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Activation Date September 3, 2013

SWOG/ NRG ONCOLOGY

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.

S1207/NSABP B-53

NCT #01674140

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AGENTS:

SWOG-Held IND Agents:
Everolimus/Placebo
(NSC- 733504) (IND-115643)

IND-Exempt Agents:
Anastrozole (NSC-719344)
Exemestane (NSC-713563)
Goserelin Acetate (NSC-606864)
Letrozole (NSC-719345)
Leuprolide Acetate (NSC-377526)
Tamoxifen (NSC-180973)

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Medical Queries (treatment or toxicity related questions):	Email: S1207medicalquery@swog.org or call: Dr. Mariana Chavez-MacGregor at: Phone: 713/792-2817
S1207-E01 BAHO Questionnaire questions:	Contact NRG Oncology by phone at 1-800-477-7227 or E-mail ccd@nsabp.org
Investigational Drug questions:	See Protocol Section 3.0
Requests for Investigator's Brochures:	See Protocol Section 3.0
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Sections 13.3 and 13.5 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Participant Transfers:	patienttransfer@crab.org
Serious Adverse Event Reporting questions:	See Protocol Section 16.1 Email: adr@swog.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS)

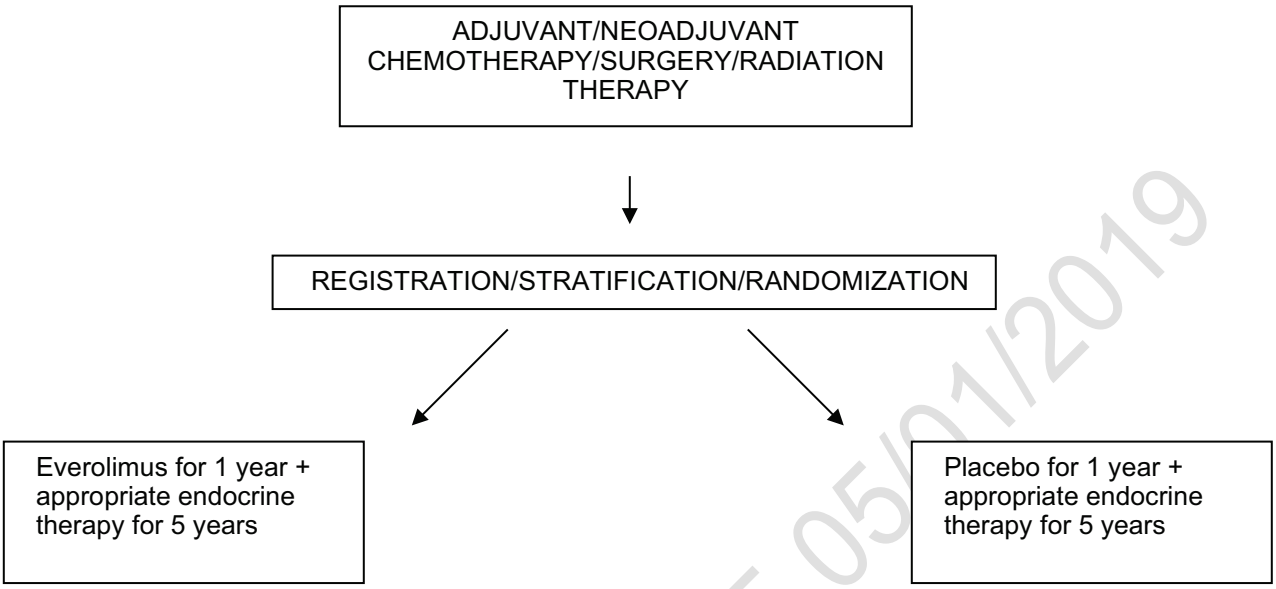
For participant eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:
Phone: 206/652-2267
Email: breastquestion@crab.org

For treatment or toxicity related questions contact the Study Chairs by Email:
S1207medicalquery@swog.org.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)

Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

a. The primary objective of this study is 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.

1.2 Secondary Objective

a. 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.

b. 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.

c. 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.

1.3 Other Objectives

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

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

NOTE: Objectives for the **S1207-E01** Behavioral and Health Outcomes (BAHO) Substudy are located in Appendix 18.1.

2.0 BACKGROUND

Prospective randomized trials indicate that some patients with HR-positive primary breast cancer benefit from the addition of chemotherapy to adjuvant endocrine treatment. *(1,2)* **SWOG-8814** demonstrated that this advantage was greater in women with ≥ 4 positive lymph nodes. *(3)* However, further analysis incorporating determination of recurrence score (RS) by RT-PCR showed that after adjusting for number of lymph nodes involved, patients with high recurrence score had worse outcomes. *(4)* Patients treated with chemotherapy (CAF x 6) followed by tamoxifen had a 10-year DFS of 55% and a 10-year OS of 68%. *(5)* Despite optimal therapies and more modern chemotherapy combinations, there are patients that still have a substantial risk of treatment failure. It has been well described that high RS, high grade tumors, lymph node involvement and residual disease after neoadjuvant chemotherapy are risk factors for recurrence. High-risk groups, therefore, include patients with node negative disease and high RS, patients with 1-3 positive lymph nodes and high RS or high-grade tumors and those with four or more positive lymph nodes. *(6,7,8,9,10)* Therefore, there is a need to develop additional, effective treatments for this patient population.

