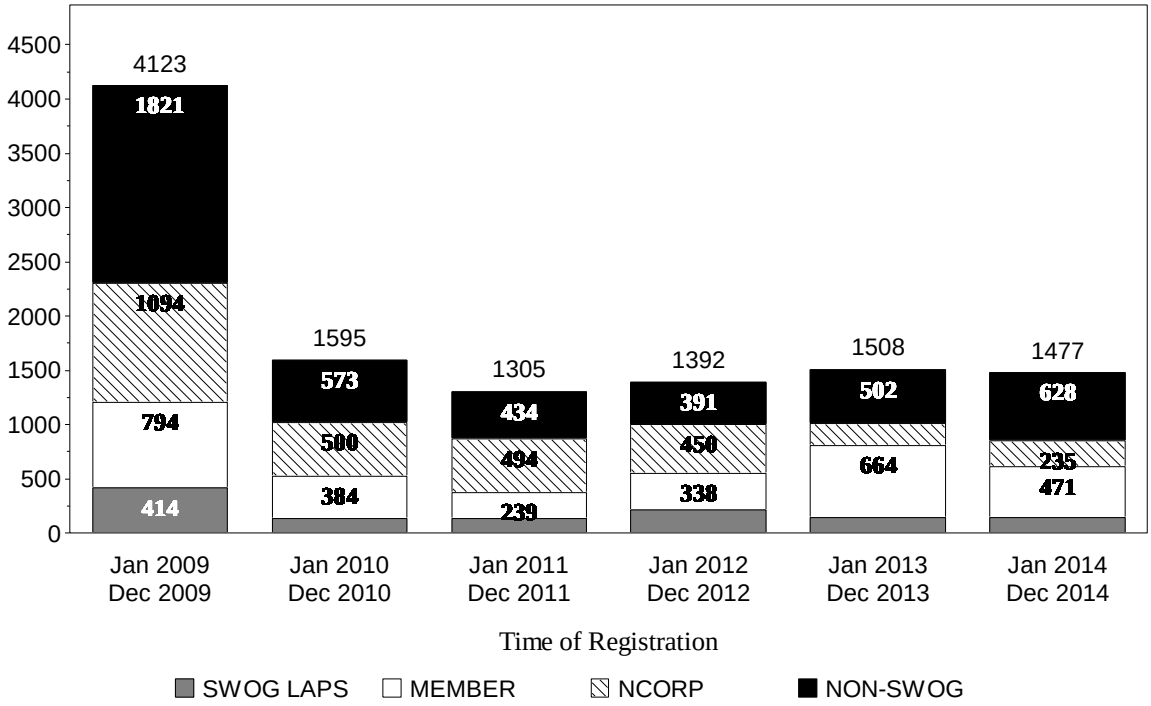
BREAST COMMITTEE

CONTENTS

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

	Jul 2014 Dec 2014	Jan 2014 Jun 2014	Jul 2013 Dec 2013	All Patients
S1007 Breast, Adj, N1, Endocrine+/-Chemo				
Initial Registration				
Recurrence Score testing	950	1,116	1,123	6,247
Randomization				
Chemo and Endocrine Therapy	245	291	291	1,570
Endocrine Therapy Alone	243	294	287	1,566
	488	585	578	3,136
S1207 Breast, Adj, Endocrine+/-Everolimus				
Randomization				
Blinded drug + Endocrine	134	67	25	226
S1222 Breast, Fulvestrant +/- Everolimus +/- Anastrozole				
Randomization				
Blinded treatment	24	6	0	30
A011106 Breast, Neoadj, ALTERNATE study*				
Total Registrations	3	1	0	4
A011202 Breast, Nodal XRT +/- ALND*				
Total Registrations	4	2	0	6
B43 Breast, DCIS, HER2+, RT +/- Tras*				
Total Registrations	5	15	18	66
B47 Breast, Chemo vs Chemo + Trastuzumab*				
Total Registrations	18	33	20	150
B49 Breast, Adj, TC vs Anthracycline*				
Total Registrations	0	0	47	127
B51 Breast, Regional Nodal XRT*				
Total Registrations	1	1	0	2
B52 Breast, Neoadj TCHP +/- AI*				
Total Registrations	1	0	0	1

	Jul 2014 Dec 2014	Jan 2014 Jun 2014	Jul 2013 Dec 2013	All Patients
E1Z11 Breast, Genetic Predictors of AIMSS*				
Total Registrations	11	54	32	97
E2108 Breast, Early Local Tx for Intact Primary Tumor*				
Total Registrations	8	6	12	42
R1005 Breast, Accelerated vs Standard WBRT*				
Total Registrations	0	8	9	17
Z11102 Breast Conserv. Surgery for MIBC*				
Total Registrations	0	2	0	2

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

S0221 Phase III

Coordinating Group: SWOG

Phase III Trial of Continuous Schedule AC + G Vs. Q 2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

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Participants:
SWOG, CTSU (endorsed by NCIC CTG, ECOG, CALGB, and NCCTG)

Study Chairs:
G Budd, H Moore

Statisticians:
W Barlow, D Lew

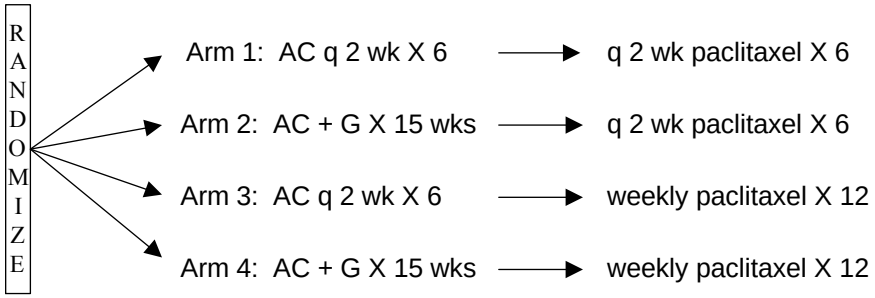
Data Coordinators:
J Barce, J Jardine

Date Activated:
11/01/2003

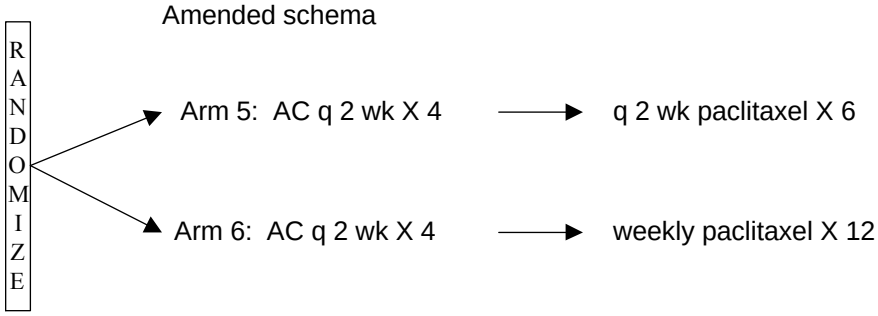
Date Closed:
01/15/2012

SCHEMA

Original schema (closed to accrual 11/10/10)



Amended schema



Objectives

To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with the combination of doxorubicin and cyclophosphamide given every 2 weeks with pegfilgrastim support with that of patients treated with weekly doxorubicin and daily oral cyclophosphamide with filgrastim support (AC+G), with both treatments to be followed by paclitaxel given according to one of two schedules.

To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with either weekly paclitaxel or paclitaxel given every 2 weeks with pegfilgrastim support following treatment with one of the two randomized doxorubicin/cyclophosphamide regimens discussed above.

To compare the disease-free survival of patients with node-positive or high-risk node-negative breast cancer treated with either weekly paclitaxel or paclitaxel given every 2 weeks with pegfilgrastim support following treatment with four two-week cycles of doxorubicin and cyclophosphamide with pegfilgrastim support and then overall adjusting for the three regimens of doxorubicin and cyclophosphamide administration.

To compare the overall survival on the four treatment arms.

To compare the toxicity of the four treatment arms.

To examine the association of putative prognostic markers with outcome and the interaction of these markers with treatment.

Patient Population

Patients must be women or men with a histologically confirmed diagnosis of operable Stage I, II, or III invasive breast cancer with known estrogen or progesterone receptor status. Patients with bilateral synchronous breast cancer diagnosed within one month of each other are eligible if the higher stage primary tumor meets the eligibility criteria for this trial. Patients must be high risk as defined in the protocol.

Patients must have had either a modified radical mastectomy or local excision of all tumor plus an axillary lymph node dissection or sentinel node resection. Final resection margins for the primary tumor must be histologically negative for invasive cancer and DCIS. Patients must be registered so that protocol treatment begins within 84 days from the final surgical procedure required to adequately treat the primary tumor or axilla. Patients must not have received prior cytotoxic chemotherapy for this breast cancer. Patients must not have had prior chemotherapy with an anthracycline, anthracenedione, or a taxane for any condition. Patients must not have received prior radiation therapy for the current malignancy, except for partial breast irradiation following lumpectomy.

Patients must be of age 18 or greater, with a Zubrod performance status of 0-2. Patients must have adequate hematologic, renal, hepatic, and cardiac function. Sexually active pre-menopausal patients must have a negative pregnancy test determined within 28 days prior to study entry.

Accrual Goals

A total of 3,250 eligible patients will be accrued. Six interim analyses will be performed after approximately 30%, 41%, 54%, 66%, 77%, and 88% of the expected events have occurred.

Summary Statement

This study was closed on January 15, 2012, after accrual of 3,294 patients. The study results were published in the *Journal of Clinical Oncology* on January 1, 2015: Interim analyses crossed the futility boundaries for demonstrating superiority of both once-per-week regimens and once-every-2-weeks regimens. After a median follow-up of 6 years, a significant interaction developed between the two randomization factors (DFS $p = .024$; OS $p = .010$) in the 2,716 patients randomly assigned in the original design, which precluded interpretation of the two factors separately. Comparing all four arms showed a significant difference in OS ($p = .040$) but not in DFS ($p = .11$), with all treatments given once every 2 weeks associated with the highest OS. This difference in OS seemed confined to patients with hormone receptor-negative/human epidermal growth factor receptor 2 (HER2) -negative tumors ($p = .067$), with no differences seen with hormone receptor-positive/HER2-negative ($p = .90$) or HER2-positive tumors ($p = .40$).

