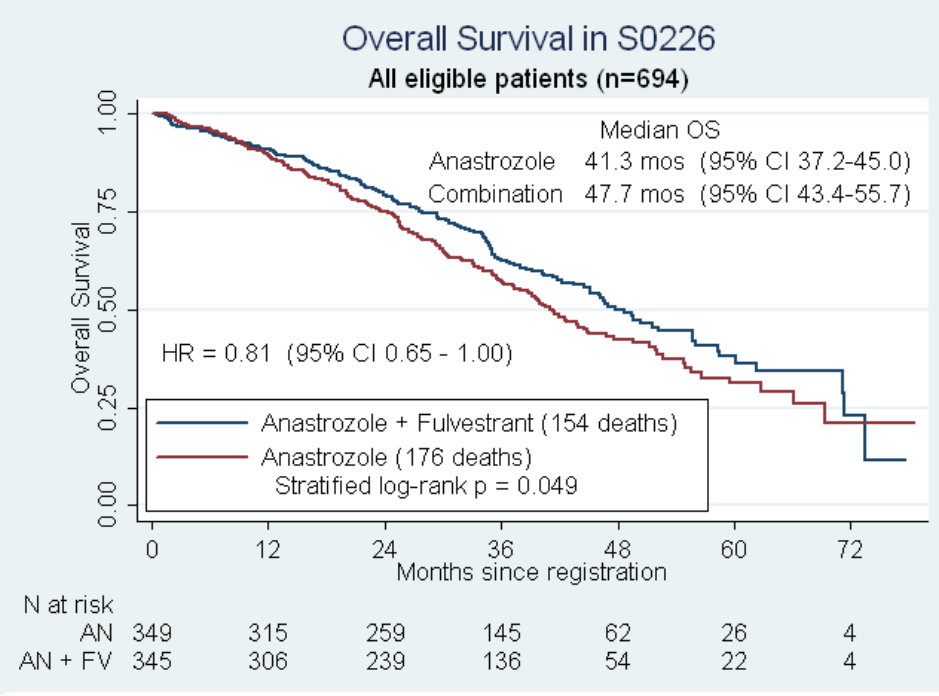
Data in the advanced disease setting suggested superiority of fulvestrant (FIRST trial) *(Robertson, J.F., et al., Breast Cancer Res Treat, 2012. **136**(2): p. 503-11.)*

Rationale to Study Fulvestrant + Anastrozole

PFS



OS



*Mehta, R.S., et al., The New England journal of medicine, 2012. **367**(5): p. 435-44.*

Data in the advanced disease setting suggested fulvestrant in combination with anastrozole (S0226 trial) maybe superior than anastrozole for endocrine naïve ER+ cancer.

Primary Objectives

- To compare the efficacy of three neoadjuvant endocrine therapy regimens in achieving modified PEPI 0 (1st Phase)
  - Anastrozole alone
  - Fulvestrant alone
  - Fulvestrant/Anastrozole combination
- To demonstrate the 5-year RFS rate in patients with a modified PEPI score of 0 is at least 95% (2nd Phase)
  - Anastrozole alone
  - Fulvestrant alone (if efficacy superior than anastrozole in the 1st Phase analysis)
  - Fulvestrant/Anastrozole combination (if efficacy superior than anastrozole in the 1st Phase analysis)

Study Objectives

Primary Objectives

- To compare the efficacy of three neoadjuvant endocrine therapy regimens in achieving modified PEPI 0 (1st Phase)
  - Anastrozole alone
  - Fulvestrant alone
  - Fulvestrant/Anastrozole combination
- To demonstrate the 5-year RFS rate in patients with a modified PEPI score of 0 is at least 95% (2nd Phase)
  - Anastrozole alone
  - Fulvestrant alone (if efficacy superior than anastrozole in the 1st Phase analysis)
  - Fulvestrant/Anastrozole combination (if efficacy superior than anastrozole in the 1st Phase analysis)

Secondary Objectives

- To assess 5-year RFS in patients with PEPI score of 0
- To examine differences in surgical outcome, clinical and radiological response rates, and safety profile of three neoadjuvant endocrine therapy regimens
- To examine pCR rate of neoadjuvant paclitaxel in patients with 4-week or 12-week Ki67>10%
- To examine pCR rate of standard neoadjuvant chemotherapy in patients with 4-week or 12-week Ki67>10%
- To summarize the frequency of severe adverse events encountered with neoadjuvant paclitaxel
- To assess RFS for patients with endocrine resistant tumors
  - 1) Ki67 >10% at week 4
  - 2) Ki67 >10% at week 12
  - 3) modified PEPI score of non-zero