Abnormalities of the PI3kinase/AKT/mTOR signaling network are some of the most common molecular anomalies in breast cancer, and most of them are detected in HR-positive tumors. *(11)* There is increasing clinical and preclinical evidence that cell membrane growth factor-regulated kinase signaling pathways may be involved in resistance of HR-positive breast tumors to endocrine therapies. *(12)* The effect of kinase activation on resistance to hormonal modification may be mediated through several mechanisms, including direct stimulation of proliferation or survival, down

regulation and loss of ERα and PR by protein degradation and/or transcriptional inactivation in addition to hormone-independent phosphorylation of the receptors at multiple sites by direct interaction. *(13,14,15)* It is now known that PIK3CA is mutationally activated in up to 40% of ERα-positive tumors, PTEN levels are decreased in a similar proportion, and AKT2 (up to 5%) and p70S6K (10-20%) may also be overexpressed by amplification in some breast tumors. *(16)*

Everolimus, an mTOR-inhibitor, has been in development for patients with various solid and hematologic malignancies since 2002, and has been evaluated either as a single agent or in combination with other antitumor agents, tyrosine kinase inhibitors, antibodies and aromatase inhibitors. Everolimus is approved for treating patients with metastatic renal cell carcinoma who failed to benefit from a previous VEGF receptor tyrosine kinase inhibitor, and clinical trials have evaluated its use in many tumor types. In patients with advanced breast cancer with HR-positive tumors, everolimus has demonstrated important activity when used in combination with endocrine therapy. **S1207** proposes a simple parallel two-group randomization, placebo-controlled clinical trial to evaluate the use of endocrine adjuvant therapy +/- one year everolimus among a population of high-risk, HR-positive, HER2-negative breast cancer patients to determine if the use of one year of everolimus improves DFS. This patient population will be enriched for hormone-resistant tumors, where the activity of an mTOR-inhibitor might be most likely to work in combination with endocrine therapy.

There is evidence for the benefit of adding an mTOR inhibitor to endocrine therapy in this patient population to improve DFS. **S1207** proposes to randomize patients to receive one year of blinded drug or placebo. This trial has the potential to change current medical practice if this trial demonstrates that the addition of one year of everolimus to endocrine therapy in high-risk patients is superior to endocrine therapy alone. Thus, there is rationale to study the benefit of adding a targeted agent directed to a pathway that has been related to endocrine resistance in patients with high-risk, HR-positive, HER2-negative breast cancer. The findings of this trial will allow for a better selection of high-risk patients for different adjuvant treatments, increasing the ability of developing personalized cancer therapies and improving outcomes.

Several studies using everolimus have been completed in HR-positive breast cancer. A Phase Ib study of escalating doses of everolimus (5-10 mg PO daily) in combination with letrozole (2.5 mg PO daily) in patients with advanced breast cancer (n=19) showed 1 DLT (Grade 3 thrombocytopenia) at 10 mg/day. The results suggested anti-tumor activity of the combination in patients not achieving an objective response to letrozole alone. A randomized Phase II neoadjuvant study indicated that the addition of four months of everolimus to letrozole resulted in increased biological activity, higher response rates and increased pharmacodynamic effects than letrozole alone. *(17)*

In patients with metastatic breast cancer, the TAMRAD study randomized patients who had previously received aromatase inhibitors to receive tamoxifen and everolimus or tamoxifen alone. The time to progression increased from 4.5 months in the tamoxifen arm to 8.6 months in the combination arm (hazard ratio 0.53; 95% CI 0.35-0.81); there was also a significant benefit in survival (hazard ratio 0.31; 95% CI 0.15-0.68). *(18)* The recently published BOLERO-2 study randomized 724 patients with metastatic HR-positive breast cancer that had progressed to prior estrogen-deprivation therapy to receive exemestane or exemestane in combination with everolimus. The initial analysis, based on investigator assessment, demonstrated a significant improvement in progression-free survival (hazard ratio 0.43; 95% CI 0.35-0.54). On central review, the median time to progression was 4.1 months in the exemestane arm and 10.6 months in the combination arm. In addition, response rate and clinical benefit rate were both significantly superior with the combination, and while there was some increase in toxicity, there was no difference in quality of life during treatment in the two arms of the study. *(19)* The most common Grade 3 or 4 adverse events were stomatitis, anemia, hyperglycemia, fatigue and pneumonitis. Therefore, the combination of endocrine therapy and everolimus resulted in an increased antitumor effect in groups of patients without prior therapy, limited prior therapy and even extensive prior endocrine treatment suggesting that targeting mTOR activation may be implicated in restoring endocrine resistance. Based on the previously described activity of everolimus and hormone therapy, **S1207** proposes to explore the benefit of everolimus in the adjuvant setting; the hypothesis is that the

addition of everolimus to standard adjuvant endocrine therapy will reduce the risk of recurrent/metastatic disease.

