# BREAST COMMITTEE

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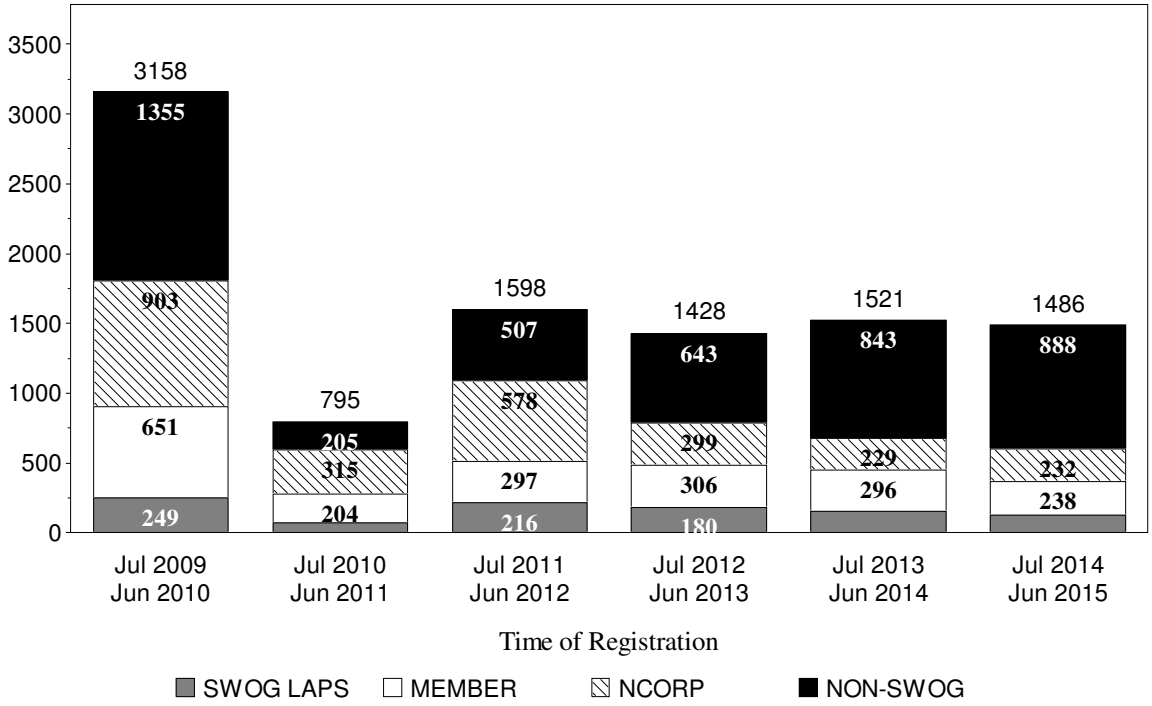
# Patient Registrations to Studies

By 12 Month Intervals
**BREAST COMMITTEE**




Screening registrations and registrations to Biologic only studies are excluded

# Patient Registrations by Study and Arm

## BREAST COMMITTEE

| | Jan 2015 Jun 2015 | Jul 2014 Dec 2014 | Jan 2014 Jun 2014 | All Patients |
|---|---|---|---|---|
| **S1007 Breast, Adj, N1, Endocrine+/-Chemo** | | | | |
| **Initial Registration** | | | | |
| Recurrence Score testing | 1,048 | 950 | 1,116 | 7,295 |
| **Randomization** | | | | |
| Chemo and Endocrine Therapy | 284 | 245 | 291 | 1,854 |
| Endocrine Therapy Alone | 279 | 243 | 294 | 1,845 |
| | 563 | 488 | 585 | 3,699 |
| **S1207 Breast, Adj, Endocrine+/-Everolimus** | | | | |
| **Randomization** | | | | |
| Blinded drug + Endocrine | 156 | 134 | 67 | 382 |
| **S1222 Breast, Fulvestrant +/- Everolimus +/- Anastrozole** | | | | |
| **Randomization** | | | | |
| Blinded treatment | 7 | 24 | 6 | 37 |
| **A011106 Breast, Neoadj, ALTERNATE Study*** | | | | |
| Total Registrations | 6 | 3 | 1 | 10 |
| **A011202 Breast, Nodal XRT +/- ALND*** | | | | |
| Total Registrations | 10 | 4 | 2 | 16 |
| **B43 Breast, DCIS, HER2+, RT +/- Tras*** | | | | |
| Total Registrations | 0 | 5 | 15 | 66 |
| **B47 Chemo vs Chemo + Trastuzumab*** | | | | |
| Total Registrations | 5 | 18 | 33 | 155 |
| **B51 Breast, Regional Nodal XRT*** | | | | |
| Total Registrations | 0 | 1 | 1 | 2 |
| **B52 Breast, Neoadj TCHP +/- AI*** | | | | |
| Total Registrations | 3 | 1 | 0 | 4 |
| **B55 Breast, Adj Olaparib for BRCA, TNBC*** | | | | |
| Total Registrations | 2 | 0 | 0 | 2 |

| | Jan 2015 Jun 2015 | Jul 2014 Dec 2014 | Jan 2014 Jun 2014 | All Patients |
|---|---|---|---|---|
| **E1Z11 Breast, Genetic Predictors of AIMSS*** | | | | |
| Total Registrations | 23 | 11 | 54 | 120 |
| **E2108 Breast, Early Local Tx for Intact Primary Tumor*** | | | | |
| Total Registrations | 9 | 8 | 6 | 51 |
| **E2112 Breast, Adv, Exemestane+/-Entinostat*** | | | | |
| Total Registrations | 1 | 0 | 0 | 1 |
| **R1005 Breast, Accelerated vs Standard WBRT*** | | | | |
| Total Registrations | 0 | 0 | 8 | 17 |
| **Z11102 Breast Conserv. Surgery for MIBC*** | | | | |
| Total Registrations | 4 | 0 | 2 | 6 |

* For non-SWOG coordinated studies only SWOG registrations are shown.

# S1007 Phase III

**Coordinating Group: SWOG**

# A Phase III Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer with Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

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**Participants:**
SWOG, CTSU (endorsed by NRG, Allaince, ECOG-ACRIN, NCIC CTG, GEICAM, and UNICANCER)

**Date Activated:**
01/15/2011

**Study Chairs:**
K Kalinsky, J Gralow, G Hortobagyi, K Albain

**Statisticians:**
W Barlow, D Lew

**Data Coordinators:**
L Kaye, J Barce

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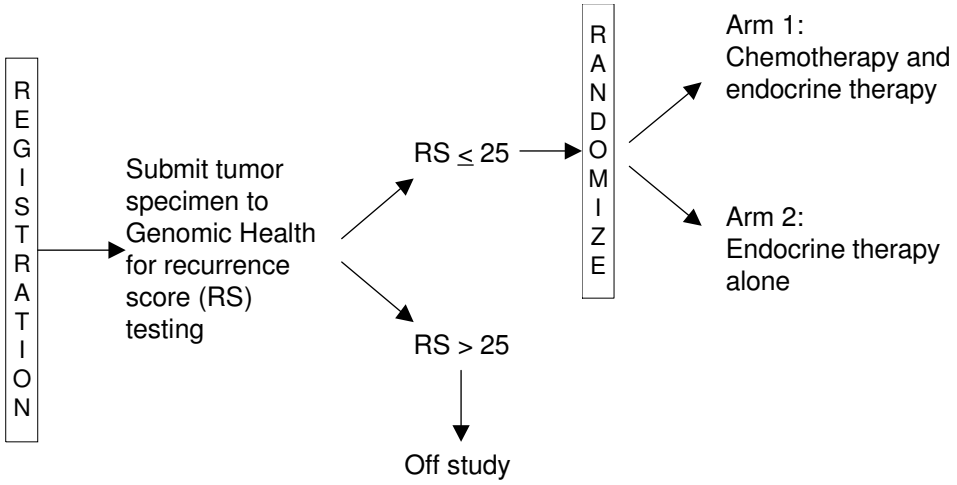
## SCHEMA




**Objectives**

To determine the effect of chemotherapy in patients with node-positive breast cancer who do not have high Recurrence Scores (RS) by Oncotype DX®. In patients with 1-3 positive nodes, and hormone receptor (HR)-positive, HER2-negative breast cancer with RS ≤ 25 treated with endocrine therapy we will

test whether the difference in disease-free survival for patients treated with chemotherapy compared to no chemotherapy depends directly on the magnitude of RS. If benefit depends on the RS score, the trial will determine the optimal cutpoint for recommending chemotherapy or not.

To compare overall survival (OS), distant disease-free survival (DDFS) and local disease-free interval (LDFI) by receipt of chemotherapy or not and its interaction with RS.

To compare the toxicity across the treatment arms.

To perform other assays or tests (in particular the PAM50 risk of relapse score), as they are developed and validated, that measure potential benefit of chemotherapy and compare them to Oncotype DX®.

To determine the impact of management with Oncotype DX® on patient-reported anxiety (co-primary Health-Related Quality of Life [HRQL] outcome) prior to screening, after disclosure of test results, and during the randomized trial.

To determine the impact of Oncotype DX® on the initial management cost of node-positive, HR-positive, HER2-negative breast cancer.

To compare patient-reported utilities (e.g. QOL) for those randomized to chemotherapy versus no chemotherapy.

Using modeling and DFS information from the trial, to estimate the cost-effectiveness of management with Oncotype DX® versus usual care.

To determine the role of other assays (e.g. PAM50) as predictors of DFS, DDFS and LDFI for patients randomized to chemotherapy versus no chemotherapy.

To determine the impact of treatment with chemotherapy versus no chemotherapy on patient-reported fatigue and cognitive concerns (secondary HRQL outcomes).

To determine the impact of management with Oncotype DX® on patient-reported decision conflict, perceptions regarding Oncotype DX® testing, and survivor concerns prior to screening, after disclosure of test results, and during the randomized trial (secondary HRQL outcomes).

**Patient Population**

Patients must be women with a histologically confirmed diagnosis of node-positive (1-3 nodes) invasive breast carcinoma with positive estrogen and/or progesterone receptor status, and negative HER-2 status. HER-2 test result negativity must be assessed as per ASCO/CAP 2013 guidelines using IHC, ISH or both. If HER-2 IHC is 2+, evaluation for gene amplification (ISH) must be performed and the ISH must be negative; ISH is not required if IHC is 0 or 1+. Patients with equivocal HER-2 are not eligible. Patients with multifocal, multicentric, and synchronous bilateral breast cancers are allowed. Patients must not have inflammatory breast cancer and must not have metastatic disease.

Patients must have had either breast-conserving surgery with planned radiation therapy or total mastectomy (with or without planned postmastectomy radiation). Patients must have clear margins from both invasive cancer and DCIS; LCIS at the margins is allowed. Patients must have undergone axillary staging by sentinel node biopsy or axillary lymph node dissection. Patients with positive sentinel node are not required to undergo full axillary lymph node dissection; this is at the discretion of the treating physician. Patients with micrometastases as the only nodal involvement (pN1mi) are not eligible. Patients must not have begun chemotherapy or endocrine therapy for their breast cancer prior to registration. Patients must be able to receive taxane and/or anthracycline based chemotherapy. Patients must not have received an aromatase inhibitor (AI) or a selective estrogen receptor modulator (SERM) such as tamoxifen or raloxifene within five years prior to registration. Partial breast irradiation (including brachytherapy) is not allowed. Radiation in the opposite breast is acceptable. Patients with a prior diagnosis of contralateral DCIS are eligible if they underwent a mastectomy or lumpectomy with whole breast radiation. Patients with a prior diagnosis of ipsilateral DCIS or invasive breast cancer who received radiation to that breast are not eligible.

Registration of patients who have not yet undergone Oncotype DX® screening must occur no later than 56 days after definitive surgery. For all patients, randomization (Step 2 Registration) must occur within 84 days after definitive surgery. If the Oncotype DX® Breast Cancer Assay has not been performed, patients must be willing to submit tissue samples directly to Genomic Health for testing to determine Recurrence Score value. If the Oncotype DX® Recurrence Score is already known and is 25 or less, the patient must be randomized (registered to

Step 2) immediately following initial registration. If the Oncotype DX® Recurrence Score is already known and is greater than 25, the patient is ineligible.

Patients must have a Zubrod performance status of 0-2 and must not require chronic treatment with systemic steroids (inhaled steroids are allowed) or other immunosuppressive agents.

**Stratification/Descriptive Factors**

Patient randomization will be stratified by the following factors: (1) Recurrence Score: 0-13 vs 14-25; (2) menopausal status: pre vs post; and (3) type of nodal dissection: axillary lymph node dissection (with or without sentinel node mapping) vs sentinel node biopsy without axillary lymph node dissection.

**Accrual Goals**

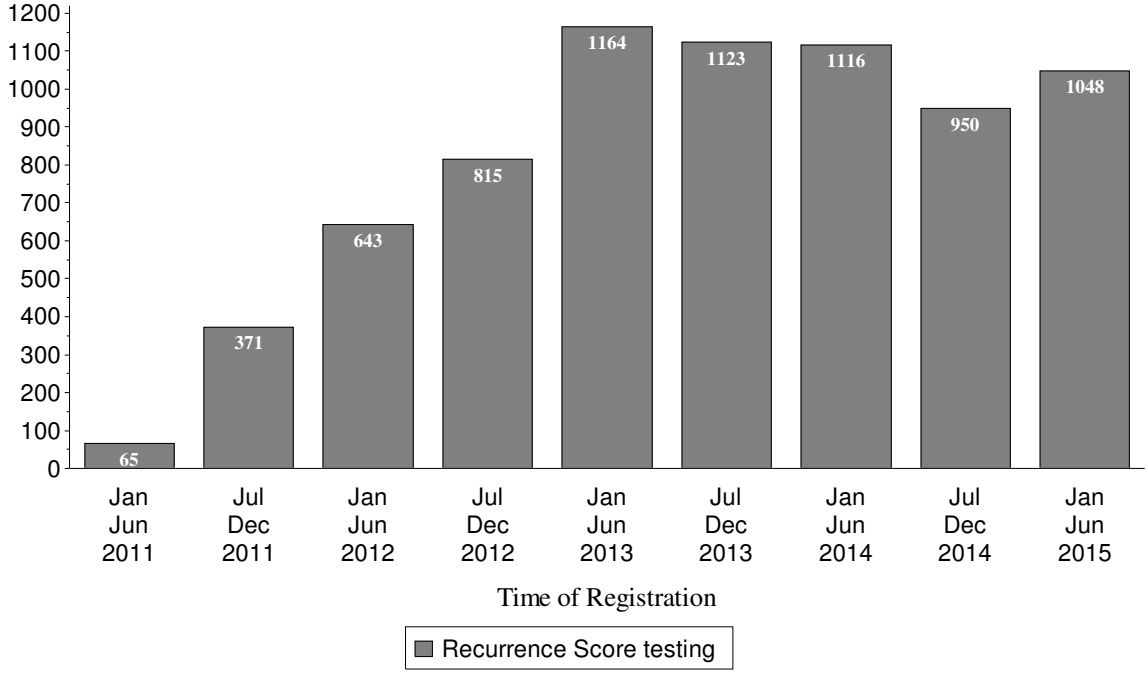
The accrual goal for the randomized trial is 4,000 eligible patients, which will require approximately 9,400 women to be screened for inclusion. An additional 1,000 eligible patients from UNICANCER in France will be randomized. Annual interim analyses are planned beginning when 24% of the events have been observed, approximately 6.6 years after initiation of the study.

**Summary Statement**

This study was activated on January 15, 2011. As of June 30, 2015, there had been 7,295 registrations to the screening step and 3,699 patients with Oncotype DX® Recurrence Score $\leq$ 25 randomized. Fifty-seven patients are currently ineligible, the most common reason being margins not clear (23 patients). One patient who refused randomization and withdrew consent for all follow-up is not analyzable for any endpoint. Major deviations are coded for 319 additional patients (9%) who refused their randomized treatment assignment, did not receive any protocol treatment, or received a non-approved chemotherapy regimen. These 319 patients are not evaluable for adverse events.

There have been four treatment-related deaths reported among 2,804 patients evaluated for adverse events: one due to small bowel, colon, and liver necrosis (listed as "GI disorders - other, specify"), one due to stroke (also coded "Death NOS"), one due to typhlitis, and one due to sepsis. An additional 88 patients reported Grade 4 adverse events as maximum degree, primarily hematologic, including two more cases of neutropenia currently coded as “Blood/lymph disorder-Other.” The Grade 4 “Infections/infestations-Other” was infection at port-a-cath. Toxicities are reviewed by treatment group by the Data Safety and Monitoring Committee, the SWOG Breast Committee leadership, and the Study Chair.

