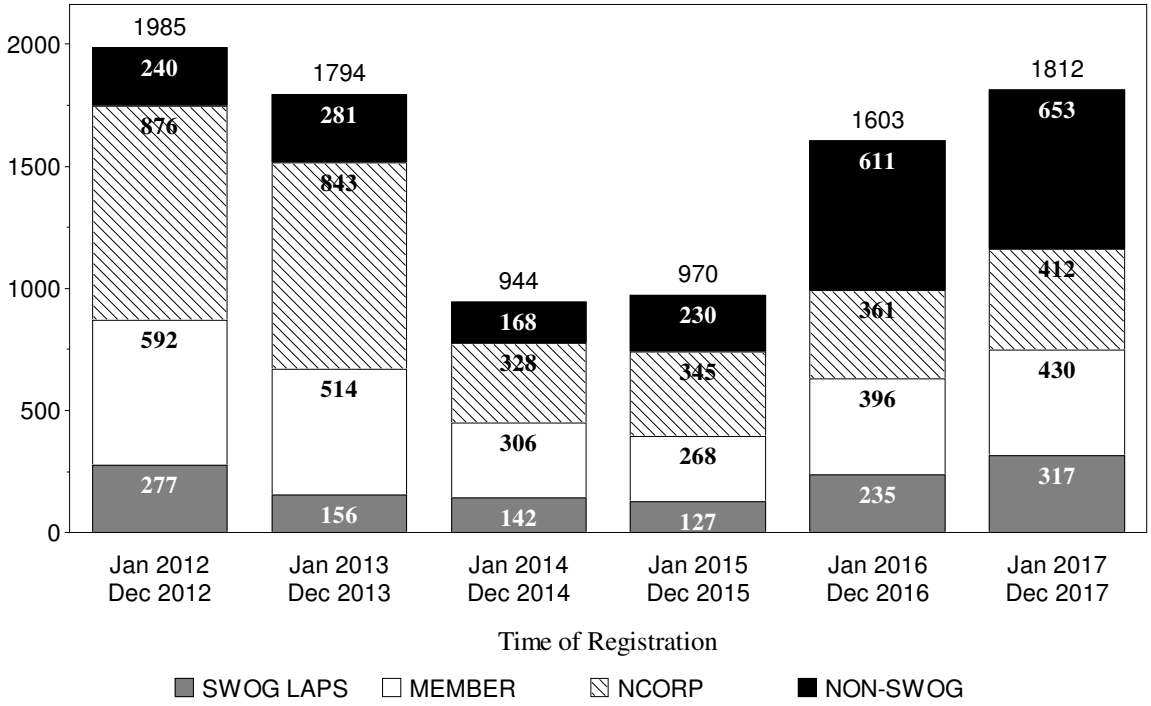
SYMPTOM CONTROL AND QOL COMMITTEE

CONTENTS

S1007 Phase III....10
S1200 Phase III....13
S1202 Phase III....16
S1207 Phase III....22
S1400I Phase III....24
S1404 Phase III....26
S1418 Phase III....28
S1600 Phase III....30
S1602 Phase III....32
S1706 Phase II....34

Patient Registrations to Studies

By 12 Month Intervals
SYMPTOM CONTROL AND QOL COMMITTEE



Screening registrations and registrations to Biologic only studies are excluded.

Patient Registrations by Study and Arm

SYMPTOM CONTROL AND QOL COMMITTEE

	Jul 2017 Dec 2017	Jan 2017 Jun 2017	Jul 2016 Dec 2016	All Patients
S1013 Validation Study of FACT-EGFRI				
Initial registration				
EGFRI-induced skin-related tox	0	0	8	146
S1200 Breast,AI Joint Pain,Acupuncture				
Randomization				
Blinded Treatment/Waitlist Control	0	8	27	226
S1207 Brst,Adj,Endocrine+/-Everolimus				
Randomization				
Blinded drug + Endocrine	188	231	211	1,454
S1400I Non-Match: Nivo + Ipi vs Nivo				
Randomization				
Nivolumab + Ipilimumab	25	23	44	126
Nivolumab	21	27	47	125
	46	50	91	251
S1404 Melan, Adv, HD-IFN/Ipilimumab vs MK-3475				
Randomization				
FDA approved regimen	110	265	204	678
MK-3475 (Pembrolizumab)	102	260	208	667
	212	525	412	1,345
S1418 Breast, Adj, TNBC, MK-3475 (Pembrolizumab)				
Randomization				
Observation	42	17	0	59
MK-3475 (Pembrolizumab)	37	16	0	53
	79	33	0	112
S1602 Blad, HG NMIBC, TICE/Tokyo/Prime+Tokyo BCG				
Registration				
TICE BCG	15	5	0	20
Tokyo-172 BCG	16	3	0	19
Prime + Tokyo-172 BCG	17	3	0	20
	48	11	0	59
A011104 Preoperative Breast MRI*				
Total Registrations	3	3	2	11
A011401 Breast, adj, Stage II/III HER2-, weight loss*				
Total Registrations	42	43	10	95
A031102 GCT, Recur, Std Chemo(TIP) vs HD Chemo(TI-CE)*				
Total Registrations	0	1	1	2
A221101 Glioma, Nuvigil/Placebo Fatigue*				
Total Registrations	2	1	1	17
A221102 Brst,AI Arthralgia,Testosterone*				
Total Registrations	0	1	5	10
B51 Breast, Regional Nodal XRT*				
Total Registrations	9	6	0	23
B55 Brst, Adj Olaparib for BRCA,TNBC*				
Total Registrations	4	7	2	22

Patient Registrations by Study and Arm (continued)

SYMPTOM CONTROL AND QOL COMMITTEE

	Jul 2017 Dec 2017	Jan 2017 Jun 2017	Jul 2016 Dec 2016	All Patients
C30610 SCLC, Thoracic RT*				
Total Registrations	5	0	0	55
C51101 CNS, myelo/non-myelo chemo, PhII*				
Total Registrations	0	1	3	9
E1411 MCL, RB+R, RBV+R, RB+LR, RBV+LR*				
Total Registrations	0	0	4	86
E1A11 MM, frontline, BLD vs CLD*				
Total Registrations	33	37	39	158
E1Q11 EROS: Reproductive Health in Cancer Survivors*				
Total Registrations	3	4	0	7
E1Z11 Brst,Genetic Predictors of AIMSS*				
Total Registrations	5	4	6	147
E2112 Brst,Adv,Exemestane+/-Entinostat*				
Total Registrations	9	9	10	44
E2810 Renal, Pazopanib vs Placebo*				
Total Registrations	1	2	6	48
E3311 Oroph,Srg + Low or Std IMRT *				
Total Registrations	0	2	5	38
E3A06 AMM, Lenalidomide vs Observation*				
Total Registrations	1	2	3	35
EA1141 Breast, Abbrev. MRI vs Digital Tomosynthesis*				
Total Registrations	38	6	0	44
EA2133 Anal, local recur/met, Cis+5FU vs Taxol/Carbo*				
Total Registrations	0	1	0	1
EA6134 Adv, BRAF mut, D+T/Ipi+Niv vs Ipi+Niv/D+T*				
Total Registrations	8	3	6	24
EA8143 RCC, HR, Surg +/- Nivolumab (PROSPER)*				
Total Registrations	5	0	0	5
EAQ152 Communication & education in tumor profiling*				
Total Registrations	0	10	1	11
G0263 Cerv, Stg I/IIA, adjv RT vs chemoRT*				
Total Registrations	1	0	0	1
G0281 Ovar, Recur/prog LG, IC chemo vs trametinib*				
Total Registrations	0	1	0	1
N1048 Rectal,LocalAdv,ChemoRT+/-FOLFOX*				
Total Registrations	17	13	20	136
NRGCC003 SCLC, PCI or HA-PCI*				
Total Registrations	1	2	1	4

Patient Registrations by Study and Arm (continued)