Inclusion of Women and Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. Women/men of all races and ethnic groups are eligible for this study. Differences among treatment arms are not expected to be a function of race or ethnicity. Thus the study is not designed to detect differences within race or ethnicity subsets. This will be explored as part of the final analysis.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	130	1	131
Not Hispanic or Latino	1,759	10	1,769
Total Ethnic	1,889	11	1,900
Racial Category			
American Indian or Alaskan Native	12	0	12
Asian	74	1	75
Black or African American	226	1	227
Native Hawaiian or other Pacific Islander	7	0	7
White	1,570	9	1,579
Racial Category: Total of all Patients	1,889	11	1,900

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy #15 (www.swog.org). For this study blinded drug is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808. For this study, anastrozole, exemestane, goserelin acetate, letrozole, leuprolide acetate and tamoxifen are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

3.1 Everolimus (Afinitor®, Zortress®) (NSC-733504) (SWOG IND-115643)/Placebo

a. PHARMACOLOGY

Mechanism of Action: Everolimus binds to the cytosolic immunophyllin FKBP12; both agents inhibit growth factor-driven cell proliferation, including that of T-cells and vascular smooth muscle cells. The everolimus and FKBP12 complex selectively inhibits mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation of neoplastic cells, specifically in the progression of cells from G1 to S phase. Everolimus also reduces angiogenesis by inhibiting VEGF and HIF-1 expression.

b. PHARMACOKINETICS

1. Absorption: Everolimus levels peak in 1-3 hours after oral administration. There is rapid but moderate absorption.

2. Distribution: Everolimus is about 74% protein bound in healthy subjects and patients with moderate hepatic impairment.

3. Metabolism: Everolimus is extensively metabolized by CYP3A4 and forms 6 weak metabolites. It is also a P-glycoprotein substrate.

4. Elimination: Everolimus is extensively eliminated via the bile. The elimination half-life of everolimus is about 30 hours and is prolonged in patients with hepatic impairment. Everolimus is primarily excreted through the feces.

c. ADVERSE EFFECTS

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3033 patients.* Below is the CAEPR for Everolimus (RAD-001).

Version 2.5, July 3, 2018[1]

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
Diarrhea[2]		
Mucositis oral[3]		
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Wound complication[5]
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Aspartate aminotransferase increased	
	Cholesterol high	
	Creatinine increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia[6]	
	Hypertriglyceridemia	
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
	Headache	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
	Pneumonitis[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Pruritus	
Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)[8]

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
2 Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.
3 Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.
4 Infection includes all 75 infection sites under the INFECTIONS AND

INFESTATIONS SOC.

5 Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.

6 Hyperglycemia may result in either exacerbation of or development of new onset diabetes mellitus.

7 Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.

8 Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

9 Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

Adverse events reported on everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that everolimus (RAD-001) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Hypothyroidism; Testosterone deficiency

EYE DISORDERS - Blurred vision; Keratitis

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bicarbonate decreased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; GGT increased; INR increased; Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia).

METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hyperlipidemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Myalgia

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)

NERVOUS SYSTEM DISORDERS - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia

PSYCHIATRIC DISORDERS - Agitation; Anxiety[9]; Delirium; Depression; Insomnia; Irritability; Mania

RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary frequency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Rhinorrhea; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration
VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage)

Note: Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. Pregnancy and Lactation: Pregnancy category D. It is not known if everolimus is excreted in human milk.

2. Drug Interactions: Everolimus is a substrate of cytochrome P450 3A4 (CPY3A4) and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Due to the extensive number of everolimus drug interactions, a complete patient medication list, including everolimus, should be screened prior to initiation of everolimus (as indicated in Section 7.3 and Appendix 18.4).

   Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

3. Hepatic Impairment: Dosage adjustment of everolimus is recommended in hepatic impairment. If a patient's hepatic (Child-Pugh) status changes during treatment refer to Section 8.0 Dosage Modification.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Everolimus should be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets should be swallowed whole with a glass of water. Grapefruit or grapefruit juice should be avoided. The tablets must not be chewed and crushed. If unable to swallow whole tablet, may disperse tablet completely in 30 mL water and drink immediately; rinse container with additional 30 mL water and swallow.

3. Blister packets should be opened only immediately prior to ingestion as the drug is both hygroscopic and light-sensitive.

e. STORAGE & STABILITY

The intact blister packs should be stored at controlled room temperature (15°-30°C) and protected from light. Current stability data permit shelf life of 24 months

for 5 mg tablet variant based on solid dispersion dried by paddle dryer and 36 months for 5 mg tablet variant based on solid dispersion dried by evaporation/drying oven if stored below 30° C in the original double sided aluminum blister and protected from light and moisture. Blister package should be opened ONLY immediately prior to ingestion.

f. HOW SUPPLIED

1. Everolimus or matching placebo will be supplied as tablets blister-packed under aluminum foil in units of 10 tablets. Blisters should be opened only immediately prior to ingestion as the drug is both hygroscopic and light-sensitive.

   Everolimus or matching placebo 5 mg tablets are white to slightly yellow, elongated tablets with a beveled edge and no score, engraved with “5” on one side and “NVR” on the other. Excipients present in both the everolimus tablet and the placebo tablet include: Butylated hydroxytoluene (BHT), magnesium stearate, hydroxypropyl methylcellulose, crospovidone, lactose. The excipients comply with the requirements of the applicable compendia monographs (Ph. Eur., USP/NF).