## Initial Registrations By 6 Month Intervals



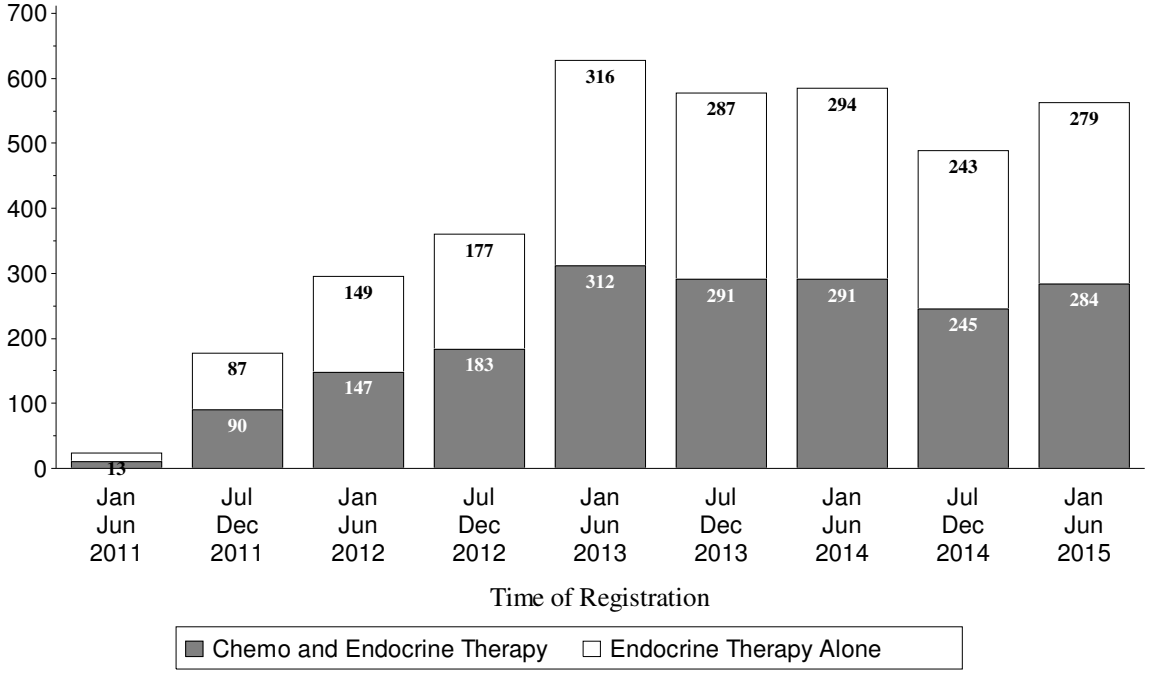
# Registration by Institution

Screening Registration

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| ECOG-ACRIN | 1338 | Virginia Mason MC/Northwest NCORP | 24 |
| NMC | 1161 | Kentucky, U of | 23 |
| Alliance | 996 | Lahey Hosp & Med Ctr | 22 |
| NCIC-CTG | 677 | S Georgia Med Ctr/Brooke Army Med Ctr | 21 |
| NRG | 569 | Henry Ford Hosp | 20 |
| MD Anderson CC | 261 | CRC West MI NCORP | 18 |
| National Cancer Ctr | 162 | Good Samaritan Hosp/CORA NCORP | 18 |
| Michigan CRC NCORP | 129 | Dayton NCORP | 17 |
| INCan | 123 | McLaren Cancer Inst/Wayne State Univ | 17 |
| Michigan, U of | 95 | San Diego, U of CA | 17 |
| City of Hope Med Ctr | 86 | Sacred Heart Hosp/Arkansas, U of | 16 |
| Cleveland Clinic OH | 78 | Montana NCORP | 15 |
| Wichita NCORP | 68 | INC, Bogota | 14 |
| Kaiser Vallejo NCORP | 53 | St Joseph Med Ctr/PCRC NCORP | 14 |
| Southeast COR NCORP | 52 | SW Cancer & Res Ctr/San Antonio, U of TX | 14 |
| KaiserPermanenteSCAL/Kaiser Vallejo NCORP | 49 | Atlanta Reg CCOP | 13 |
| Utah, U of | 47 | Colorado, U of | 13 |
| Kansas, U of | 46 | Singing River Hosp/Mississippi, Univ of | 13 |
| Loyola University | 46 | Cookeville Reg MC | 12 |
| Columbus NCORP | 45 | Long Beach Mem MC/Irvine, U of CA | 12 |
| Beaumont NCORP | 42 | Mem Hosp, Co Springs/Colorado, U of | 12 |
| New Mexico MU-NCORP | 42 | Rochester, Univ of | 12 |
| Yale University | 42 | Univ of Louisville | 12 |
| Wayne State Univ | 37 | Harrison Bremerton/Harrison Medical Ctr | 11 |
| St Charles Hlth Sys/PCRC NCORP | 34 | Davis, U of CA | 10 |
| St Luke's Mt State/PCRC NCORP | 34 | PCRC NCORP | 10 |
| Columbia MU-NCORP | 32 | San Antonio, U of TX | 10 |
| So Calif, U of | 32 | UF Cancer Center/Arkansas, U of | 10 |
| Poudre Valley Hosp/Colorado, U of | 31 | Providence Hosp | 9 |
| Methodist Hospital | 30 | St Mary Med Ctr/PCRC NCORP | 9 |
| Northwest NCORP | 29 | Bridgeport Hospital/Yale University | 8 |
| Hawaii MU-NCORP | 26 | Cedars-Sinai Med Ctr | 8 |
| MUSC MU-NCORP | 26 | Upstate Carolina | 8 |
| Kansas City NCORP | 25 | Utah Valley Reg Med/Intermountain MC | 8 |
| Ozarks NCORP | 25 | All Other Institutions | 208 |
| U of Tennessee MC/Tennessee, U of | 25 | **Total (138 Institutions)** | **7295** |
| Heartland NCORP | 24 | | |

## Randomization By 6 Month Intervals



## Registration by Institution

Randomization

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| NMC | 716 | Virginia Mason MC/Northwest NCORP | 16 |
| ECOG-ACRIN | 640 | Columbia MU-NCORP | 14 |
| Alliance | 486 | Sacred Heart Hosp/Arkansas, U of | 14 |
| NCIC-CTG | 296 | So Calif, U of | 14 |
| NRG | 249 | Wayne State Univ | 13 |
| MD Anderson CC | 143 | Good Samaritan Hosp/CORA NCORP | 12 |
| National Cancer Ctr | 131 | Atlanta Reg CCOP | 11 |
| INCan | 87 | Hawaii MU-NCORP | 11 |
| Wichita NCORP | 48 | Henry Ford Hosp | 11 |
| City of Hope Med Ctr | 42 | Poudre Valley Hosp/Colorado, U of | 11 |
| KaiserPermanenteSCAL/Kaiser Vallejo NCORP | 42 | Colorado, U of | 10 |
| Michigan CRC NCORP | 42 | Kansas City NCORP | 10 |
| Kansas, U of | 30 | San Antonio, U of TX | 10 |
| Beaumont NCORP | 29 | St Luke's Mt State/PCRC NCORP | 10 |
| Southeast COR NCORP | 29 | Harrison Bremerton/Harrison Medical Ctr | 9 |
| Kaiser Vallejo NCORP | 28 | Heartland NCORP | 9 |
| Cleveland Clinic OH | 26 | INC, Bogota | 9 |
| New Mexico MU-NCORP | 23 | Long Beach Mem MC/Irvine, U of CA | 9 |
| Loyola University | 22 | Northwest NCORP | 9 |
| Kentucky, U of | 21 | Montana NCORP | 8 |
| Michigan, U of | 20 | PCRC NCORP | 8 |
| Yale University | 20 | Providence Hosp | 8 |
| MUSC MU-NCORP | 17 | Univ of Louisville | 8 |
| Columbus NCORP | 16 | All Other Institutions | 220 |
| Lahey Hosp & Med Ctr | 16 | **Total (120 Institutions)** | **3699** |
| Utah, U of | 16 | | |

## Registration, Eligibility, and Evaluability

Randomization

Registrations ending June 30, 2015; Data as of August 27, 2015

| | TOTAL | Chemo and Endocrine Therapy | Endocrine Therapy Alone |
|---|---|---|---|
| NUMBER REGISTERED | 3699 | 1854 | 1845 |
| INELIGIBLE | 57 | 34 | 23 |
| ELIGIBLE | 3642 | 1820 | 1822 |
| Analyzable, Pend. Elig. | 167 | 77 | 90 |
| Not Analyzable | 1 | 1 | 0 |
| ADVERSE EVENT ASSESSMENT | | | |
| Evaluable | 2804 | 1343 | 1461 |
| Not Evaluable | 319 | 221 | 98 |
| Too Early | 518 | 255 | 263 |

# Patient Characteristics

Randomization

Registrations ending June 30, 2015; Data as of August 27, 2015

| | Total (n=3641) | |
|---|---|---|
| AGE | | |
| Median | 57.5 | |
| Minimum | 18.4 | |
| Maximum | 87.7 | |
| HISPANIC | | |
| Yes | 570 | 16% |
| No | 2979 | 82% |
| Unknown | 92 | 3% |
| RACE | | |
| White | 2877 | 79% |
| Black | 233 | 6% |
| Asian | 283 | 8% |
| Pacific Islander | 12 | 0% |
| Native American | 22 | 1% |
| Multi-Racial | 5 | 0% |
| Unknown | 209 | 6% |
| RECURRENCE SCORE | | |
| 0-13 | 1537 | 42% |
| 14-25 | 2104 | 58% |
| MENOPAUSAL STATUS | | |
| Pre-menopausal | 1161 | 32% |
| Post-menopausal | 2480 | 68% |
| NODAL DISSECTION | | |
| Axillary lymph node dissection (with or without sentinel node mapping) | 2073 | 57% |
| Sentinel node biopsy without axillary lymph node dissection | 1568 | 43% |

## Treatment Summary

Registrations ending June 30, 2015; Data as of August 27, 2015

| | Total |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 3362 |
| NUMBER OFF PROTOCOL TREATMENT | 279 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 0 |
| Adverse Event or side effects | 6 |
| Refusal unrelated to adverse event | 172 |
| Progression/relapse | 37 |
| Death | 13 |
| Other - not protocol specified | 27 |
| Reason under review | 24 |
| MAJOR PROTOCOL DEVIATIONS | 319 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed

Registrations ending June 30, 2015; Data as of August 27, 2015

| | Total (n=2804) Grade | | | |
|---|---|---|---|---|
| **ADVERSE EVENTS** | **<=2** | **3** | **4** | **5** |
| ALT increased | 2800 | 4 | 0 | 0 |
| AST increased | 2802 | 2 | 0 | 0 |
| Abdominal pain | 2797 | 7 | 0 | 0 |
| Acute kidney injury | 2803 | 1 | 0 | 0 |
| Alkaline phosphatase increased | 2803 | 1 | 0 | 0 |
| Allergic reaction | 2800 | 4 | 0 | 0 |
| Anemia | 2787 | 15 | 2 | 0 |
| Anorexia | 2803 | 1 | 0 | 0 |
| Anxiety | 2803 | 1 | 0 | 0 |
| Arthralgia | 2761 | 43 | 0 | 0 |
| Atrial fibrillation | 2802 | 2 | 0 | 0 |
| Back pain | 2802 | 2 | 0 | 0 |
| Blood/lymph disorder-Other | 2801 | 1 | 2 | 0 |
| Bone pain | 2792 | 12 | 0 | 0 |
| Breast infection | 2802 | 2 | 0 | 0 |
| CD4 lymphocytes decreased | 2803 | 1 | 0 | 0 |
| Catheter related infection | 2803 | 1 | 0 | 0 |
| Chest pain - cardiac | 2803 | 1 | 0 | 0 |
| Chest wall pain | 2803 | 1 | 0 | 0 |
| Colitis | 2801 | 3 | 0 | 0 |
| Constipation | 2801 | 3 | 0 | 0 |
| Death NOS | 2803 | 0 | 0 | 1 |
| Dehydration | 2794 | 10 | 0 | 0 |
| Depression | 2801 | 3 | 0 | 0 |
| Dermatitis radiation | 2800 | 4 | 0 | 0 |

| | Total (n=2804) Grade | | | |
|---|---|---|---|---|
| **ADVERSE EVENTS** | **<=2** | **3** | **4** | **5** |
| Device related infection | 2800 | 3 | 1 | 0 |
| Diarrhea | 2777 | 27 | 0 | 0 |
| Dizziness | 2802 | 2 | 0 | 0 |
| Dry skin | 2803 | 1 | 0 | 0 |
| Dyspareunia | 2803 | 1 | 0 | 0 |
| Dyspepsia | 2802 | 2 | 0 | 0 |
| Dyspnea | 2803 | 1 | 0 | 0 |
| Ear pain | 2802 | 2 | 0 | 0 |
| Edema limbs | 2803 | 1 | 0 | 0 |
| Erythema multiforme | 2803 | 1 | 0 | 0 |
| Erythroderma | 2803 | 1 | 0 | 0 |
| Esophagitis | 2802 | 2 | 0 | 0 |
| Fatigue | 2769 | 35 | 0 | 0 |
| Febrile neutropenia | 2755 | 42 | 7 | 0 |
| Fever | 2803 | 1 | 0 | 0 |
| Flank pain | 2803 | 1 | 0 | 0 |
| Flu like symptoms | 2803 | 1 | 0 | 0 |
| GI disorders-Other, specify | 2803 | 0 | 0 | 1 |
| Gastric hemorrhage | 2803 | 1 | 0 | 0 |
| Gastric ulcer | 2803 | 1 | 0 | 0 |
| Gastrointestinal pain | 2803 | 1 | 0 | 0 |
| Gen disorders/admin site cond | 2802 | 2 | 0 | 0 |
| Generalized muscle weakness | 2800 | 4 | 0 | 0 |
| Hand-Foot syndrome | 2799 | 5 | 0 | 0 |
| Headache | 2798 | 6 | 0 | 0 |
| Heart failure | 2803 | 1 | 0 | 0 |
| Hot flashes | 2791 | 13 | 0 | 0 |
| Hyperglycemia | 2791 | 13 | 0 | 0 |
| Hypertension | 2797 | 7 | 0 | 0 |
| Hypokalemia | 2800 | 4 | 0 | 0 |
| Hyponatremia | 2802 | 2 | 0 | 0 |
| Hypotension | 2800 | 4 | 0 | 0 |
| INR increased | 2803 | 1 | 0 | 0 |
| Infections/infestations-Other | 2801 | 2 | 1 | 0 |
| Injection site reaction | 2803 | 1 | 0 | 0 |
| Insomnia | 2799 | 5 | 0 | 0 |
| Irregular menstruation | 2803 | 1 | 0 | 0 |
| Kidney infection | 2803 | 1 | 0 | 0 |
| LV systolic dysfunction | 2803 | 1 | 0 | 0 |
| Leukocytosis | 2800 | 3 | 1 | 0 |
| Localized edema | 2802 | 2 | 0 | 0 |
| Lung infection | 2799 | 4 | 1 | 0 |
| Lymphedema | 2802 | 2 | 0 | 0 |
| Lymphocyte count decreased | 2788 | 15 | 1 | 0 |
| Mucositis oral | 2787 | 17 | 0 | 0 |
| Myalgia | 2782 | 22 | 0 | 0 |
| Myocardial infarction | 2803 | 1 | 0 | 0 |
| Nail infection | 2803 | 1 | 0 | 0 |
| Nausea | 2789 | 15 | 0 | 0 |
| Neck pain | 2802 | 2 | 0 | 0 |
| Neoplasms, all | 2803 | 1 | 0 | 0 |

| | Total (n=2804) Grade | | | |
|---|---|---|---|---|
| **ADVERSE EVENTS** | **<=2** | **3** | **4** | **5** |
| Nervous sys disorders-Other | 2802 | 2 | 0 | 0 |
| Neutrophil count decreased | 2705 | 32 | 67 | 0 |
| Pain | 2801 | 3 | 0 | 0 |
| Pain in extremity | 2801 | 3 | 0 | 0 |
| Paresthesia | 2803 | 1 | 0 | 0 |
| Peripheral ischemia | 2803 | 1 | 0 | 0 |
| Peripheral motor neuropathy | 2801 | 2 | 1 | 0 |
| Peripheral sensory neuropathy | 2788 | 15 | 1 | 0 |
| Platelet count decreased | 2803 | 1 | 0 | 0 |
| Pneumonitis | 2798 | 6 | 0 | 0 |
| Pruritus | 2801 | 3 | 0 | 0 |
| ROM decreased | 2803 | 1 | 0 | 0 |
| RT recall reaction, derm | 2803 | 1 | 0 | 0 |
| Rash acneiform | 2803 | 1 | 0 | 0 |
| Rash maculo-papular | 2799 | 5 | 0 | 0 |
| Renal/urinary disorders-Other | 2803 | 1 | 0 | 0 |
| Sepsis | 2800 | 0 | 3 | 1 |
| Skin infection | 2799 | 5 | 0 | 0 |
| Skin/subq tissue ds-Other | 2803 | 1 | 0 | 0 |
| Stroke | 2803 | 0 | 0 | 1 |
| Suicidal ideation | 2803 | 1 | 0 | 0 |
| Syncope | 2802 | 2 | 0 | 0 |
| Thromboembolic event | 2796 | 6 | 2 | 0 |
| Tinnitus | 2803 | 1 | 0 | 0 |
| Typhlitis | 2803 | 0 | 0 | 1 |
| Upper GI hemorrhage | 2803 | 0 | 1 | 0 |
| Urinary tract infection | 2801 | 3 | 0 | 0 |
| Urticaria | 2801 | 3 | 0 | 0 |
| Uterine hemorrhage | 2803 | 1 | 0 | 0 |
| Vaginal dryness | 2801 | 3 | 0 | 0 |
| Vascular access complication | 2803 | 1 | 0 | 0 |
| Vomiting | 2792 | 12 | 0 | 0 |
| Watering eyes | 2800 | 4 | 0 | 0 |
| Weight gain | 2803 | 1 | 0 | 0 |
| Weight loss | 2802 | 2 | 0 | 0 |
| White blood cell decreased | 2754 | 33 | 17 | 0 |
| Wound dehiscence | 2803 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 2422 | 290 | 88 | 4 |

# S1008 Phase II

# Feasibility Study of a Physical Activity and Dietary Change Weight Loss Intervention in Breast and Colorectal Cancer Survivors, Phase II

**Study Chairs:**
H Greenlee, D Hershman

**Statisticians:**
D Lew, J Unger

**Data Coordinator:**
D Marrah

**Date Activated:**
03/01/2012

**Date Closed:**
07/01/2014

**Objectives**

To determine the feasibility of a 12-month community-situated combined physical activity and dietary change weight loss intervention in overweight and sedentary female breast and colorectal cancer survivors recruited via SWOG. Feasibility will be assessed based on study accrual, intervention adherence, and study retention. Analyses will be conducted separately for breast and colorectal cancer survivors.