SYMPTOM CONTROL AND QOL COMMITTEE

NRGGY004 Ovar, Recur HG, VEGFi vs VEGFi+PARPi vs chemo*				
Total Registrations	2	1	3	6
NRGGY005 OVAR, Cedir vs Olaparib vs C+O vs Std of Care*				
Total Registrations	0	1	2	3
NRGHN001 Nasopharyngeal , Indiviual Tx EBV*				
Total Registrations	1	1	0	4
NRGHN002 HN, Adv, Orophyx RT vs RT+ Chemo*				
Total Registrations	0	0	1	1
R0724 Cervical, Chem+RT +/- Adj. Chemo*				
Total Registrations	0	0	1	1
R0920 HN, Adv, Postop IMRT ± Cetuximab*				
Total Registrations	1	1	0	11
R0924 Pros, NADT+WPRT vs. NADT+P&SV RT*				
Total Registrations	14	13	14	61
Z11102 Breast Conserv. Surgery for MIBC*				
Total Registrations	0	0	1	14

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

Non-SWOG Studies with SWOG-Credited Registrations

SYMPTOM CONTROL AND QOL COMMITTEE

Studies with Accrual from July 2016 - December 2017

	SWOG Champion	Date Activated	Date Closed	Total Accrued
A011104 Preoperative Breast MRI *Most Recent Progress Report*		02/21/14		200
A011401 Breast, adj, Stage II/III HER2-, weight loss *Most Recent Progress Report*	D Hershman	08/29/16		1025
A021202 Carcinoid, Pazopanib vs Placebo *Most Recent Progress Report*	A Phan	06/21/13	10/07/16	171
A031102 GCT, Recur, Std Chemo(TIP) vs HD Chemo(TI-CE) *Most Recent Progress Report*	D Quinn	07/01/15		72
A091105 Desmoid, Sorafenib vs Placebo *Most Recent Progress Report*		03/21/14	12/01/16	87
A221101 Glioma, Nuvigil/Placebo Fatigue *Most Recent Progress Report*		06/03/13		225
A221102 Brst,AI Arthralgia,Testosterone *Most Recent Progress Report*		09/07/12	12/01/17	228
B51 Breast, Regional Nodal XRT *No Progress Report Available*		01/31/04		821
B55 Brst, Adj Olaparib for BRCA,TNBC *No Progress Report Available*	P Sharma	07/03/14		146
C30610 SCLC, Thoracic RT *Most Recent Progress Report*		03/21/08		636
C51101 CNS, myelo/non-myelo chemo, PhII *Most Recent Progress Report*	N Mohile	06/22/12	05/02/17	113
E1411 MCL, RB+R, RBV+R, RB+LR, RBV+LR *Most Recent Progress Report*	B Till	06/08/12	09/09/16	373
E1A11 MM, frontline, BLD vs CLD *Most Recent Progress Report*	J Zonder	11/22/13		762
E1Q11 EROS: Reproductive Health in Cancer Survivors *Most Recent Progress Report*		09/30/15		123
E1Z11 Brst,Genetic Predictors of AIMSS *Most Recent Progress Report*	N Henry	05/10/13		1005
E2112 Brst,Adv,Exemestane+/-Entinostat *Most Recent Progress Report*	M Royce	01/02/14		517
E2810 Renal, Pazopanib vs Placebo *Most Recent Progress Report*	S Pan	04/17/12	07/25/17	130
E2906 AML, Age 60+, Clo vs Dauno+Cy *Most Recent Progress Report*		02/24/11		727
E3311 Oroph,Srg + Low or Std IMRT *Most Recent Progress Report*		03/01/14	07/07/17	520
E3A06 AMM, Lenalidomide vs Observation *Most Recent Progress Report*	M Dhodapkar	11/08/10	07/14/17	226

Non-SWOG Studies with SWOG-Credited Registrations (cont.)

SYMPTOM CONTROL AND QOL COMMITTEE

Studies with Accrual from July 2016 - December 2017

	SWOG Champion	Date Activated	Date Closed	Total Accrued
EA1141 Breast, Abbrev. MRI vs Digital Tomosynthesis *Most Recent Progress Report*		09/02/16	11/07/17	1518
EA2133 Anal, local recur/met, Cis+5FU vs Taxol/Carbo *Most Recent Progress Report*		01/29/16	09/27/17	12
EA6134 MELAN, Adv, BRAF mut, **Dabrafenib/Trametinib → Ipilimumab/Nivolumab** **vs** **Ipilimumab/Nivolumab → Dabrafenib/Trametinib** *Most Recent Progress Report*	B Chmielowski	12/15/15		119
EA8143 RCC, HR, Surg +/- Nivolumab (PROSPER) *Most Recent Progress Report*	P Lara, B Shuch	02/02/17		28
EAQ152 Communication & education in tumor profiling *Most Recent Progress Report*		09/26/16		262
G0263 Cerv, Stg I/IIA, adjv RT vs chemoRT *Most Recent Progress Report*		04/12/10		271
G0281 Ovar, Recur/prog LG, IC chemo vs trametinib *Most Recent Progress Report*		02/27/14		225
G0286B Adv Endometrial,Metformin/Chemo *Most Recent Progress Report*		07/17/14	02/01/18	469
N1048 Rectal,LocalAdv,ChemoRT+/-FOLFOX *Most Recent Progress Report*	C Eng	01/13/12		941
NRGCC003 SCLC, PCI or HA-PCI *No Progress Report Available*	L Gaspar	12/07/15		182
NRGGY004 Ovar, Recur HG, VEGFi vs VEGFi+PARPi vs chemo *Most Recent Progress Report*		02/04/16	11/10/17	572
NRGGY005 OVAR, Cedir vs Olaparib vs C+O vs Std of Care *Most Recent Progress Report*		02/06/16		213
NRGHN001 Nasopharyngeal, Indiviual Tx EBV *Most Recent Progress Report*		04/21/14		218
NRGHN002 HN, Adv, Orophyx RT vs RT+ Chemo *Most Recent Progress Report*		10/27/14	02/07/17	308
R0724 Cervical, Chem+RT +/- Adj. Chemo *Most Recent Progress Report*		01/15/14		187
R0848 Panc, Adj, Erlotinib v ChemoRT *Most Recent Progress Report*	P Philip	03/01/14		288
R0920 HN, Adv, Postop IMRT ± Cetuximab *Most Recent Progress Report*		12/24/13		614
R0924 Pros, NADT+WPRT vs. NADT+P&SV RT *Most Recent Progress Report*		07/07/11		1914

Non-SWOG Studies with SWOG-Credited Registrations (cont.)

SYMPTOM CONTROL AND QOL COMMITTEE

Studies with Accrual from July 2016 - December 2017

	SWOG Champion	Date Activated	Date Closed	Total Accrued
R1216 HN, Adv,Cis vs Dtx vs Dtx+Cetux *Most Recent Progress Report*		03/18/13		204
Z11102 Breast Conserv. Surgery for MIBC *Most Recent Progress Report*		02/06/14	08/19/16	271

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, CCTG,GEICAM and UNICANCER)

Study Chairs:
K Kalinsky, J Gralow, P Rastogi (NRG), N Lin (Alliance), L Goldstein (ECOG-ACRIN), S Chia (CCTG), E Alba Conejo (GEICAM), S DeLaloge (UNICANCER)

Statisticians:
W Barlow, D Lew, J Miao

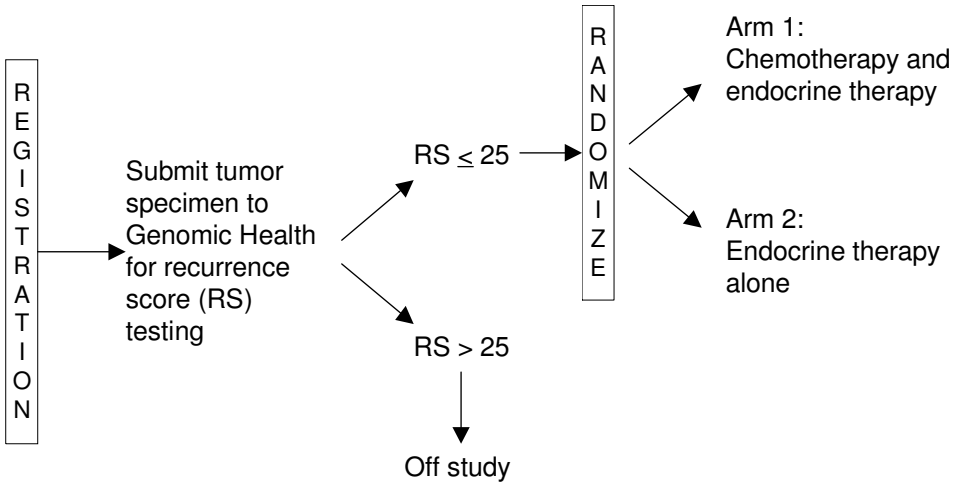
Data Coordinators:
L Kaye, J Scurlock

Date Activated:
01/15/2011

Date Closed*:
10/01/2015

* Open to UNICANCER only

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

Registration of patients who have not yet undergone Oncotype DX® screening must occur no later than 56 days after definitive surgery. For all patients, randomization (Step 2 Registration) must occur

within 84 days after definitive surgery. If the Oncotype DX® Breast Cancer Assay has not been performed, patients must be willing to submit tissue samples directly to Genomic Health for testing to determine Recurrence Score value. If the Oncotype DX® Recurrence Score is already known and is 25 or less, the patient must be randomized (registered to Step 2) immediately following initial registration. If the Oncotype DX® Recurrence Score is already known and is greater than 25, the patient is ineligible.