Registration by Institution

Institutions	Total Reg	Institutions	Total Reg
Alliance	775	Mansfield Gen Hosp/Cleveland Clinic OH	26
ECOG-ACRIN	419	Cleveland Clinic OH	24
Hawaii MU-NCORP	107	Breslin Cancer Ctr/Henry Ford Hosp	23
NCIC	96	Colorado, U of	23
Michigan CRC NCORP	92	Columbia University	23
Columbus NCORP	77	Greenville NCORP	22
Montana NCORP	67	Madigan Army Med Ctr/Northwest NCORP	21
LSU-Shreveport	66	Virginia Mason MC/Northwest NCORP	20
LSU-Shreveport/Gulf South MU-NCORP	64	Harrison Bremerton/PCRC NCORP	19
Wayne State Univ	64	Providence Hosp	18
Loyola University	62	San Antonio, U of TX	18
NRG	56	St Bernards Reg MC/Arkansas, U of	18
Northwest NCORP	49	McKay-Dee Hospital/Utah, U of	17
PCRC NCORP	46	Mercy Hosp Ft Smith/Arkansas, U of	17
So Calif, U of	45	Gulf South MU-NCORP	16
Ozarks NCORP	44	Wichita NCORP	16
CTSU-nos	43	St Luke's Mt State/PCRC NCORP	15
Southeast CCC NCORP	43	SW Cancer & Res Ctr/San Antonio, U of TX	15
Beaumont NCORP	41	Kansas, U of	14
Heartland NCORP	39	Sutter General Hosp/Sutter Cancer RC	14
Arizona MC, U of	38	Tennessee, U of	13
City of Hope Med Ctr	36	Mem Hosp, Co Springs/Colorado, U of	11
California Ca Ctr/San Diego, U of CA	34	Singing River Hosp/Mississippi, Univ of	10
Michigan, U of	33	Highlands Onc Group/Arkansas, U of	9
S Georgia Med Ctr/Brooke Army Med Ctr	33	Sutter Cancer RC	9
New Mexico MU-NCORP	32	Arkansas, U of	8
Kansas City NCORP	30	Good Samaritan Hosp/Cincinnati MC, U of	8
Edward Hospital/Loyola University	29	Prov Portland MC/PCRC NCORP	8
Scott & White CCOP	27	Schumpert St Mary/San Antonio, U of TX	8
West Michigan NCORP	27	All Other Institutions	191
Davis, U of CA	26	**Total (112 Institutions)**	**3294**

Registration, Eligibility, and Evaluability

Data as of March 25, 2015

	TOTAL	AC+PEG-Gx6 then q2wk T +PEG-Gx6	AC+Gx15wks then q2wk T +PEG-Gx6	AC+PEG-Gx6 then weekly T x 12
NUMBER REGISTERED	3294	678	693	697
INELIGIBLE	54	13	10	16
ELIGIBLE	3240	665	683	681
Not Analyzable	1	0	1	0
ADVERSE EVENT ASSESSMENT				
Evaluable	3179	654	661	674
Not Evaluable	51	9	16	5
Too Early	9	2	5	2

	AC+Gx15wks then weekly T x 12	AC+PEG-Gx4 then q2wk T +PEG-Gx6	AC+PEG-Gx4 then weekly T x 12
NUMBER REGISTERED	648	282	296
INELIGIBLE	8	5	2
ELIGIBLE	640	277	294
Not Analyzable	0	0	0
ADVERSE EVENT ASSESSMENT			
Evaluable	624	275	291
Not Evaluable	16	2	3
Too Early	0	0	0

Patient Characteristics

Data as of March 25, 2015

	AC+PEG-Gx6 then q2wk T +PEG-Gx6 (n=665)		AC+Gx15wks then q2wk T +PEG-Gx6 (n=682)		AC+PEG-Gx6 then weekly T x 12 (n=681)		AC+Gx15wks then weekly T x 12 (n=640)		AC+PEG-Gx4 then q2wk T +PEG-Gx6 (n=277)		AC+PEG-Gx4 then weekly T x 12 (n=294)	
AGE												
Median	50.5		50.9		51.8		50.7		52.7		53.2	
Minimum	25.8		23.2		23.2		21.0		31.2		23.7	
Maximum	77.5		79.4		86.3		76.1		79.4		76.2	
SEX												
Males	6	1%	4	1%	5	1%	3	0%	2	1%	3	1%
Females	659	99%	678	99%	676	99%	637	100%	275	99%	291	99%
HISPANIC												
Yes	51	8%	38	6%	38	6%	29	5%	23	8%	27	9%
No	553	83%	578	85%	592	87%	550	86%	235	85%	250	85%
Unknown	61	9%	66	10%	51	7%	61	10%	19	7%	17	6%
RACE												
White	543	82%	549	80%	544	80%	505	79%	227	82%	232	79%
Black	73	11%	77	11%	74	11%	79	12%	31	11%	44	15%
Asian	27	4%	30	4%	25	4%	29	5%	7	3%	5	2%
Pacific Islander	1	0%	2	0%	6	1%	3	0%	0	0%	0	0%
Native American	5	1%	5	1%	4	1%	3	0%	1	0%	2	1%
Multi-Racial	2	0%	1	0%	3	0%	9	1%	2	1%	0	0%
Unknown	14	2%	18	3%	25	4%	12	2%	9	3%	11	4%

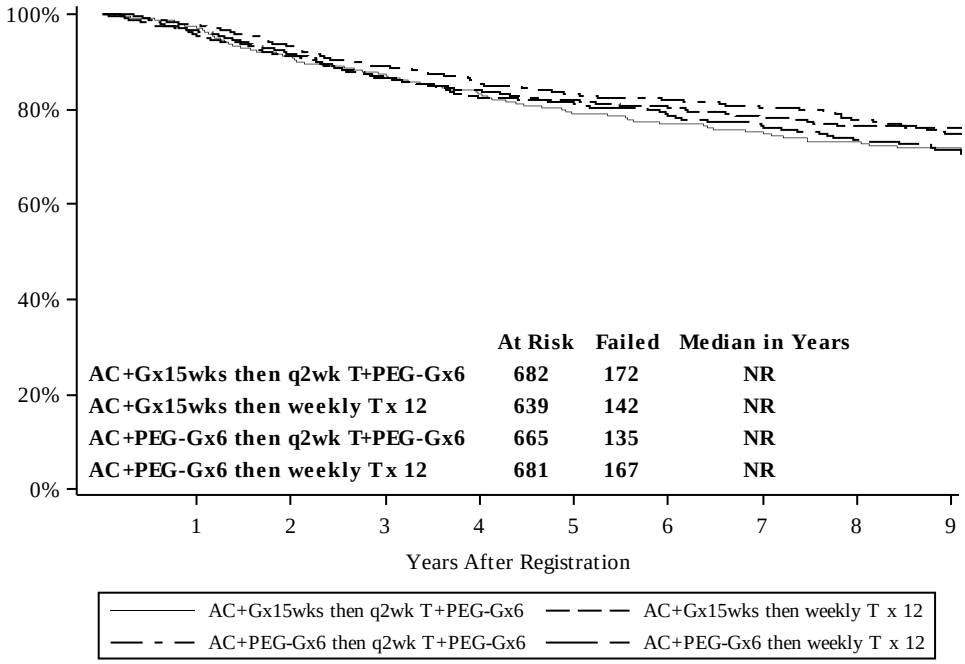
Treatment Summary

Data as of March 25, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	0
NUMBER OFF PROTOCOL TREATMENT	3239
REASON OFF TREATMENT	
Treatment completed as planned	2388
Adverse Event or side effects	608
Refusal unrelated to adverse event	128
Progression/relapse	20
Death	14
Other - not protocol specified	74
Reason under review	7
MAJOR PROTOCOL DEVIATIONS	117

Progression-Free Survival

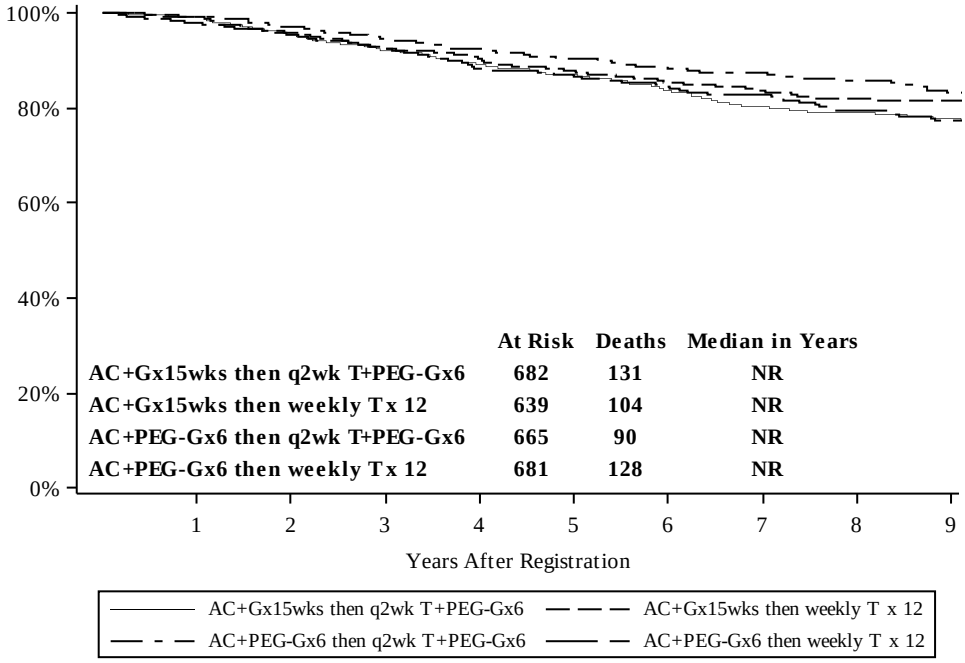
Data as of March 25, 2015



	At Risk	Failed	Median in Years
AC+Gx15wks then q2wk T+PEG-Gx6	682	172	NR
AC+Gx15wks then weekly T x 12	639	142	NR
AC+PEG-Gx6 then q2wk T+PEG-Gx6	665	135	NR
AC+PEG-Gx6 then weekly T x 12	681	167	NR

Overall Survival

Data as of March 25, 2015



	At Risk	Deaths	Median in Years
AC+Gx15wks then q2wk T+PEG-Gx6	682	131	NR
AC+Gx15wks then weekly T x 12	639	104	NR
AC+PEG-Gx6 then q2wk T+PEG-Gx6	665	90	NR
AC+PEG-Gx6 then weekly T x 12	681	128	NR

S0230 Phase III Intergroup

Coordinating Group: SWOG

Phase III Trial of LHRH Analog Administration During Chemotherapy to Reduce Ovarian Failure Following Chemotherapy in Early Stage, Hormone-Receptor Negative Breast Cancer

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Intergroup Participants:
SWOG, CALGB, ECOG, IBCSG

Date Activated:
10/01/2003

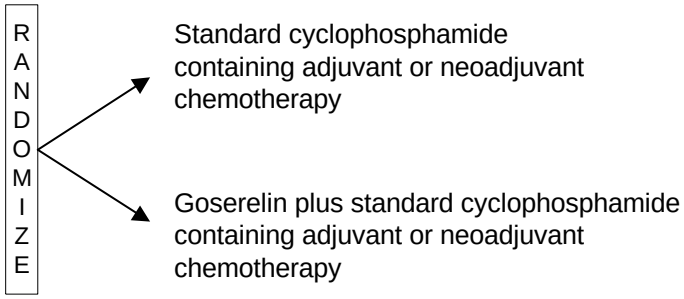
Study Chairs:
H Moore, K Albain, S Martino, A Partridge (CALGB), L Goldstein (ECOG), K Phillips (IBCSG)

Date Closed:
06/01/2011

Statisticians:
J Unger, D Lew

Data Coordinator:
I Syquia

SCHEMA



Objectives

The primary objective of this study is to compare the rate of premature ovarian failure at two years following standard adjuvant or neoadjuvant chemotherapy with or without the addition of ovarian suppression with a LHRH analog during chemotherapy in premenopausal women with early stage, hormone-receptor negative breast cancer.

The secondary objectives are to compare rates of ovarian dysfunction at one year and two years following standard adjuvant or neoadjuvant chemotherapy with or without ovarian suppression and to evaluate ovarian reserve in the two groups at one and two years. In addition, this study will describe pregnancy and other fertility information in the two groups after treatment and during the five year follow-up period.

Patient Population
Patients must be premenopausal women with a histologically confirmed diagnosis of operable Stage I, II, or IIIA invasive breast cancer. Patients must have tumors that are both estrogen receptor negative and progesterone receptor negative. Patients must be registered within 84 days after the final surgical procedure required to adequately treat the primary tumor or axilla, or after biopsy demonstrating cancer if receiving pre-operative chemotherapy.

Patients must not have received any prior cytotoxic chemotherapy. Patients must not have received estrogens, antiestrogens, selective estrogen receptor modulators, aromatase inhibitors, or hormonal forms of contraception within the past three months, with the exception of women under age 35 and those receiving hormonal interventions for the purposes of in vitro fertilization and cryopreservation of embryos or oocytes. The patient's planned treatment must include 3 to 6 months or 4 to 8 cycles of an alkylating agent containing postoperative chemotherapy regimen, either anthracycline-based or non-anthracycline-based.