To estimate the effect size of the intervention on weight loss at 12 months.

To measure changes from baseline to 6 and 12 months in anthropometric measures (body mass index [BMI], waist and hip circumference) and changes from baseline to 12 months in body composition (% body fat as assessed by DXA scan).

To measure changes from baseline to 6 and 12 months in minutes spent per week in moderate-to-vigorous aerobic activity using Curves® attendance records and a 7-day physical activity assessment.

To measure changes from baseline to 6 and 12 months in self-reported dietary intake via three separate 24-hour diet recalls at each time point.

To measure changes from baseline to 6 and 12 months in dietary intake of carotenoids via serum carotenoid measures.

To measure changes from baseline to 6 and 12 months in metabolic and hormonal biomarkers associated with breast and colorectal cancer recurrence risk (fasting insulin, fasting glucose, hemoglobin A1C, bioavailable estradiol, free testosterone, and adiponectin).

To assess changes from baseline to 6 and 12 months in anxiety, depression, fatigue, sleep, satisfaction with social roles, pain and physical function using the PROMIS-43.

To assess changes from baseline to 6 and 12 months in perceived benefit of dietary change, physical activity and weight loss after a cancer diagnosis.

To assess the diversity of subjects who enroll and complete the intervention.

To assess baseline predictors (medical history, health behaviors, quality of life) of subjects who adhere to and complete the intervention.

To assess the safety of the Curves® fitness centers for this population by assessing self-reported changes in lymphedema and any injuries as measured at 6 and 12 months.

To assess the availability and acceptability of the Curves® fitness centers at 12 months.

To assess the acceptability of the dietary change component of the intervention at 12 months.

To explore changes in DNA methylation.

To assess the intervention and study process via open-ended interviews with SWOG sites and Curves® franchises.

To measure changes in anthropometric measures and assess feasibility of extended follow-up at 24 and 36 months.

**Patient Population**

Participants must be women with a previous diagnosis of invasive breast cancer or colorectal cancer, Stage I, II, or III, with no evidence of metastatic disease (M0). Participants must have no evidence of disease at the time of registration and no history of metastases. Participants must be post-menopausal as defined in the protocol.

Participants must be 90 days to 7 years post-surgery, chemotherapy, and radiation therapy. Concurrent cytotoxic therapies, including Herceptin, are not allowed among breast cancer patients. Other concurrent therapies are allowed among breast cancer patients, including IV bisphosphonates (e.g., Zometa), RANK ligand inhibitors (e.g., Xgeva, Prolia), and anti-hormonal therapies (e.g., aromatase inhibitors). Participants must not have had weight loss surgery.

Participants must be considered sedentary as defined in the protocol, have a BMI $\geq$ 25 kg/m2 and a Zubrod performance status of 0. Participants must have no abnormal changes on cardiovascular exercise stress test as measured by EKG. Participants must not be active smokers or have evidence of uncontrolled hypertension. Participants with diabetes, pre-diabetes, and/or metabolic syndrome must have HgbA1C $\leq$ 8. Participants must be willing and able to attend a Curves® fitness center at least three times per week for 12 months and agree to participate in the behavioral counseling sessions and telephone interviews. Participants must be willing to submit blood samples for biomarkers. Participants must have physician clearance to participate, regular access to the internet, a home phone or cell phone, and be able to understand, speak and read English.

**Stratification/Descriptive Factors**

Participants will be stratified at time of registration by type of cancer: breast vs colorectal.

**Accrual Goals**

The accrual goal is 25 eligible breast cancer survivors and 25 eligible colorectal cancer survivors.

**Summary Statement**

For the current status of this study, please refer to the Cancer Survivorship chapter.

# S1200 Phase III

# Randomized Blinded Sham- and Waitlist-Controlled Trial of Acupuncture for Joint Symptoms Related to Aromatase Inhibitors in Women with Early Stage Breast Cancer

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**Study Chairs:**
D Hershman, K Crew

**Date Activated:**
03/27/2012

**Statisticians:**
J Unger, D Lew

**Data Coordinator:**
D Marrah

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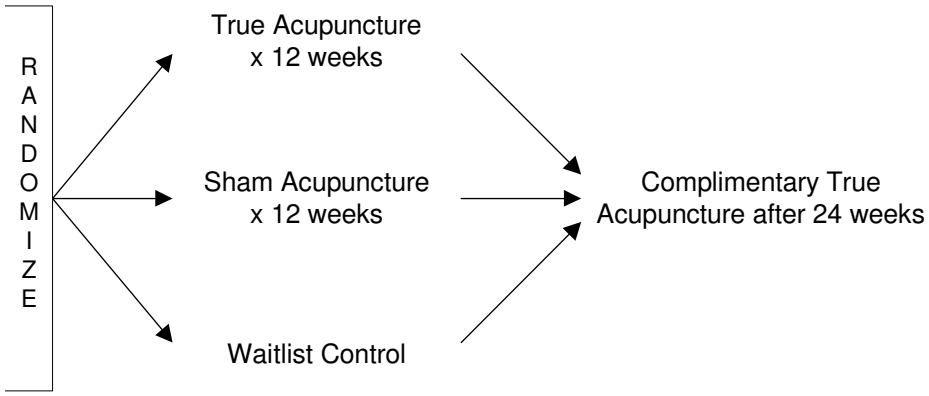
## SCHEMA




**Objectives**

To determine whether true acupuncture administered twice weekly for six weeks compared to sham acupuncture and waitlist control causes a significant reduction in joint pain related to aromatase inhibitors (AIs) in women with early stage breast cancer as measured by the Brief Pain Inventory-Short Form (BPI-SF) worst pain score at six weeks.

To evaluate the effects of acupuncture on the Brief Pain Inventory-Short Form (BPI-SF) worst pain, worst stiffness, pain severity, and pain-related interference scores.

To evaluate the effects of acupuncture on Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (pain, stiffness, and function) for the hips and knees.

To evaluate the effects of acupuncture on Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) (pain, stiffness, and function).

To evaluate the effects of acupuncture on the PROMIS Pain Impact-Short Form (PROMIS PI-SF).

To evaluate the effects of acupuncture on quality of life (QOL) as assessed by the Functional Assessment of Cancer Therapy-Endocrine Subscales (FACT-ES).

To evaluate the effects of acupuncture on functional testing with grip strength and "Timed Get Up and Go" (TGUG) test.

To evaluate the effects of acupuncture on analgesic and opioid use.

To evaluate the effects of acupuncture on self-reported AI adherence.

To assess AI adherence via urine AI metabolites.

To evaluate the effects of acupuncture on serum hormones (estradiol, FSH, LH) and inflammatory biomarkers (serum TNFá, IL-6, IL-12, CRP and urine CTX-II).

To evaluate whether polymorphisms in CYP19A1 aromatase gene predict severity of AI-related joint symptoms.

To assess the safety and tolerability of acupuncture in this study population.

**Patient Population**

Patients must be women with histologically confirmed primary invasive carcinoma of the breast (Stage I, II, or III) with no evidence of metastatic disease (M0), or with histologically confirmed DCIS. Patients must have ER and/or PgR positive disease.

If patient has undergone breast cancer surgery, she must have recovered from all side-effects of the surgery. Patients must currently be taking a third-generation aromatase inhibitor (anastrazole, letrozole, or exemestane) for at least the previous 30 days prior to registration, with plans to continue for at least an additional one year. Patients may have switched AIs provided that they have been on a stable dose for at least 30 days. Concurrent trastuzumab (Herceptin) is allowed.

Patients must have had two or fewer acupuncture treatments within the past 12 months for any reason except for joint symptoms. Patients must not have had prior acupuncture treatment for joint symptoms at any time. Patients must not be on narcotics or have received topical analgesics to the study joint or any other analgesics with the exception of NSAIDS and acetaminophen within 14 days prior to registration. Patients must not have received oral corticosteroids, intramuscular corticosteroids, or intra-articular steroids for joint symptoms within 28 days prior to registrations. Patients must not have received or implemented any other medical therapy, alternative therapy, or physical therapy for the treatment of joint pain/stiffness within 28 days prior to registration. Therapeutic massage is allowed. Patients must not have a history of bone fracture or surgery of the afflicted knees and/or hands within six months prior to registration.

Patients must be post-menopausal as defined in the protocol and have a Zubrod performance status of 0-1. Patients must have completed the S1200 Brief Pain Inventory - Short Form within 14 days prior to registration and have a worst pain score of at least 3 that has started or increased since starting AI therapy. Patients must not have a severe bleeding disorder, an allergy to latex, or concurrent medical/arthritic disease that could confound or interfere with evaluation of pain or efficacy. Patients must be willing to submit blood and urine for correlative analyses as specified in the protocol. Patients must be able to complete study questionnaires in English or Spanish.

**Stratification/Descriptive Factors**

Patients will be randomized using a 2:1:1 ratio to true acupuncture vs. sham acupuncture vs. waitlist control. Patient randomization will be dynamically balanced according to study site at time of registration.

**Accrual Goals**

A total of 228 patients will be enrolled to achieve 208 eligible patients.

**Summary Statement**

For the current status of this study, please refer to the Symptom Control and QOL chapter.

# S1202 Phase III

# A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer

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**Study Chairs:**
N Henry, A Schott

**Date Activated:**
05/15/2013

**Statisticians:**
J Unger, D Lew

**Data Coordinator:**
R Topacio

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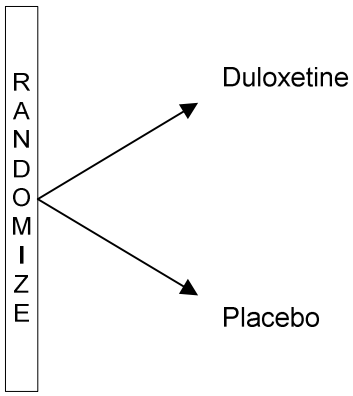
## SCHEMA




**Objectives**

To assess whether daily duloxetine decreases average joint pain in women with aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), as measured at 12 weeks by the modified Brief Pain Inventory Short Form (BPISF).

To assess whether daily duloxetine decreases worst joint pain in women with AIMSS, as measured at 12 weeks by the modified BPI-SF.

To assess whether daily duloxetine decreases pain interference in women with AIMSS, as measured at 12 weeks by the modified BPI-SF.

To investigate whether daily duloxetine improves functioning, pain, and stiffness in the knees/hips according to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scale.

To investigate whether daily duloxetine improves function, pain and stiffness in the hands according to the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH).

To investigate whether daily duloxetine improves functional quality of life as measured by the Functional Assessment of Cancer Therapy-Endocrine Scale (FACT-ES).

To investigate whether daily duloxetine improves the proportion of patients reporting changes for the better versus worst as measured by the Global Rating of Change Scale.

To investigate whether daily duloxetine improves/decreases analgesic use.

To investigate whether daily duloxetine improves/increases adherence to, and reduces the discontinuation rate for, aromatase inhibitor (AI) therapy.

To assess whether patients receiving duloxetine as compared to placebo have improved depression as measured by the Patient Health Questionnaire (PHQ-9) at Weeks 6 and 12 (for patients experiencing depression at baseline).

To explore the relationship between inherited variants in genes responsible for duloxetine metabolism and activity (COMT, HTR3A, SLC6A2, SLC6A4, CYP1A2, CYP2D6) and aromatase (CYP19A1) andchange inpain with 12 weeks of treatment.

To explore the impact of treatment on serum inflammatory cytokine levels with 12 weeks of treatment at baseline and 12 weeks.

To bank blood samples for future correlative analyses.

**Patient Population**

Patients must be women with histologically confirmed ER and/or PgR positive invasive carcinoma of the breast with no evidence of metastatic disease (M0).

Patients must have completed mastectomy or breast sparing surgery and have recovered from all side-effects of the surgery. Any chemotherapy and/or radiation therapy must be completed at least 28 days prior to registration, and patients must have recovered from all Grade 2 or higher side effects with the exception of alopecia and peripheral neuropathy. Concurrent bisphosphonate and trastuzumab therapies are allowed. Patients must currently be taking one of the following aromatase inhibitor (AI) doses for at least 21 days with plans to continue for at least an additional 180 days after registration: anastrozole 1 mg daily, letrozole 2.5 mg daily, or exemestane 25 mg daily. Patients may have received any number of prior AI therapies, but the first AI therapy must have started no more than 36 months prior to registration. Patients must not have previously taken the serotonin norepinephrine reuptake inhibitors (SNRI) duloxetine or milnacipran. Patients must not require selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants during study participation. Prior venlafaxine is allowed as long as it was not taken for treatment of pain (e.g., prior treatment for hot flashes is permitted). Patients must not take MAO-inhibitors for 14 days before registration or any time during study treatment. Concommitant therapy with heparin and warfarin is also not permitted at registration or while on protocol treatment. Aspirin is permitted.

Patients must be post-menopausal as defined in the protocol and have adequate renal and hepatic function and a Zubrod performance status of 0-2. Patients must have AI associated musculoskeletal symptoms that began or increased after starting AI therapy. New musculoskeletal pain must not be due specifically to fracture or traumatic injury. Patients must have completed the S1202 Brief Pain Inventory - Short Form within 7 days prior to registration and have an average pain score of at least 4 (BPI-SF item #4). Patients must have no known allergy or hypersensitivity to duloxetine or any of the inactive ingredients in the matching placebo. Patients must not have any contraindicated concurrent illnesses or be taking any contraindicated medications listed on the duloxetine package insert including anticoagulation medicine. Patients must not have concurrent medical/arthritic disease that could confound or interfere with evaluation of pain or efficacy. Patients who are receiving treatment with narcotics, tramadol, gabapentin, and/or pregabalin must have been taking a stable dose for at least 30 days prior to registration. Patients must be willing to submit blood samples for correlative analyses as specified in the protocol. Patients must be able to complete study questionnaires in English or Spanish.

**Stratification/Descriptive Factors**

Patient randomization will be dynamically balanced according to the following stratification factors: (1) baseline pain score (BPI-SF item #4): 4-6 vs 7-10; and (2) prior taxane use: yes vs no.

**Accrual Goals**

A total of 294 patients will be enrolled to achieve 270 eligible patients.

**Summary Statement**

For the current status of this study, please refer to the Symptom Control and QOL chapter.

# S1204 Surveillance

# A Sero-Epidemiologic Survey and Cost-Effectiveness Study of Screening for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Among Newly Diagnosed Cancer Patients

**Study Chairs:**
S Ramsey, R Loomba, R Chugh, D Hershman, J Hwang

**Date Activated:**
08/29/2013

**Statisticians:**
J Unger, K Arnold

**Data Coordinator:**
M Yee

**Objectives**

Among newly diagnosed cancer patients presenting to SWOG-affiliated community and academic oncology clinics, estimate the prevalence of human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) infection.

Evaluate known sociodemographic, clinical, and behavioral factors that are significantly associated with previously undiagnosed HIV, HBV, and/or HCV infection in a population of people with newly diagnosed cancer.

Among patients who are identified as having HIV, HBV, and/or HCV, evaluate the timing and type of treatments received, both for the viral infections and the cancers.

Evaluate type and rate of cancer treatment-related adverse events in patients with HIV, HBV, and/or HCV infection.

Determine the cost-effectiveness of (1) routine, universal screening and (2) risk factor-directed screening of newly diagnosed cancer patients for HIV, HBV and/or HCV versus current care.

Create a biorepository of stored serum for future translational medicine studies that may include identifying genomic and viral factors that increase the risk of serious adverse effects among participants infected with HIV, HBV, and/or HCV being treated for invasive cancers.

**Patient Population**

Patients must be presenting for evaluation or treatment for the first diagnosis of a new solid or hematologic cancer malignancy. Confirmed diagnosis date must be within 120 days prior to first clinic visit as a newly diagnosed cancer patient at the registering clinic. Patients presenting for "second opinions" of confirmed malignancies are eligible, including those who have started cancer treatment at other facilities. Patients must be registered within 90 days after their first clinic visit. Patients must not have been diagnosed with a malignancy other than the current malignancy within the past five years, with the exception of basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ breast cancer. Patients must have no evidence of disease for a prior malignancy for at least five years prior to randomization except as noted above.