Correlatives Science Objectives

- To compare the degree of Ki67 suppression at week 4 among the three neoadjuvant endocrine therapy regimens
- To examine the impact of post-neoadjuvant ER level on RFS
- To examine pathologic tumor stage (T1 vs T2) on RFS in modified PEPI 0 group
- To correlate degree of week 4 Ki67 suppression with modified PEPI 0 rate and RFS
- To correlate gene expression and mutation profiles with Ki67 response and RFS
- To assess the pCR/RCB-1 rate post neoadjuvant chemotherapy in endocrine resistant population (Ki67>10% at week 4 or 12)
- To evaluate Cycle 1, day 2 tumor biopsy following the initiation of paclitaxel to develop early molecular markers of response
- To evaluate tumor tissue, serum, and plasma specimens for biomarker discovery that aim to understand signaling pathways associated with endocrine therapy and taxane therapy sensitivity and resistance
  - Genomic analysis of tumors with 4-week Ki67>10% vs <10%

Eligibility Criteria

Key Inclusion Criteria

- Postmenopausal women
- Clinical T2-T4c, any N, M0 invasive breast cancer
  - Patients with multifocal invasive breast cancer are not eligible
- Invasive breast cancer is ER+ with an Allred score of 6, 7 or 8 and HER2 negative defined as 0 or 1+ by IHC or with a FISH ratio (HER2 gene copy/chromosome 17) < 2 if IHC 2+.
- ECOG performance status 0-2
- Must agree to undergo the required research biopsies at baseline, week 4 and at surgery.

Please refer to the Protocol Section 4 for a full description of the Eligibility Criteria

Key Exclusion Criteria

- An excisional biopsy of this breast cancer
- Surgical axillary staging procedure prior to study entry

  Note: FNA or core needle biopsy of axillary node is permitted
- Treatment for this cancer including surgery, radiation therapy, chemotherapy, biotherapy, hormonal therapy or investigational agent prior to study entry
- History of invasive breast cancer or contralateral DCIS

Please refer to the Protocol Section 4 for a full description of the Eligibility Criteria

Correlative Sample Collections

- Required tumor collection
  - Pre-treatment
    - 4 cores: 2 formalin fixed, 2 immediately frozen in OCT
  - 4-week
    - 4 cores: 2 formalin fixed, 2 immediately frozen in OCT
  - Surgery post 6 cycles of neoadjuvant endocrine therapy
    - 4 cores collected at surgery (2 formalin fixed, 2 immediately frozen in OCT)
    - 10 Superfrost Plus slides after surgery
  - Surgery post neoadjuvant chemotherapy
    - 4 cores: 2 formalin fixed, 2 immediately frozen in OCT

Please refer to the Protocol Section 7 for a full description on specimen submission

Correlative Sample Collections

- Optional tumor collection
  - 4 cores: 2 formalin fixed, 2 immediately frozen in OCT
  - 12-week on neoadjuvant endocrine therapy if clinical response is less than Partial Response (PR)
  - Cycle 1 day 2 on neoadjuvant paclitaxel
  - At disease progression at surgery
- Optional blood collection at the time point of tumor collection

Please refer to the Protocol Section 7 for a full description on specimen submission

Biopsy/Shipment Kit

- Biopsy/shipment Kit (provided)
  - 1 formalin containing cup
  - 2 OCT chamber with OCT included for frozen cores
  - Blood collection tube
    - One 10 cc red top tube (or other “clot-tube”) for serum
    - Two 10 cc EDTA tube (1 for plasma and 1 for DNA)
    - Cryovials
  - 14-G biopsy gun (Achieve)
- Two chamber that allows shipping of both frozen and ambient