Patients must be of age 18 or greater and under age 50. Patients must have a Zubrod performance status of 0-2.

Stratification/Descriptive Factors
Patient randomization will be stratified by the following: (1) age: < 40 vs 40-49; and (2) planned chemotherapy regimen: 3-4 month/cycle anthracycline-based vs 6-8 month/cycle anthracycline-based vs 3-4 month/cycle non-anthracycline-based vs 6-8 month/cycle non-anthracycline-based regimen.

Cancer Control Credits
The NCI Division of Cancer Prevention and Control has assigned 1.0 cancer control credit per registration to this study.

Accrual Goals
The accrual goal is 416 eligible patients. Interim analyses will be performed when 50% and 80% of patients have passed the one-year time point from chemotherapy initiation.

Summary Statement
This study was permanently closed effective June 1, 2011, due to drug supply/distribution issues. There were 257 patients registered, 218 of them eligible and able to be evaluated for the study endpoints.

The results of this study were published in the *New England Journal of Medicine* on March 5, 2015, including the following results: Among 135 patients with complete primary end-point data, the ovarian failure rate was 8% in the goserelin group and 22% in the chemotherapy-alone group (odds ration, 0.30; 95% confidence interval, 0.09 to 0.97; two-sided p=0.04). Among the 218 patients who could be evaluated, pregnancy occurred in more women in the goserelin group than in the chemotherapy-alone group (21% vs. 11%, p=0.03); women in the goserelin group also had improved disease-free survival (p=0.04) and overall survival (p=0.05).

Registration by Institution

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	86	Ozarks NCORP	2
ANZ BCTG/ IBCSG	58	Southeast CCC NCORP	2
FSS/ IBCSG	46	Sutter Cancer RC	2
Alliance	14	Tennessee, U of	2
Wichita NCORP	8	Columbus NCORP	1
So Calif, U of	6	Dayton NCORP	1
Cleveland Clinic OH	3	Eisenhower Army MC/Brooke Army Med Ctr	1
King Faisal Spec Hos	3	Finger Lakes Hem/Onc/Rochester, Univ of	1
Michigan, U of	3	Greenville NCORP	1
City of Hope Med Ctr	2	Harrison Bremerton/PCRC NCORP	1
Loyola University	2	Henry Ford Hosp	1
MD Anderson	2	Kansas, U of	1
Montana NCORP	2	PCRC NCORP	1
Orange Reg Med Ctr/Columbia University	2	Salem Hospital/Oregon Hlth Sci Univ	1
Oregon Hlth Sci Univ	2	**Total (29 Institutions)**	**257**

Registration, Eligibility, and Evaluability

Data as of March 24, 2015

	TOTAL	Standard chemo	Standard chemo + Goserelin
NUMBER REGISTERED	257	131	126
INELIGIBLE	23	11	12
Insufficient Documentation	19	9	10
Irreversible	19	9	10
ELIGIBLE	234	120	114
Not Analyzable	16	7	9
ADVERSE EVENT ASSESSMENT			
Evaluable	214	111	103
Not Evaluable	4	2	2

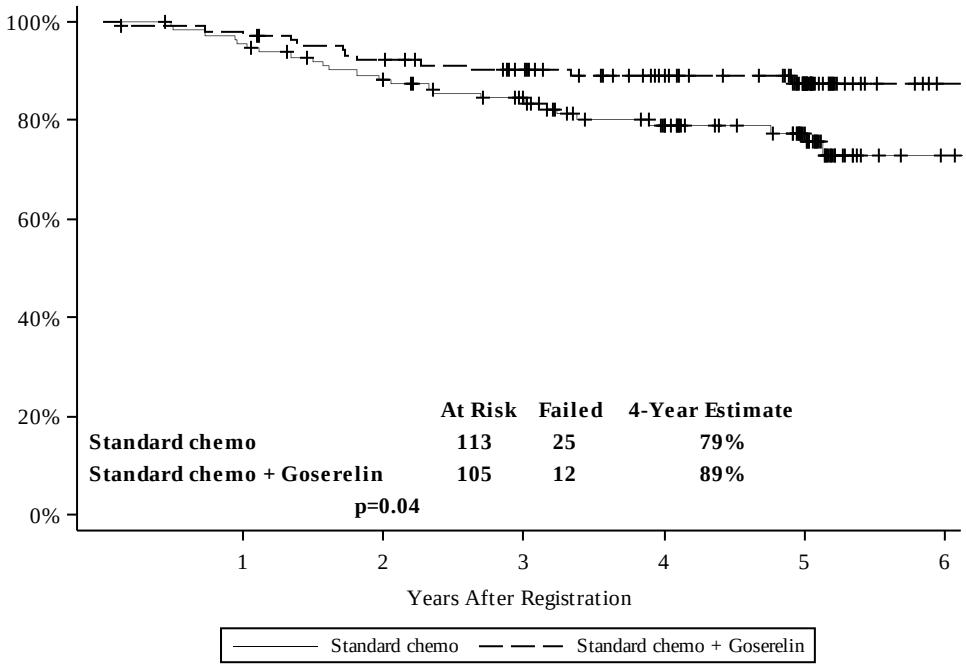
Patient Characteristics

Data as of March 24, 2015

	Standard chemo (n=113)		Standard chemo + Goserelin (n=105)	
AGE				
Median	38.7		37.6	
Minimum	25.1		26.1	
Maximum	50.0		48.6	
HISPANIC				
Yes	34	30%	33	31%
No	26	23%	33	31%
Unknown	53	47%	39	37%
RACE				
White	57	50%	65	62%
Black	6	5%	5	5%
Asian	2	2%	0	0%
Native American	1	1%	0	0%
Unknown	47	42%	35	33%
AGE				
< 40	70.0	62%	68.0	65%
40-49	43.0	38%	37.0	35%
PLANNED CHEMOTHERAPY REGIMEN				
3-4 month/cycle anthracycline based	22	19%	24	23%
6-8 month/cycle anthracycline based	80	71%	72	69%
6-8 month/cycle non-anthracycline based	4	4%	4	4%
3-4 month/cycle non-anthracycline based	7	6%	5	5%

Progression-Free Survival

Data as of March 24, 2015

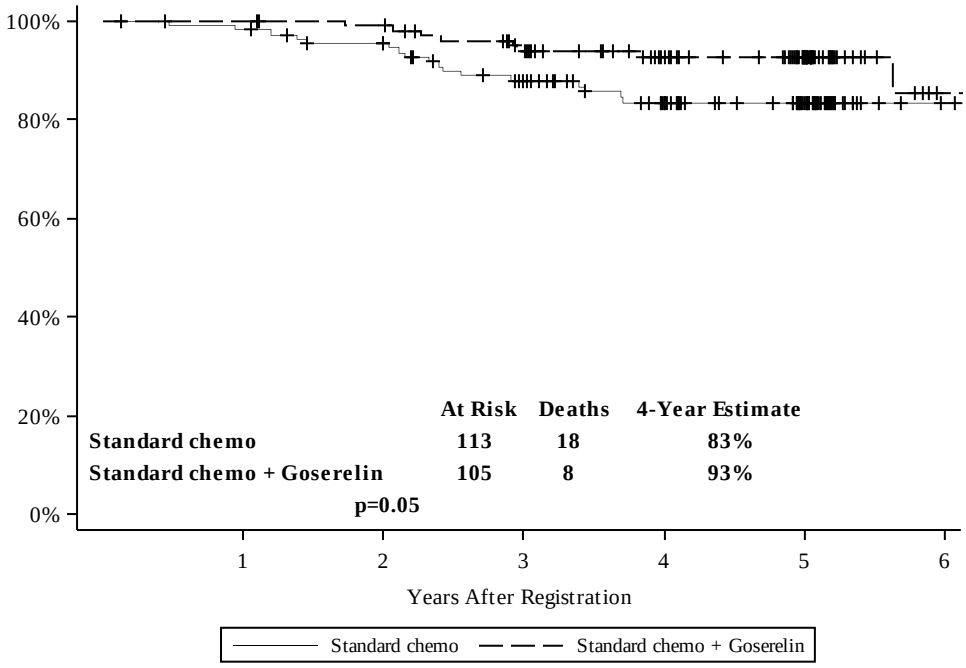


	At Risk	Failed	4-Year Estimate
Standard chemo	113	25	79%
Standard chemo + Goserelin	105	12	89%

p=0.04

Overall Survival

Data as of March 24, 2015



	At Risk	Deaths	4-Year Estimate
Standard chemo	113	18	83%
Standard chemo + Goserelin	105	8	93%

p=0.05

S0812 Phase IIB

Coordinating Group: SWOG

A Randomized Double-Blind Placebo-Controlled Biomarker Modulation Study of High Dose Vitamin D in Premenopausal Women at High Risk for Breast Cancer, Phase IIB

Participants:
SWOG, CTSU

Study Chairs:
K Crew, D Hershman

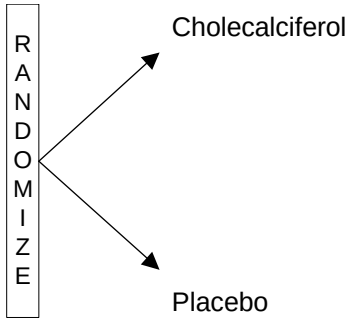
Statisticians:
G Anderson, D Lew

Data Coordinator:
M Yee

Date Activated:
11/01/2011

Date Closed:
08/15/2014

SCHEMA



Objectives

To assess whether mammographic density is reduced in premenopausal women at high risk of breast cancer taking high dose vitamin D3 (cholecalciferol 20,000 IU PO weekly) compared to high risk women taking placebo for one year.

To assess whether proliferation as measured by Ki-67 staining of breast epithelial cells is reduced in premenopausal women at high risk of breast cancer taking high dose vitamin D3 compared to high risk women taking placebo for one year.

To explore the difference in the expression of other biomarkers in breast tissue obtained from women taking high dose vitamin D3 as compared to tissue obtained from women taking placebo for one year. Additional biomarkers to be examined include cleaved caspase-3 (apoptosis marker), ER, vitamin D receptor (VDR), and 1α-hydroxylase expression in breast tissue.

To assess whether parathyroid hormone (PTH), IGF-1, IGFBP-3, 25(OH)D, and 1,25(OH)D serum levels are altered at baseline, 6 months and 12 months in women at high risk of breast cancer taking high dose vitamin D3 as compared to women taking placebo.

To explore whether a change in mammographic density correlates with polymorphisms in the VDR gene.

To assess other sources of vitamin D (sunlight exposure, diet) in this study population using a validated questionnaire administered at baseline, 12 months and 24 months.

To collect and bank serum, plasma, and breast tissue from premenopausal women at high risk of breast cancer prior to and after a one year intervention with vitamin D for future biomarker analysis.

To assess the toxicity of high dose vitamin D3 compared to placebo in this setting.

Patient Population

Participants must be premenopausal women with an elevated risk of breast cancer as defined by at least one of the following: diagnosis of resected DCIS; ADH, ALH, or LCIS; diagnosis of resected Stage I (T1b-c N0-N1mi) - Stage II breast cancer for which the participant has been disease-free for at least 5 years and has completed all adjuvant treatment; a known deleterious mutation in BRCA1, BRCA2, PTEN or TP53; modified Gail/CARE model risk at 5 years $\geq$ 1.67% or lifetime risk $\geq$ 20%; or mammographic breast density $\geq$ 50% (heterogeneously dense).

Participants must have at least one breast available for imaging and biopsy (not previously irradiated). Participants must have a baseline mammogram performed within 10 days after starting their menstrual period, with a mammographic density > 10%. Participants must not have bilateral breast implants, but prior breast reduction surgery is allowed.