2. Everolimus is commercially available, however is considered investigational for this study. Everolimus 5 mg tablets and placebo to match everolimus 5 mg tablets will be supplied by Novartis Pharmaceuticals Corporation and will be distributed by the Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC). Each participating Institution must have a Pharmacy ID Number, in addition to their Institution Number, before randomization of subjects can begin. SWOG institutions already have a pharmacy associated with them, so they do not need to report a Pharmacy ID number since that information is already linked in the SWOG database. However, Institutions registering via CTSU must be assigned a pharmacy ID number by the PCC. (Please do not use an existing Pharmacy ID number from a different trial. You must obtain a new Pharmacy ID specifically for the **S1207** trial.) With the initial and each subsequent randomization, the Institution registering via CTSU will be required to provide their Institution’s Pharmacy ID Number. No randomizations can be completed without a Pharmacy ID Number. For CTSU Participating Institutions, each Institution must call the PCC at (505) 248-3203 to register their Institution with the PCC and receive a Pharmacy ID Number. This registration by CTSU Participating Institutions with the PCC must be completed **at least 1 working day prior to the randomization of the first subject** at the site or randomization of the first subject will have to be postponed. When calling the PCC, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct PCC staff, the caller should indicate the “SWOG protocol - S1207”. To register an Institution, the PCC will require:

   - the name of the receiving individual,
   - complete street address, and phone number,
   - e-mail address of the receiving individual.

   Everolimus or matching placebo will be packaged by the PCC and supplied to the Institutions in kits of 10 blister cards, with each kit containing sufficient drug for a single reporting period of treatment (6 weeks) (100 tablets) for Reporting Periods 1, 2 and 6. For Reporting Periods 3, 4 and 5, the PCC will send sufficient drug for one reporting period of treatment (twelve weeks) (2 kits; 20 blister cards or 200 tablets).

No supply of unassigned everolimus or matching placebo will be maintained at the Institutions. Rather everolimus or matching placebo will be supplied to the site in a "just in time" manner. **Upon notification of a randomization by the SWOG Statistics and Data Management Center, the PCC will ship the first patient-specific kit to an Institution to arrive within four working days.** Each kit will be labeled specifically for an individual subject with the subject's SWOG Patient Number.

Due to the temperature sensitivities of everolimus/placebo, the drug is not shipped out over the weekend. Patients registered on Thursday or Friday will not have their kit shipped out until the following Monday or Tuesday (if federal holiday falls on Monday).

Subsequent patient-specific kits will automatically be shipped to the Institution approximately two weeks prior to the needed reporting period. The blister card and kits labels will be permanently attached. The site will write down the kit numbers on the Drug Accountability Record Form when the kit is dispensed.

Should a patient stop taking study drug, please inform PCC at (505) 248-3203 so that future shipments can be altered accordingly.

If a subject requires a replacement kit (Emergency Kit) for lost (etc.) medication, an Emergency Kit should be supplied by calling the PCC at (505) 248-3203.

Prior to dispensing the next kit of study medication, or at the study visit at the end of blinded drug treatment, the old blister cards and any unused tablets are to be collected from the subjects and quantity remaining logged on to the Drug Accountability Records.

3. Drug Handling and Accountability

a. Drug accountability**:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and return of all study drugs received from the distributor using the NCI Oral Drug Accountability Record Form (NCI Oral DARF)**,** available at http://ctep.cancer.gov. A separate record must be maintained for each patient on this protocol. For emergency unblinding guidelines see Appendix 18.3. Expiration dates will be centrally monitored by PCC and sites will be notified of any drug that should not be dispensed.

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.

4. Drug Return and/or Disposition Instruction

a. Drug Returns: All unused drug, unopened and unused blister cards remaining when a subject goes off treatment, and expired blister cards should be destroyed on-site in accordance with institutional policy. Partially used blister cards with remaining tablets should be documented in the patient-specific accountability record (i.e., logged in as "# of tablets returned") and destroyed on-site in accordance with institutional policy. In the event that a site does not have documented destruction procedures in place, call PCC at (505) 248-3203 for instructions on how to return leftover study drug.

b. Drug Transfers: Blister cards **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g. a patient moves from one participating institution to another participating institution) must be approved **in advance** by calling the PCC at (505) 248-3203.

5. Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PCC at (505) 248-3203.

3.2 Anastrozole (Arimidex®) (NSC-719344)

a. PHARMACOLOGY

Mechanism of Action: Anastrozole is a selective non-steroidal aromatase inhibitor. Estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. Anastrozole significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.

b. PHARMACOKINETICS

1. Absorption: Anastrozole is well absorbed (85% bioavailability) and its absorption is not affected by food. Maximum plasma concentrations occur within 2 hours. Plasma concentrations approach steady-state levels by about the seventh day of once daily dosing.

2. Distribution: Anastrozole is distributed throughout the systemic circulation and is approximately 40% protein bound.

3. Metabolism: Anastrozole is extensively (85%) hepatically metabolized via N-dealkylation, hydroxylation, and glucuronidation. Three metabolites have been identified in plasma and urine, and there are several unidentified minor metabolites. The main circulating metabolite, triazole, is inactive. The other known metabolites are a glucuronide conjugate of hydroxy-anastrozole and a glucuronide conjugate of anastrozole. Although hepatic cirrhosis reduces apparent oral clearance of anastrozole, no dosage adjustments are needed because plasma concentrations remain within the same range for patients without hepatic disease.