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

Stratification/Descriptive Factors

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

Accrual Goals

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

Summary Statement

For the current status of this study, please refer to the Breast 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

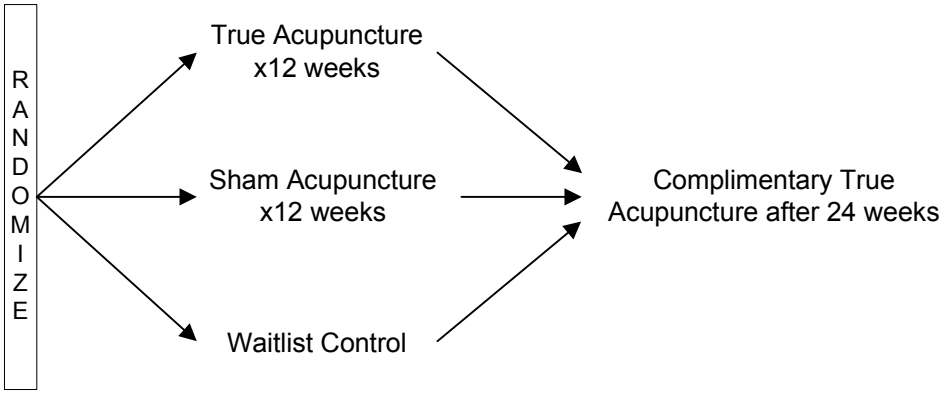
Statisticians:
J Unger, D Lew

Data Coordinator:
R Topacio

Date Activated:
03/27/2012

Date Closed:
02/15/2017

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 TNFα, IL-6, IL-12, CRP and urine CTX-II).

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

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

Patient Population

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

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

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

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

Stratification/Descriptive Factors

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

Accrual Goals

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

Summary Statement

The final analysis for this study was reported as an oral presentation at the 2017 San Antonio Breast Cancer Symposium and the abstract is provided as follows:

Background: Musculoskeletal symptoms are the most common side effect of aromatase inhibitors (AIs) and can result in decreased quality of life and discontinuation of therapy. Pilot data from two prior single institution studies showed that acupuncture decreased AI-induced joint symptoms in breast cancer (BC) patients.

Methods: We conducted a SWOG multicenter randomized controlled trial among postmenopausal women with early stage BC. Patients taking an AI for

≥30 days and having a worst pain score of ≥3 out of 10 using the Brief Pain Inventory (BPI-WP) were eligible. Subjects were randomized at a 2:1:1 ratio to true acupuncture (TA) vs. sham acupuncture (SA) vs. waitlist control (WC). The TA protocol used a standardized protocol of body and auricular acupoints tailored to joint symptoms. The similarly standardized SA protocol utilized superficial needling of non-acupoints. Both the TA and SA protocols consisted of a 12-week intervention, with 12 sessions administered over 6 weeks, followed by 1 session per week for 6 additional weeks. The primary endpoint was change in the BPI-WP (worst pain) score at 6 weeks. Secondary outcomes included other BPI scores, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for the hips and knees, the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH), and functional testing with grip strength and "Timed Get Up and Go" (TGUG). The design specified alpha=.025 two-sided tests to account for two independent comparisons (TA vs. SA and TA vs. WC).

Results: Among 226 patients registered, 110 were randomized to TA, 59 to SA, and 57 to WC. Baseline characteristics were similar between the groups. In a linear regression adjusting for the baseline score and stratification factors, 6-week mean BPI-WP scores were 0.92 points lower (correlating with less pain) in the TA compared to SA arm (95% CI: 0.20-1.65, p=.01), and were 0.96 points lower in the TA compared to WC arm (95% CI: 0.24-1.67, p=.01). The proportion of patients experiencing a clinically meaningful (>2) reduction (i.e., improvement) in BPI-WP was 58% for TA compared to 33% on SA and 31% on WC. Patients randomized to TA had improved symptoms compared to SA at week 6 according to all other BPI pain measures (average pain, p=.04; pain interference, p=.02; pain severity, p=.05; worst stiffness, p=.02). Results were similar compared to WC. Patients randomized to TA compared to SA or WC had statistically significant or marginally statistically significant improvements in BPI pain measures at week 12. Patients randomized to TA had generally improved symptoms compared to SA or WC at week 6 and at week 12 according to the M-SACRAH and WOMAC measures (p<0.05). With regard to adverse events, more patients on the TA arm experienced Grade 1 bruising compared to SA (47% vs. 25%, p=.01). No other differences by arm for selected adverse events were observed.

Conclusions: This study was the first large multicenter trial to investigate the effect of acupuncture in treating AI-induced joint symptoms in BC patients. According to multiple measures, TA generated better outcomes than either SA or WC with minimal toxicity.

Registration by Institution

Institutions	Total Reg	Institutions	Total Reg
CRC West MI NCORP	68	Lahey Hosp & Med Ctr	10
Kaiser Perm NCORP	56	Good Samaritan Hosp/Oregon Hlth Sci Univ	9
Columbia MU-NCORP	29	PCRC NCORP	6
Greenville NCORP	15	So Calif, U of	5
St Luke's Mt State/PCRC NCORP	14	Utah, U of	3
Fred Hutchinson CRC	11	**Total (11 Institutions)**	**226**

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

Study Chairs:
N Henry, A Schott

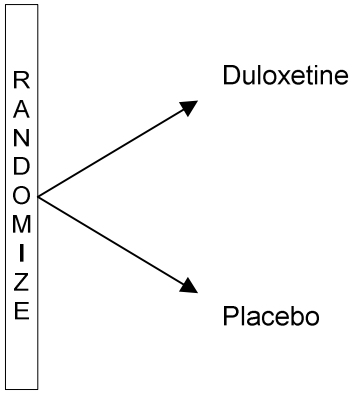
Statisticians:
J Unger, D Lew, A Moseley

Data Coordinator:
R Topacio

Date Activated:
05/15/2013

Date Closed:
10/01/2015

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 (BPI-SF).

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.

Patient Population

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

Patients must have completed mastectomy or breast sparing surgery and have recovered from all side-effects of the surgery. Any chemotherapy and/or radiation therapy must be completed at least 28 days prior to registration, and patients must have recovered from all Grade 2 or higher side effects with the exception of alopecia and peripheral neuropathy. Concurrent bisphosphonate and trastuzumab therapies are allowed. Patients must currently be

taking one of the following aromatase inhibitor (AI) doses for at least 21 days with plans to continue for at least an additional 180 days after registration: anastrozole 1 mg daily, letrozole 2.5 mg daily, or exemestane 25 mg daily. Patients may have received any number of prior AI therapies, but the first AI therapy must have started no more than 36 months prior to registration. Patients must not have previously taken the serotonin norepinephrine reuptake inhibitors (SNRI) duloxetine or milnacipran. Patients must not require selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants during study participation. Prior venlafaxine is allowed as long as it was not taken for treatment of pain (e.g., prior treatment for hot flashes is permitted). Patients must not take MAO-inhibitors for 14 days before registration or any time during study treatment. Concommitant therapy with heparin and warfarin is also not permitted at registration or while on protocol treatment. Aspirin is permitted.