Patients must be 18 years of age or older. Patients must have had their blood drawn for viral status testing for HIV, HBV and HCV or provide acceptable viral status documentation prior to registration, as defined in the protocol. Note that patients must have blood drawn for testing prior to registration for any of the three viruses not covered by the documentation. Patients are allowed to participate in other clinical trials.

**Accrual Goals**

A total of 3,000 eligible patients will be accrued.

**Summary Statement**

For the current status of this study, please refer to the Cancer Care Delivery chapter.

# S1207 Phase III

**Coordinating Groups: SWOG and NRG**

# Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine Therapy +/- One Year of Everolimus in Patients with High-Risk, Hormone Receptor-Positive and Her2/neu Negative Breast Cancer

## e3 Breast Cancer Study - evaluating everolimus with endocrine therapy

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**Participants:**
SWOG, CTSU, NRG

**Date Activated:**
09/03/2013

**Study Chairs:**
M Chavez MacGregor, P Ganz (NRG), L Pusztai, P Rastogi (NRG)

**Statisticians:**
W Barlow, D Lew

**Data Coordinators:**
J Barrett, I Syquia

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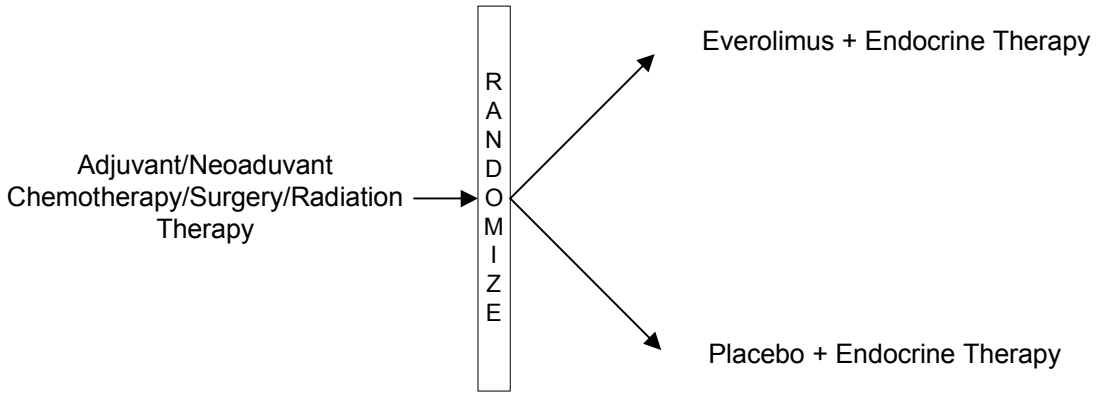
## SCHEMA




**Objectives**

To compare whether the addition of one year of everolimus (10 mg daily) to standard adjuvant endocrine therapy improves invasive disease-free survival (IDFS) in patients with high-risk, hormone-receptor (HR) positive and HER2-negative breast cancer.

To compare whether the addition of one year of everolimus to standard adjuvant endocrine therapy improves overall survival (OS) and distant recurrence-free survival (DRFS) in this patient population.

To evaluate the safety, toxicities, and tolerability of one year of everolimus in combination with standard

adjuvant endocrine therapy and compare it with standard adjuvant endocrine therapy plus placebo in this patient population.

To determine whether the benefit of one year of everolimus use in addition to standard adjuvant endocrine therapy varies by recurrence score (RS), nodal status, or other commonly used prognostic factors.

To evaluate adherence to 1-year treatment of everolimus in comparison to placebo in addition to standard adjuvant endocrine therapy in this patient population.

To collect specimens in order to evaluate biomarkers of therapeutic efficacy.

**Patient Population**

Patients must have histologically confirmed invasive breast carcinoma with positive ER and/or PgR status and negative HER-2, for whom standard adjuvant endocrine therapy is planned. Patients must not have metastatic breast cancer. Patients with multifocal, multicentric, synchronous bilateral, and primary inflammatory breast cancers are allowed. Patients must be high risk as defined in the protocol, based on Recurrence Score and grade, number of positive nodes, and prior therapy. Patients with micrometastases as the only nodal involvement (pN1mi) are not eligible.

Patients must have completed either breast-conserving surgery or total mastectomy with negative margins and appropriate axillary staging. Patients must have completed appropriate radiation therapy as described in the protocol. Patients must have completed standard neoadjuvant or adjuvant taxane and/or anthracycline based chemotherapy prior to randomization. Patients may have started endocrine therapy at any time after the diagnosis of the current breast cancer. Patients must not be receiving or planning to receive trastuzumab. Concurrent bisphosphonate therapy is allowed. Patients must not have prior exposure to mTOR inhibitors.

Patients must have a Zubrod performance status of 0-2 and adequate hematologic, hepatic, renal, and cardiac function. Patients must not have received immunization with an attenuated live vaccine within seven days prior to registration. Patients must be able to take oral medications. Patients at NCORP institutions who have not already started endocrine therapy must be offered the opportunity to participate in the Behavioral and Health Outcomes (BAHO) substudy.

**Stratification/Descriptive Factors**

Patient randomization will be stratified by risk level as described in the protocol based on Recurrence Score and grade, number of positive nodes, and prior therapy.

**Accrual Goals**

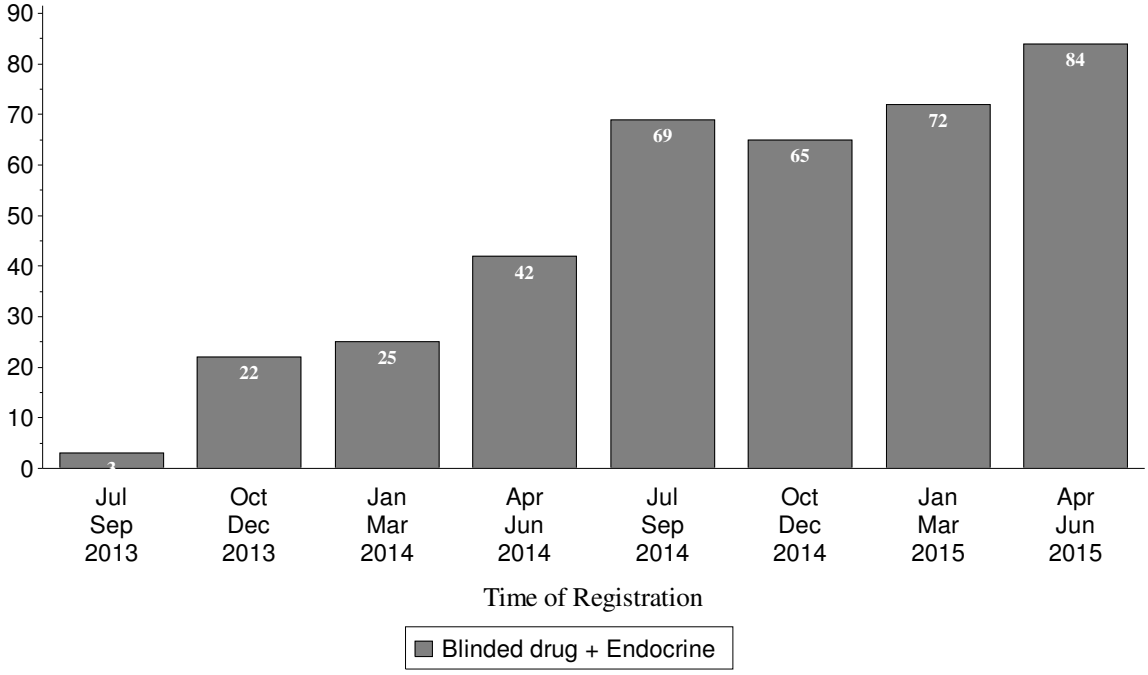
The accrual goal is 3,500 eligible patients. Interim analyses are planned for after approximately 39%, 60%, and 81% of the events in the control arm have been observed.

**Summary Statement**

This study was activated on September 3, 2013. As of June 30, 2015, there had been 382 patients enrolled. Twenty-two patients are currently ineligible, the most common reasons being registration on study too soon after completion of radiation therapy or too late after completion of chemotherapy. Major deviations are coded for nine patients who received no protocol treatment; these nine patients are not evaluable for adverse events, along with an additional patient who discontinued protocol treatment without being assessed for adverse events.

There have been six patients with Grade 4 toxicities reported among 317 patients evaluated for adverse events, including three with Grade 4 hypertriglyceridemia. Fifty patients experienced Grade 3 adverse events as maximum degree, including nine cases of mucositis oral. The Grade 3 "Investigations-Other, specify" was decreased neutrophils, the Grade 3 "Eye disorders - Other, specify" was herpes simplex keratoconjunctivitis, the Grade 3 "GI disorders - Other, specify" was enteritis requiring two hospitalizations, and the four cases of Grade 3 "Infections/infestations-Other" were abscess, cellulitis, continued soft tissue infection, and pending review. Toxicities are reviewed by treatment group by the Data Safety and Monitoring Committee, the SWOG Breast Committee leadership, and the Study Chair.

## Initial Registrations By 3 Month Intervals




## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Alliance | 83 | CRC West MI NCORP | 3 |
| ECOG-ACRIN | 68 | Davis, U of CA | 3 |
| NRG | 56 | Kaiser Vallejo NCORP | 3 |
| MD Anderson CC | 10 | Michigan CRC NCORP | 3 |
| Michigan, U of | 8 | Northwestern Univ/San Diego, U of CA | 3 |
| Yale University | 8 | Ozarks NCORP | 3 |
| Cedars-Sinai Med Ctr | 7 | Southeast COR NCORP | 3 |
| Fred Hutchinson CRC | 6 | Sutter Cancer RC | 3 |
| Gulf South MU-NCORP | 6 | Thompson Ca Surv Ctr/San Antonio, U of TX | 3 |
| Arizona MC, U of | 5 | Baylor Univ Med Ctr | 2 |
| City of Hope Med Ctr | 5 | Beaumont NCORP | 2 |
| Heartland NCORP | 5 | Columbia MU-NCORP | 2 |
| Kansas, U of | 5 | Loma Linda Univ | 2 |
| MUSC MU-NCORP | 5 | LSU-Shreveport/Gulf South MU-NCORP | 2 |
| New Mexico MU-NCORP | 5 | Mem Hosp, Co Springs/Colorado, U of | 2 |
| Oklahoma, Univ of | 5 | PCRC NCORP | 2 |
| Wichita NCORP | 5 | Rochester, Univ of | 2 |
| Columbus NCORP | 4 | Sacred Heart Hosp/Arkansas, U of | 2 |
| Good Samaritan Hosp/Oregon Hlth Sci Univ | 4 | San Antonio, U of TX | 2 |
| H Lee Moffitt CC | 4 | St Charles Hlth Sys/PCRC NCORP | 2 |
| Wayne State Univ | 4 | All Other Institutions | 19 |
| Cincinnati MC, U of | 3 | **Total (62 Institutions)** | **382** |
| Cleveland Clinic OH | 3 | | |

## Registration, Eligibility, and Evaluability

Registrations ending June 30, 2015; Data as of August 25, 2015

| | Total |
|---|---|
| NUMBER REGISTERED | 382 |
| INELIGIBLE | 22 |
| ELIGIBLE | 360 |
| Analyzable, Pend. Elig. | 19 |
| ADVERSE EVENT ASSESSMENT | |
| Evaluable | 317 |
| Not Evaluable | 10 |
| Too Early | 33 |

## Patient Characteristics

Registrations ending June 30, 2015; Data as of August 25, 2015

| | Total (n=360) | |
|---|---|---|
| AGE | | |
| Median | 54.5 | |
| Minimum | 29.4 | |
| Maximum | 76.2 | |
| SEX | | |
| Males | 1 | 0% |
| Females | 359 | 100% |
| HISPANIC | | |
| Yes | 24 | 7% |
| No | 327 | 91% |
| Unknown | 9 | 2% |
| RACE | | |
| White | 314 | 87% |
| Black | 19 | 5% |
| Asian | 13 | 4% |
| Pacific Islander | 1 | 0% |
| Native American | 3 | 1% |
| Multi-Racial | 1 | 0% |
| Unknown | 9 | 2% |
| RISK GROUP | | |
| Node-negative and RS > 25 treated with adjuvant chemotherapy | 29 | 8% |
| 1-3 positive lymph nodes and RS > 25 or Grade III disease treated with adjuvant chemotherapy | 42 | 12% |
| ≥ 4 positive lymph nodes (any RS value) treated with adjuvant chemotherapy | 219 | 61% |
| ≥ 1 positive lymph node (any RS value) with neoadjuvant chemotherapy | 70 | 19% |

## Treatment Summary

Registrations ending June 30, 2015; Data as of August 25, 2015

| | Total |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 205 |
| NUMBER OFF PROTOCOL TREATMENT | 155 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 44 |
| Adverse Event or side effects | 55 |
| Refusal unrelated to adverse event | 26 |
| Progression/relapse | 8 |
| Death | 0 |
| Other - not protocol specified | 4 |
| Reason under review | 18 |
| MAJOR PROTOCOL DEVIATIONS | 9 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending June 30, 2015; Data as of August 25, 2015

| | Total (n=317) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| ALT increased | 291 | 21 | 3 | 2 | 0 | 0 |
| AST increased | 286 | 27 | 2 | 2 | 0 | 0 |
| Abdominal pain | 309 | 5 | 1 | 2 | 0 | 0 |
| Agitation | 315 | 1 | 1 | 0 | 0 | 0 |
| Alkaline phosphatase increased | 305 | 10 | 2 | 0 | 0 | 0 |
| Allergic rhinitis | 316 | 1 | 0 | 0 | 0 | 0 |
| Alopecia | 307 | 10 | 0 | 0 | 0 | 0 |
| Anal mucositis | 316 | 1 | 0 | 0 | 0 | 0 |
| Anemia | 282 | 24 | 10 | 1 | 0 | 0 |
| Anorexia | 292 | 20 | 5 | 0 | 0 | 0 |
| Anxiety | 313 | 4 | 0 | 0 | 0 | 0 |
| Arthralgia | 276 | 26 | 15 | 0 | 0 | 0 |
| Arthritis | 313 | 2 | 2 | 0 | 0 | 0 |
| Ataxia | 316 | 1 | 0 | 0 | 0 | 0 |
| Atrial fibrillation | 316 | 0 | 1 | 0 | 0 | 0 |
| Back pain | 311 | 5 | 1 | 0 | 0 | 0 |
| Bladder infection | 315 | 0 | 2 | 0 | 0 | 0 |
| Bloating | 313 | 3 | 1 | 0 | 0 | 0 |
| Blood/lymph disorder-Other | 316 | 1 | 0 | 0 | 0 | 0 |
| Bone pain | 312 | 4 | 1 | 0 | 0 | 0 |
| Breast infection | 315 | 0 | 1 | 1 | 0 | 0 |
| Bronchial infection | 315 | 0 | 2 | 0 | 0 | 0 |
| Bullous dermatitis | 315 | 1 | 1 | 0 | 0 | 0 |
| CPK increased | 316 | 0 | 1 | 0 | 0 | 0 |
| Chest wall pain | 316 | 1 | 0 | 0 | 0 | 0 |
| Chills | 312 | 5 | 0 | 0 | 0 | 0 |