4. Elimination: Anastrozole is eliminated predominantly through the feces (75%) with some renal excretion (10%). Anastrozole has a terminal elimination half-life of approximately 50 hours. Renal clearance of anastrozole does decrease proportionally with creatinine clearance, but overall this has very little effect on total body clearance. No dosage adjustments are therefore necessary for patients with impaired renal function

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Anastrozole		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Leukopenia	
CARDIAC DISORDERS		
Vasodilatation	Edema	Angina
	Hypertension	Ischemic cerebrovascular event
		Myocardial infarction
		Venous thromboembolic event
EYE DISORDERS		
	Cataracts	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Nausea	
	Vomiting	
	Xerostomia	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hot flashes	Fever	Neoplasms
	Pain	Tumor Flare
	Malaise	
	Thrombophlebitis	

Adverse Events with Possible Relationship to Anastrozole		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
INFECTIONS AND INFESTATIONS		
	Flu-like syndrome	
INVESTIGATIONS		
		Alkaline phosphatase increased
		Liver function tests increased
METABOLISM AND NUTRITION DISORDERS		
	Weight gain or loss	
	Hypercholesterolemia	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Arthralgia	Fracture
	Arthritis	
	Back pain	
	Breast pain	
	Carpal tunnel syndrome	
	Myalgia	
	Neck pain	
	Osteoporosis	
	Paresthesia	
	Weakness	
NERVOUS SYSTEM DISORDERS		
	Confusion	
	Dizziness	
	Fatigue	
	Headache	
	Somnolence	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Depression	
	Insomnia	
	Mood disturbance	
	Nervousness	
RENAL AND URINARY DISORDERS		
	Pelvic pain	
	Urinary tract infection	
	Vaginal bleeding	
	Vaginal discharge	
	Vaginitis	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Bronchitis
	Pharyngitis	Dyspnea
	Rhinitis	
	Sinusitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Pruritis	
	Rash	
VASCULAR DISORDERS		

Adverse Events with Possible Relationship to Anastrozole		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
		Lymphedema

< 1%, postmarketing, and case reports: anaphylaxis, angioedema, bilirubin increased, CVA, cerebral ischemia, cerebral infarct, cutaneous vasculitis (including Henoch-Schönlein purpura), endometrial cancer, erythema multiforme, hepatitis, jaundice, joint pain, joint stiffness, liver inflammation, liver pain, liver swelling, myocardial ischemia, pulmonary embolus, retinal vein thrombosis, skin reactions (eg, blisters, lesions, ulcers); Stevens-Johnson syndrome, trigger finger, urticaria.

2. Pregnancy and Lactation: Pregnancy category X. Fetal toxicity was observed in animal studies. It is not known if anastrozole is excreted into breast milk.

3. Drug Interactions: Anastrozole is a weak CYP3A4 inhibitor. Due to potential drug interactions, a complete patient medication list, including anastrozole, should be screened prior to initiation of anastrozole. Refer to the current FDA-approved package insert for additional information.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Anastrozole should be administered orally, with or without food.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Anastrozole is available in 1 mg tablets.

2. Anastrozole is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.3 Exemestane (Aromasin®) (NSC-713563)

a. PHARMACOLOGY

Mechanism of Action: Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition." Exemestane significantly lowers circulating estrogen concentrations in postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone.

b. PHARMACOKINETICS

1. Absorption: Following oral administration of radiolabeled exemestane, at least 42% of radioactivity was absorbed from the gastrointestinal tract. Exemestane plasma levels increased by approximately 40% after a high-fat breakfast.

2. Distribution: Exemestane is distributed extensively into tissues. Exemestane is 90% bound to plasma proteins and the fraction bound is independent of the total concentration. Albumin and α_1-acid glycoprotein both contribute to the binding. The distribution of exemestane and its metabolites into blood cells is negligible.

3. Metabolism: Exemestane is extensively metabolized, with levels of the unchanged drug in plasma accounting for less than 10% of the total radioactivity. The initial steps in the metabolism of exemestane are oxidation of the methylene group in position 6 and reduction of the 17-keto group with subsequent formation of many secondary metabolites. Each metabolite accounts only for a limited amount of drug-related material. The metabolites are inactive or inhibit aromatase with decreased potency compared with the parent drug. One metabolite may have androgenic activity (see Pharmacodynamics, Other Endocrine Effects). Studies using human liver preparations indicate that cytochrome P-450 3A4 (CYP 3A4) is the principal isoenzyme involved in the oxidation of exemestane.

4. Elimination: Following administration of radiolabeled exemestane to healthy postmenopausal women, the cumulative amounts of radioactivity excreted in urine and feces were similar (42 ± 3% in urine and 42 ± 6% in feces over a 1-week collection period). The amount of drug excreted unchanged in urine was less than 1% of the dose.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Exemestane		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
CARDIAC DISORDERS		
	Edema	Cardiac failure
	Chest pain	Ischemic events (MI, angina)

Adverse Events with Possible Relationship to Exemestane		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Hypertension	
EYE DISORDERS		
	Visual disturbances	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Anorexia	
	Appetite increased	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hot flashes	Endometrial hyperplasia	Trigger finger
	Fever	
	Pain	
	Hypoesthesia	
	Uterine polyps	
INFECTIONS AND INFESTATIONS		
	Influenza-like syndrome	Infection
INVESTIGATIONS		
	Serum creatinine increased	Alkaline phosphatase increased
		Bilirubin increased
		Transaminases increased
METABOLISM AND NUTRITION DISORDERS		
	Weight gain	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Arthralgia	Back pain	Fracture
	Carpal tunnel syndrome	Neuropathy
	Cramping	Osteochondrosis
	Limb pain	
	Osteoarthritis	
	Osteoporosis	
	Paresthesia	
	Weakness	
NERVOUS SYSTEM DISORDERS		
	Confusion	
	Dizziness	
	Fatigue	
	Headache	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Depression	

