ALTernate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment (ALTERNATE) in postmenopausal women: A Phase III Study (A011106) Protocol version Update #2

Cynthia X. Ma, M.D., Ph.D. Associate Professor Medical Oncology Washington University in Saint Louis
Eligibility
Post-menopausal
Clinical Stage II or III
ER+ (Allred 6-8) HER2-

ALTERNATE Schema

BEFORE SURGERY

6 cycles (each cycle is 4 weeks)

Arm I
Arm II
Arm III

Ki67 <10%

Neoadjuvant Chemotherapy Group
Chemotherapy (4-6 cycles)

Ki67 >10%

Modified PEPI 0
Chemo NOT recommended

Modified PEPI > 0
Chemo recommended

Surgery

AFTER SURGERY

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

Endocrine therapy of Physician’s Choice

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

<table>
<thead>
<tr>
<th>Post-therapy factors</th>
<th>RFS</th>
<th>Breast Cancer Specific Survival</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
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<tr>
<td>Tumor stage (T1/2 vs T3/4)</td>
<td>2.8 (1.4 to 5.4)</td>
<td>.003</td>
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<tr>
<td>Node status (pos vs neg)</td>
<td>3.2 (1.5 to 6.9)</td>
<td>.004</td>
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<tr>
<td>Ki67 level per 2.7-fold increase</td>
<td>1.3 (1.1 to 1.6)</td>
<td>.003</td>
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<tr>
<td>ER, Allred score (0,2 vs 3-8)</td>
<td>2.8 (1.2 to 6.4)</td>
<td>.02</td>
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</tbody>
</table>

PEPI Score

The PEPI Score was developed using results of the 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.


<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
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<th>BCSS</th>
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<tr>
<td></td>
<td>HR</td>
<td>Points</td>
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<tr>
<td>Tumor Size</td>
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<td></td>
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<tr>
<td>T1/2</td>
<td>—</td>
<td>0</td>
<td>—</td>
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<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
<td>4.4</td>
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<tr>
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<td>0</td>
<td>—</td>
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<tr>
<td>Positive</td>
<td>3.2</td>
<td>3</td>
<td>3.9</td>
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<tr>
<td>Ki67 level</td>
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<tr>
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<td>0</td>
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<td>&gt;2.7–7.3%</td>
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<td>1</td>
<td>1.4</td>
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<td>2.0</td>
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<td>2.7</td>
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<td>&gt;53.1%</td>
<td>2.9</td>
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<td>3.8</td>
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<tr>
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Modified PEPI excludes ER
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)


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

<table>
<thead>
<tr>
<th></th>
<th>% PEPI 0</th>
<th>RFS (events), median F/U 5 years</th>
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</thead>
<tbody>
<tr>
<td><strong>POL 4W Ki67</strong></td>
<td></td>
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<tr>
<td>&gt;10%</td>
<td>1/19 (5%)</td>
<td>8/21 (38%)</td>
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<tr>
<td>≤10%</td>
<td>10/36 (28%)</td>
<td>3/45 (7%)</td>
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<tr>
<td><strong>P Value</strong></td>
<td>P=0.08 (Fisher)</td>
<td>P=0.003</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>% PEPI 0</th>
<th>RFS (events), median F/U 37 months</th>
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</thead>
<tbody>
<tr>
<td><strong>IMPACT 2W Ki67</strong></td>
<td></td>
<td></td>
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<tr>
<td>&gt;10%</td>
<td>0/32 (0%)</td>
<td>9/35 (26%)</td>
</tr>
<tr>
<td>≤10%</td>
<td>21/101 (21%)</td>
<td>13/118 (11%)</td>
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<tr>
<td><strong>P Value</strong></td>
<td>P=0.004 (Fisher)</td>
<td>P=0.008 (log rank)</td>
</tr>
</tbody>
</table>

**POL**

- **ER+ Stage 2/3**

- **Letrozole**

**IMPACT**

- **ER+ Stage 2/3**

- **Anastrozole**

- **Combination**

- **Tamoxifen**

*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.
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 (1\textsuperscript{st} 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\% (2\textsuperscript{nd} Phase)
  – Anastrozole alone
  – Fulvestrant alone (if efficacy superior than anastrozole in the 1\textsuperscript{st} Phase analysis)
  – Fulvestrant/Anastrozole combination (if efficacy superior than anastrozole in the 1\textsuperscript{st} 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°C)

Please refer to the Protocol Section 7 for a full description on specimen submission
Biopsy/Shipment Kit

- cryovials
- Formalin cup inside
- Blood draw kit
- OCT and chamber
Biopsy/Shipmen Kit

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

- OCT frozen tissue block

- Serum, plasma cryovials

- Room temperature samples
  - Formalin cup
  - EDTA whole blood

- Biopsy gun
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
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**

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

<table>
<thead>
<tr>
<th>Surgical Specimen</th>
<th>Modified PEPI points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>0</td>
</tr>
<tr>
<td>T3/4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Node status</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
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<tr>
<td><strong>Ki67 level</strong></td>
<td></td>
</tr>
<tr>
<td>0-2.7%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.7-7.3%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;7.3-19.7%</td>
<td>1</td>
</tr>
<tr>
<td>19.7-53.1%</td>
<td>2</td>
</tr>
<tr>
<td>&gt;53.1%</td>
<td>3</td>
</tr>
</tbody>
</table>

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:  \[ \text{(mm)} \times \text{(mm)} \]
   Overall Cancer Cellularity (as percentage of area):  \[ \text{\%} \]
   Percentage of Cancer That Is in situ Disease:  \[ \text{\%} \]

(2) Lymph Nodes
   Number of Positive Lymph Nodes:
   Diameter of Largest Metastasis:  \[ \text{(mm)} \]

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
<table>
<thead>
<tr>
<th>Questions</th>
<th>Contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient eligibility, treatment, and dose modification</td>
<td>Study Chair, Nursing Liaison, Protocol Coordinator, or Data Manager</td>
</tr>
<tr>
<td>Data submission, RAVE or follow-up</td>
<td>Data Manager</td>
</tr>
<tr>
<td>Protocol document</td>
<td>Protocol Coordinator</td>
</tr>
<tr>
<td>IRB issues, model consent revisions, and AdEERS reporting</td>
<td>Regulatory Affairs Manager</td>
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<tr>
<td></td>
<td>Email: <a href="mailto:regulatory@calgb.org">regulatory@calgb.org</a></td>
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<td>Biospecimen Submission</td>
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<tr>
<td>Interpretation of Ki67 result, Modified PEPI calculation, Residual Cancer Burden</td>
<td>Study Chair, Pathology Co-chair, Correlative Science Co-chair</td>
</tr>
<tr>
<td>Role</td>
<td>Name</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Study Chair</td>
<td>Cynthia Ma, MD, PhD</td>
</tr>
<tr>
<td>Community Oncology Co-chair</td>
<td>Gary W. Unzeitig, MD, FRCP</td>
</tr>
<tr>
<td>Surgery Co-chair</td>
<td>A. Marilyn Leitch, MD, FACS</td>
</tr>
<tr>
<td>Correlative Science Co-chair</td>
<td>Matthew Ellis, MB, BChir, PhD</td>
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<tr>
<td>Study Statistician</td>
<td>Vera Suman, PhD</td>
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<tr>
<td>Study Pathologist</td>
<td>Souzan Sanati</td>
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<td>Alliance Biorepository</td>
<td>Mark Watson, MD, PhD</td>
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<td>Wendy Lindeman</td>
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<tr>
<td>Pharmacy Contact</td>
<td>Zoe Ngo, Pharm D</td>
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