| | Total (n=317) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| Cholesterol high | 238 | 64 | 14 | 1 | 0 | 0 |
| Cognitive disturbance | 316 | 1 | 0 | 0 | 0 | 0 |
| Concentration impairment | 316 | 1 | 0 | 0 | 0 | 0 |
| Confusion | 316 | 1 | 0 | 0 | 0 | 0 |
| Constipation | 304 | 12 | 1 | 0 | 0 | 0 |
| Cough | 302 | 14 | 1 | 0 | 0 | 0 |
| Creatinine increased | 315 | 2 | 0 | 0 | 0 | 0 |
| Dehydration | 316 | 1 | 0 | 0 | 0 | 0 |
| Delayed orgasm | 316 | 1 | 0 | 0 | 0 | 0 |
| Depression | 315 | 2 | 0 | 0 | 0 | 0 |
| Diarrhea | 274 | 33 | 8 | 2 | 0 | 0 |
| Dizziness | 308 | 8 | 1 | 0 | 0 | 0 |
| Dry eye | 316 | 1 | 0 | 0 | 0 | 0 |
| Dry mouth | 292 | 22 | 3 | 0 | 0 | 0 |
| Dry skin | 302 | 13 | 2 | 0 | 0 | 0 |
| Dysgeusia | 295 | 20 | 2 | 0 | 0 | 0 |
| Dyspareunia | 316 | 1 | 0 | 0 | 0 | 0 |
| Dyspepsia | 312 | 5 | 0 | 0 | 0 | 0 |
| Dysphagia | 315 | 2 | 0 | 0 | 0 | 0 |
| Dyspnea | 299 | 12 | 5 | 1 | 0 | 0 |
| Ear pain | 316 | 0 | 1 | 0 | 0 | 0 |
| Edema face | 316 | 1 | 0 | 0 | 0 | 0 |
| Edema limbs | 303 | 9 | 5 | 0 | 0 | 0 |
| Edema trunk | 315 | 2 | 0 | 0 | 0 | 0 |
| Epistaxis | 313 | 4 | 0 | 0 | 0 | 0 |
| Eye disorders - Other, specify | 312 | 3 | 1 | 1 | 0 | 0 |
| Eye infection | 316 | 0 | 1 | 0 | 0 | 0 |
| Facial nerve disorder | 316 | 1 | 0 | 0 | 0 | 0 |
| Fatigue | 210 | 74 | 28 | 5 | 0 | 0 |
| Fever | 314 | 2 | 1 | 0 | 0 | 0 |
| Flatulence | 313 | 4 | 0 | 0 | 0 | 0 |
| Floaters | 316 | 1 | 0 | 0 | 0 | 0 |
| Flu like symptoms | 316 | 0 | 1 | 0 | 0 | 0 |
| Flushing | 313 | 4 | 0 | 0 | 0 | 0 |
| GI disorders-Other, specify | 301 | 13 | 2 | 1 | 0 | 0 |
| Gastrointestinal pain | 316 | 1 | 0 | 0 | 0 | 0 |
| Gen disorders/admin site cond | 313 | 3 | 1 | 0 | 0 | 0 |
| Generalized muscle weakness | 315 | 2 | 0 | 0 | 0 | 0 |
| Hand-Foot syndrome | 315 | 0 | 2 | 0 | 0 | 0 |
| Headache | 283 | 26 | 8 | 0 | 0 | 0 |
| Hemoglobin increased | 316 | 1 | 0 | 0 | 0 | 0 |
| Hoarseness | 316 | 1 | 0 | 0 | 0 | 0 |
| Hot flashes | 285 | 27 | 4 | 1 | 0 | 0 |
| Hypercalcemia | 316 | 1 | 0 | 0 | 0 | 0 |
| Hyperglycemia | 278 | 31 | 4 | 4 | 0 | 0 |
| Hyperhidrosis | 316 | 0 | 0 | 1 | 0 | 0 |
| Hyperkalemia | 316 | 1 | 0 | 0 | 0 | 0 |
| Hypertension | 305 | 7 | 5 | 0 | 0 | 0 |
| Hypertriglyceridemia | 257 | 40 | 13 | 4 | 3 | 0 |
| Hypoalbuminemia | 309 | 7 | 1 | 0 | 0 | 0 |
| Hypocalcemia | 315 | 2 | 0 | 0 | 0 | 0 |

| | Total (n=317) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| Hypokalemia | 310 | 4 | 2 | 1 | 0 | 0 |
| Hypomagnesemia | 316 | 1 | 0 | 0 | 0 | 0 |
| Hyponatremia | 315 | 2 | 0 | 0 | 0 | 0 |
| Hypoxia | 316 | 0 | 0 | 1 | 0 | 0 |
| Immune sys disorders-Other | 314 | 3 | 0 | 0 | 0 | 0 |
| Infections/infestations-Other | 311 | 1 | 1 | 4 | 0 | 0 |
| Insomnia | 293 | 21 | 2 | 1 | 0 | 0 |
| Investigations-Other, specify | 314 | 2 | 0 | 1 | 0 | 0 |
| Irregular menstruation | 316 | 1 | 0 | 0 | 0 | 0 |
| Libido decreased | 316 | 0 | 1 | 0 | 0 | 0 |
| Libido increased | 316 | 1 | 0 | 0 | 0 | 0 |
| Lip infection | 316 | 1 | 0 | 0 | 0 | 0 |
| Lipase increased | 316 | 0 | 0 | 0 | 1 | 0 |
| Lung infection | 313 | 0 | 2 | 2 | 0 | 0 |
| Lymph node pain | 316 | 1 | 0 | 0 | 0 | 0 |
| Lymphedema | 312 | 2 | 3 | 0 | 0 | 0 |
| Lymphocyte count decreased | 273 | 20 | 19 | 4 | 1 | 0 |
| MS/connective tissue disorder | 309 | 6 | 2 | 0 | 0 | 0 |
| Malaise | 312 | 3 | 2 | 0 | 0 | 0 |
| Metab/nutrition disorders-Oth | 315 | 2 | 0 | 0 | 0 | 0 |
| Mucosal infection | 314 | 0 | 3 | 0 | 0 | 0 |
| Mucositis oral | 204 | 69 | 35 | 9 | 0 | 0 |
| Muscle weakness upper limb | 316 | 1 | 0 | 0 | 0 | 0 |
| Myalgia | 306 | 8 | 3 | 0 | 0 | 0 |
| Myositis | 316 | 1 | 0 | 0 | 0 | 0 |
| Nail discoloration | 315 | 2 | 0 | 0 | 0 | 0 |
| Nail loss | 316 | 1 | 0 | 0 | 0 | 0 |
| Nausea | 275 | 34 | 6 | 2 | 0 | 0 |
| Neoplasms, all | 316 | 1 | 0 | 0 | 0 | 0 |
| Nervous sys disorders-Other | 316 | 0 | 1 | 0 | 0 | 0 |
| Neuralgia | 316 | 0 | 0 | 1 | 0 | 0 |
| Neutrophil count decreased | 294 | 10 | 11 | 2 | 0 | 0 |
| Non-cardiac chest pain | 314 | 2 | 1 | 0 | 0 | 0 |
| Oral dysesthesia | 316 | 1 | 0 | 0 | 0 | 0 |
| Oral pain | 309 | 5 | 3 | 0 | 0 | 0 |
| Otitis externa | 316 | 0 | 1 | 0 | 0 | 0 |
| Otitis media | 315 | 0 | 2 | 0 | 0 | 0 |
| Pain | 309 | 7 | 1 | 0 | 0 | 0 |
| Pain in extremity | 309 | 7 | 1 | 0 | 0 | 0 |
| Palpitations | 315 | 2 | 0 | 0 | 0 | 0 |
| Paresthesia | 313 | 3 | 1 | 0 | 0 | 0 |
| Pelvic pain | 316 | 1 | 0 | 0 | 0 | 0 |
| Periorbital edema | 316 | 1 | 0 | 0 | 0 | 0 |
| Peripheral motor neuropathy | 315 | 0 | 2 | 0 | 0 | 0 |
| Peripheral sensory neuropathy | 305 | 9 | 1 | 2 | 0 | 0 |
| Personality change | 314 | 1 | 2 | 0 | 0 | 0 |
| Pharyngitis | 316 | 0 | 1 | 0 | 0 | 0 |
| Photosensitivity | 316 | 0 | 1 | 0 | 0 | 0 |
| Platelet count decreased | 293 | 18 | 5 | 1 | 0 | 0 |
| Pneumonitis | 312 | 1 | 3 | 1 | 0 | 0 |
| Postnasal drip | 316 | 1 | 0 | 0 | 0 | 0 |

| | Total (n=317) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| Presyncope | 315 | 0 | 2 | 0 | 0 | 0 |
| Productive cough | 316 | 0 | 0 | 1 | 0 | 0 |
| Pruritus | 301 | 14 | 2 | 0 | 0 | 0 |
| ROM decreased | 315 | 2 | 0 | 0 | 0 | 0 |
| Rash acneiform | 295 | 19 | 3 | 0 | 0 | 0 |
| Rash maculo-papular | 288 | 23 | 6 | 0 | 0 | 0 |
| Resp/thoracic/mediastinal ds | 315 | 2 | 0 | 0 | 0 | 0 |
| Sepsis | 316 | 0 | 0 | 0 | 1 | 0 |
| Sinusitis | 316 | 0 | 1 | 0 | 0 | 0 |
| Skin infection | 311 | 0 | 2 | 4 | 0 | 0 |
| Skin/subq tissue ds-Other | 308 | 7 | 2 | 0 | 0 | 0 |
| Sore throat | 316 | 1 | 0 | 0 | 0 | 0 |
| Stomach pain | 315 | 2 | 0 | 0 | 0 | 0 |
| Stomal ulcer | 316 | 0 | 1 | 0 | 0 | 0 |
| Thromboembolic event | 314 | 0 | 1 | 2 | 0 | 0 |
| Upper respiratory infection | 314 | 0 | 3 | 0 | 0 | 0 |
| Urinary frequency | 314 | 3 | 0 | 0 | 0 | 0 |
| Urinary tract infection | 316 | 0 | 0 | 1 | 0 | 0 |
| Urinary tract pain | 316 | 1 | 0 | 0 | 0 | 0 |
| Urinary urgency | 316 | 1 | 0 | 0 | 0 | 0 |
| Urticaria | 316 | 1 | 0 | 0 | 0 | 0 |
| Vaginal discharge | 315 | 2 | 0 | 0 | 0 | 0 |
| Vaginal dryness | 313 | 2 | 2 | 0 | 0 | 0 |
| Vaginal hemorrhage | 316 | 0 | 1 | 0 | 0 | 0 |
| Vaginal pain | 316 | 0 | 1 | 0 | 0 | 0 |
| Vascular access complication | 316 | 0 | 0 | 1 | 0 | 0 |
| Vertigo | 315 | 1 | 1 | 0 | 0 | 0 |
| Vomiting | 310 | 4 | 3 | 0 | 0 | 0 |
| Watering eyes | 316 | 1 | 0 | 0 | 0 | 0 |
| Weight gain | 312 | 4 | 1 | 0 | 0 | 0 |
| Weight loss | 308 | 7 | 2 | 0 | 0 | 0 |
| White blood cell decreased | 262 | 33 | 21 | 1 | 0 | 0 |
| Wound complication | 315 | 0 | 1 | 1 | 0 | 0 |
| Wound dehiscence | 316 | 0 | 0 | 1 | 0 | 0 |
| Wound infection | 314 | 0 | 2 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 68 | 81 | 112 | 50 | 6 | 0 |

# S1222 Phase III

# Fulvestrant Alone Versus Fulvestrant and Everolimus versus Fulvestrant, Everolimus and Anastrozole: A Phase III Randomized Placebo-Controlled Trial in Postmenopausal Patients with Hormone-Receptor-Positive Stage IV Breast Cancer

---

**Study Chairs:**
G Somlo, H Moore, D Hayes, P Kuhn, J Hicks

**Statisticians:**
W Barlow, D Lew

**Data Coordinator:**
L Kaye

**Date Activated:**
05/09/2014

**Date Closed:**
02/24/2015

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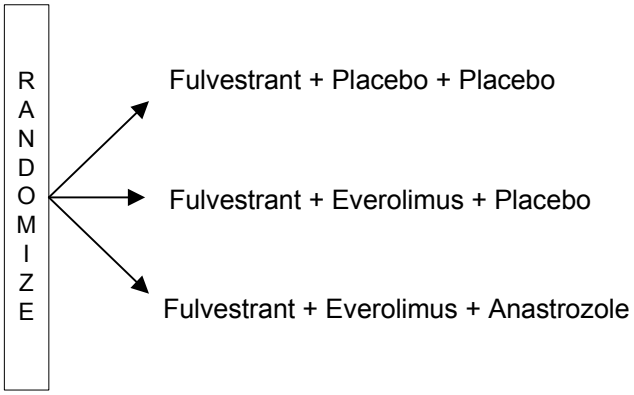
## SCHEMA




**Objectives**

To test the benefit of interfering with the function of the estrogen receptor (ER) and providing downstream target inhibition (PI3K/AKT/mTOR) with a combination of optimal dose fulvestrant and everolimus to improve progression-free survival compared to the optimal dose fulvestrant alone.

To test the benefit of adding the non-steroidal aromatase inhibitor anastrozole to optimal dose fulvestrant and everolimus in order to improve progression-free survival over optimal dose fulvestrant.

To compare progression-free survival among those receiving fulvestrant + everolimus + anastrozole versus fulvestrant + everolimus.

To compare overall survival among the treatment arms in post-menopausal patients with hormone-receptor positive (HR+) Stage IV breast cancer.

To assess and compare toxicities, feasibility and compliance among the study regimens.

To compare response rates and clinical benefit rates among the study regimens.

To test molecular determinants of response to endocrine therapy and everolimus in circulating tumor cells: CTC-Endocrine Therapy Index (CTC ETI) on the CellSearch® platform, and CTC-Next Generation Sequencing Analysis (CTC-NGS) of single cells captured on the HD-CTC® platform.

To collect and bank the following specimens for future research: Circulating Cell-Free DNA, Cancer Tissue, Germline DNA.

**Patient Population**

Patients must be post-menopausal women with a histologically confirmed diagnosis of metastatic invasive breast carcinoma with positive estrogen and/or progesterone receptor status, and negative HER-2, for whom endocrine therapy is planned. Pathologic confirmation of histology is preferable. Cytology-based diagnosis is allowed only if morphology, hormone-receptor and HER2 status can be assessed on such specimen. In the case of bone metastases only, biopsy-proven metastatic disease of solitary site, or multiple sites of involvement are required.

Patients must have measurable or non-measurable disease, with a chest/abdominal CT scan (PET/CT of diagnostic quality, coventional or spiral) and bone scan. Patients with a history of prior chemotherapy or hormone therapy or immunotherapy for recurrent or metastatic disease are not eligible. Prior adjuvant or neoadjuvant chemotherapy, if completed more than 12 months prior to registration, is acceptable. Any number of prior hormone therapy regimens for the adjuvant setting but not for metastatic or recurrent disease is allowed; prior adjuvant or neoadjuvant treatment with an aromatase inhibitor is allowed, if completed more than 12 months prior to registration. Patients who have taken LHRH analogue as adjuvant therapy are eligible provided they have discontinued such therapy at least 12 months prior to registration and have not resumed their menstrual periods. Patients must not have had prior exposure to fulvestrant or mTOR inhibitors. Radiation therapy to any site must be completed at least seven days prior to registration. Concurrent bisphosphonate therapy is allowed.

Patients must have a Zubrod performance status of 0-2 and adequate cardiac coagulation factors, triglycerides, hematologic, hepatic, and renal function. Patients with bleeding diathesis or long-term anti-coagulant therapy (other than anti-platelet therapy) are not eligible. Patients with presence of life-threatening metastatic visceral disease are not eligible. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not significantly compromised as a result of disease in the opinion of the investigator. Patients must not have uncontrolled diabetes. Patients must not have an organ allograft or other history of immune compromise. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed. Patients known to be HIV positive may be enrolled if meet protocol criteria. Patients with known chronic or active hepatitis are not eligible. Patients must not have any known uncontrolled underlying pulmonary disease. Patients must be able to take oral medications. Patients may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus. Patients must not have received immunization with an attenuated live vaccine within seven days prior to registration. Patients must not have taken within 14 days prior to registration, be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors, and/or CYP3A4 inducers. Specimen submission as outlined in the protocol is mandatory.

**Stratification/Descriptive Factors**

Patients will be stratified according to the following factors: (1) disease: measurable vs evaluable non-measurable disease; and (2) prior hormonal therapy: prior adjuvant hormonal therapy completed more than 5 years ago vs prior adjuvant hormonal therapy completed 1-5 years ago vs de novo presentation of metastatic disease or no prior adjuvant hormonal therapy.

**Accrual Goals**

The accrual goal is 825 eligible patients. Two interim analyses are planned at 50% and 75% of the expected events in Arm 1.

**Summary Statement**

This is not an NCI sponsored study. The study was activated on May 9, 2014, and closed on February 24, 2015, due to slow accrual. The sponsor subsequently made the decision to withdraw support and permanently close the study, with all patients being unblinded to treatment assignment and given the option to continue receiving the active agents on their assigned treatment arm. There were 37 patients registered prior to closure, with 19 currently still on treatment. A major deviation is recorded for one patient who received no protocol treatment; this patient is not evaluable for adverse events.

Among 36 patients assessed for adverse events, one experienced Grade 4 hypophosphatemia. Nine patients experienced Grade 3 toxicities as maximum degree.