Participants must be between 18 and 50 years of age and have a Zubrod performance status of 0-1. Participants must have adequate renal function and serum 25(OH)D level $\leq$ 32 ng/mL. Participants must not have a known hypersensitivity to vitamin D or known allergy to soy, and must agree not to take calcium and additional vitamin D supplements.

Stratification/Descriptive Factors

Participant randomization will be dynamically balanced according to the following stratification factors: (1) baseline serum 25(OH)D level: < 20 ng/ml vs 20-32 ng/ml (or < 50 nmol/L vs 50-80 nmol/L); (2) baseline mammographic density: 11-50% vs > 50%; and (3) designated biopsy institution: yes vs no.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit per registration to this study.

Accrual Goals

The accrual goal is 200 eligible participants.

Summary Statement

For the current status of this study, please refer to the Prevention and Epidemiology chapter.

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

---

Participants:
SWOG, CTSU (supported by NRG, Alliance, ECOG-ACRIN, NCIC CTG, GEICAM, and UNICANCER)

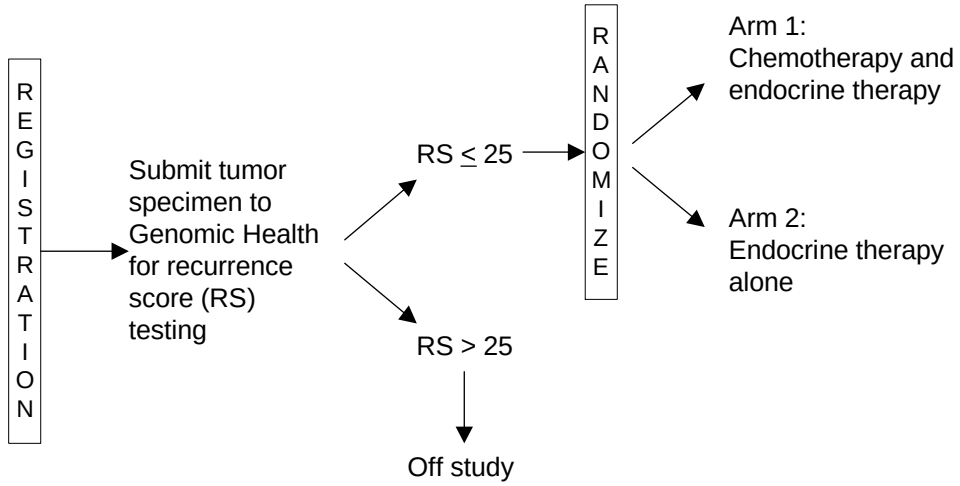
Date Activated:
01/15/2011

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

Statisticians:
W Barlow, D Lew

Data Coordinators:
L Highleyman, J Barce

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 $\leq$ 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 with a prior diagnosis of DCIS are eligible if they received mastectomy alone (i.e., no therapeutic radiation or endocrine therapy).

Patients must have had either breast-conserving surgery with planned radiation therapy or total mastectomy (with or without planned post-mastectomy radiation), with clear margins. 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.

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.

Cancer Control Credits

No cancer control credits are awarded for this study.

Accrual Goals

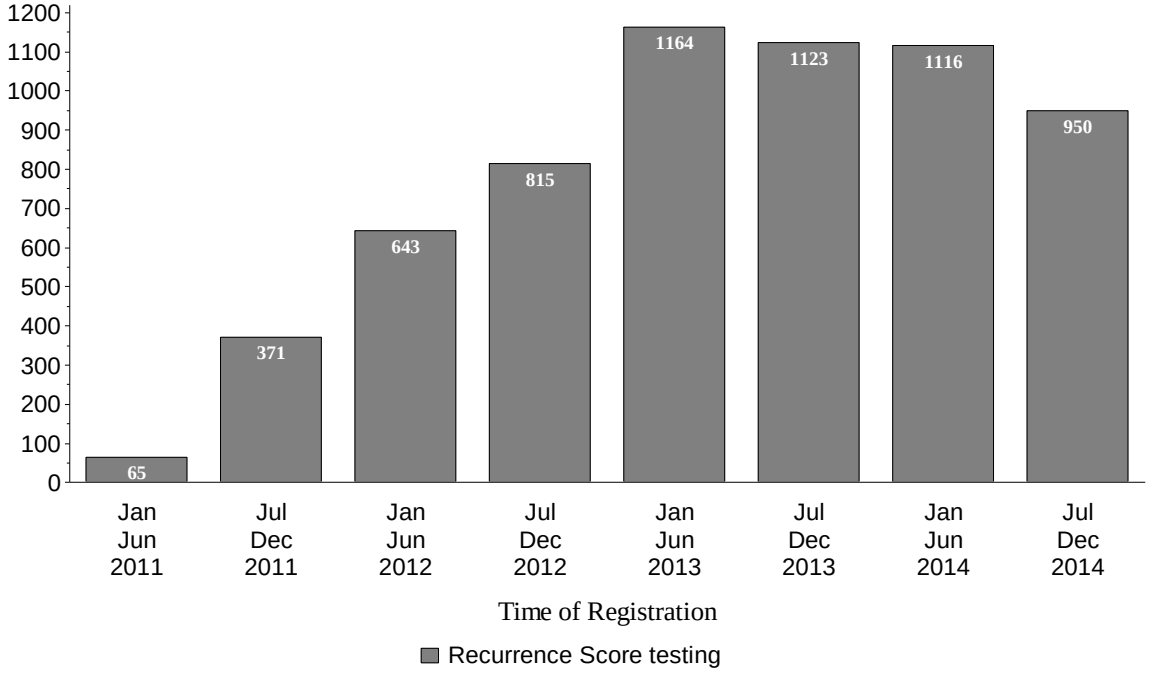
The accrual goal for the randomized trial is 4,000 eligible patients, which will require approximately 9,400 women to be screened for inclusion. An additional 1,000 eligible patients from UNICANCER in France will be randomized. Annual interim analyses are planned beginning when 24% of the events have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

Summary Statement

This study was activated on January 15, 2011. As of December 31, 2014, there had been 6,247 registrations to the screening step and 3,136 patients with Oncotype DX® Recurrence Score $\leq$ 25 randomized. One hundred sixty-five patients are currently ineligible, 114 due to incomplete baseline data. Available data for these 114 patients are included in the tables with the eligible patients. The most common other reason for ineligibility is 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 266 additional patients (8%) who refused their randomized treatment assignment, did not receive any protocol treatment, or received a non-approved chemotherapy regimen. These 266 patients are not evaluable for adverse events.

There have been four treatment-related deaths reported among 2,424 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 78 patients reported Grade 4 adverse events as maximum degree, primarily hematologic. 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



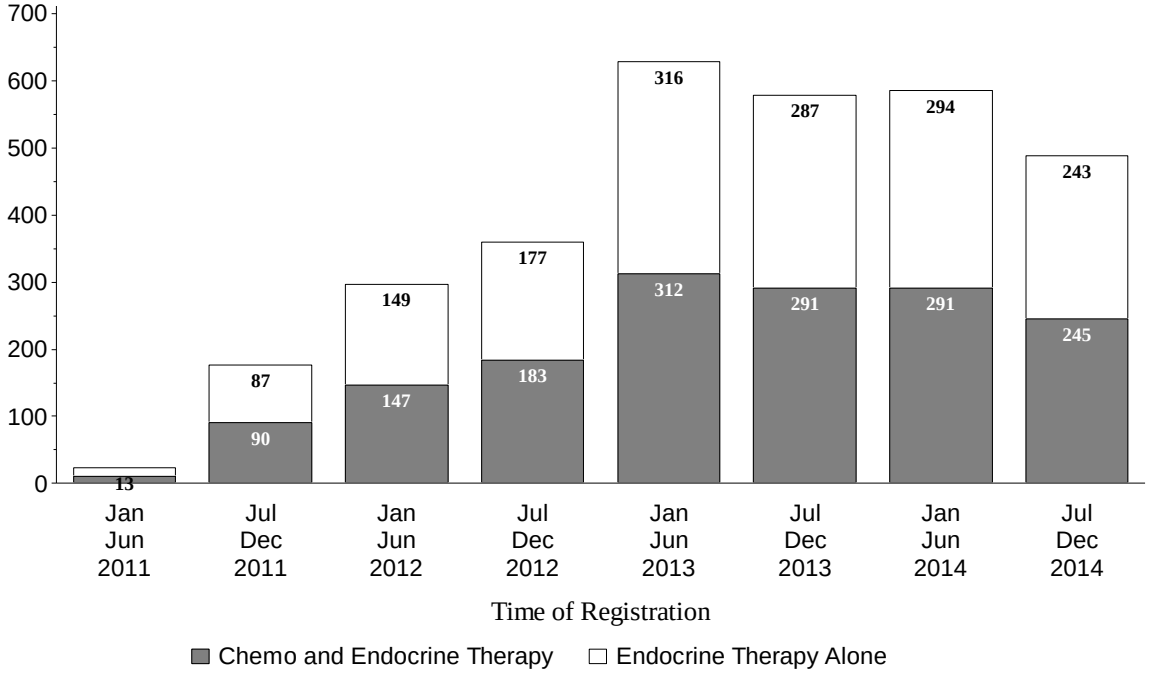
Registration by Institution

Screening Registration

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	1140	Heartland NCORP	21
GEICAM	951	Kentucky, U of	21
Alliance	865	Hawaii MU-NCORP	19
NCIC-CTG	574	Henry Ford Hosp	19
NRG	494	Lahey Hosp & Med Ctr	19
MD Anderson	244	S Georgia Med Ctr/Brooke Army Med Ctr	18
National Cancer Ctr	140	Good Samaritan Hosp/Cincinnati MC, U of	17
INCan	110	McLaren Cancer Inst/Wayne State Univ	16
Michigan CRC NCORP	107	Sacred Heart Hosp/Arkansas, U of	16
Michigan, U of	87	West Michigan NCORP	16
City of Hope Med Ctr	71	Dayton NCORP	15
Cleveland Clinic OH	69	Ozarks NCORP	15
Wichita NCORP	59	Kansas City NCORP	14
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	48	San Diego, U of CA	14
Kaiser Vallejo NCORP	43	St Joseph Med Ctr/PCRC NCORP	14
Yale University	41	Atlanta Reg CCOP	13
Loyola University	40	Montana NCORP	13
Southeast CCC NCORP	40	Singing River Hosp/Mississippi, Univ of	13
Utah, U of	40	Mem Hosp, Co Springs/Colorado, U of	12
Beaumont NCORP	36	Cookeville Reg MC	11
Columbus NCORP	36	Harrison Bremerton/PCRC NCORP	11
Kansas, U of	36	Univ of Louisville	11
New Mexico MU-NCORP	36	Colorado, U of	10
Wayne State Univ	36	SW Cancer & Res Ctr/San Antonio, U of TX	10
St Luke's Mt State/PCRC NCORP	34	UF Cancer Center/Arkansas, U of	10
St Charles Hlth Sys/PCRC NCORP	33	Long Beach Mem MC/Irvine, U of CA	9
Columbia MU-NCORP	31	St Mary Med Ctr/PCRC NCORP	9
Poudre Valley Hosp/Colorado, U of	31	Davis, U of CA	8
Methodist Hospital	27	INC, Bogota	8
So Calif, U of	27	Providence Hosp	8
MUSC MU-NCORP	26	Upstate Carolina	8
Northwest NCORP	26	Utah Valley Reg Med/Utah, U of	8
Tennessee, U of	24	All Other Institutions	195
Virginia Mason MC/Northwest NCORP	24	**Total (131 Institutions)**	**6247**