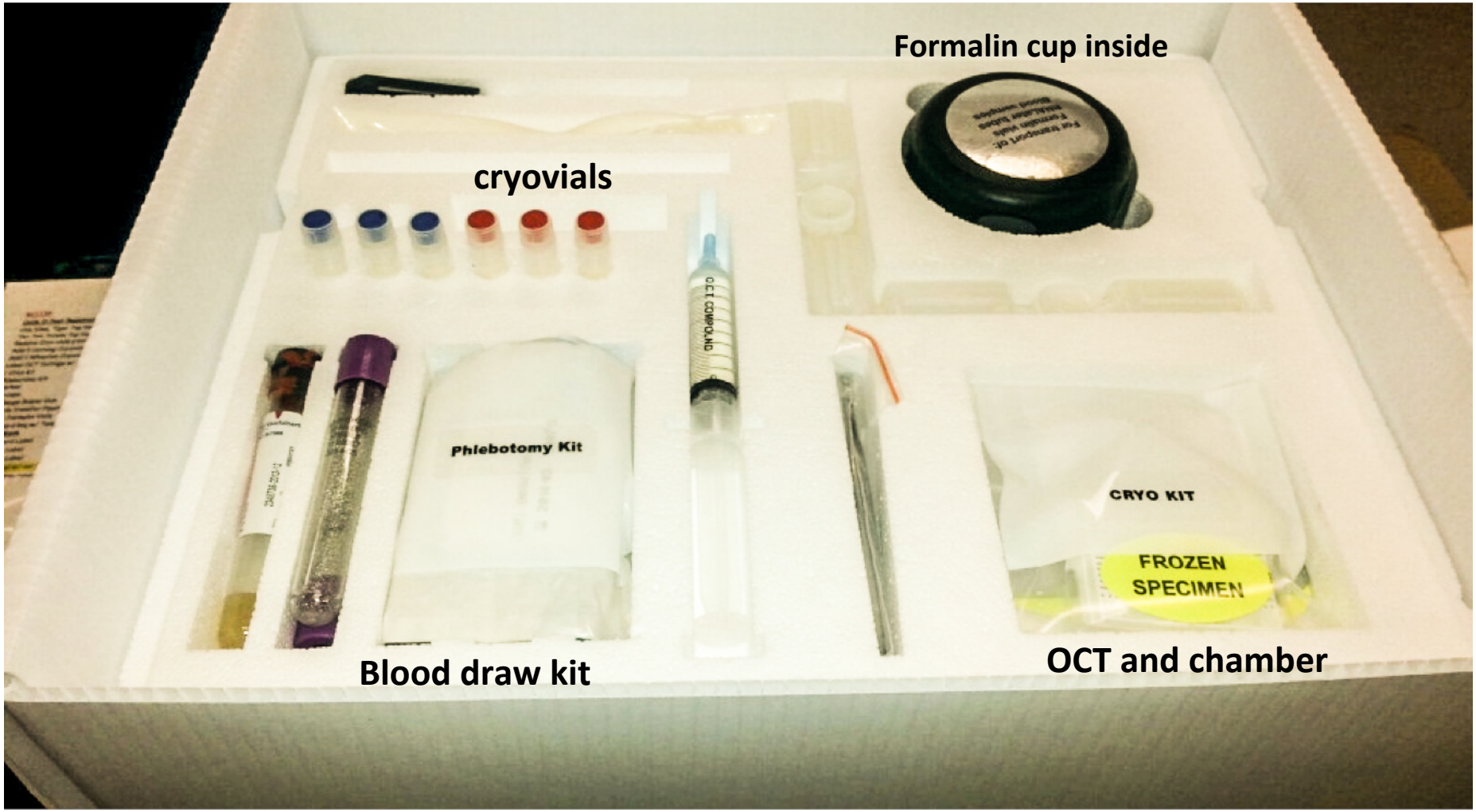
Please refer to the Protocol Section 7 for a full description on specimen submission