Adverse Events with Possible Relationship to Exemestane		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Insomnia	
RENAL AND URINARY DISORDERS		
	Urinary tract infection	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Bronchitis
	Pharyngitis	Dyspnea
	Rhinitis	
	Sinusitis	
	Upper respiratory infection	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Hyperhidrosis	
	Pruritis	
	Rash	
VASCULAR DISORDERS		
		Lymphedema
		Thromboembolism

2. Pregnancy and Lactation: Pregnancy Category X. Exemestane is not indicated for premenopausal women and should not be given to women who are breast-feeding their infants. It is not known if exemestane is excreted into human breast milk; however, it has been detected in the breast milk of animals.

3. Drug Interactions: Exemestane is an inducer of CYP3A4 (weak/moderate) and a substrate of CYP3A4 (major). Due to potential exemestane drug interactions, a complete patient medication list, including exemestane, should be screened prior to initiation of exemestane.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Exemestane is administered orally once daily after a meal.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Exemestane is available in 25 mg tablets.

2. Exemestane is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.4 Goserelin Acetate (Zoladex®) (NSC-606864)

a. PHARMACOLOGY

Mechanism of Action: Following initial administration in males, goserelin causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to goserelin leads to suppression of gonadotropin secretion, a decrease in serum estradiol levels consistent with the postmenopausal state, and would be expected to lead to a reduction in ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone-responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the patients enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within four weeks after initial administration of drug and are usually maintained at that range with continued use of goserelin.

b. PHARMACOKINETICS

1. Absorption: Goserelin 3.6 mg is released slowly in first 8 days, and then rapid and continuous release for the remainder of the 28 day dosing period. Time to peak concentration for goserelin 3.6 mg is 12-15 days in males and 8-22 days in females. Goserelin 10.8 mg exhibits an initial rapid release resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin produces a reasonably stable systemic exposure.

2. Distribution: Apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. Goserelin is approximately 27% protein bound.

3. Metabolism: Metabolism of goserelin by hydrolysis of the C-terminal amino acids is the major clearance mechanism. The half-life elimination ($t_{1/2}$) is approximately 4 hours in males and 2 hours in females

4. Elimination: Clearance of goserelin is very rapid and occurs primarily via

5. urinary excretion (>90%; 20% as unchanged drug).

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Goserelin		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
	Congestive heart failure	Cerebrovascular accident
	Hypertension	Myocardial infarction
	Palpitation	
	Vasodilatation	
	Tachycardia	
EYE DISORDERS		
	Amblyopia	
	Dry eyes	
GASTROINTESTINAL DISORDERS		
	Anorexia	
	Appetite increased	
GASTROINTESTINAL DISORDERS (contd.)		
	Nausea	
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Flatulence	
	Ulcer	
	Vomiting	
	Xerostomia	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Sweating	Injection site reactions	
Tumor flare	Voice alterations	
IMMUNE SYSTEM DISORDERS		
	Fever	
INFECTIONS AND INFESTATIONS		
	Infection	
	Flu syndrome	
METABOLISM AND NUTRITION DISORDERS		
	Weight gain / loss	
	Hyperglycemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Bone mineral density decreased	Weakness	
	Arthralgia	
	Back pain	

Adverse Events with Possible Relationship to Goserelin		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Hypertonia	
	Bone / joint pain	
	Leg cramps	
	Myalgia	
	Paresthesia	
NERVOUS SYSTEM DISORDERS		
Headache	Dizziness	
	Pain	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Depression	
	Insomnia	
	Emotional lability	
RENAL AND URINARY DISORDERS		
	Urinary frequency	
	Urinary obstruction	
	Urinary tract infection	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Hot flashes	Vaginal hemorrhage	
Libido decreased	Vulvovaginitis	
Sexual dysfunction	Pelvic symptoms	
Vaginitis	Dyspareunia	
Breast atrophy	Breast enlargement	
	Erections decreased	
	Libido increased	
	Breast pain/swelling	
	Dysmenorrhea	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pharyngitis	
	Upper respiratory infection	
	Chronic obstructive pulmonary disease	
	Cough	
	Bronchitis	
	Sinusitis	
	Epistaxis	
	Rhinitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acne	Hair disorders	
Seborrhea	Hirsutism	
	Pruritus	
	Rash	
	Skin discoloration / bruising	
VASCULAR DISORDERS		
Peripheral edema	Hemorrhage	Thromboembolism

Adverse effects occurring in <1%, postmarketing, and/or case reports: ALT increased, anaphylaxis, AST increased, diabetes, glucose tolerance

decreased, hypercalcemia, hypercholesterolemia, hyperlipidemia, hypersensitivity reactions, hypotension, ovarian cyst, pituitary apoplexy, psychotic disorders, urticaria.

2. Pregnancy and Lactation: Pregnancy category X in patients with endometriosis and endometrial thinning. Pregnancy category D in patients with advanced breast cancer. It is not known if goserelin is excreted in human milk, however goserelin is excreted in the milk of lactating rats.