Randomization By 6 Month Intervals



Registration by Institution

Randomization

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
GEICAM	588	MUSC MU-NCORP	16
ECOG-ACRIN	523	Virginia Mason MC/Northwest NCORP	16
Alliance	430	Columbia MU-NCORP	14
NCIC-CTG	242	Columbus NCORP	14
NRG	215	Sacred Heart Hosp/Arkansas, U of	14
MD Anderson	133	Lahey Hosp & Med Ctr	13
National Cancer Ctr	113	So Calif, U of	13
INCan	75	Utah, U of	12
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	42	Wayne State Univ	12
Wichita NCORP	41	Atlanta Reg CCOP	11
City of Hope Med Ctr	35	Good Samaritan Hosp/Cincinnati MC, U of	11
Michigan CRC NCORP	34	Poudre Valley Hosp/Colorado, U of	11
Beaumont NCORP	26	Henry Ford Hosp	10
Southeast CCC NCORP	23	St Luke's Mt State/PCRC NCORP	10
Cleveland Clinic OH	22	Colorado, U of	9
Kansas, U of	22	Harrison Bremerton/PCRC NCORP	9
Kaiser Vallejo NCORP	21	Heartland NCORP	8
Loyola University	20	Kansas City NCORP	8
New Mexico MU-NCORP	20	Northwest NCORP	8
Kentucky, U of	19	Univ of Louisville	8
Yale University	19	All Other Institutions	228
Michigan, U of	18	**Total (115 Institutions)**	**3136**

Registration, Eligibility, and Evaluability

Randomization

Registrations ending December 31, 2014; Data as of March 19, 2015

	TOTAL	Chemo and Endocrine Therapy	Endocrine Therapy Alone
NUMBER REGISTERED	3136	1570	1566
INELIGIBLE	51	29	22
ELIGIBLE	3085	1541	1544
Not Analyzable	1	1	0
ADVERSE EVENT ASSESSMENT			
Evaluable	2424	1164	1260
Not Evaluable	266	180	86
Too Early	394	196	198

Patient Characteristics

Randomization

Registrations ending December 31, 2014; Data as of March 19, 2015

	Total (n=3084)	
AGE		
Median	57.8	
Minimum	18.4	
Maximum	87.7	
HISPANIC		
Yes	478	15%
No	2522	82%
Unknown	84	3%
RACE		
White	2445	79%
Black	205	7%
Asian	223	7%
Pacific Islander	10	0%
Native American	18	1%
Multi-Racial	4	0%
Unknown	179	6%
RECURRENCE SCORE		
0-13	1299	42%
14-25	1785	58%
MENOPAUSAL STATUS		
Pre-menopausal	961	31%
Post-menopausal	2123	69%
NODAL DISSECTION		
Axillary lymph node dissection (with or without sentinel node mapping)	1735	56%
Sentinel node biopsy without axillary lymph node dissection	1349	44%

Treatment Summary

Registrations ending December 31, 2014; Data as of March 19, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	2870
NUMBER OFF PROTOCOL TREATMENT	214
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	3
Refusal unrelated to adverse event	151
Progression/relapse	26
Death	11
Other - not protocol specified	23
Reason under review	0
MAJOR PROTOCOL DEVIATIONS	266

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 December 31, 2014; Data as of March 19, 2015

	Total (n=2424)			
	Grade			
ADVERSE EVENT	**<=2**	**3**	**4**	**5**
ALT increased	2420	4	0	0
AST increased	2422	2	0	0
Abdominal pain	2418	6	0	0
Acute kidney injury	2423	1	0	0
Alkaline phosphatase increased	2423	1	0	0
Allergic reaction	2420	4	0	0
Anemia	2408	14	2	0
Anorexia	2423	1	0	0
Anxiety	2423	1	0	0
Arthralgia	2386	38	0	0
Back pain	2422	2	0	0
Blood/lymph disorder-Other	2421	1	2	0
Bone pain	2413	11	0	0
Breast infection	2423	1	0	0
CD4 lymphocytes decreased	2423	1	0	0
Catheter related infection	2423	1	0	0
Chest pain - cardiac	2423	1	0	0
Chest wall pain	2423	1	0	0
Colitis	2422	2	0	0
Constipation	2422	2	0	0
Death NOS	2423	0	0	1
Dehydration	2418	6	0	0

	Total (n=2424)			
	Grade			
ADVERSE EVENT	**<=2**	**3**	**4**	**5**
Depression	2421	3	0	0
Dermatitis radiation	2421	3	0	0
Device related infection	2420	3	1	0
Diarrhea	2398	26	0	0
Dizziness	2423	1	0	0
Dry skin	2423	1	0	0
Dyspepsia	2422	2	0	0
Dyspnea	2423	1	0	0
Ear pain	2422	2	0	0
Edema limbs	2423	1	0	0
Erythema multiforme	2423	1	0	0
Erythroderma	2423	1	0	0
Esophagitis	2422	2	0	0
Fatigue	2392	32	0	0
Febrile neutropenia	2384	34	6	0
Fever	2423	1	0	0
Flank pain	2423	1	0	0
Flu like symptoms	2423	1	0	0
GI disorders-Other, specify	2423	0	0	1
Gastric hemorrhage	2423	1	0	0
Gastric ulcer	2423	1	0	0
Gastrointestinal pain	2423	1	0	0
Generalized muscle weakness	2421	3	0	0
Hand-Foot syndrome	2419	5	0	0
Headache	2418	6	0	0
Heart failure	2423	1	0	0
Hot flashes	2414	10	0	0
Hyperglycemia	2412	12	0	0
Hypertension	2419	5	0	0
Hypokalemia	2421	3	0	0
Hyponatremia	2422	2	0	0
Hypotension	2422	2	0	0
INR increased	2423	1	0	0
Infections/infestations-Other	2422	1	1	0
Injection site reaction	2423	1	0	0
Insomnia	2419	5	0	0
Irregular menstruation	2423	1	0	0
Kidney infection	2423	1	0	0
LV systolic dysfunction	2423	1	0	0
Leukocytosis	2420	3	1	0
Localized edema	2422	2	0	0
Lung infection	2419	4	1	0
Lymphedema	2422	2	0	0
Lymphocyte count decreased	2411	12	1	0
Mucositis oral	2408	16	0	0
Myalgia	2403	21	0	0
Myocardial infarction	2423	1	0	0
Nausea	2412	12	0	0
Neck pain	2422	2	0	0
Nervous sys disorders-Other	2422	2	0	0
Neutrophil count decreased	2335	29	60	0

	Total (n=2424)			
	Grade			
ADVERSE EVENT	**<=2**	**3**	**4**	**5**
Pain	2423	1	0	0
Pain in extremity	2422	2	0	0
Paresthesia	2422	2	0	0
Peripheral motor neuropathy	2421	2	1	0
Peripheral sensory neuropathy	2409	14	1	0
Platelet count decreased	2423	1	0	0
Pneumonitis	2418	6	0	0
Pruritus	2423	1	0	0
ROM decreased	2423	1	0	0
Rash acneiform	2423	1	0	0
Rash maculo-papular	2419	5	0	0
Sepsis	2420	0	3	1
Skin infection	2420	4	0	0
Skin/subq tissue ds-Other	2423	1	0	0
Stroke	2423	0	0	1
Suicidal ideation	2423	1	0	0
Syncope	2422	2	0	0
Thromboembolic event	2417	6	1	0
Tinnitus	2423	1	0	0
Typhlitis	2423	0	0	1
Upper GI hemorrhage	2423	0	1	0
Urinary tract infection	2421	3	0	0
Urticaria	2422	2	0	0
Uterine hemorrhage	2423	1	0	0
Vaginal dryness	2422	2	0	0
Vascular access complication	2423	1	0	0
Vomiting	2414	10	0	0
Watering eyes	2422	2	0	0
Weight loss	2422	2	0	0
White blood cell decreased	2380	30	14	0
Wound dehiscence	2423	1	0	0
MAX. GRADE ANY ADVERSE EVENT	2096	246	78	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.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit per registration to this study.

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

---

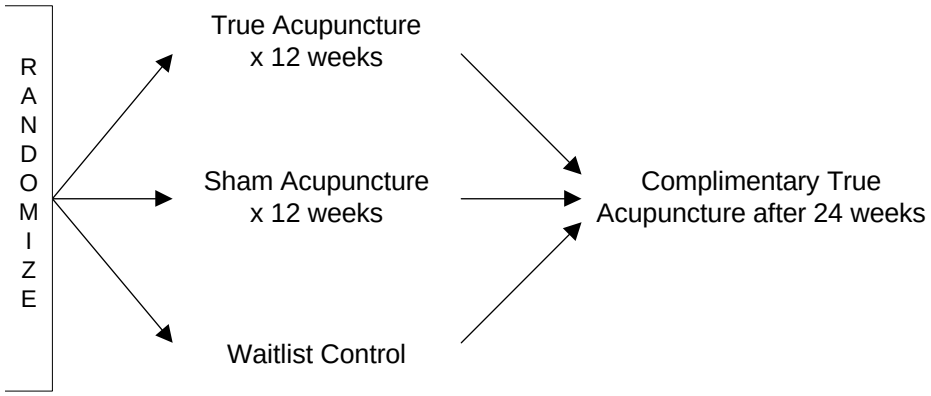
Study Chairs:
D Hershman, K Crew

Date Activated:
03/27/2012

Statisticians:
J Unger, D Lew

Data Coordinator:
D Marrah

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.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit (1.6 credits for High Performance sites) per registration to this study.

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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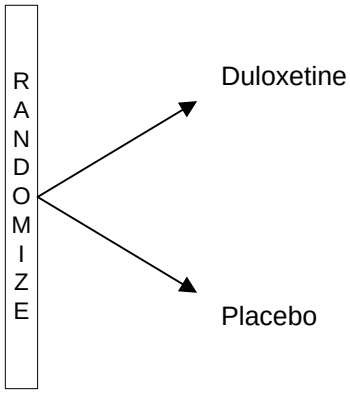
Study Chairs:
N Henry, A Schott

Date Activated:
05/15/2013

Statisticians:
J Unger, D Lew

Data Coordinator:
R Topacio

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.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit (1.6 credits for High Performance sites) per registration to this study. There are potential additional cancer control credits for specimen submission.

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

Statisticians:
J Unger, K Arnold

Data Coordinator:
M Yee

Date Activated:
08/29/2013

Date Closed*:
12/15/2014

*Temporary closure

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 cancer malignancy (including hematologic). Confirmed pathologic diagnosis must be within 120 days of registration. Patients presenting for "second opinions" of confirmed malignancies are eligible, including those who have started cancer treatment at other facilities. Individuals are ineligible if they 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. Individuals are eligible if they have had no evidence of disease for a prior malignancy, except as noted above, for at least five years prior to randomization.

Patients must be 18 years of age or older. Patients must have had their blood drawn for testing for HIV, HBV and HCV prior to registration. Patients who have had HIV, HBV and/or HCV testing within 60 days prior to registration and who do not wish to be retested are eligible, provided supporting documents can be obtained confirming viral test results for all three viruses. Patients who are viral positive for either HIV, HBV, and/or HCV and who do not wish to be retested are eligible, provided documentation of viral load within 120 days prior to registration can be obtained. Note that these patients must be tested for

or provide current viral load for all three viruses to be eligible. All documentation must be obtained prior to registration. Patients are allowed to participate in other clinical trials.

Cancer Control Credits
No cancer control credits are awarded for this study.