Sample Processing

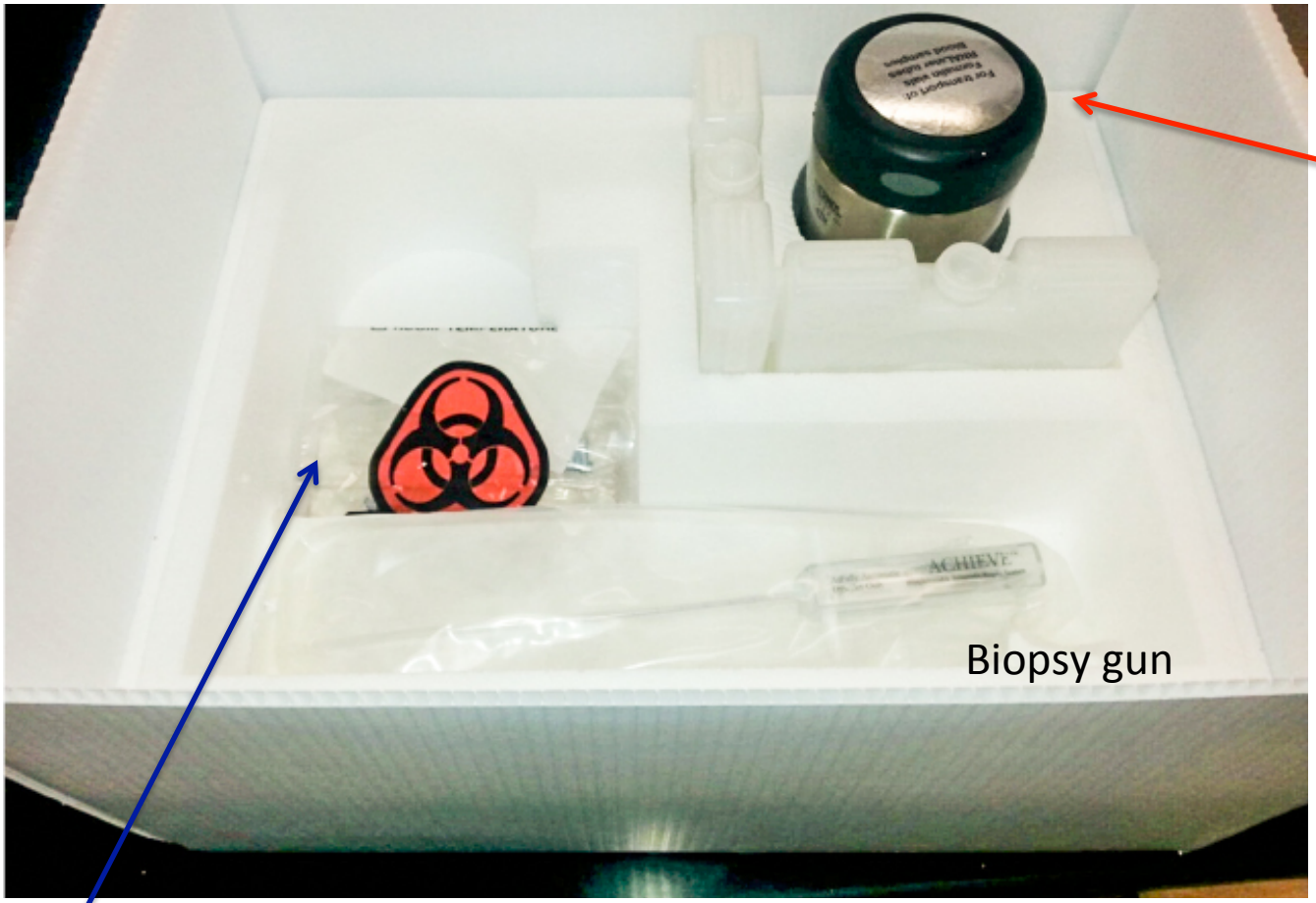
- Tumor cores:
  - Place 2 cores in 1 formalin cup, at room temperature
  - Place 2 cores in 2 separate OCT blocks, frozen at bed side
- Blood samples:
  - Serum and plasma samples are processed on site and frozen until shipment
  - 1 EDTA whole blood at room temperature
- Add dry ice in one of the chambers for the frozen samples
  - OCT-embedded tumor
  - Processed serum and plasma
- Place the anti-coagulated whole blood and formalin-fixed samples in the canister (15^0C)

Please refer to the Protocol Section 7 for a full description on specimen submission

Biopsy/Shipment Kit



Biopsy/Shipment Kit



Room temperature samples
- Formalin cup
- EDTA whole blood

dry ice and frozen samples
- OCT frozen tissue block
- Serum, plasma cryovials

Integral and Integrated Biomarkers

- Ki67 (centrally tested at Wash U AMP)
  - Baseline (results not provided to sites)
  - 4-week (results provided to sites)
  - 12-week (results provided to sites)
  - Surgery post 6 cycles of neoadjuvant endocrine therapy (results provided to sites)
- ER (centrally tested at Wash U AMP)
  - Baseline (results not provided to sites)
  - Surgery post 6 cycles of neoadjuvant endocrine therapy (results not provided to sites)