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

Stratification/Descriptive Factors

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

Accrual Goals

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

Summary Statement

This study was activated on May 15, 2013, and closed on October 1, 2015, after meeting its accrual goal with 299 patients registered.

Ten patients were ineligible for the following reasons: three started their AI over 36 months prior to registration, two had previously taken venlafaxine for pain, two were not postmenopausal, one had baseline creatinine clearance too low, one had baseline average pain score less than 4, and one had noninvasive breast cancer.

Major deviations are recorded for 15 other patients: four who received only one day of intervention, nine who did not receive any protocol intervention and are therefore not evaluable for adverse events, one who did not begin protocol intervention until over a month after registration, and one who changed AI and was not removed from protocol intervention. One additional patient discontinued treatment before adverse events were assessed by the site and is not included in the analysis of adverse events.

Three patients were removed from protocol treatment for reasons other than adverse events, patient refusal, or progression: one due to non-compliance, one due to change of AI therapy after registration, and one due to concurrent venlafaxine. These patients did not receive any protocol intervention and are among those recorded as major deviations.

Seventeen patients have experienced Grade 3 toxicities among 279 patients assessed for adverse events, including 5 cases of Grade 3 insomnia (4 of them on the duloxetine arm). There have been no Grade 4 or 5 toxicities reported.

Results

The results of this trial were published in the Journal of Clinical Oncology in November, 2017. Analyses of average pain, worst pain, and pain interference used multivariable linear mixed models with a random effect for patient and including the protocol-specified stratification factors, a continuous variable for time, and baseline score as covariates ("Mixed Models" columns in Table 1). The main analyses for each outcome included assessments completed within the protocol-specified windows (± 7 days at week 2

and ± 14 days at weeks 6 and 12). Sensitivity analyses included all observations within 14 weeks of randomization, regardless of timing. Multivariable linear regression analyses by assessment time were used to identify potential critical effectiveness times ("Linear Models" columns in Table 1). Model covariates for linear regressions were the same as described above, excluding the variable for time. Secondary endpoints were analyzed similarly, with longitudinal and assessment time-specific analyses of Global Rating of Change (GRC) scale improvement in pain and stiffness using generalized linear mixed models and logistic regression, respectively, since these were binary outcomes.

Patients were evaluable for the main analysis of average pain if they had a baseline BPI-SF score and at least one follow-up BPI-SF score at week 2, 6, or 12 within the protocol-specified windows. For this analysis, there were 127 evaluable patients on the duloxetine arm and 128 on the placebo arm. Other models used slightly different numbers of patients due to differing patterns of missing data across different patient-reported outcomes and assessment times.

In mixed models, average pain was 0.82 points less on the duloxetine arm than on the placebo arm (95% Confidence Interval [CI] -1.24 to -0.40, p=0.0002). The results were similar when all BPI-SF assessments within 14 weeks after registration were included in the models (-0.76; 95% CI -1.17 to -0.34; p=0.004). When each time point was analyzed separately using linear regression, duloxetine patients showed significant reductions in average pain over placebo patients at weeks 2, 6, and 12. There was not a significant difference in average pain score between arms at week 24, however, which was 12 weeks after completion of the full-dose study intervention. Analysis results for the primary and secondary objectives are shown in Table 1, below.

Registration by Institution

Institutions	Total Reg	Institutions	Total Reg
Kaiser Perm NCORP	40	MUSC MU-NCORP	2
Southeast COR NCORP	17	PCRC NCORP	2
Gulf South MU-NCORP	15	Porter Memorial Hosp/Loyola University	2
Wichita NCORP	13	Schumpert St Mary/San Antonio, U of TX	2
Heartland NCORP	11	Texas Tech Univ HSC/San Antonio, U of TX	2
Sacred Heart Hosp/Arkansas, U of	10	Columbia MU-NCORP	1
Michigan CRC NCORP	9	Columbus NCORP	1
Dayton NCORP	6	Greenville NCORP	1
Intermountain MC/Northwest NCORP	5	Highline Medical Ctr/Franciscan Res Ctr	1
Montana NCORP	5	Loyola University	1
Tulane University	5	McLaren Cancer Inst/Wayne State Univ	1
Prov Portland MC/PCRC NCORP	4	Nevada CRF NCORP	1
Cedars-Sinai Med Ctr	3	New Mexico MU-NCORP	1
Hawaii MU-NCORP	3	Northwest NCORP	1
LSU-Shreveport/Gulf South MU-NCORP	3	Ozarks NCORP	1
PIH Health Hosp/Irvine, U of CA	3	S Georgia Med Ctr/Brooke Army Med Ctr	1
Sutter Cancer RC	3	The Watson Clinic/H Lee Moffitt CC	1
Wayne State Univ	3	Tulane Univ MBCCOP	1
Baptist MU-NCORP	2	NRG	44
Beaumont NCORP	2	ALLIANCE	43
Kansas City NCORP	2	ECOG-ACRIN	23
Michigan, U of	2	**Total (43 Institutions)**	**299**

Registration, Eligibility, and Evaluability

Data as of January 24, 2018

	TOTAL	Placebo	Duloxetine
NUMBER REGISTERED	299	149	150
INELIGIBLE	10	5	5
ELIGIBLE	289	144	145
ADVERSE EVENT ASSESSMENT			
Evaluable	279	141	138
Not Evaluable	10	3	7

Patient Characteristics

All eligible and selected ineligible patients included

Data as of January 24, 2018

	Placebo (n=144)		Duloxetine (n=145)	
AGE				
Median	60.2		60.7	
Minimum	27.4		40.7	
Maximum	82.2		83.4	
HISPANIC				
Yes	6	4%	5	3%
No	137	95%	140	97%
Unknown	1	1%	0	0%
RACE				
White	120	83%	128	88%
Black	17	12%	10	7%
Asian	3	2%	6	4%
Pacific Islander	0	0%	1	1%
Native American	2	1%	0	0%
Multi-Racial	1	1%	0	0%
Unknown	1	1%	0	0%
BASELINE PAIN SCORE				
4-6	110	76%	110	76%
7-10	34	24%	35	24%
PRIOR TAXANE USE				
Yes	79	55%	77	53%
No	65	45%	68	47%

Treatment Summary

All eligible and selected ineligible patients included

Data as of January 24, 2018

	TOTAL	Placebo	Duloxetine
NUMBER ON PROTOCOL TREATMENT	0	0	0
NUMBER OFF PROTOCOL TREATMENT	289	144	145
REASON OFF TREATMENT			
Treatment completed as planned	219	108	111
Adverse Event or side effects	40	19	21
Refusal unrelated to adverse event	25	15	10
Progression/relapse	2	2	0
Death	0	0	0
Other - not protocol specified	3	0	3
Reason under review	0	0	0
MAJOR PROTOCOL DEVIATIONS	15	2	13

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

Adverse Events Unlikely or Not Related to Treatment Excluded

All Eligible and Selected Ineligible Patients Included

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

Data as of January 24, 2018

	Placebo (n=141) Grade						Duloxetine (n=138) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Abdominal pain	136	3	2	0	0	0	132	5	0	1	0	0
Arthralgia	126	7	7	1	0	0	126	5	6	1	0	0
Diarrhea	135	6	0	0	0	0	119	15	3	1	0	0
Fatigue	123	15	3	0	0	0	94	28	15	1	0	0
Headache	123	13	4	1	0	0	108	26	4	0	0	0
Hypersomnia	140	0	0	1	0	0	138	0	0	0	0	0
Insomnia	134	3	3	1	0	0	119	8	7	4	0	0
Myalgia	131	4	6	0	0	0	118	11	8	1	0	0
Nausea	132	8	1	0	0	0	94	36	7	1	0	0
Pain	129	5	6	1	0	0	130	3	5	0	0	0
Pain in extremity	139	2	0	0	0	0	134	0	2	2	0	0
ROM decreased	134	6	1	0	0	0	128	4	5	1	0	0
Vomiting	140	1	0	0	0	0	134	1	2	1	0	0
MAX. GRADE ANY ADVERSE EVENT	71	32	33	5	0	0	29	54	43	12	0	0