## Registration by Institution

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Heartland NCORP | 6 | Yale University | 2 |
| City of Hope Med Ctr | 4 | Arkansas, U of | 1 |
| Michigan CRC NCORP | 4 | Bridgeport Hospital/Yale University | 1 |
| Montana NCORP | 3 | Dayton NCORP | 1 |
| Southeast COR NCORP | 3 | Hawaii MU-NCORP | 1 |
| Lahey Hosp & Med Ctr | 2 | Loyola University | 1 |
| Michigan, U of | 2 | Sinai Hospital/San Antonio, U of TX | 1 |
| PCRC NCORP | 2 | Utah, U of | 1 |
| Prov Portland MC/PCRC NCORP | 2 | **Total (17 Institutions)** | **37** |

## Registration, Eligibility, and Evaluability

Data as of August 27, 2015

| | Total |
|---|---|
| NUMBER REGISTERED | 37 |
| ELIGIBLE | 37 |
| RESPONSE ASSESSMENT | |
| Determinable | 34 |
| Not Determinable | 2 |
| Too Early | 1 |
| ADVERSE EVENT ASSESSMENT | |
| Evaluable | 36 |
| Not Evaluable | 1 |

## Patient Characteristics

Data as of August 27, 2015

| | Total (n=37) | |
|---|---|---|
| AGE | | |
| Median | 62.1 | |
| Minimum | 45.7 | |
| Maximum | 88.0 | |
| HISPANIC | | |
| Yes | 3 | 8% |
| No | 34 | 92% |
| RACE | | |
| White | 28 | 76% |
| Black | 5 | 14% |
| Asian | 1 | 3% |
| Multi-Racial | 1 | 3% |
| Unknown | 2 | 5% |
| DISEASE | | |
| Measurable | 28 | 76% |
| Evaluable non-measurable disease | 9 | 24% |
| PRIOR HORMONE | | |
| Prior adjuvant hormonal therapy completed more than 5 years ago | 6 | 16% |
| Prior adjuvant hormonal therapy completed 1-5 years ago | 15 | 41% |
| De novo presentation of metastatic disease or no prior adjuvant hormonal therapy | 16 | 43% |

## Treatment Summary

Data as of August 27, 2015

| | Total |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 19 |
| NUMBER OFF PROTOCOL TREATMENT | 18 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 0 |
| Adverse Event or side effects | 2 |
| Refusal unrelated to adverse event | 2 |
| Progression/relapse | 11 |
| Death | 0 |
| Other - not protocol specified | 3 |
| Reason under review | 0 |
| MAJOR PROTOCOL DEVIATIONS | 1 |

# Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Data as of August 27, 2015

| | Total (n=36) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| ALT increased | 30 | 3 | 3 | 0 | 0 | 0 |
| AST increased | 28 | 7 | 0 | 1 | 0 | 0 |
| Abdominal pain | 31 | 2 | 2 | 1 | 0 | 0 |
| Acute kidney injury | 35 | 1 | 0 | 0 | 0 | 0 |
| Alkaline phosphatase increased | 33 | 3 | 0 | 0 | 0 | 0 |
| Alopecia | 34 | 2 | 0 | 0 | 0 | 0 |
| Anemia | 22 | 9 | 5 | 0 | 0 | 0 |
| Anorexia | 30 | 2 | 2 | 2 | 0 | 0 |
| Arthralgia | 31 | 4 | 1 | 0 | 0 | 0 |
| Arthritis | 35 | 1 | 0 | 0 | 0 | 0 |
| Ascites | 35 | 1 | 0 | 0 | 0 | 0 |
| Atelectasis | 35 | 0 | 1 | 0 | 0 | 0 |
| Back pain | 34 | 2 | 0 | 0 | 0 | 0 |
| Blood bilirubin increased | 35 | 1 | 0 | 0 | 0 | 0 |
| Blood/lymph disorder-Other | 34 | 1 | 1 | 0 | 0 | 0 |
| Bone pain | 31 | 2 | 3 | 0 | 0 | 0 |
| Burn | 35 | 1 | 0 | 0 | 0 | 0 |
| Cardiac disorder-Other, spec | 35 | 1 | 0 | 0 | 0 | 0 |
| Chills | 34 | 2 | 0 | 0 | 0 | 0 |
| Cholesterol high | 21 | 13 | 2 | 0 | 0 | 0 |
| Constipation | 31 | 5 | 0 | 0 | 0 | 0 |
| Cough | 31 | 5 | 0 | 0 | 0 | 0 |
| Creatinine increased | 33 | 2 | 1 | 0 | 0 | 0 |
| Dehydration | 32 | 0 | 1 | 3 | 0 | 0 |
| Depression | 35 | 1 | 0 | 0 | 0 | 0 |
| Diarrhea | 28 | 4 | 3 | 1 | 0 | 0 |
| Dizziness | 35 | 1 | 0 | 0 | 0 | 0 |
| Dry mouth | 33 | 3 | 0 | 0 | 0 | 0 |
| Dry skin | 34 | 2 | 0 | 0 | 0 | 0 |
| Dysesthesia | 35 | 1 | 0 | 0 | 0 | 0 |
| Dysgeusia | 31 | 4 | 1 | 0 | 0 | 0 |
| Dyspepsia | 32 | 2 | 2 | 0 | 0 | 0 |
| Dysphagia | 34 | 0 | 2 | 0 | 0 | 0 |
| Dyspnea | 33 | 2 | 1 | 0 | 0 | 0 |
| ECG QT corrected int prolong | 35 | 0 | 1 | 0 | 0 | 0 |
| Ear/labyrinth disorders-Other | 35 | 0 | 1 | 0 | 0 | 0 |
| Edema limbs | 31 | 5 | 0 | 0 | 0 | 0 |
| Epistaxis | 35 | 1 | 0 | 0 | 0 | 0 |
| Erythema multiforme | 35 | 1 | 0 | 0 | 0 | 0 |
| Esophagitis | 35 | 0 | 1 | 0 | 0 | 0 |
| Fatigue | 16 | 14 | 4 | 2 | 0 | 0 |
| Fever | 35 | 1 | 0 | 0 | 0 | 0 |
| Flu like symptoms | 35 | 0 | 0 | 1 | 0 | 0 |
| GI disorders-Other, specify | 34 | 2 | 0 | 0 | 0 | 0 |
| Gen disorders/admin site cond | 35 | 1 | 0 | 0 | 0 | 0 |

| | Total (n=36) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| Generalized muscle weakness | 34 | 0 | 1 | 1 | 0 | 0 |
| Glucose intolerance | 35 | 1 | 0 | 0 | 0 | 0 |
| Headache | 30 | 5 | 1 | 0 | 0 | 0 |
| Hot flashes | 22 | 11 | 3 | 0 | 0 | 0 |
| Hyperglycemia | 24 | 10 | 1 | 1 | 0 | 0 |
| Hypernatremia | 35 | 1 | 0 | 0 | 0 | 0 |
| Hypertension | 32 | 0 | 1 | 3 | 0 | 0 |
| Hypertriglyceridemia | 20 | 12 | 4 | 0 | 0 | 0 |
| Hypoalbuminemia | 32 | 2 | 2 | 0 | 0 | 0 |
| Hypocalcemia | 34 | 0 | 1 | 1 | 0 | 0 |
| Hypokalemia | 31 | 2 | 0 | 3 | 0 | 0 |
| Hypomagnesemia | 35 | 1 | 0 | 0 | 0 | 0 |
| Hyponatremia | 32 | 3 | 0 | 1 | 0 | 0 |
| Hypophosphatemia | 34 | 1 | 0 | 0 | 1 | 0 |
| Hypotension | 35 | 0 | 0 | 1 | 0 | 0 |
| Ileus | 35 | 0 | 1 | 0 | 0 | 0 |
| Infections/infestations-Other | 35 | 0 | 1 | 0 | 0 | 0 |
| Injection site reaction | 34 | 1 | 1 | 0 | 0 | 0 |
| Insomnia | 35 | 1 | 0 | 0 | 0 | 0 |
| Lipase increased | 35 | 1 | 0 | 0 | 0 | 0 |
| Localized edema | 34 | 1 | 0 | 1 | 0 | 0 |
| Lymphocyte count decreased | 28 | 2 | 5 | 1 | 0 | 0 |
| MS/connective tissue disorder | 35 | 1 | 0 | 0 | 0 | 0 |
| Malaise | 35 | 0 | 1 | 0 | 0 | 0 |
| Metab/nutrition disorders-Oth | 34 | 2 | 0 | 0 | 0 | 0 |
| Mucosal infection | 35 | 1 | 0 | 0 | 0 | 0 |
| Mucositis oral | 18 | 8 | 9 | 1 | 0 | 0 |
| Myalgia | 31 | 4 | 1 | 0 | 0 | 0 |
| Nasal congestion | 34 | 2 | 0 | 0 | 0 | 0 |
| Nausea | 27 | 5 | 4 | 0 | 0 | 0 |
| Nervous sys disorders-Other | 35 | 1 | 0 | 0 | 0 | 0 |
| Neutrophil count decreased | 32 | 2 | 0 | 2 | 0 | 0 |
| Oral pain | 30 | 4 | 2 | 0 | 0 | 0 |
| Pain | 33 | 3 | 0 | 0 | 0 | 0 |
| Pain in extremity | 35 | 1 | 0 | 0 | 0 | 0 |
| Paresthesia | 34 | 2 | 0 | 0 | 0 | 0 |
| Peripheral sensory neuropathy | 34 | 2 | 0 | 0 | 0 | 0 |
| Platelet count decreased | 28 | 7 | 1 | 0 | 0 | 0 |
| Pleural effusion | 35 | 0 | 1 | 0 | 0 | 0 |
| Pneumonitis | 33 | 2 | 1 | 0 | 0 | 0 |
| Rash acneiform | 31 | 4 | 1 | 0 | 0 | 0 |
| Rash maculo-papular | 32 | 3 | 0 | 1 | 0 | 0 |
| Rectal hemorrhage | 35 | 1 | 0 | 0 | 0 | 0 |
| Resp/thoracic/mediastinal ds | 35 | 0 | 0 | 1 | 0 | 0 |
| Sinus tachycardia | 34 | 1 | 1 | 0 | 0 | 0 |
| Skin hyperpigmentation | 35 | 1 | 0 | 0 | 0 | 0 |
| Skin induration | 35 | 1 | 0 | 0 | 0 | 0 |
| Skin/subq tissue ds-Other | 35 | 1 | 0 | 0 | 0 | 0 |
| Sore throat | 33 | 2 | 0 | 1 | 0 | 0 |
| Upper respiratory infection | 34 | 0 | 2 | 0 | 0 | 0 |
| Urinary frequency | 34 | 2 | 0 | 0 | 0 | 0 |

| | Total (n=36) Grade | | | | | |
|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** |
| Urinary tract infection | 35 | 0 | 1 | 0 | 0 | 0 |
| Vasc disorders-Other, spec | 35 | 1 | 0 | 0 | 0 | 0 |
| Vertigo | 35 | 0 | 1 | 0 | 0 | 0 |
| Vomiting | 32 | 2 | 1 | 1 | 0 | 0 |
| Weight gain | 35 | 1 | 0 | 0 | 0 | 0 |
| Weight loss | 26 | 5 | 5 | 0 | 0 | 0 |
| Wheezing | 35 | 1 | 0 | 0 | 0 | 0 |
| White blood cell decreased | 29 | 5 | 1 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 3 | 6 | 17 | 9 | 1 | 0 |

# S1416 Phase II

# Phase II Randomized Placebo-Controlled Trial of Cisplatin with or without ABT-888 (Veliparib) in Metastatic Triple-Negative Breast Cancer and/or BRCA Mutation-Associated Breast Cancer

---

**Study Chairs:**
E Rodler, P Sharma

**Statisticians:**
W Barlow, D Lew

**Data Coordinator:**
J Barce

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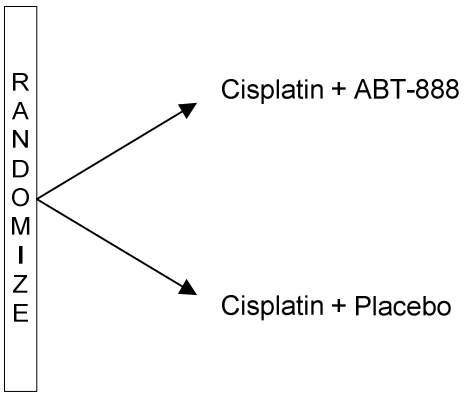
## SCHEMA




**Objectives**

To compare the efficacy of cisplatin with or without ABT-888 (veliparib) on progression-free survival (PFS) in each of the following groups:

- Patients with germline *BRCA* (*gBRCA*) mutation-associated breast cancer
- Patients with germline *BRCA* wild-type breast cancer who have evidence of BRCAness phenotype
- Patients with germline *BRCA* wild-type breast cancer who do not have evidence of BRCAness phenotype.

To compare the efficacy of cisplatin with or without ABT-888 on overall survival (OS), response rate (RR), and clinical benefit rate in each of the three groups.

To compare the differential benefit of ABT-888 across the three groups using both PFS and OS as outcomes.

To compare toxicities of ABT-888 to placebo in each of the three groups separately.

To evaluate the impact of Homologous Recombination Deficiency score (independent of other BRCAness markers) on RR and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

To evaluate the overlap among various markers utilized to define the BRCAness phenotype.

To evaluate the impact of PAM50 basal signature (independent of *gBRCA* status and other BRCAness markers) on RR and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

To evaluate the impact of BRCA1 mRNA expression (independent of *gBRCA* status and other BRCAness markers) on RR and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

**Patient Population**

Patients must have metastatic breast cancer (Stage IV disease) and be HER2 non-over expressing per 2013 ASCO-CAP HER testing guidelines, and must also meet at least one of the following criteria: histologically confirmed primary and/or metastatic site that is ER- and PR-negative (≤ 1%) and HER2-negative, or previously confirmed deleterious *BRCA1* or *BRCA2* germline mutation. Patients must have measurable or non-measurable disease with a chest/abdominal CT scan and bone scan prior to registration. Patients with known brain metastases must have clinically controlled neurologic symptoms, defined as surgical excision and/or radiation therapy followed by 14 days of stable neurologic function prior to registration.

Patients must have had no more than one prior cytotoxic regimen for metastatic disease. Patients must not have received any prior chemotherapy, radiation therapy, and hormonal therapy at least 14 days prior to registration; any immunotherapy, biologic, or any investigational drug within 28 days prior to registration; or any bevacizumab within 42 days prior to registration. Patients must not have received prior cisplatin or PARP inhibitors. Prior carboplatin in the adjuvant/neoadjuvant setting and prior treatment with iniparib is allowed, if completed more than six months prior to study entry. Patients may receive bisphosphonates or denosumab concurrently with study treatment provided it has been started at least seven days prior to registration. Patients must have recovered to ≤ Grade 2 following a significant adverse event or toxicity attributed to previous anti-cancer treatment.

Patients must be at least 18 years of age and have a Zubrod performance status of 0-2. Patients must have adequate hematologic, hepatic, and renal function. Patients must not have a clinically relevant hearing impairment ≥ Grade 2 or baseline neuropathy that exceeds Grade 1 and must be able to swallow whole capsules. Patients must have a complete history and physical examination within 28 days prior to registration, have adequate tissue available, and agree to have specimens submitted for germline DNA sequencing and other correlative studies.

**Stratification/Descriptive Factors**

Patients with be stratified at randomization by number of prior cytotoxic regimens for metastatic disease: 0 vs 1.

**Accrual Goals**

The accrual goal is 235 eligible patients.

# A011106 Phase III SWOG Supported CTSU Study

**Coordinating Group: Alliance**

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

---

**Participants:**
Alliance, CTSU

**Date Activated:**
02/15/2014

**Study Chairs:**
C Ma (Alliance), A Forero (SWOG)

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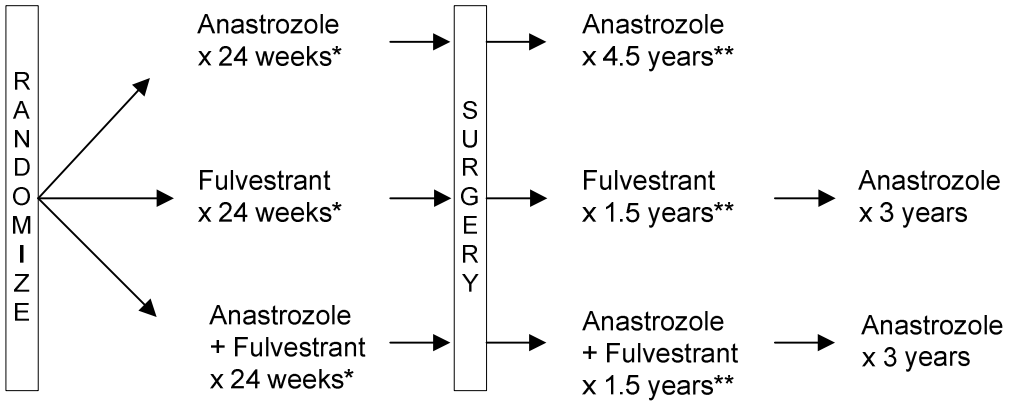
## SCHEMA




*Patients who have an endocrine resistant tumor at week 4 or week 12 will discontinue endocrine protocol therapy, with recommended switch to neoadjuvant chemotherapy.

**Patients with modified PEPI score of 0 will continue assigned endocrine treatment. Those with modified PEPI >0 after completion of surgery will receive adjuvant chemotherapy +/- endocrine therapy of physician's choice.

**Objectives**

To determine whether fulvestrant administered for 24 weeks as neoadjuvant endocrine treatment decreases the proportion of endocrine resistant tumors (as defined in the protocol) relative to patients treated with anastrozole.

To determine whether fulvestrant in combination with anastrozole, administered for 24 weeks as neoadjuvant endocrine treatment, decreases the proportion of endocrine resistant tumors (as defined in the protocol) relative to patients treated with anastrozole.

To assess whether the 5-year RFS rate among women with a modified preoperative endocrine prognostic index (PEPI) score of 0 following 24 weeks of neoadjuvant anastrozole treatment is at least 95%.

To assess whether the 5-year RFS rate among women with a modified PEPI score of 0 following 24 weeks of neoadjuvant fulvestrant, or fulvestrant in combination with anastrozole, is at least 95%. Note that this objective will only be tested if the selected fulvestrant arm was shown to be superior to anastrozole in objective 1 or 2.