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

---

Participants:
SWOG, CTSU, NRG

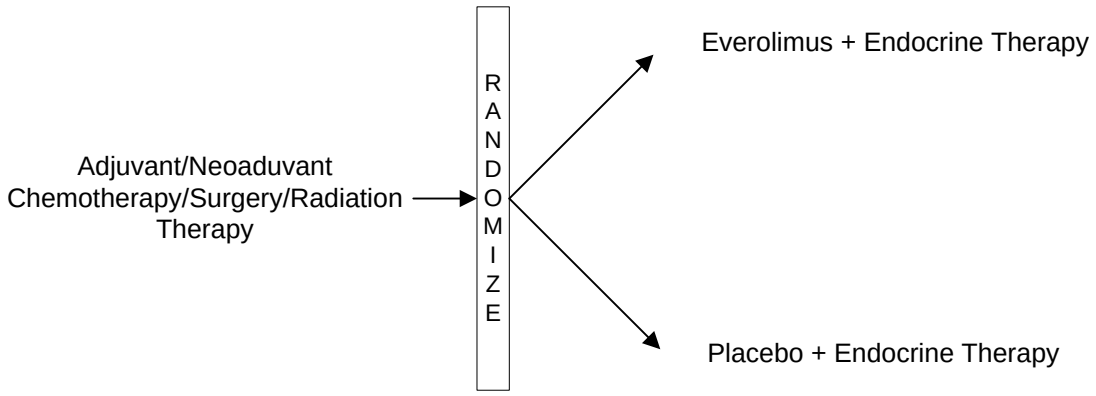
Date Activated:
09/03/2013

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

Statisticians:
W Barlow, D Lew

Data Coordinators:
J Barrett, I Syquia

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.

Cancer Control Credits

The NCI Division of Cancer Prevention has not assigned cancer control credits for registration to this study. There are potential cancer control credits for the BAHO portion of this study.

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

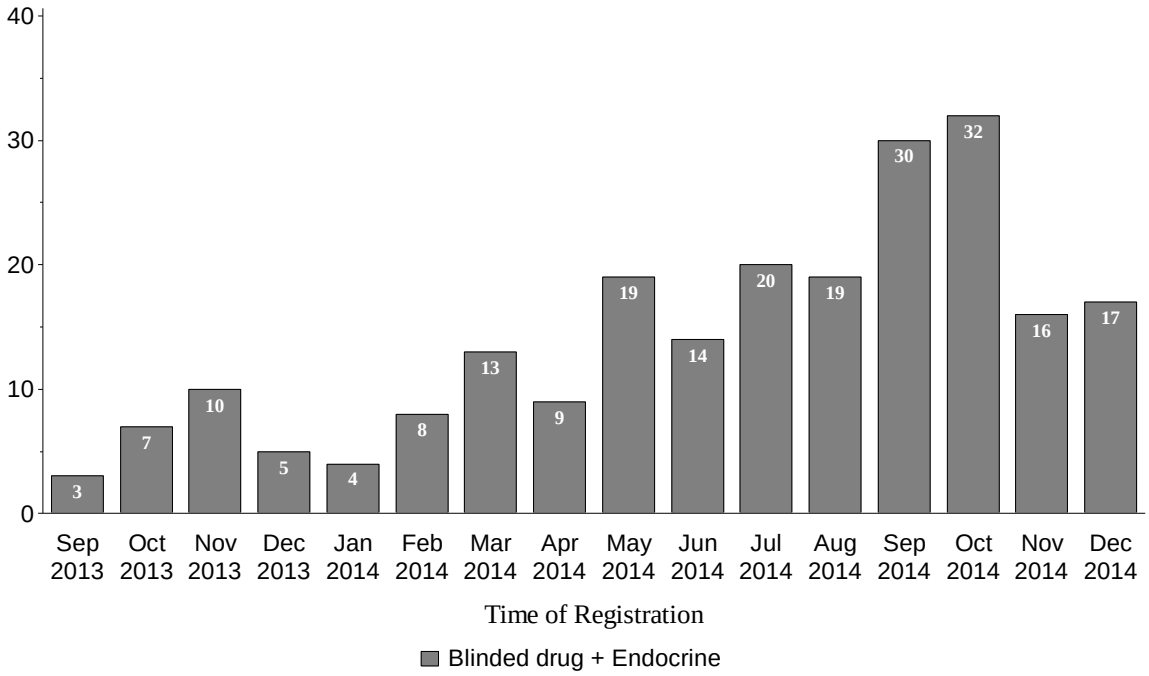
This study was activated on September 3, 2013. As of December 31, 2014, there had been 226 patients enrolled. Sixty-four patients are currently ineligible, including 40 patients with incomplete baseline data and 9 patients with missing baseline specimen submission; available data for these 49 patients are included in the tables with the eligible patients. Other reasons for ineligiblity include registration on study too soon after completion of radiation therapy (6 patients), registration on study too late after completion of chemotherapy (2), insufficient blood counts (3), omission of required radiation therapy (2) and positive HER-2 (2). Major deviations are coded for six patients who received no protocol treatment; these six patients are not evaluable for adverse events.

There has been one Grade 4 lymphocytopenia reported among 192 patients evaluated for adverse events. Thirty-five patients experienced Grade 3 adverse events as maximum degree, including six

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.

Revision #3 distributed January 1, 2015, expanded eligibility to include patients with 1-3 positive nodes and unknown RS and Grade III disease, and patients with any number of positive nodes treated with neoadjuvant chemotherapy. Patients with nicrometastases as the only nodal involvement (pN1mi) are not eligible.

Initial Registrations By 1 Month Intervals



Registration by Institution

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	51	Wayne State Univ	3
Alliance	50	Cleveland Clinic OH	2
NRG	22	Columbus NCORP	2
MD Anderson	6	Fred Hutchinson CRC	2
Arizona MC, U of	5	Kansas, U of	2
Michigan, U of	5	LSU-Shreveport/Gulf South MU-NCORP	2
Cedars-Sinai Med Ctr	4	Mem Hosp, Co Springs/Colorado, U of	2
City of Hope Med Ctr	4	Ozarks NCORP	2
Good Samaritan Hosp/Oregon Hlth Sci Univ	4	Sacred Heart Hosp/Arkansas, U of	2
H Lee Moffitt CC	4	St Charles Hlth Sys/PCRC NCORP	2
Heartland NCORP	4	Sutter Cancer RC	2
MUSC MU-NCORP	4	Thompson Ca Surv Ctr/San Antonio, U of TX	2
Wichita NCORP	4	Yale University	2
Davis, U of CA	3	All Other Institutions	26
New Mexico MU-NCORP	3	**Total (54 Institutions)**	**226**

Registration, Eligibility, and Evaluability

Registrations ending December 31, 2014; Data as of March 24, 2015

	Total
NUMBER REGISTERED	226
INELIGIBLE	15
ELIGIBLE	211
Analyzable, Pend. Elig.	7
ADVERSE EVENT ASSESSMENT	
Evaluable	192
Not Evaluable	6
Too Early	13

Patient Characteristics

Registrations ending December 31, 2014; Data as of March 24, 2015

	Total (n=211)	
AGE		
Median	54.9	
Minimum	29.4	
Maximum	76.1	
SEX		
Males	1	0%
Females	210	100%
HISPANIC		
Yes	13	6%
No	194	92%
Unknown	4	2%
RACE		
White	187	89%
Black	10	5%
Asian	5	2%
Pacific Islander	1	0%
Native American	2	1%
Multi-Racial	1	0%
Unknown	5	2%
RISK GROUP		
Node-negative and RS > 25 treated with adjuvant chemotherapy	20	9%
1-3 positive lymph nodes and RS > 25 or Grade III disease treated with adju	20	9%
>= 4 positive lymph nodes (any RS value) treated with adjuvant chemotherapy	131	62%
>= 1 positive lymph node (any RS value) with neoadjuvant chemotherapy	40	19%

Treatment Summary

Registrations ending December 31, 2014; Data as of March 24, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	132
NUMBER OFF PROTOCOL TREATMENT	79
REASON OFF TREATMENT	
Treatment completed as planned	17
Adverse Event or side effects	32
Refusal unrelated to adverse event	15
Progression/relapse	5
Death	0
Other - not protocol specified	3
Reason under review	7
MAJOR PROTOCOL DEVIATIONS	6

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

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending December 31, 2014; Data as of March 24, 2015

	Total (n=192)					
	Grade					
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
ALT increased	177	12	1	2	0	0
AST increased	174	17	0	1	0	0
Abdominal pain	186	3	0	3	0	0
Alkaline phosphatase increased	187	4	1	0	0	0
Allergic rhinitis	191	1	0	0	0	0
Alopecia	185	7	0	0	0	0
Anal mucositis	191	1	0	0	0	0
Anemia	172	13	7	0	0	0
Anorexia	178	10	4	0	0	0
Anxiety	190	2	0	0	0	0
Arthralgia	172	12	8	0	0	0
Arthritis	190	1	1	0	0	0
Back pain	189	2	1	0	0	0
Bladder infection	191	0	1	0	0	0
Bloating	191	0	1	0	0	0
Bone pain	188	3	1	0	0	0
Breast infection	191	0	1	0	0	0
CPK increased	191	0	1	0	0	0
Chest wall pain	191	1	0	0	0	0
Chills	190	2	0	0	0	0
Cholesterol high	146	38	8	0	0	0

	Total (n=192)					
	Grade					
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Concentration impairment	191	1	0	0	0	0
Confusion	191	1	0	0	0	0
Constipation	184	7	1	0	0	0
Cough	182	10	0	0	0	0
Creatinine increased	191	1	0	0	0	0
Dehydration	191	1	0	0	0	0
Depression	191	1	0	0	0	0
Diarrhea	170	16	4	2	0	0
Dizziness	188	4	0	0	0	0
Dry mouth	181	9	2	0	0	0
Dry skin	185	6	1	0	0	0
Dysgeusia	185	7	0	0	0	0
Dyspareunia	191	1	0	0	0	0
Dyspepsia	190	2	0	0	0	0
Dyspnea	178	11	2	1	0	0
Edema face	191	1	0	0	0	0
Edema limbs	182	9	1	0	0	0
Edema trunk	190	2	0	0	0	0
Epistaxis	189	3	0	0	0	0
Eye disorders - Other, specify	189	1	1	1	0	0
Facial nerve disorder	191	1	0	0	0	0
Fatigue	128	44	18	2	0	0
Fever	191	0	1	0	0	0
Flatulence	190	2	0	0	0	0
Flu like symptoms	191	0	1	0	0	0
Flushing	189	3	0	0	0	0
GI disorders-Other, specify	183	8	0	1	0	0
Gen disorders/admin site cond	190	2	0	0	0	0
Generalized muscle weakness	191	1	0	0	0	0
Hand-Foot syndrome	190	0	2	0	0	0
Headache	168	20	4	0	0	0
Hemoglobin increased	191	1	0	0	0	0
Hot flashes	173	15	3	1	0	0
Hypercalcemia	191	1	0	0	0	0
Hyperglycemia	173	16	2	1	0	0
Hyperhidrosis	191	0	0	1	0	0
Hypertension	182	5	5	0	0	0
Hypertriglyceridemia	161	22	6	3	0	0
Hypoalbuminemia	188	3	1	0	0	0
Hypocalcemia	191	1	0	0	0	0
Hypokalemia	187	2	2	1	0	0
Hyponatremia	190	2	0	0	0	0
Hypoxia	191	0	0	1	0	0
Immune sys disorders-Other	191	1	0	0	0	0
Infections/infestations-Other	187	0	1	4	0	0
Insomnia	183	7	1	1	0	0
Investigations-Other, specify	191	0	0	1	0	0
Libido decreased	190	1	1	0	0	0
Lung infection	191	0	1	0	0	0
Lymph node pain	191	1	0	0	0	0
Lymphedema	190	1	1	0	0	0