Table 1: Analysis Results

Coefficient for treatment term (duloxetine vs. placebo)*

	Mixed Models		Linear Models by Assessment Time			
Outcome	**In window**	**Any w/in 14 weeks**	**Week 2**	**Week 6**	**Week 12**	**Week 24**
Average pain	-0.82 (-1.24,-0.40) P=0.0002	-0.76 (-1.17,-0.34) P=0.0004	-0.82 (-1.35,-0.29) P=0.0024	-0.97 (-1.49,-0.46) P=0.0002	-0.56 (-1.11,-0.01) P=0.0472	-0.07 (-0.61,0.48) P=0.8044
Worst pain	-1.06 (-1.57,-0.55) P<.0001	-1.09 (-1.57,-0.61) P<.0001	-1.00 (-1.64,-0.36) P=0.0025	-1.29 (-1.92,-0.65) P<.0001	-0.76 (-1.47,-0.05) P=0.0351	0.15 (-0.54,0.84) P=0.6629
Pain interference	-0.95 (-1.35,-0.55) P<.0001	-0.98 (-1.36,-0.59) P<.0001	-0.93 (-1.43,-0.43) P=0.0003	-1.14 (-1.65,-0.64) P<.0001	-0.59 (-1.10,-0.07) P=0.0251	-0.38 (-0.91,0.14) P=0.1518
Functioning, pain, and stiffness (WOMAC)	-11.90 (-15.81,-8.00) P<.0001	-11.74 (-15.57,-7.91) P<.0001	-12.62 (-17.32,-7.92) P<.0001	-12.35 (-17.24,-7.45) P<.0001	-9.38 (-14.10,-4.66) P=0.0001	-0.84 (-5.80,4.11) P=0.7375
Function, pain, and stiffness (M-SACRAH)	-13.56 (-18.24,-8.88) P<.0001	-13.42 (-17.75,-9.09) P<.0001	-11.03 (-15.36,-6.70) P<.0001	-10.14 (-14.19,-6.10) P<.0001	-4.40 (-9.04,0.25) P=0.0634	-3.29 (-7.77,1.19) P=0.1490
Functional quality of life (FACT-ES)	3.65 (1.16,6.13) P=0.0042	3.16 (0.81,5.50) P=0.0085	3.07 (0.04,6.11) P=0.0472	4.70 (1.70,7.70) P=0.0023	2.57 (-0.40,5.54) P=0.0892	0.64 (-2.52,3.79) P=0.6912
Depression (PHQ-9)	-0.52 (-1.22,0.19) P=0.1478	-0.40 (-1.10,0.30) P=0.2619		-0.74 (-1.58,0.10) P=0.0836	-0.30 (-1.09,0.48) P=0.4439	
GRC pain is better	1.69 (1.15,2.50) P=0.0085	3.07 (1.57,6.00) P=0.0012	2.30 (1.25,4.24) P=0.0079	1.60 (0.95,2.72) P=0.0780	1.22 (0.72,2.06) P=0.4649	1.03 (0.60,1.76) P=0.9155
GRC stiffness is better	3.80 (1.82,7.92) P=0.0004	3.95 (2.01,7.75) P<.0001	3.38 (1.85,6.18) P=0.0001	1.59 (0.94,2.68) P=0.0804	1.20 (0.70,2.04) P=0.5001	1.08 (0.63,1.86) P=0.7762

*Results are displayed as: coefficient (95% CI) p-value. GRC results indicate odds ratios for the treatment term (duloxetine vs. placebo) instead of coefficients.

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, NRG, CTSU (Supported by Alliance)

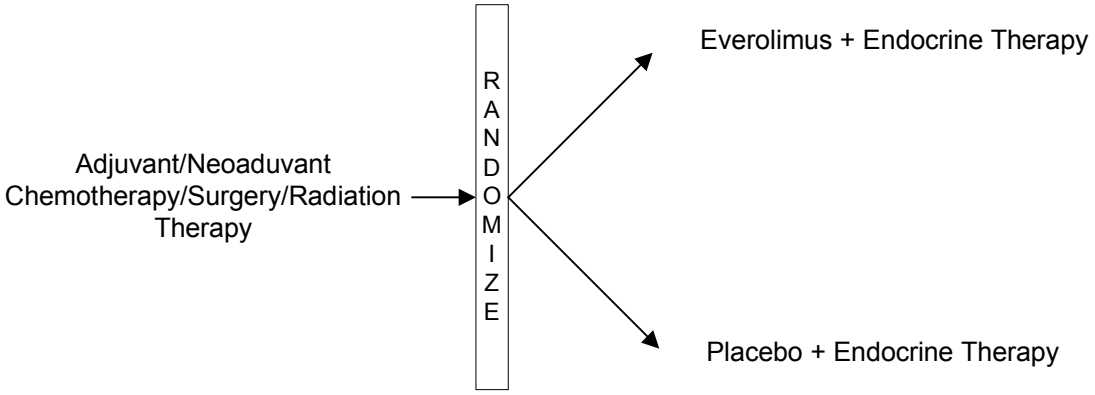
Date Activated:
09/03/2013

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

Statisticians:
W Barlow, J Miao, D Lew

Data Coordinator:
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.

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 or MammaPrint and grade, number of positive nodes, and prior therapy. Patients with micrometastases as the only nodal involvement (pN1mi) will be categorized as node negative.

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 be at least 18 years of age, have a Zubrod performance status of 0-2, and have 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 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 or MammaPrint and grade, number of positive nodes, and prior therapy.

Accrual Goals

The accrual goal is 1,900 patients. Interim analyses are planned for after approximately 40%, 60%, and 80% of the events in the control arm have been observed.

Summary Statement

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

S1400I Phase III

Coordinating Group: SWOG

A Phase III Randomized Study of Nivolumab Plus Ipilimumab versus Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarker (Lung-MAP Sub-Study)

Participants:
SWOG, CTSU (Supported by Alliance, ECOG-ACRIN and NRG)

Date Activated:
12/18/2015

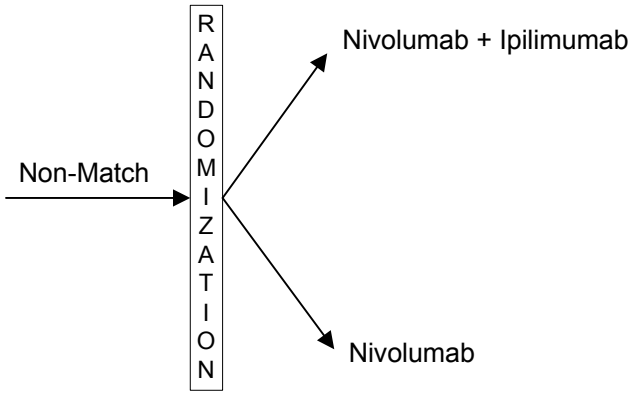
Study Chairs:
S Gettinger, L Bazhenova (Alliance)

Statisticians:
M Redman, K Griffin

Project Manager:
S Basse

Data Coordinators:
L Highleyman, K Pagarigan

SCHEMA



Objectives

To compare overall survival (OS) in patients with advanced stage refractory SCCA of the lung randomized to nivolumab plus ipilimumab versus nivolumab.

To compare investigator-assessed progression-free survival (IA-PFS) in patients with advanced stage refractory SCCA of the lung randomized to receive nivolumab plus ipilimumab versus nivolumab.

To compare the response rates (confirmed and unconfirmed, complete and partial) per RECIST 1.1 among patients randomized to receive nivolumab plus ipilimumab versus nivolumab.

To compare the response rates (confirmed only, complete and partial) per RECIST 1.1 among patients randomized to receive nivolumab plus ipilimumab versus nivolumab.

To evaluate the frequency and severity of toxicities associated with nivolumab plus ipilimumab versus nivolumab.

To evaluate if there is a differential treatment effect on OS, IA-PFS, and Response by tumor PD-L1 expression status.

To examine patient reported outcomes by treatment arm.

Patient Population

Patients must have been eligible for the S1400 screening study and must have been assigned to the S1400I sub-study based on biomarker profiling results. Patients must have measurable disease by CT or MRI per RECIST 1.1. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease. Patients must not have leptomeningeal disease, spinal cord compression, or brain metastases unless (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to registration to S1400I.