To assess whether the 5-year RFS rate among women with a preoperative endocrine prognostic index (PEPI) score of 0 following 24 weeks of neoadjuvant anastrozole treatment is at least 95%.

To examine the differences in surgical outcome, clinical and radiological response rates, and safety profile between the fulvestrant arm and the anastrozole arm.

To examine the differences in surgical outcome, clinical and radiological response rates, and safety profile between patients randomized to fulvestrant in combination with anastrozole and those randomized to anastrozole.

To examine the rate of pathologic complete response (pCR) of 12 weeks of neoadjuvant paclitaxel in patients with endocrine resistant disease following 4 weeks or 12 weeks of neoadjuvant endocrine therapy (with either fulvestrant or anastrozole or the combination of fulvestrant and anastrozole).

To examine the rate of pathologic complete response (pCR) among those patients with endocrine resistant disease, following 4 weeks or 12 weeks of neoadjuvant endocrine therapy (with either fulvestrant or anastrozole or the combination of fulvestrant and anastrozole), who choose not to receive neoadjuvant paclitaxel, but another standard neoadjuvant taxane and /or anthracycline containing regimen or CMF.

To summarize the frequency of severe (NCI CTCAE grade > 3) adverse events encountered with administration of paclitaxel in the neoadjuvant setting.

To assess RFS for patients with endocrine resistant tumors defined by tumor 1) Ki67 >10% at week 4, 2) Ki67 >10% at week 12 and 3) modified PEPI score of non-zero on neoadjuvant endocrine therapy, with all three groups combined or separated.

To assess whether the degree of tumor Ki67 suppression at week 4 differs between patients randomized to fulvestrant and those randomized to anastrozole.

To assess whether the degree of tumor Ki67 suppression at week 4 differs between patients randomized to fulvestrant in combination with anastrozole and those randomized to anastrozole.

To examine the impact of tumor ER expression level post-neoadjuvant endocrine therapy on RFS in each treatment arm separately.

To examine whether RFS differs with respect to pathologic tumor stage (T1 vs. T2) post-neoadjuvant endocrine therapy in the subgroup of women with a modified PEPI score of 0.

To examine whether rate of endocrine resistant tumors or RFS differs with respect to the degree of week 4 Ki67 suppression.

To examine whether the rate of week 4 Ki67 level > 10%, the rate of endocrine resistant tumors or RFS differs with respect to pre-treatment gene expression profile.

To examine whether gene expression profiles at week 4 can further refine the patient population who have modified PEPI score non-0 or shorter RFS.

To assess the pCR/RCB-1 rate in each of the following cohorts: a) Those who chose to switch to paclitaxel afterfinding their week 4 Ki67 was > 10%. b) Those who chose to switch to paclitaxel after finding their week 12 Ki67 was > 10%. c) Those patients who chose to switch to a standard neoadjuvant taxane and/or anthracycline containing regimen or CMF (rather than paclitaxel) after finding their week 4 Ki67 was > 10%. d) Those patients who chose to switch to a standard neoadjuvant taxane and/or anthracycline containing regimen or CMF (rather than paclitaxel) after finding their week 12 Ki67 was > 10%.

To evaluate Cycle 1, day 2 tumor biopsy following the initiation of paclitaxel to develop early molecular markers of tumor response to paclitaxel.

To evaluate tumor tissue, serum, and plasma specimens collected at baseline, on-therapy, and at surgery for biomarker discovery (through methods such as gene expression profiling, patterns of gains or losses of DNA, tumor whole genome and targeted DNA and RNA sequencing and proteomics) studies

that aim to understand signaling pathways associated with endocrine therapy and taxane therapy sensitivity and resistance.

**Patient Population**

Patients must be postmenopausal women with pathologic confirmation of invasive breast cancer diagnosed by core needle biopsy, clinical T2-T4c, any N, M0 by AJCC 7th edition clinical staging, with the goal being surgery to complete excision of the tumor in the breast and the lymph nodes. Patients must not have inflammatory breast cancer, contralateral invasive breast cancer and/or DCIS, or multifocal/multi-lesional breast cancer if more than one lesion is invasive cancer in the same breast. Invasive breast cancer must be estrogen receptor positive with an Allred score of 6, 7 or 8 by local institution standard protocol and HER2 negative defined as 0 or 1+ by IHC or with a FISH ratio < 2 if IHC 2+ by local institution standard protocol. If an Allred Score is not reported on the diagnostic pathology report, ER positivity in > 66% cells is eligible. If ER positivity is ≤ 66%, the staining intensity (weak, intermediate, strong) is needed to calculate the Allred Score to determine eligibility.

Patients must have documentation of mammogram and ultrasound (including DCIS and invasive cancer) of the diseased breast performed within 42 days prior to registration, with mammogram of the unaffected contralateral breast within 12 months prior to registration. Patients must not have received treatment for this cancer including surgery, radiation therapy, chemotherapy, biotherapy, hormonal therapy or investigational agent prior to study entry. Patients must not have hormone replacement therapy of any type within one week prior to registration.

Patients must be at least 18 years of age and have an ECOG performance status of 0-2. Patients must have adequate hematologic, renal, and hepatic function and agree to provide the required research biopsies at baseline, week 4 and at surgery for biomarker and correlative studies.

**Stratification/Descriptive Factors**

Patient randomization will be stratified by the following factors: (1) clinical tumor stage: T2 vs T3 vs T4a-c; (2) clinical lymph node status: positive vs negative; and (3) performance status: 0 or 1 vs 2.

**Accrual Goals**

A maximum of 2,820 eligible patients will be enrolled on the study.

**Summary Statement**

CTSU reports that 203 patients had been registered to this study as of June 30, 2015, including 10 SWOG registrations. The complete November 2014 summary of this study from Alliance is available on the SWOG web site.

## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg |
|---|---|
| Arizona MC, U of | 5 |
| Baptist MU-NCORP | 4 |
| New Mexico MU-NCORP | 1 |
| **Total (3 Institutions)** | **10** |

# B47 Phase III SWOG Supported CTSU Study

**Coordinating Group: NRG**

# A Randomized Phase III Trial of Adjuvant Therapy Comparing Chemotherapy Alone (Six Cycles of TC or Four Cycles of AC Followed by Four Cycles of Weekly Paclitaxel) to Chemotherapy Plus Trastuzumab in Women with Node-Positive or High-Risk Node-Negative HER2-Low Invasive Breast Cancer

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**Participants:**
NRG, CTSU

**Date Activated:**
01/07/2011

**Study Chairs:**
L Fehrenbacher (NRG), K Albain (SWOG)

**Date Closed:**
02/10/2015

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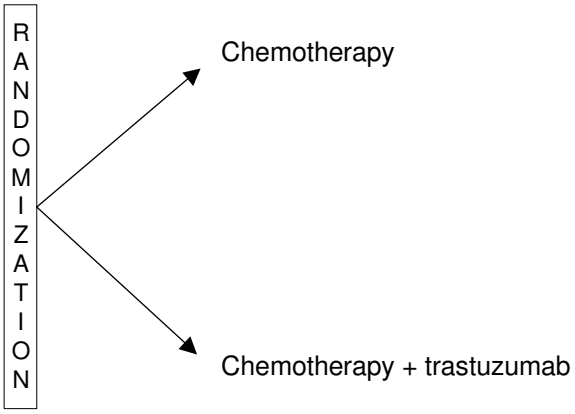
## SCHEMA




**Objectives**

To determine whether the addition of trastuzumab to chemotherapy (TC or AC->WP) improves invasive disease-free survival (IDFS) in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

To determine whether the addition of trastuzumab to chemotherapy (TC or AC->WP) improves disease-free survival (DFS-DCIS), breast cancer-free survival (BCFS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI), and overall survival (OS) in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

To evaluate the associations between amenorrhea and circulating reproductive hormone levels, and the associations between chemotherapy regimen, amenorrhea, and IDFS benefit in premenopausal women eligible at baseline for the menstrual history assessments.

To evaluate the toxicity associated with each of the regimens.

To test the hypothesis that the HER2 mRNA level is the predictor of the degree of benefit from trastuzumab and the threshold for benefit in the adjuvant setting is lower than defined by current ASCO/CAP Guidelines for HER2 assays (IHC and FISH).

To identify and/or validate molecular predictors of the degree of benefit from the addition of trastuzumab to chemotherapy (TC or AC->WP).

To test the alternative hypothesis that the main determinant of trastuzumab response in the adjuvant setting of HER2-low breast cancer is through ADCC by demonstrating that the polymorphism of the Fcã receptor gene is predictive of the degree of benefit from the addition of trastuzumab to chemotherapy (TC or AC->WP).

To examine the relationship between behavioral host factors (obesity, tobacco, alcohol) and comorbid conditions that may influence systemic inflammation and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

To examine the relationship between medication exposures that may influence systemic inflammation and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

To examine the relationship between comorbid conditions, medication exposures and behavioral host factors together and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

**Patient Population**

Patients must be women with unilateral invasive adenocarcinoma of the breast on histologic examination, with primary tumor pT1-3 and no evidence of metastatic disease. Patients with pathologic node negative disease must have primary tumor pT2 with either both ER and PgR negative; or ER positive with Grade 3 histology or Oncotype DX® Recurrence Score ≥ 25; or pT3 regardless of hormone receptor status, histologic grade, and Oncotype DX® Recurrence Score. HER2 status of the primary tumor must be HER2-low as defined in the protocol. Patients must have known ER status, and known PgR status if ER negative.

Patients must have undergone either a total mastectomy or breast-conserving surgery, with sentinel lymphadenectomy or axillary lymphadenectomy as described in the protocol. The interval between the last surgery for breast cancer and randomization must be no more than 84 days. Patients must not have had chemotherapy or HER2-targeted therapy administered for the currently diagnosed breast cancer or prior therapy with anthracyclines, taxanes, or trastuzumab for any malignancy.

Patients must be ≥ 18 years old with an ECOG performance status of 0-1. Patients must have adequate hematologic, hepatic, renal, and cardiac function. Patients must not have uncontrolled hypertension, history of cardiac disease, poorly controlled diabetes mellitus, or nervous system disorder ≥ Grade 2.

**Stratification/Descriptive Factors**

Patient randomization will be dynamically balanced by the following factors: (1) IHC score: 1+ vs 2+; (2) pathologic nodal status: 0-3 vs 4-9 vs 10+ positive nodes; (3) hormone receptor status: ER-positive and/or PgR-positive vs ER- and PgR-negative; and (4) intended chemotherapy regimen: TC vs AC->WP.

**Accrual Goals**

The accrual goal is 3,260 patients.

**Summary Statement**

CTSU reports that 3,270 patients had been registered to this study prior to closure on February 10, 2015, including 155 SWOG registrations. The complete October 2014 summary of this study from NRG is available on the SWOG web site.

# Registration by Institution

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Michigan, U of | 17 | Greenville NCORP | 2 |
| Yale University | 17 | McLaren Cancer Inst/Wayne State Univ | 2 |
| Wayne State Univ | 13 | Sinai Hospital/San Antonio, U of TX | 2 |
| LSU-Shreveport/Gulf South MU-NCORP | 9 | Skagit Valley Hosp/Fred Hutchinson CRC | 2 |
| Cleveland Clinic OH | 7 | St Elizabeth's MC/Davis, U of CA | 2 |
| Columbia MU-NCORP | 7 | Watson Clinic Center/H Lee Moffitt CC | 2 |
| PCRC NCORP | 7 | Cadence CC-Warren/Cleveland Clinic OH | 1 |
| St Joseph's/Candler/H Lee Moffitt CC | 7 | Carolinas Med Ctr/San Antonio, U of TX | 1 |
| Rochester, Univ of | 6 | Columbia University | 1 |
| St Joseph Med Ctr/PCRC NCORP | 5 | Good Samaritan Hosp/CORA NCORP | 1 |
| Atlanta Reg CCOP | 4 | Good Samaritan Hosp/Oregon Hlth Sci Univ | 1 |
| Fowler Family Center/Baptist MU-NCORP | 4 | Heartland NCORP | 1 |
| Harrison Bremerton/Harrison Medical Ctr | 4 | NE Alabama Reg MC/Mississippi, Univ of | 1 |
| Loyola University | 4 | Northwest NCORP | 1 |
| MidMichigan Med Ctr/Michigan, U of | 4 | Ozarks NCORP | 1 |
| Highline Medical Ctr/Franciscan Res Ctr | 3 | Providence Hosp | 1 |
| KaiserPermanenteSCAL/Kaiser Vallejo NCORP | 3 | Southeast COR NCORP | 1 |
| Salem Hospital/Oregon Hlth Sci Univ | 3 | Univ of Louisville | 1 |
| Stormont-Vail Health/Kansas, U of | 3 | Upstate Carolina | 1 |
| Sutter General Hosp/Sutter Cancer RC | 3 | **Total (39 Institutions)** | **155** |

# B55 Phase III SWOG Supported CTSU Study

**Coordinating Group: NRG**

# A Randomised, Double-Blind, Parallel Group, Placebo-Controlled Multi-Centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients with Germline *BRCA1/2* Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy

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**Participants:**
NRG, CTSU

**Date Activated:**
07/03/2014

**Study Chairs:**
C Geyer (NRG), P Sharma (SWOG)

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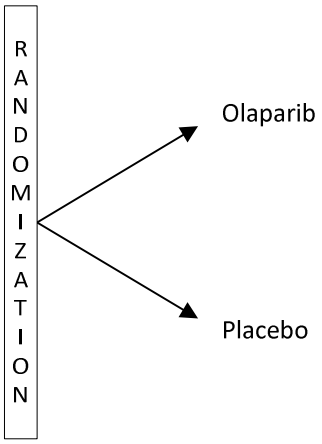
## SCHEMA




**Objectives**

The primary objective is to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS).

To assess the safety and tolerability of adjuvant treatment with olaparib.

To assess the effect of adjuvant treatment with olaparib on overall survival (OS).

To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS).

To assess the effect of adjuvant treatment with olaparib on the incidence of new invasive breast primary cancer and/or new epithelial ovarian cancer.

To assess the effect of olaparib on patient reported outcomes using the FACIT fatigue scale and EORTC QLQ-C30 QoL scale.

To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future germline *BRCA* mutation assays (gene sequencing and large rearrangement analysis).

**Patient Population**

Patients must have histologically confirmed non-metastatic primary triple negative invasive adenocarcinoma of the breast that is high risk as described in the protocol, with documented mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious.

Patients must have completed adequate breast and axilla surgery with clear margins as defined in the protocol. Patients must have completed at least six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or the combination of both. Prior platinum as potentially curative treatment for prior cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed. Patients must not have received systemic chemotherapy within three weeks prior to start of study treatment, adjuvant radiotherapy within two weeks prior to start of study treatment, exposure to an investigational product within 30 days or five half lives (whichever is longer) prior to randomization, or any previous treatment with a PARP inhibitor.

Patients must be at least 18 years of age and have ECOG performance status 0-1 and adequate hematologic, hepatic, cardiac, and renal function. Female patients must be postmenopausal or evidence of non-childbearing status as defined in the protocol. Patients must not have known active Hepatitis B or C, HIV, previous allogeneic bone marrow transplant, or whole blood tranfusions in the 120 days prior to study entry which may interfere with *gBRCA* testing. FFPE tumor sample from the primary tumor is required unless waived by Study Team if tumor is not available.

**Stratification/Descriptive Factors**

Patients will be stratified at randomization by the following baseline factors: (1) prior therapy: neoadjuvant vs adjuvant; and (2) prior platinum therapy for current breast cancer: yes vs no.

**Accrual Goals**

Approximately 1,320 patients will be randomized into the study. An interim analysis will be performed once a minimum of 165 IDFS events have been observed from the first 660 patients recruited, estimated to be approximately 4.5 years after the first patient is randomized.

**Summary Statement**

CTSU reports that 14 patients had been registered to this study as of June 30, 2015, including two from SWOG institutions, one each from Cedars-Sinai Medical Center and University of Michigan.

# E1Z11 SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Cohort Study to Evaluate Genetic Predictors of Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS)

**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
05/31/2013

**Study Chairs:**
V Stearns (ECOG-ACRIN), N Henry (SWOG)

**Objectives**

To validate previously identified associations between 10 specific single nucleotide polymorphisms (SNPs) and discontinuation of treatment with aromatase inhibitors (AIs) due to the development of musculoskeletal symptoms (MSS) among women with breast cancer.

To determine whether other SNPs in CYP, UGT, Vitamin D, serotonin and other receptors are associated with discontinuation of treatment due to the development of severe AIMSS.

To determine whether other SNPs in CYP, UGT, Vitamin D, serotonin and other receptors are associated with the development of other potential complications of AI therapy.

To develop a gene signature that can identify patients at risk for developing severe anastrozole-related AIMSS and other potential complications of AI therapy.

To determine the epidemiology and predictors of severe AIMSS and of AI discontinuation.

To describe patient reported outcomes for minority patients with breast cancer treated with AIs.

To assess the utility of the PROMIS system to collect patient reported outcomes in a cooperative group study, and validate the PROMIS Physical Function 20a form in patients with AIMSS.

To develop a model that incorporates patient ratings of treatment burden, fear of recurrence and adherence behaviors to describe patient decisions to continue or discontinue anastrozole.