	Total (n=192)					
	Grade					
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Lymphocyte count decreased	166	9	13	3	1	0
MS/connective tissue disorder	187	3	2	0	0	0
Malaise	188	2	2	0	0	0
Metab/nutrition disorders-Oth	191	1	0	0	0	0
Mucosal infection	191	0	1	0	0	0
Mucositis oral	124	41	21	6	0	0
Muscle weakness upper limb	191	1	0	0	0	0
Myalgia	185	4	3	0	0	0
Nail discoloration	190	2	0	0	0	0
Nail loss	191	1	0	0	0	0
Nausea	167	21	3	1	0	0
Neoplasms, all	191	1	0	0	0	0
Neuralgia	191	0	0	1	0	0
Neutrophil count decreased	174	8	9	1	0	0
Non-cardiac chest pain	190	1	1	0	0	0
Oral dysesthesia	191	1	0	0	0	0
Oral pain	187	3	2	0	0	0
Otitis media	191	0	1	0	0	0
Pain	190	1	1	0	0	0
Pain in extremity	189	2	1	0	0	0
Palpitations	190	2	0	0	0	0
Paresthesia	188	3	1	0	0	0
Periorbital edema	191	1	0	0	0	0
Peripheral motor neuropathy	191	0	1	0	0	0
Peripheral sensory neuropathy	186	4	1	1	0	0
Personality change	191	0	1	0	0	0
Platelet count decreased	175	13	3	1	0	0
Pneumonitis	189	0	2	1	0	0
Postnasal drip	191	1	0	0	0	0
Presyncope	191	0	1	0	0	0
Productive cough	191	0	0	1	0	0
Pruritus	184	6	2	0	0	0
ROM decreased	191	1	0	0	0	0
Rash acneiform	180	11	1	0	0	0
Rash maculo-papular	176	14	2	0	0	0
Resp/thoracic/mediastinal ds	191	1	0	0	0	0
Skin infection	190	0	0	2	0	0
Skin/subq tissue ds-Other	187	4	1	0	0	0
Stomach pain	191	1	0	0	0	0
Stomal ulcer	191	0	1	0	0	0
Thromboembolic event	189	0	1	2	0	0
Tinnitus	191	1	0	0	0	0
Upper respiratory infection	188	0	4	0	0	0
Urinary frequency	189	3	0	0	0	0
Urinary tract infection	191	0	0	1	0	0
Urinary tract pain	191	1	0	0	0	0
Urinary urgency	191	1	0	0	0	0
Urticaria	191	1	0	0	0	0
Vaginal dryness	191	0	1	0	0	0
Vaginal hemorrhage	191	0	1	0	0	0
Vaginal pain	191	0	1	0	0	0

	Total (n=192)					
	Grade					
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Vomiting	189	1	2	0	0	0
Watering eyes	191	1	0	0	0	0
Weight gain	190	2	0	0	0	0
Weight loss	187	5	0	0	0	0
White blood cell decreased	161	16	15	0	0	0
Wound complication	190	0	1	1	0	0
Wound infection	191	0	1	0	0	0
MAX. GRADE ANY ADVERSE EVENT	44	47	65	35	1	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

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

Statisticians:
W Barlow, D Lew

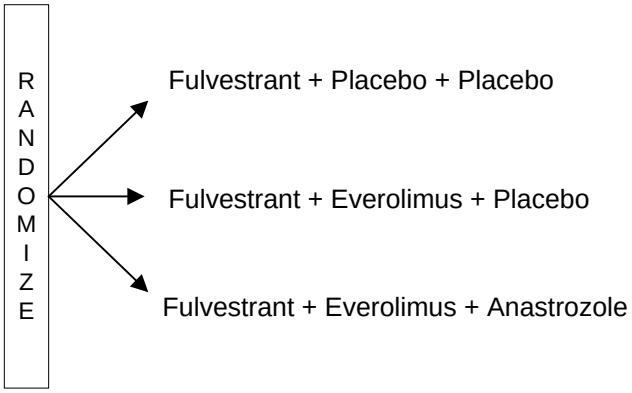
Data Coordinator:
L Kaye

Date Activated:
05/09/2014

Date Closed*:
02/24/2015

*Temporary closure

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. This study was activated on May 9, 2014. As of December 31, 2014, there had been 30 patients registered to this study. The study was temporarily closed to accrual on February 24, 2015, for statistical reasons. A major deviation is recorded for one patient who received no protocol treatment; this patient is not evaluable for adverse events. Among 29 patients assessed for adverse events, one experienced Grade 4 hypophosphatemia. Eight patients experienced Grade 3 toxicities as maximum degree.

Registration by Institution

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
Heartland NCORP	6	Lahey Hosp & Med Ctr	1
City of Hope Med Ctr	4	Loyola University	1
Montana NCORP	3	PCRC NCORP	1
Southeast CCC NCORP	3	Prov Portland MC/PCRC NCORP	1
Michigan CRC NCORP	2	Sinai Hospital/San Antonio, U of TX	1
Michigan, U of	2	Thompson Ca Surv Ctr/San Antonio, U of TX	1
Yale University	2	Utah, U of	1
Hawaii MU-NCORP	1	**Total (15 Institutions)**	**30**

Registration, Eligibility, and Evaluability

Registrations ending December 31, 2014; Data as of March 20, 2015

	Total
NUMBER REGISTERED	30
ELIGIBLE	30
RESPONSE ASSESSMENT	
Determinable	24
Too Early	6
ADVERSE EVENT ASSESSMENT	
Evaluable	29
Not Evaluable	1

Patient Characteristics

Registrations ending December 31, 2014; Data as of March 20, 2015

	Total (n=30)	
AGE		
Median	63.7	
Minimum	45.7	
Maximum	88.0	
HISPANIC		
Yes	3	10%
No	27	90%
RACE		
White	23	77%
Black	3	10%
Asian	1	3%
Multi-Racial	1	3%
Unknown	2	7%
DISEASE		
Measurable	22	73%
Evaluable non-measurable disease	8	27%
PRIOR HORMONE		
Prior adjuvant hormonal therapy completed more than 5 years ago	6	20%
Prior adjuvant hormonal therapy completed 1-5 years ago	12	40%
De novo presentation of metastatic disease or no prior adjuvant hormonal therapy	12	40%

Treatment Summary

Registrations ending December 31, 2014; Data as of March 20, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	20
NUMBER OFF PROTOCOL TREATMENT	10
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	2
Refusal unrelated to adverse event	1
Progression/relapse	5
Death	0
Other - not protocol specified	2
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

Registrations ending December 31, 2014; Data as of March 20, 2015

	Total (n=29)	Grade				
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
ALT increased	25	1	3	0	0	0
AST increased	22	6	0	1	0	0
Abdominal pain	25	1	2	1	0	0
Acute kidney injury	28	1	0	0	0	0
Alkaline phosphatase increased	26	3	0	0	0	0
Anemia	19	6	3	1	0	0
Anorexia	24	1	2	2	0	0
Arthralgia	27	2	0	0	0	0
Atelectasis	28	0	1	0	0	0
Back pain	27	2	0	0	0	0
Blood bilirubin increased	28	1	0	0	0	0
Bone pain	27	2	0	0	0	0
Cardiac disorder-Other, spec	28	1	0	0	0	0
Chills	27	2	0	0	0	0
Cholesterol high	19	8	2	0	0	0
Constipation	26	3	0	0	0	0
Cough	26	3	0	0	0	0
Creatinine increased	27	1	1	0	0	0
Dehydration	25	0	1	3	0	0
Diarrhea	23	2	3	1	0	0
Dizziness	28	1	0	0	0	0
Dry mouth	27	2	0	0	0	0
Dry skin	28	1	0	0	0	0
Dysesthesia	28	1	0	0	0	0
Dysgeusia	27	2	0	0	0	0
Dyspepsia	26	2	1	0	0	0
Dysphagia	28	0	1	0	0	0
Dyspnea	27	2	0	0	0	0
ECG QT corrected int prolong	28	0	1	0	0	0
Edema limbs	28	1	0	0	0	0
Erythema multiforme	28	1	0	0	0	0
Esophagitis	28	0	1	0	0	0
Fatigue	15	10	2	2	0	0
Fever	28	1	0	0	0	0
Generalized muscle weakness	27	0	1	1	0	0
Headache	26	3	0	0	0	0
Hot flashes	20	8	1	0	0	0
Hyperglycemia	21	6	2	0	0	0
Hypernatremia	28	1	0	0	0	0
Hypertension	28	0	0	1	0	0
Hypertriglyceridemia	19	6	4	0	0	0
Hypoalbuminemia	26	1	2	0	0	0
Hypocalcemia	27	0	1	1	0	0

	Total (n=29)	Grade				
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Hypokalemia	25	2	0	2	0	0
Hypomagnesemia	28	1	0	0	0	0
Hyponatremia	27	1	0	1	0	0
Hypophosphatemia	27	1	0	0	1	0
Hypotension	28	0	0	1	0	0
Ileus	28	0	1	0	0	0
Infections/infestations-Other	27	0	1	1	0	0
Injection site reaction	27	1	1	0	0	0
Insomnia	28	1	0	0	0	0
Lipase increased	28	1	0	0	0	0
Localized edema	28	0	0	1	0	0
Lymphocyte count decreased	24	1	3	1	0	0
Malaise	28	0	1	0	0	0
Metab/nutrition disorders-Oth	28	1	0	0	0	0
Mucosal infection	28	1	0	0	0	0
Mucositis oral	15	6	7	1	0	0
Myalgia	27	2	0	0	0	0
Nasal congestion	28	1	0	0	0	0
Nausea	21	4	4	0	0	0
Neutrophil count decreased	26	2	0	1	0	0
Oral pain	25	3	1	0	0	0
Pain	27	2	0	0	0	0
Pain in extremity	28	1	0	0	0	0
Paresthesia	28	1	0	0	0	0
Platelet count decreased	25	3	1	0	0	0
Pneumonitis	26	1	1	1	0	0
Rash acneiform	26	2	1	0	0	0
Rash maculo-papular	26	2	0	1	0	0
Sinus tachycardia	27	1	1	0	0	0
Skin hyperpigmentation	28	1	0	0	0	0
Sore throat	28	0	0	1	0	0
Upper respiratory infection	28	0	1	0	0	0
Urinary frequency	28	1	0	0	0	0
Vomiting	25	2	1	1	0	0
Weight loss	23	2	4	0	0	0
Wheezing	28	1	0	0	0	0
White blood cell decreased	23	4	1	1	0	0
MAX. GRADE ANY ADVERSE EVENT	2	6	12	8	1	0

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

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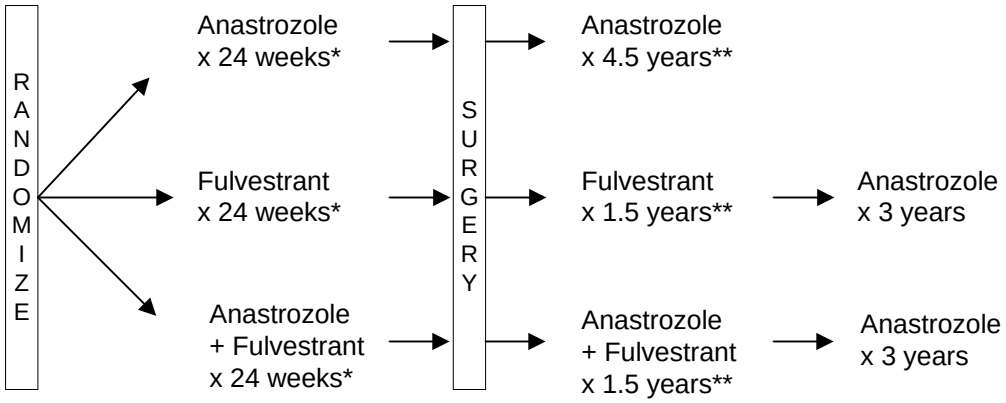
Participants:
Alliance, CTSU

Date Activated:
02/15/2014

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

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

Alliance reports that 101 patients had been registered to this study as of December 31, 2014, including four CTSU patients from SWOG institution, three from U of Arizona MC and one from Baptist MU-NCORP. The complete November 2014 summary of this study from NRG is available on the SWOG web site.