Patients must not have received any prior systemic therapy within 21 days prior to S1400I registration. Patients must not have received any radiation therapy within 14 days prior to S1400I registration. Patients must not have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways. Patients must not have received systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days prior to registration to S1400I.

Patients must have Zubrod performance status of 0-1 and adequate hematologic, hepatic, cardiac, and renal function. Patients must not have an active, known, or suspected autoimmune disease. Patients must not have a known positive test for HIV, AIDS, hepatitis B, or hepatitis C. Patients with a positive hepatitis C antibody with a negative viral load are allowed. Patients must not have interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

English-speaking patients who registered after September 1, 2016 are required to complete the patient reported outcomes.

Stratification/Descriptive Factors

Treatment randomization will be stratified by the following: (1) gender: male vs female; (2) number of prior therapies: one vs two or more.

Accrual Goals

The accrual goal is 332 eligible patients. Interim analyses will be performed when 50% and 75% of the expected deaths have been observed.

Summary Statement

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

S1404 Phase III

Coordinating Group: SWOG

A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma

---

Participants:
SWOG, CTSU (Supported by CCTG, ECOG-ACRIN)

Study Chairs:
K Grossmann, S Patel, A Tarhini (ECOG-ACRIN), T Petrella (CCTG)

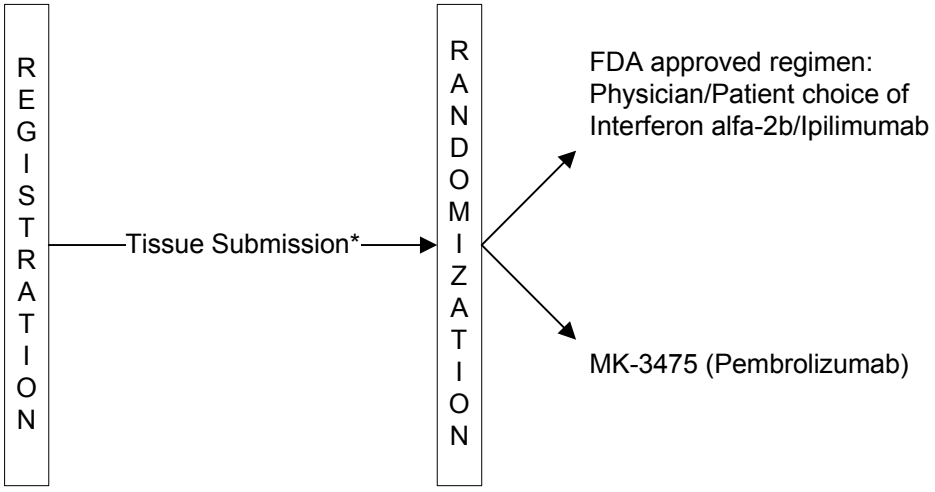
Statisticians:
M Othus, H Li, J Moon, M Latkovic-Taber

Data Coordinators:
J Dur, K Pagarigan, L Kingsbury, J Jardine, V Kim

Date Activated:
10/15/2015

Date Closed:
08/15/2017

SCHEMA



*PD-L1 status determined by central laboratory and blinded to the investigator and patient

Objectives
Co-Primary Objectives:

To compare overall survival (OS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose

interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

To compare OS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab) among patients who are PD-L1 positive.

To compare relapse-free survival (RFS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

To compare RFS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab) among patients who are PD-L1 positive.

Secondary Objectives:

To estimate OS and RFS for patients who are PD-L1 negative or PD-L1 indeterminate in this population.

To compare OS and RFS between the two arms within the PD-L1 positive and PD-L1 negative subgroups and to investigate the interaction between PD-L1 status (positive versus negative) and treatment arm.

To assess the safety and tolerability of the regimens.

Patient Population

Patients must have histologically confirmed selected Stage III (IIIA/N2a, IIIB, IIIC) or Stage IV melanoma of cutaneous or mucosal origin or unknown primary. Patients must not have melanoma of ocular origin. Patients are eligible for this trial either at initial presentation of their melanoma, at time of first detected nodal, satellite/in-transit, distant metastases, or recurrent disease in prior lymphadenectomy basin or distant site. Patients must not have a history of brain metastases. Patients who have multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted. All disease must have been completely resected with negative pathologic margins and no clinical, radiologic, or pathologic evidence of any incompletely resected melanoma. Patients must have available and be willing to submit adequate tissue for PD-L1 testing.

Patients may have received prior radiotherapy, including after the surgical resection that rendered the patient disease-free. Patients must not have received neoadjuvant treatment for their melanoma. Patients must not have received prior immunotherapy, including but not limited to ipilimumab, interferon alfa-2b, pegylated interferon, high dose IL-2, anti-PD-1, anti-PD-L1 intra-tumoral or vaccine therapies. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

Patients must have a Zubrod performance status of 0-1, and have adequate renal, hepatic, hematologic, and cardiac function. Patients must not have active autoimmune disease that has required systemic treatment in the past two years.Patients must not have an active infection requiring systemic therapy. Patients must not have pneumonitis or a history of non-infectious pneumonitis that required steroids. Patients known to be HIV positive must have adequate CD4 counts and low viral load. Patients must not have known active hepatitis B or C infections. Patients must not have received live vaccines within 42 days prior to enrollment. Women of childbearing potential must have a negative pregnancy test within 28 days prior to randomization.

Stratification/Descriptive Factors

Treatment randomization will be stratified by the following: (1) surgically resected AJCC stage: IIIA(N2a) vs IIIB vs IIIC vs IV; (2) PD-L1 status: positive vs negative vs indeterminate; (3) planned control arm regimen: high dose interferon vs ipilimumab.

Accrual Goals

The accrual goal of this study is to randomize 1,240 eligible patients. Up to two formal interim analyses of overall survival will be performed when 55% and 85% of the expected deaths across both arms combined have been observed. There will be no interim analyses of relapse-free survival (RFS) and the final analysis of RFS is expected to be one year after the last eligible patients is randomized.

Summary Statement

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

S1418 Phase III

Coordinating Groups: SWOG and NRG

A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of MK-3475 (Pembrolizumab) as Adjuvant Therapy for Triple Receptor-Negative Breast Cancer with ≥ 1 cm Residual Invasive Cancer or Positive Lymph Nodes (ypN+) after Neoadjuvant Chemotherapy

---

Participants:
SWOG, NRG, CTSU

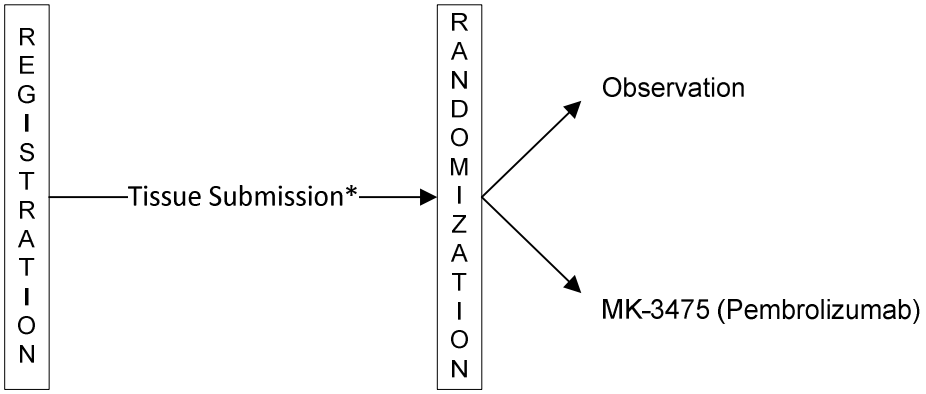
Date Activated:
11/15/2016

Study Chairs:
L Pusztai, J Mammen, P Ganz (NRG)

Statisticians:
W Barlow, J Miao, D Lew

Data Coordinators:
I Syquia, J Scurlock

SCHEMA



*PD-L1 status determined by central laboratory

Objectives

To compare invasive disease-free survival (IDFS) of patients with triple-negative breast cancer (TNBC) who have either ≥1 cm residual invasive breast cancer and/or positive lymph nodes (>ypN+) after neoadjuvant chemotherapy randomized to 1 year of MK-3475 (pembrolizumab) adjuvant therapy compared to no MK-3475 (pembrolizumab), in both the entire study population and also in the PD-L1 positive subset.