Refer to Protocol Section 15 for a full description of integral and integrated biomarkers

Shipping Instruction

- Log in **BioMS** to register specimen

(http://bioms.allianceforclinicaltrialsinoncology.org)

  - Complete the **Biomarker Assay Request Form** downloaded from BioMS for the following samples and place in the kit:
    - Pre-treatment
    - 4-week biopsy
    - 12-week biopsy
    - Surgery core (post neoadjuvant endocrine therapy only)
    - Surgery slides (post neoadjuvant endocrine therapy only)
  - **Do not** need the Biomarker Assay Request Form for the following samples:
    - Samples collected at disease progression
    - Samples collected from patients on neoadjuvant chemotherapy group
      - Cycle 1 day 2
      - Surgery
  - Print shipping manifest

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY Protocol Number: A011106 (ALTERNATE Trial)

Biomarker Assay Request Form

(Only for patients receiving Neoadjuvant Endocrine Therapy)

Note: Ki67 analysis is only done for patients on neoadjuvant endocrine therapy at baseline, 4-week, 12-week, or surgery. Please DO NOT fill this form for samples collected on the Neoadjuvant Chemotherapy Group or at disease progression.

Patient Initial (First, Middle, Last):_____ **Alliance ID:**_____

Collection Date (MM/DD/YYYY):____/____/____ **Time:**_____ **AM/PM**

CRA Ordering Test (please print):

Name (First, Last):_____ Institution:_____

Adrress:_____
Street

_____
City State Zip

Phone: (__)_____ Fax: (__)_____ Email:_____

Check One	Study Timepoint	Specimen type (enter number of specimens)	WU AMP Instructions		Ki67 Report
	Pre-Treatment	tissue cores in 10% formalin (number:____)	Embed both cores in 1 block	1 H&E 1 ER 1 Ki67	Not Real Time
	4-Week*	tissue cores in 10% formalin (number:____)		1 H&E 1 Ki67	Real Time
	12-Week*	tissue cores in 10% formalin (number:____)			Real Time
	Surgery* (core)	tissue cores in 10% formalin (number:____)		No H&E No IHC	Not required
	Surgery* (resection)	Preferred: ☐ unstained Superfrost slides (number:_____) Alternatively (not preferred): ☐Tumor rich block (number_____)	1 H&E, 1 ER and 1 Ki67		Real Time

*post neoadjuvant endocrine therapy (anastrozole and/or fulvestrant) only.

Please check mark the correct time point above and ship this order form with the sample
Shipping Address: Alliance Central Specimen Bank, 425 S. Euclid Ave, Room 5120, St. Louis, MO 63110-1005
Phone: (314) 454-7615; Fax: (314) 454-5525; E-mail: tbank@wudosis.wustl.edu

- Fedex only on Mondays and Thursdays and No shipments to be made on Fridays or the day before a holiday.
- On the day that specimens are sent to the specimen bank, please contact the bank by phone, fax, or e-mail to notify what is being sent and when the shipment is expected to arrive.

caTissue Label

W☐☐-☐☐☐☐

Please refer to the Protocol Section 7 for a full description on specimen submission

Shipping Instruction

- Ship kit (contain both tumor and blood samples) to Alliance Biorepository

Alliance Biorepository at Washington University
425 S. Euclid Ave, Room 5120
St. Louis, MO 63110-1005
Phone: (314) 454-7615
Fax: (314) 454-5525
E-mail: tbank@wudosis.wustl.edu

- No shipment on Friday or before a holiday
- Tumor collection should not be done on Fridays or before a 2-day holiday if overnight shipment is needed as the formalin samples need to be processed within 72 hours of collection.
- Refer to protocol section 7 for storage instruction if immediate shipment is not possible.
- Label samples with patient study ID number, patient initials, and sample collection date and time.

Please refer to the Protocol Section 7 for a full description on specimen shipment

Ki67 Reporting

- Ki67 result for clinical decision making (neoadjuvant endocrine therapy **4-week or 12-week biopsy** and **surgical resection slides**) will be emailed or faxed sites.
  - The person whose contact information has been entered on the **Biomarker Assay Request Form** which should be the same person whose name appears in RAVE, will receive the result.
- Contact the specimen coordinator (email:AlternateTrial@dom.wustl.edu) with questions regarding sample and Ki67 result tracking.