To collect serum samples for future testing for biomarkers of AIMSS.

**Patient Population**

Patients must be female and post-menopausal as defined in the protocol, with estrogen and/or progesterone receptor positive histologically confirmed Stage I-III adenocarcinoma of the breast. Patients must not have prior history of ovarian, endometrial, or fallopian tube carcinoma, and/or primary peritoneal carcinomatosis.

Patients must have completed planned local therapy (i.e., definitive surgery and radiation therapy) and adjuvant chemotherapy for breast cancer, with plans to treat with anastrozole for at least 12 months. Concomitant treatment with ongoing trastuzumab (Herceptin®) or other targeted/biologic agents is allowed. Concomitant treatment with any other type of chemotherapy or hormonal therapy is not allowed. Patients must not have received prior AI therapy with exemestane, letrozole, or anastrozole as preoperative/adjuvant therapy or for prevention of breast cancer. Prior tamoxifen is allowed.

Patients must have adequate hepatic, hematologic and renal functioning to be able to be administered anastrozole at the discretion of the treating physician. Patients must have worst pain rated as no worse than 3 out of 10 on the following question (i.e., a pain

score of 0, 1, 2, or 3): "In the past week, how much pain have you had on a scale of 0 to 10, where 0 equals no pain and 10 means the worst pain you can imagine." NOTE: This question regarding patient's pain should be completed within one week prior to registration. This pain item may be completed orally prior to consent up to seven days prior to registration. Patients must not be currently taking (or have taken in the past six months) medication for active, chronic conditions, including rheumatoid arthritis, carpal tunnel syndrome, tenosynovitis, systemic lupus erythematosus, gout, fibromyalgia, or severe osteoarthritis involving the hands, wrists, hips, knees, feet or ankles. This includes analgesic medications or medications being taken with the purpose of treating pain or that may have an effect on pain (e.g. anti-depressants for help with pain or neuropathy, corticosteroid shots for arthritis). Patients taking daily low dose aspirin are allowed to participate in this trial.

Patients must be at least 18 years old, have an ECOG performance status of 0-2, and must not have a prior history of deep vein thrombosis (DVT) or pulmonary embolism in the past five years.

**Accrual Goals**

The accrual goal is 1000 patients, including 200 Asian and 200 African American.

**Summary Statement**

CTSU reports that as of June 30, 2015, there had been 905 registrations to this study, including 119 SWOG registrations. The Caucasian/Other Races cohort was closed to accrual on February 24, 2014, and the African American cohort was closed to accrual on July 20, 2015. The Asian and Native Hawaiian/Pacific Islanders cohort remains open to accrual. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| KaiserPermanenteSCAL/Kaiser Vallejo NCORP | 17 | Beaumont NCORP | 3 |
| Columbia MU-NCORP | 15 | Columbus NCORP | 2 |
| Greenville NCORP | 12 | CRC West MI NCORP | 2 |
| Michigan, U of | 11 | Dayton NCORP | 2 |
| Ozarks NCORP | 9 | Greenwich Hospital/Yale University | 2 |
| St Joseph's/Candler/H Lee Moffitt CC | 8 | Providence Hosp | 2 |
| Hawaii MU-NCORP | 6 | Cincinnati MC, U of | 1 |
| Prov Portland MC/PCRC NCORP | 6 | Fowler Family Center/Baptist MU-NCORP | 1 |
| LSU-Shreveport/Gulf South MU-NCORP | 5 | Good Samaritan Hosp/CORA NCORP | 1 |
| MUSC MU-NCORP | 5 | NorthBay Med Ctr/Davis, U of CA | 1 |
| Montana NCORP | 4 | Poudre Valley Hosp/Colorado, U of | 1 |
| Baptist Health/Cincinnati MC, U of | 3 | **Total (23 Institutions)** | **119** |

# E2108 Phase III SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

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**Participants:**
ECOG-ACRIN, CTSU

**Study Chairs:**
S Khan (ECOG-ACRIN), C Lee (SWOG)

**Date Activated:**
02/28/2011

**Date Closed:**
07/23/2015

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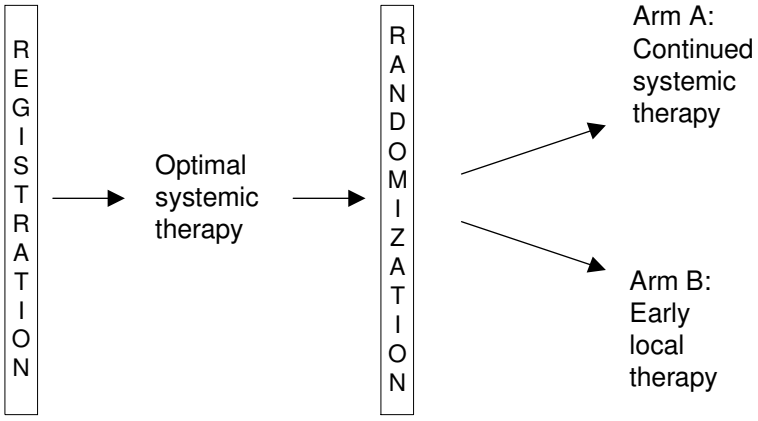
## SCHEMA




**Objectives**

To evaluate whether early local therapy of intact primary disease in women with Stage IV breast cancer whose disease does not progress during initial optimal systemic therapy, will result in prolonged survival, compared to women who receive local therapy for palliation only.

To compare the time to uncontrolled chest wall disease between patients who receive early local therapy versus patients who receive palliative local therapy.

To determine whether there is a difference in HRQOL between patients who receive early local therapy and those who receive palliative local therapy.

To determine whether the absolute value of the CTC burden at six months following randomization will be lower in Arm B than Arm A and whether this value is inversely related to survival.

To collect tumor and blood specimens for future exploration of the biological interactions between the primary tumor and metastatic lesions and the effect of primary tumor resection.

**Patient Population**

Patients must have an intact biopsy-proven primary (not recurrent) invasive carcinoma of the breast. Patients must not have bilateral disease. Patients should have at least one site of distant metastatic disease; if only a single metastatic lesion, this must be proven by biopsy. Radiology reports documenting status of disease must be available. Patients must not

have experienced distant disease progression since the start of systemic therapy.

Patients must have completed at least 16 weeks of optimal systemic therapy (appropriate to the tumor biological profile and patient's age and menopausal status). Patients must be randomized between 16 and 32 weeks of initiation of optimal systemic therapy and must not have experienced disease progression. Patients must be judged to be candidates for complete resection with free margins followed by radiation therapy. Local disease at the primary site must be asymptomatic.

Patients must have adequate organ function to undergo local therapy.

**Stratification/Descriptive Factors**

Patient randomization will be stratified by the following factors: (1) marker status and treatment plan: ER+ or PR+, HER2-, and plan to treat with endocrine therapy alone vs ER+ or PR+, HER2-, and plan to treat with chemotherapy (with or without endocrine therapy) vs ER- or PR-, HER2- vs HER2+; and (2) number of organ systems with metastatic involvement: 1 vs >1.

**Accrual Goals**

Target accrual is 368 patients to accrue 258 responders to the randomized trial.

**Summary Statement**

CTSU reports that there were 388 registrations to this study prior to closure on July 23, 2015, including 52 SWOG registrations. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending July 23, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Beaumont NCORP | 5 | Gulf South MU-NCORP | 1 |
| Rochester, Univ of | 4 | H Lee Moffitt CC | 1 |
| Baylor Univ Med Ctr | 3 | King Faisal Spec Hos | 1 |
| Montana NCORP | 3 | MD Anderson CC | 1 |
| Northwest NCORP | 3 | MUSC MU-NCORP | 1 |
| St Luke's Mt State/PCRC NCORP | 3 | PCRC NCORP | 1 |
| Kansas City NCORP | 2 | Providence Hosp | 1 |
| Mississippi, Univ of | 2 | Singing River Hosp/Mississippi, Univ of | 1 |
| So Calif, U of | 2 | St Elizabeth's MC/Davis, U of CA | 1 |
| Sutter Cancer RC | 2 | St Joseph Med Ctr/PCRC NCORP | 1 |
| Wayne State Univ | 2 | St Louis CCOP | 1 |
| Winthrop-Univ Hosp/Yale University | 2 | St Luke's-Roosevelt/Columbia University | 1 |
| City of Hope Med Ctr | 1 | St Mary Med Ctr/PCRC NCORP | 1 |
| CORA NCORP | 1 | Tulane University | 1 |
| Dayton NCORP | 1 | Winthrop-Univ Hosp/Columbia University | 1 |
| Greenville NCORP | 1 | **Total (31 Institutions)** | **52** |

# E3108 Phase II SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Phase II Prospective Trial Correlating Progression-Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

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**Participants:**
ECOG-ACRIN, CTSU

**Study Chairs:**
V Stearns (ECOG-ACRIN), C Lohrisch (SWOG)

**Date Activated:**
10/08/2010

**Date Closed*:**
06/21/2013

*Temporary closure

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**Objectives**

To correlate CYP2D6 score (0 vs. 1+2) and progression-free survival.

To correlate CYP2D6 score (0 vs. 1 vs. 2) and progression-free survival.

To correlate CYP2D6 score (0 vs. 1+2) and proportion of patients who are progression-free at 6 months.

To correlate endoxifen concentration with response.

To correlate CYP2D6 score with response.

To correlate the presence of candidate estrogen receptor (ESR) 1 and 2 variant alleles, UGT7, SULT1A1, and other candidate genes to progression-free survival.

**Patient Population**

Patients must have estrogen and/or progesterone receptor positive, histologically confirmed adenocarcinoma of the breast. Patients must have measurable or non-measurable Stage III/locally advanced or metastatic carcinoma of the breast where surgery is not possible. Patients with a history of central nervous system metastasis are allowed provided they have been treated (surgery, radiation, or radiosurgery) at least four weeks prior to initiating study drug and do not require medication(s) to control symptoms. Patients with leptomeningeal disease are not eligible.

Patients must not have had more than two lines of non-hormonal treatment in the locally advanced or metastatic setting, including trastuzumab, bevacizumab, or other agents; treatment in the locally advanced or metastatic setting must have completed at least two weeks prior to study registration. Chemotherapy, trastuzumab or bevacizumab in the adjuvant setting is allowed but must have been completed at least four weeks prior to study registrattion. Other prior non-hormonal investigational agents in the adjuvant setting must have been completed at least four weeks prior to study registration and should be discussed with the study PI. Patients who have received agents that modulate or downregulate the estrogen receptor for breast cancer prevention (e.g., tamoxifen, raloxifene, fulvestrant) or bone health (raloxifene) are eligible if they were on treatment for at least six months, did not have a diagnosis of breast cancer on the medication, and have discontinued the agents six months prior to study registration. Prior tamoxifen as adjuvant treatment is allowed as long as the patient did not have disease relapse or progression while on adjuvant tamoxifen or within four weeks of last dose, and treatment was discontinued at least six months prior to study registration. Patients who have received other agents that modulate or downregulate the estrogen receptor (e.g., raloxifene, fulvestrant) in the adjuvant setting are eligible if they were on treatment

for at least 6 months prior to disease progression in the locally advanced or metastatic setting, and treatment was discontinued at least six months prior to study registration. Prior aromatase inhibitors (e.g., anastrozole, letrozole, exemestane, amino-glutethamide) are allowed in the adjuvant, locally advanced or metastatic settings. Prior tamoxifen is not allowed in the locally advanced or metastatic setting. Patients who have received other agents that modulate or downregulate the estrogen receptor (e.g., raloxifene, fulvestrant) in the locally advanced or metastatic setting are eligible if they were on treatment for at least 6 months, and treatment was discontinued at least six months prior to study registration. Concurrent chemotherapy or non-protocol hormonal therapy is not allowed. Patients may receive concurrent radiation therapy to painful sites of bony disease or areas of impending fracture as long as the radiation therapy is initiated prior to study entry and sites of measurable disease and non-measurable disease outside the radiation therapy port are available to follow. Patients who have received prior radiationtherapy must have recovered from toxicity.

Patients must have adequate hematologic, hepatic, and renal function, and an ECOG performance status of 0-2. Patients must not take the following medications that are strong to moderate inhibitors of CYP2D6 and may alter tamoxifen metabolism: paroxetine (Paxil), fluoxetine (Prozac), buproprion (Wellbutrin) and quindine (Cardioquin) within two weeks of registration.

**Accrual Goals**

A total of 240 patients will be enrolled in this study.

**Summary Statement**

CTSU reports that as of June 30, 2015, there had been 125 registrations to this study, including 17 SWOG registrations. The study has been temporarily closed to accrual since June 21, 2013 to assess feasibility. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg |
|---|---|
| BC Cancer Agency | 13 |
| Davis, U of CA | 1 |
| Hawaii MU-NCORP | 1 |
| Wayne State Univ | 1 |
| Yale University | 1 |
| **Total (5 Institutions)** | **17** |

# EAY131 Master Protocol / Phase II

## Coordinating Group: ECOG-ACRIN

## NCI-MATCH: Molecular Analysis for Therapy Choice

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**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
08/12/2015

**Study Chairs:**
K Flaherty (ECOG-ACRIN), A Chen (NCI), P O'Dwyer (ECOG-ACRIN), B Conley (NCI)

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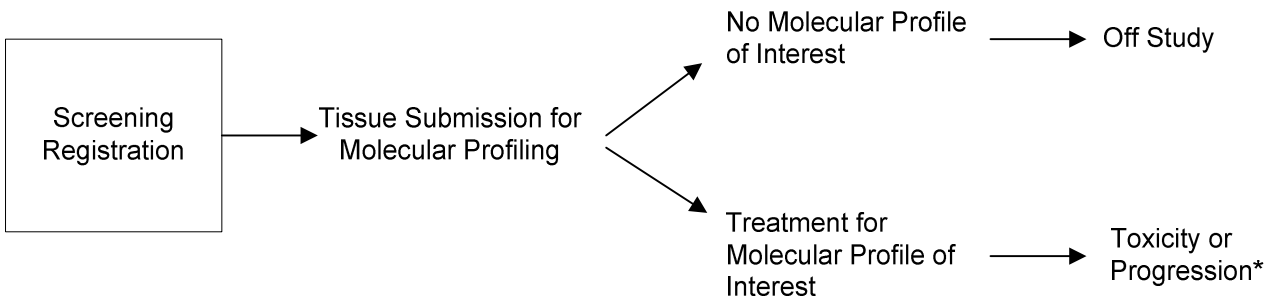
## SCHEMA




*Upon progression or inability to tolerate protocol treatment, patients may be re-screened for additional molecular profiles of interest and corresponding protocol treatment.

**Objectives**

To evaluate the proportion of patients with objective response (OR) to targeted study agent(s) in patients with advanced refractory cancers/lymphomas.

To evaluate the proportion of patients alive and progression free at six months of treatment with targeted study agent in patients with advanced refractory cancers/lymphomas.

To evaluate the time until death or disease progression.

To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned or resistance mechanisms using additional genomic, RNA and protein-based assessment platforms.

**Patient Population**

Patients must have histologically documented solid tumors or histologically confirmed diagnosis of lymphoma that has progressed following at least one line of standard systemic therapy and/or for whose disease no standard treatment exists that has been shown to prolong survival. Patients must have measurable disease, have tumor amenable to image guided or direct vision biopsy, and be willing and able to undergo biopsy for molecular profiling.

Patients must not currently be receiving any other investigational agents. Any prior therapy, radiotherapy (except palliative radiation therapy of 30 Gy or less), or major surgery must have been completed at least four weeks prior to treatment on NCI-MATCH and patient must be recovered from adverse events due to prior therapy (except alopecia

and lymphopenia). Palliative radiation therapy must have been completed at least two weeks prior to enrollment on a NCI-MATCH treatment subprotocol, and patient must have recovered from any adverse events of this therapy. Patients with brain metastases or primary brain tumors must have completed treatment , surgery, or radiation therapy at least four weeks prior to initial registration. Patients must not require the use of full dose coumarin-derivative anticoagulants such as warfarin. Low molecular weight heparin is permitted for prophylactic or therapeutic use.

Patients must be at least 18 years of age, have an ECOG performance status of 0 or 1 and must be able to swallow tablets. Patients must have adequate hematologic, hepatic, renal, cardiac and marrow function. HIV-positive patients are eligible provided they meet protocol criteria. Each subprotocol will have additional eligibility criteria that will be outlined in Section 2.0 of the agent-specific subprotocol.

**Accrual Goals**

The target screening accrual for this study is approximately 3,000 patients, with the goal of accruing 35 patients in each treatment subprotocol. If after screening 500 patients, the total number of patients with actionable tumor alteration (therefore qualifying for treatment) is below 50, results will be presented to the steering committee for consideration of terminating the trial. Within any given subprotocol, if rate of enrollment is such that it is unlikely accrual can be completed in 7.5 years, then the steering committee may consider terminating accrual in that subgroup due to lack of feasibility. An interim analysis of the assay results will be performed after biopsies from approximately the first 200 patients are processed.

**Summary Statement**

This study activated on August 12, 2015, with ten subprotocols included in the activation. Only sites utilizing the CIRB as their IRB of record will be able to participate in the trial.