3. Drug Interactions: Luteinizing hormone-releasing hormone analogs may diminish the therapeutic effect of antidiabetic agents. No formal drug-drug interaction studies have been performed. Please refer to the current FDA-approved package insert for additional information.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Goserelin is administered subcutaneously into the anterior abdominal wall below the navel line using aseptic technique.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Goserelin acetate implant is available in a 3.6 mg or 10.8 mg disposable syringe device. The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.

2. Goserelin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.5 Letrozole (Femara®) (NSC-719345)

a. PHARMACOLOGY

Mechanism of Action: Letrozole binds to the heme group of aromatase, which catalyzes the conversion of androgens to estrogens. Inhibition of aromatase significantly decreases plasma estrogen levels.

b. PHARMACOKINETICS

1. Absorption: Letrozole is rapidly and well absorbed. Absorption is not affected by food.

2. Distribution: The volume of distribution of letrozole is approximately 1.9 L/kg. It is weakly protein bound.

3. Metabolism: Letrozole is metabolized in the liver via CYP3A4 and CYP2A6 to an inactive carbinol metabolite. Letrozole is also a strong inhibitor of CYP2A6 in vitro.

4. Elimination: Letrozole is primarily excreted in the urine, predominantly as a glucuronide carbinol metabolite. The elimination half-life is approximately 2 days.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Letrozole		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
CARDIAC DISORDERS		
	Edema	Chest pain
	Hypertension	Cerebrovascular event
		Thromboembolic event
EYE DISORDERS		
	Cataracts	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hot flashes	Night sweats	
	Pain	
INFECTIONS AND INFESTATIONS		
		Infection
		Influenza
		Viral infection
METABOLISM AND NUTRITION DISORDERS		
	Hypercalcemia	
	Hypercholesterolemia	
	Weight gain or loss	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Arthralgia	Fracture
	Arthritis	
	Back pain	
	Bone pain	
	Limb pain	
	Myalgia	
	Osteoporosis	
	Weakness	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Fatigue	
	Headache	
	Somnolence	
PSYCHIATRIC DISORDERS		
	Anxiety	

Adverse Events with Possible Relationship to Letrozole		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Depression	
RENAL AND URINARY DISORDERS		
	Urinary tract infection	
	Vaginal bleeding	
	Vaginal irritation	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Dyspnea
		Pleural effusion
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Pruritis	
	Rash	

< 1%, postmarketing, and case reports: anaphylactic reaction, angioedema, appetite increased, arterial thrombosis, blurred vision, cardiac failure, carpal tunnel syndrome, dry skin, dysesthesia, endometrial cancer, endometrial hyperplasia, endometrial proliferation, erythema multiforme, eye irritation, fever, hepatitis, hypoesthesia, irritability, leukopenia, liver enzymes increased, memory impairment, nervousness, palpitations, paresthesia, stomatitis, tachycardia, taste disturbance, thirst, thrombocytopenia, toxic epidermal necrolysis, trigger finger, urinary frequency increased, urticaria, vaginal discharge, xerostomia

2. Pregnancy and Lactation: Pregnancy category X. It is not known if letrozole is excreted in human milk.

3. Drug Interactions: Letrozole is a strong CYP2A6 inhibitor and moderate CYP2C19 inhibitor. Due to potential drug interactions, a complete patient medication list, including letrozole, should be screened prior to initiation of letrozole. Refer to the current FDA-approved package insert for additional information.

4. Hepatic Impairment: Letrozole in metabolized in the liver and dose adjustment is recommended in hepatic impairment. Refer to Section 8 Dosage Modification.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Letrozole is administered orally once daily with or without food.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Letrozole is available in 2.5 mg tablets.

2. Letrozole is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.6 Leuprolide Acetate (Lupron Depot®) (NSC-377526)

a. PHARMACOLOGY

Mechanism of Action: Leuprolide inhibits gonadotropin secretion by acting as an luteinizing hormone-releasing hormone (LHRH) agonist. Continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also act directly on the testes as well as act by a different mechanism not directly related to reduction in serum testosterone.

b. PHARMACOKINETICS

1. Absorption: After the initial increase of leuprolide following each injection, mean serum concentrations remain relatively constant.

2. Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

3. Metabolism: Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-I) metabolite.

4. Elimination: Less than 5% of the leuprolide dose was recovered as parent and M-I metabolite in the urine following the 3.5 mg depot injection.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Leuprolide		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Edema	
CARDIAC DISORDERS		
	Hyper- / hypotension	Arrhythmia
	Tachycardia	Atrial fibrillation
	Bradycardia	Congestive heart failure
	Angina	Syncope
	Palpitation	
GASTROINTESTINAL DISORDERS		
Nausea	Altered bowel function	Gastrointestinal hemorrhage
Vomiting	Ulcer	
	Intestinal obstruction	
	Constipation	
	Diarrhea	