Refer to Protocol Section 15 for a full description of integral and integrated biomarkers

Ki67, modified PEPI, and clinical decision making

- Ki67 at 4-week or 12-week
  - If >10%, discontinue endocrine therapy, recommend chemotherapy, paclitaxel preferred
  - If ≤10%, continue endocrine therapy
- Modified PEPI score at surgery
  - If score 0
    - No adjuvant chemotherapy
    - Continue assigned endocrine therapy for 1.5 years followed by anastrozole
  - If score non-0
    - Adjuvant chemotherapy and hormonal therapy per physician choice.

Refer to Protocol Section 15 for a full description of integral and integrated biomarkers

Modified PEPI Score Determination

Surgical Specimen	Modified PEPI points
Tumor size	
T1/2	0
T3/4	3
Node status	
Negative	0
Positive	3
Ki67 level	
0-2.7%	0
>2.7-7.3%	1
>7.3-19.7%	1
19.7-53.1%	2
>53.1%	3

Site MD is required to sign off on the modified PEPI score !!!

Refer to Protocol Section 15 for a full description of integral and integrated biomarkers

Residual Cancer Burden

for patients who come off endocrine therapy
and treated in the Neoadjuvant Chemotherapy Group

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

Diameter of Largest Metastasis: _____ (mm)

Reset Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

The Residual Cancer Burden Calculator and detailed description of reporting can be found at the following web site: http://www.mdanderson.org/breastcancer_RCB

Site pathologists are responsible for the RCB report

Statistics (First Phase)

- Primary endpoint:
  - To compare the Modified PEPI 0 rate of the three neoadjuvant treatment.
- N=400 each arm (total n=1200)
  - one sided alpha=0.025 chi-square test
  - 82% chance to detect at least 0.10 difference in modified PEPI 0 rate
- Upon completion of the first phase enrollment, the anastrozole arm will continue to enroll patients for the 2nd phase of the trial while waiting for the primary endpoint analysis.
- Only the fulvestrant containing arm (s) which showed a superiority over anastrozole in the primary endpoint will be continued to the second phase.

Refer to Protocol Section 13 for a full description of statistical analysis and sample size

Statistics (Second Phase)

- Primary endpoint:
  - RFS for the modified PEPI 0 group in pts treated with neoadjuvant anastrozole or fulvestrant or anastrozole/fulvestrant if proceeded to the 2nd phase
- A sample size of 317 pts with a modified PEPI score of 0 are needed so that:
  - With a sample size of 317 patients, a one-sided alpha=0.025 nonparametric Brookmeyer-Crowley type one sample survival test will have a 90% chance of rejecting that 5 year RFS rate is 95%, when the true 5 year RFS rate is at most 90%. (That is, we will conclude that the 5 year RFS rate is significantly less than 95% if the p-value for this test is less than 0.025).
- A sample size of 940 patients (including the 400 enrolled in the first phase of the trial) in each arm is needed to reach the goal of 317 women with a modified PEPI score of 0 assuming the modified PEPI 0 rate is 33%.

Refer to Protocol Section 13 for a full description of statistical analysis and sample size

Questions	Contacts
Patient eligibility, treatment, and dose modification	Study Chair, Nursing Liaison, Protocol Coordinator, or Data Manager
Data submission, RAVE or follow-up	Data Manager
Protocol document	Protocol Coordinator
IRB issues, model consent revisions, and AdEERS reporting	Regulatory Affairs Manager Email: *regulatory@calgb.org*
Biospecimen Submission	Specimen Coordinator
Kits ordering	tbank@wudosis.wustl.edu
Tracking of sample and Ki67 results	Specimen Coordinator
Interpretation of Ki67 result, Modified PEPI calculation, Residual Cancer Burden	Study Chair, Pathology Co-chair, Correlative Science Co-chair

Study Team

Study Chair	Cynthia Ma, MD, PhD	cma@dom.wustl.edu
Community Oncology Co-chair	Gary W. Unzeitig, MD, FRCP	drgwu@laredobreastcare.com
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Nursing Liaison		
Pharmacy Contact	Zoe Ngo, Pharm D	zoe.ngo@ucsfmedctr.org