To compare the effects of MK-3475 (pembrolizumab) on overall survival (OS) and distant recurrence-free survival (DRFS) between the two randomized arms for the PD-L1 positive patients and then all patients.

To assess the toxicity and tolerability of MK-3475 (pembrolizumab) in this patient population with or without radiation therapy.

To examine the association between biomarkers of inflammation and quality of life and patient-reported outcomes between the two groups during and shortly after the end of therapy.

To examine the long-term and late effects of treatment on patient-reported outcomes.

Patient Population

Patients must have histologically confirmed ER-, PR- and HER2-negative breast cancer (triple-negative, TNBC) with residual invasive disease after completion of neoadjuvant chemotherapy. Patients with HER2 equivocal that do not receive HER2-targerted therapy are eligible. Patients with weakly ER or PR positive disease are eligible if patients are not eligible for adjuvant endocrine therapy. Residual disease must be $\geq$ 1 cm in greatest dimension, and/or have positive lymph nodes (ypN+) determined as described in the protocol. Patients must not have metastatic disease. Patients must have adequate tumor tissue for PD-L1 testing.

Patients must have received neoadjuvant chemotherapy which should include 12 to 24 weeks of a third generation chemotherapy regimen as recommended by NCCN guidelines for TNBC. Patients may receive post-operative (adjuvant) chemotherapy for up to 24 weeks, which must have been completed within 35 days prior to registration. Patients must have completed their final breast surgery with clear resection margins for invasive cancer and DCIS within 270 days or 90 days (if no adjuvant chemotherapy) prior to registration. Patients may receive concomitant radiation therapy (XRT) or XRT prior to registration; the intention to use XRT and the extent of intended XRT must be specified at registration if it has not been initiated. Patients must not have had prior immunotherapy with anti PD-L1 or anti-CTLA4 or similar drugs.

Patients must be at least 18 years of age, have a Zubrod performance status of 0-2, and must not have received live vaccines within 30 days prior to registration. Patients must not be known HIV positive or have known active hepatitis B or C. Patients must not have active autoimmune disease that has required systemic treatment in the past two years, non-infectious pneumonitis, or an active infection requiring systemic therapy. Patients who speak/read English or Spanish must agree to participate in the Behavioral and Health Outcomes (BAHO) substudy.

Patients must be registered to Step 2 for randomization within seven days of receiving e-mail notification that the patient's tissue specimen was adequate for PD-L1 testing. Patients must have adequate hematologic, hepatic, renal and thyroid function prior to randomization.

Stratification/Descriptive Factors

Randomization will be stratified by the following factors: (1) nodal stage: ypN0 vs ypN+; (2) residual tumor size: $\leq$ 2 cm vs $>$ 2 cm; (3) PD-L1 status: positive vs negative; and (4) prior use of post-operative (adjuvant) chemotherapy: yes vs no.

Accrual Goals

The accrual goal is 1,000 patients to achieve 910 eligible patients. Two interim analyses will be performed when approximately 50% and 75% of the IDFS events in the PD-L1 positive population have been observed.

Summary Statement

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

S1600 Phase III

Coordinating Group: SWOG

A Randomized Phase III Double-Blind Clinical Trial Evaluating the Effect of Immune-Enhancing Nutrition on Radical Cystectomy Outcomes

---

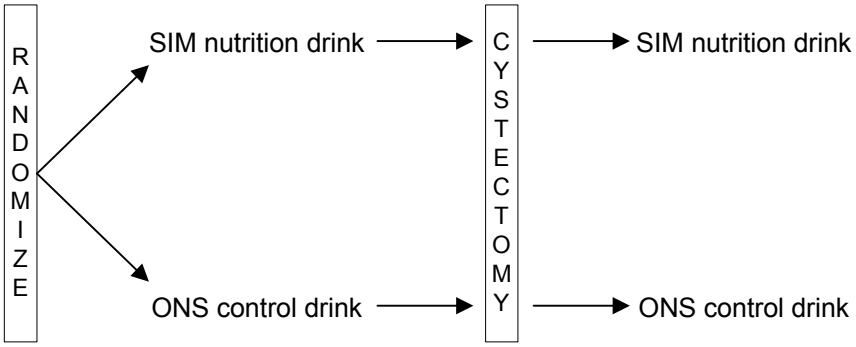
Participants:
SWOG, CTSU

Study Chairs:
J Hamilton-Reeves, J Holzbeierlein

Statisticians:
J Unger, D Lew

Data Coordinator:
H Dong

SCHEMA



Objectives

To compare the impact of consuming perioperative specialized immune-modulating drinks (SIM, Impact Advanced Recovery®, Nestlé) to oral nutrition supplement control drinks (ONS, Oral Nutrition Control, Nestlé) on post-operative complications (any vs. none) within 30 days after scheduled radical cystectomy (RC).

To assess whether SIM use compared to ONS reduces late-phase post-operative complications within 90 days after scheduled RC.

To assess whether SIM use compared to ONS reduces infections.

To assess whether SIM use compared to ONS reduces skeletal muscle wasting.

To assess whether SIM use compared to ONS reduces high grade post-operative complications.

To assess whether SIM use compared to ONS reduces readmission rates.

To assess whether SIM use compared to ONS improves quality of life.

To assess whether SIM use compared to ONS improves disease-free survival and overall survival.

Patient Population

Patients must have a tissue diagnosis of primary cell carcinoma of the bladder by TURBT or partial cystectomy. Patients may not have any evidence of unresectable disease or metastatic disease as assessed by exam under anesthesia or imaging (CT, MRI, PET). Patients must be planning to undergo radical cystectomy within 28 days after registration, and the surgery must be planned to be performed under pre-approved, study-specific surgical guidelines.

Patients must have completed any neoadjuvant chemotherapy or immunotherapy (intravesical or systemic) at least 14 days prior to registration and any toxicities resolved to ≤ Grade 2. Patients must not be planning to receive adjuvant chemotherapy within 90 days after radical cystectomy. Patients may have received prior partial cystectomy and/or prior radiation therapy; these must have been completed at least 180 days prior to registration.

Patients must be at least 18 years old, be able to understand and speak English, and not have known galactosemia or active viral infections such as HIV or hepatitis. Patients must have their baseline nutrition status assessed using the Patient-Generated Subjective Global Assessment (PG-SGA) within 14 days prior to registration and must not have a global category rating of Stage C (severely malnourished). Patients must be able to swallow liquid and have no refractory nausea, vomiting, malabsorption, or significant small bowel resection that would preclude adequate absorption. Patients on tube feeding are not eligible.

Stratification/Descriptive Factors

Patient randomization will be stratified by the following factors: (1) planned diversion type: neobladder vs other; (2) prior neoadjuvant therapy: any vs none; and (3) baseline nutrition status as assessed by the PG-SGA: well nourished (Stage A) vs moderate malnutrition (Stage B).

Accrual Goals

The accrual goal is 200 patients to achieve 190 eligible patients.

S1602 Phase III

Coordinating Group: SWOG

A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming with Intradermal BCG before Intravesical Therapy for BCG-Naïve High-Grade Non-Muscle Invasive Bladder Cancer

---

Participants:
SWOG, CTSU (Supported by Alliance, ECOG-ACRIN and NRG)

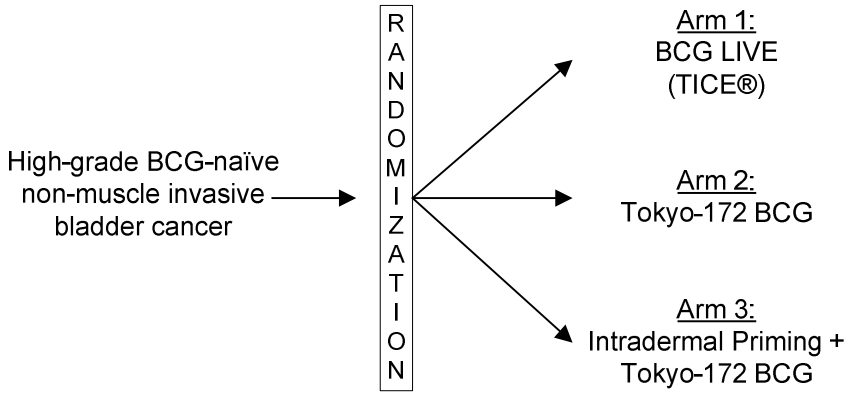
Date Activated:
02/07/2017

Study Chairs:
R Svatek, M Woods (Alliance), V Master (NRG), J Mark (ECOG-ACRIN)

Statisticians:
C Tangen, M Plets, E Mayerson

Data Coordinator:
J Sanchez

SCHEMA



Objectives

To compare whether time to high-grade recurrence (TTHGR) for patients with BCG-naïve, non-muscle invasive bladder cancer (NMIBC) receiving Tokyo-172 BCG strain (Arm 2) is non-inferior to patients receiving BCG LIVE (TICE® BCG) strain (Arm 1).