B43 Phase III SWOG Supported CTSU Study

Coordinating Group: NRG

A Phase III Clinical Trial Comparing Trastuzumab Given Concurrently with Radiation Therapy and Radiation Therapy Alone for Women with HER2-Positive Ductal Carcinoma in Situ Resected by Lumpectomy

---

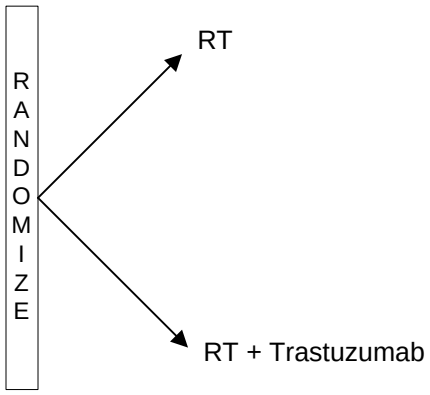
Participants:
NRG, CTSU

Study Chairs:
M Cobleigh (NRG), A Chung (SWOG)

Date Activated:
11/22/2008

Date Closed:
12/08/2014

SCHEMA



Objectives

To determine the value of trastuzumab given during radiation therapy (RT) compared to RT alone in preventing the subsequent occurrence of ipsilateral breast cancer recurrence, ipsilateral skin cancer recurrence, or ipsilateral DCIS (IIBCR-SCR-DCIS) in women with HER2-positive DCIS resected by lumpectomy.

To determine the value of trastuzumab given during RT compared to RT alone in prolonging IDFS-DCIS.

To determine the value of trastuzumab given during RT compared to RT alone in increasing invasive or DCIS recurrence-free interval.

To determine the value of trastuzumab given during RT compared to RT alone in improving regional or distant recurrence.

To determine the value of trastuzumab given during RT compared to RT alone in improving the incidence of contralateral invasive or DCIS breast cancer.

To determine the value of trastuzumab given during RT compared to RT alone in improving survival.

To explore the effect of trastuzumab on ovarian function.

To determine if the benefit of trastuzumab added to RT will be significantly higher in cMYC-amplified tumors than in the cMYC non-amplified subset.

To determine if the benefit of trastuzumab added to RT will be less in tumors with mutations in the PI3 Kinase gene than in tumors without PI3 Kinase gene mutations.

Patient Population

Patients must have histologically confirmed DCIS that is HER2-positive as determined by central testing. DCIS must not be present in more than one quadrant. ER and/or PgR status must be determined prior to randomization. Patients must not have invasive breast cancer, contralateral breast cancer (including DCIS), or nodal staging of pN1.

All DCIS must have been resected by lumpectomy, with the margins of the resected specimen histologically free of DCIS (re-excision may be performed to obtain clear margins). Patients who require mastectomy are not eligible. Axillary staging is not required, but if performed must be pN0. The interval between the last surgery for excision of DCIS and randomization must be no more than 120 days. Patients must not have prior history of breast cancer, prior whole breast irradiation, or prior anthracycline for any malignancy.

Patients must be female, at least 18 years of age, and have an ECOG performance status of 0 or 1. Patients must not have uncontrolled hypertension or cardiac disease that would preclude the use of the drugs included in the treatment regimen.

Stratification/Descriptive Factors

Patient randomization will be stratified by the following factors: (1) menopausal status: postmenopausal vs not postmenopausal; (2) hormonal therapy: yes vs no; and (3) nuclear grade: low or intermediate vs high.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit per registration to this study.

Accrual Goals

The accrual goal is 2000 eligible patients. Three formal interim analyses are planned after approximately 25%, 50%, and 75% of the expected events have been reported.

Summary Statement

NRG reports that 2,014 patients had been registered to this study prior to closure on December 8, 2014, including 66 CTSU patients from SWOG institutions. 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
Harrington CC	14	Tennessee, U of	2
Cedars-Sinai Med Ctr	6	Watson Clinic Center/H Lee Moffitt CC	2
California Ca Ctr/San Diego, U of CA	4	Asante Rogue Reg MC/Oregon Hlth Sci Univ	1
Cleveland Clinic OH	4	Central DuPage Hosp/Cleveland Clinic OH	1
McLaren Cancer Inst/Wayne State Univ	4	Christian Hosp NE/NW/St Louis University	1
Kansas City NCORP	3	Irvine, U of CA	1
Providence Hosp	3	Kaiser NCORP	1
Kansas, U of	2	Loyola University	1
Loma Linda Univ	2	Mem Hosp, Co Springs/Colorado, U of	1
Mercy Hosp Ft Smith/Arkansas, U of	2	MUSC MU-NCORP	1
Michigan, U of	2	St Joseph's/Candler/H Lee Moffitt CC	1
Mid Illinois Hem Onc/Cleveland Clinic OH	2	Sutter Cancer RC	1
Sinai Hospital/San Antonio, U of TX	2	**Total (26 Institutions)**	**66**
St Elizabeth's MC/Davis, U of CA	2		

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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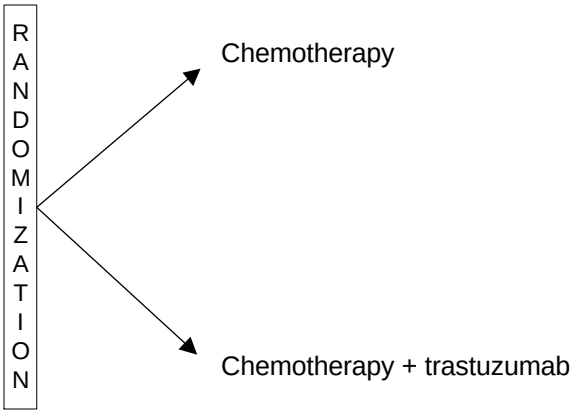
Participants:
NRG, CTSU

Date Activated:
01/07/2011

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

Date Closed:
02/10/2015

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

NRG reports that 3,156 patients had been registered to this study as of December 31, 2014, including 150 CTSU patients from SWOG institutions. The complete October 2014 summary of this study from NRG is available on the SWOG web site.

Registration by Institution

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
Michigan, U of	17	Greenville NCORP	2
Yale University	15	McLaren Cancer Inst/Wayne State Univ	2
Wayne State Univ	12	Sinai Hospital/San Antonio, U of TX	2
Cleveland Clinic OH	7	Skagit Valley Hosp/Fred Hutchinson CRC	2
Columbia MU-NCORP	7	St Elizabeth's MC/Davis, U of CA	2
LSU-Shreveport/Gulf South MU-NCORP	7	Watson Clinic Center/H Lee Moffitt CC	2
PCRC NCORP	7	Carolinas Med Ctr/San Antonio, U of TX	1
St Joseph's/Candler/H Lee Moffitt CC	7	Central DuPage Hosp/Cleveland Clinic OH	1
Rochester, Univ of	6	Columbia University	1
St Joseph Med Ctr/PCRC NCORP	5	Good Samaritan Hosp/Kansas, U of	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/PCRC NCORP	4	NE Alabama Reg MC/Mississippi, Univ of	1
Loyola University	4	Northwest NCORP	1
MidMichigan Med Ctr/Michigan, U of	4	Ozarks Reg NCORP	1
Highline Cancer Ctr/PCRC NCORP	3	Providence Hosp	1
KaiserPermanenteSCAL/Kaiser NCORP	3	Southeast CCC 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)**	**150**

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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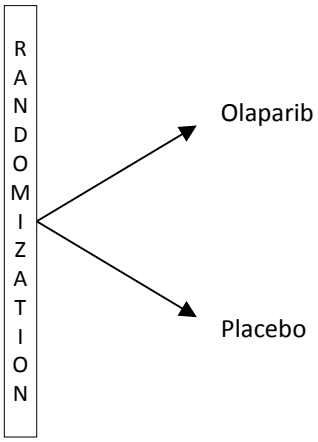
Participants:
NRG, CTSU

Date Activated:
07/03/2014

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

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.

Cancer Control Credits

No cancer control credits are awarded for this study.

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

NRG reports that three patients had been registered to this study as of December 31, 2014, none from SWOG institutions.

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.

Cancer Control Credits

The NCI Division of Cancer Prevention has assigned 1.0 cancer control credit per registration to this study.

Accrual Goals

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

Summary Statement

ECOG-ACRIN reports that as of December 31, 2014, there had been 833 registrations to this study, including 97 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
Columbia MU-NCORP	14	Dayton NCORP	2
Greenville NCORP	12	Greenwich Hospital/Yale University	2
Michigan, U of	11	Hawaii MU-NCORP	2
Ozarks NCORP	9	West Michigan NCORP	2
St Joseph's/Candler/H Lee Moffitt CC	8	Cincinnati MC, U of	1
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	6	Fowler Family Center/Baptist MU-NCORP	1
Prov Portland MC/PCRC NCORP	6	Good Samaritan Hosp/Kansas, U of	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	Providence Hosp	1
Beaumont NCORP	3	**Total (22 Institutions)**	**97**
Columbus NCORP	2		

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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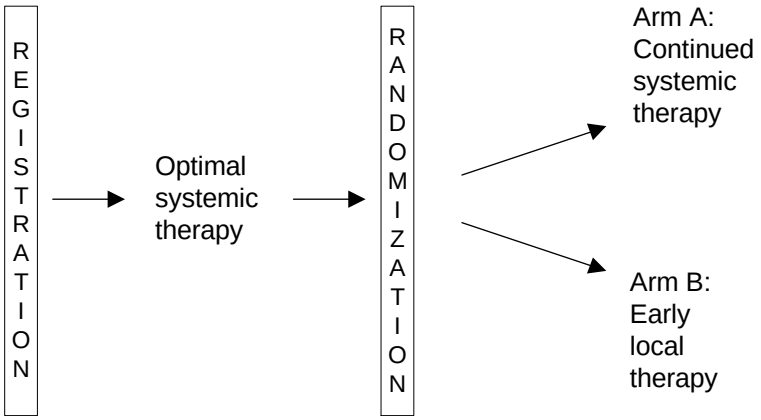
Participants:
ECOG-ACRIN, CTSU

Date Activated:
02/28/2011

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

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.

Cancer Control Credits

The NCI Division of Cancer Prevention has not assigned cancer control credits for registration to this study. There are potential cancer control credits for quality of life.

Accrual Goals

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

Summary Statement

ECOG-ACRIN reports that as of December 31, 2014, there had been 300 registrations to this study, including 42 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution

Registrations ending December 31, 2014

Institutions	Total Reg	Institutions	Total Reg
Beaumont NCORP	5	MUSC MU-NCORP	1
Baylor Univ Med Ctr	3	PCRC NCORP	1
Northwest NCORP	3	Providence Hosp	1
Kansas City NCORP	2	Singing River Hosp/Mississippi, Univ of	1
Mississippi, Univ of	2	So Calif, U of	1
Rochester, Univ of	2	St Elizabeth's MC/Davis, U of CA	1
St Luke's Mt State/PCRC NCORP	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
Dayton NCORP	1	Sutter Cancer RC	1
Greenville NCORP	1	Tulane University	1
Gulf South MU-NCORP	1	Winthrop-Univ Hosp/Columbia University	1
H Lee Moffitt CC	1	**Total (28 Institutions)**	**42**
MD Anderson	1		

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

Date Activated:
10/08/2010

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

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, aminoglute-

thimide) 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

ECOG-ACRIN reports that as of December 31, 2014, there had been 124 registrations to this study, including 17 CTSU registrations from SWOG institutions. The study has been temporarily closed to accrual since June 21, 2013 to assess feasibility. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution

Registrations ending December 31, 2014

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**