To test whether TTHGR for patients with BCG-naïve, NMIBC receiving intradermal Tokyo-172 BCG vaccination followed by intravesical Tokyo-172 BCG instillation (Arm 3) is superior to patients receiving intravesical Tokyo-172 BCG instillation without prior intradermal BCG vaccination (Arm 2).

To compare time to recurrence (TTR) with *any*-grade (AG) bladder cancer between: (1) patients receiving Tokyo-172 versus BCG LIVE (TICE® BCG) strain; and (2) patients receiving intradermal + intravesical versus intravesical only Tokyo-172 BCG.

To compare progression-free survival (PFS) between: (1) patients receiving Tokyo-172 versus BCG LIVE (TICE® BCG) strain; and (2) patients receiving intradermal + intravesical versus intravesical only Tokyo-172 BCG.

To estimate the complete response (CR) rate for CIS patients at 6 months in patients receiving intravesical Tokyo-172 BCG (Arms 2 & 3 will be evaluated separately).

To evaluate the duration of CR by treatment arm for patients with CIS who have a CR at 6 months.

To test whether TTHGR for patients with BCG-naïve, NMIBC receiving intradermal Tokyo-172 BCG vaccination followed by intravesical Tokyo-172 BCG instillation is superior to patients receiving intravesical TICE BCG strain.

To compare the change (baseline to 6 month) in patient-reported bladder cancer-specific quality of life between TICE and Tokyo BCG strains.

To compare the change (baseline to 6 month) in patient-reported quality of life between priming and no priming.

To test the hypothesis that changes in urinary symptoms during BCG treatment predict time to high-grade recurrence (TTHGR).

Patient Population

Patients must have high-grade, histologically proven Ta, carcinoma in situ (CIS) or T1 stage urothelial cell carcinoma of the bladder and must have had all visible papillary tumors removed. Patients with pure adenocarcinoma, pure squamous cell carcinoma, micropapillary components, nodal involvement or metastatic disease are excluded.

Patients must not have received prior intravesical or intradermal BCG. Patients must not be taking oral glucocorticoids and must not be planning to receive concomitant biologic therapy, hormonal therapy, chemotherapy, surgery, or other cancer therapy while on study.

Patients must not have a known history of tuberculosis and must have a negative PPD test within 90 days prior to registration. Patients must have a Zubrod performance status of 0-2. Patients who can complete Patient Reported Outcomes (PRO) forms in English or Spanish must complete the baseline Bladder Cancer Index (BCI), EORTC QLQ-C30 and AUASS forms.

Treating physician must confirm availability and access to BCG LIVE (TICE® BCG).

Stratification/Descriptive Factors

Patient randomization will be stratified according to the following factors: (1) age: ≤ 75 vs > 75; and (2) clinical stage: Ta vs T1 vs CIS only vs CIS with either Ta or T1.

Accrual Goals

The accrual goal for this study is 969 patients to achieve 924 eligible patients. Interim analyses will be conducted when 22%, 45%, and 70% of the expected number of pooled TTHGR events have occurred.

Summary Statement

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

S1706 Phase II

Coordinating Group: SWOG

A Phase II Randomized, Double-Blinded, Placebo-Controlled Trial of Olaparib (NSC-747856) Administered Concurrently with Radiotherapy for Inflammatory Breast Cancer

---

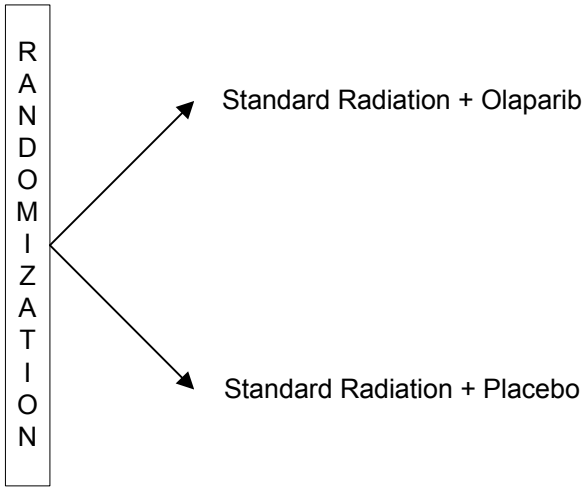
Participants:
SWOG, CTSU (Supported by NRG, Alliance and ECOG-ACRIN)

Study Chairs:
R Jagsi, P Chalasani, J White (NRG), J Bellon (Alliance), R Zellars (ECOG-ACRIN)

Statisticians:
W Barlow, D Lew, J Miao

Data Coordinator:
I Syquia

SCHEMA



Objectives

To compare the Invasive Disease-Free Survival (IDFS) of patients with inflammatory breast cancer receiving concurrent administration of olaparib with standard doses of radiotherapy to the chestwall and regional lymph nodes compared to concurrent administration of placebo with standard doses of radiotherapy to the chestwall and regional lymph nodes.

To compare the effect of concurrent administration of olaparib with radiotherapy versus placebo on improvement in locoregional control (measured by Locoregional Recurrence-Free Interval), Distant Relapse-Free Survival, and Overall Survival in inflammatory breast cancer patients.

To evaluate the toxicity (both acute and late) that develops in this setting, through standard physician-reported adverse event evaluation while on treatment and in follow-up, as well as through PRO-CTCAE measures obtained during radiotherapy.

To evaluate the association of olaparib/placebo and radiation therapy with short- and long-term quality of life assessed by patient-reported outcomes.

Patient Population

Patients must have inflammatory breast cancer without distant metastases. All biomarker subtype groups (ER, PR, HER2) are eligible.

Patients must have completed neoadjuvant chemotherapy and must have undergone modified radical mastectomy with negative margins within 3-12 weeks prior to registration. Additional adjuvant chemotherapy is allowed either completed prior to registration or planned for after completion of protocol treatment. Patients must not have a history of radiation therapy to the ipsilateral chest wall and/or regional nodes. Patients must not be planning to receive any other investigational agents during radiation therapy. Pathologic complete response (pCR) status must be determined post-surgery prior to registration.

Patients must have a Zubrod performance status of 0-2 and have adequate hematologic, renal, and hepatic function. Patients who are breastfeeding must agree to discontinue breastfeeding before receiving olaparib/placebo. Patients must not have active uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris or cardiac arrhythmia. Patients must be able to swallow and retain oral medications. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib. Patients must not have unresolved or unstable Grade 3 or greater toxicity from prior administration of another investigational drug and/or prior anti-cancer treatment.

Patients who can complete a questionnaire in English must be offered the opportunity to participate in the quality of life substudy. Patients must be offered the opportunity to participate in specimen submission for banking.

Stratification/Descriptive Factors

Randomization will be stratified by the following factors: (1) biologic subtype: HER2 positive vs HER2 negative and ER/PR positive vs triple negative (HER2/ER/PR negative); and (2) residual disease status after neoadjuvant chemotherapy: pCR vs no pCR and no planned or administered adjuvant chemotherapy vs no pCR and planned or administered adjuvant chemotherapy after surgery.

Accrual Goals

The accrual goal is 300 patients to achieve 280 eligible patients. An interim analysis for futility will be conducted at 50% of the expected IDFS events.

Summary Statement

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