Adverse Events with Possible Relationship to Leuprolide		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Gastroenteritis/colitis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Local injection site burning/stinging	Skin reaction	
IMMUNE SYSTEM DISORDERS		
	Flu-like syndrome	Allergic reaction
INFECTIONS AND INFESTATIONS		
	Urinary tract infection	
	Infection	
INVESTIGATIONS		
	BUN increased	
	Creatinine increased	
	Bicarbonate decreased	
	Hyperphosphatemia	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypoproteinemia	
METABOLISM AND NUTRITION DISORDERS		
	Dehydration	
	Hyperlipidemia	
	Weight gain/loss	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Weakness	
	Bone pain	
	Joint disorder	
	Myalgia	
	Paresthesia	
NERVOUS SYSTEM DISORDERS		
Headache	Nervousness	Seizure
Pain	Anxiety	
Insomnia	Confusion	
	Fatigue	
	Dizziness/vertigo	
PSYCHIATRIC DISORDERS		
Depression		
RENAL AND URINARY DISORDERS		
	Urinary disorders	
	Bladder spasm	
	Urinary retention	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Hot flashes / sweats	Vaginitis	
Testicular atrophy	Gynecomastia	
	Breast tenderness	
	Menstrual disorder	
	Lactation	
	Testicular Pain	
	Impotence	
	Libido decreased	
	Nocturia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		

Adverse Events with Possible Relationship to Leuprolide		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Emphysema	
	Epistaxis	
	Pleural effusion	
	Pulmonary edema	
	Dyspnea	
	Cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Acne	
	Alopecia	
	Bruising	
	Cellulitis	
	Pruritus	
	Rash	
	Hirsutism	
VASCULAR DISORDERS		
	Varicose vein	
	Deep thrombophlebitis	

< 1%, postmarketing, and/or case reports: Abdominal pain, anaphylactic/anaphylactoid reactions, asthmatic reactions, bone density decreased, coronary artery disease, diabetes; fibromyalgia-like symptoms; flushing, hemoptysis, hepatic dysfunction, hypokalemia, hypoproteinemia, injection site induration/abscess, liver injury, myocardial infarction, pelvic fibrosis, penile swelling, peripheral neuropathy, photosensitivity; pituitary apoplexy; prostate pain, pulmonary embolism, pulmonary infiltrate, seizure, spinal fracture/paralysis, stroke suicidal ideation/attempt (rare), tenosynovitis-like symptoms, thrombocytopenia, transient ischemic attack, uric acid increased, urticaria, WBC decreased/increased.

2. Pregnancy and Lactation: Leuprolide is pregnancy category X and excretion into breast milk is unknown / contraindicated.

3. Drug Interactions: Luteinizing hormone-releasing hormone analogs may diminish the therapeutic effect of antidiabetic agents. No pharmacokinetic-based drug-drug interaction studies have been performed. Because leuprolide is a peptide that is primarily degraded by peptidase and not by Cytochrome P-450 enzymes and the drug is only about 46% protein bound, drug interactions would not be expected to occur.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Leuprolide is administered intramuscular (Lupron Depot®) or subcutaneous (Eligard®) injection based on commercial depot formulation. Injection sites should be varied periodically.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Leuprolide acetate is available in 3.75 mg, 7.5 mg, 11.25 mg, 22.5 mg, 30mg, or 45 mg depot formulation kit with accompanying diluent. The prefilled dual-chamber syringe contains lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.

2. Leuprolide is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.7 Tamoxifen Citrate (Nolvadex®) (NSC-180973)

a. PHARMACOLOGY

Mechanism of Action: Tamoxifen is an antiandrogen that competitively binds to estrogen receptors on tumors and competes with estrogen binding sites, therefore inhibiting estrogen effects; cells accumulate in the G0 and G1 phases.

b. PHARMACOKINETICS

1. Absorption: Tamoxifen is well absorbed from the GI tract. The time to peak concentration is approximately 5 hours. The steady state concentration is reached in approximately 4 weeks.

2. Distribution: High concentrations of tamoxifen are found in the uterus, endometrial and breast tissue. Tamoxifen is 99% protein bound. The distribution half-life is 7 to 14 hours.

3. Metabolism: Tamoxifen is metabolized hepatically through CYP2D6 to 4-hydroxytamoxifen and CYP3A4/5 to N-desmethyl-tamoxifen. Both metabolites are further metabolized to endoxifen. The metabolites are more potent than tamoxifen. Tamoxifen is an inhibitor of P-glycoprotein.

4. Elimination: The half-life elimination of tamoxifen is approximately 5 to 7 days; the half-life elimination of N-desmethyl-tamoxifen is approximately 14 days. Tamoxifen is primarily excreted in the feces with some excretion in the urine.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Tamoxifen		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Thrombocytopenia	
CARDIAC DISORDERS		
Flushing	Edema	Angina
Vasodilation	Hypertension	Ischemic cerebrovascular event
		Myocardial infarction
		Venous thromboembolic event
EYE DISORDERS		
	Cataracts	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hot flashes	Amenorrhea	Allergic reaction
	Diaphoresis	Breast neoplasm
	Irregular menses	Tumor Flare
	Oligomenorrhea	
	Pain	
INFECTIONS AND INFESTATIONS		
	Flu-like syndrome	Infection
INVESTIGATIONS		
	Serum creatinine increased	AST increased
		Serum bilirubin increased
METABOLISM AND NUTRITION DISORDERS		
	Weight gain or loss	
	Hypercholesterolemia	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Arthralgia	Fracture
	Arthritis	
	Back pain	
	Bone pain	
	Breast pain	
	Myalgia	
	Osteoporosis	
	Paresthesia	

Adverse Events with Possible Relationship to Tamoxifen		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Weakness	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Fatigue	
	Headache	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Depression	
	Insomnia	
	Mood changes	
RENAL AND URINARY DISORDERS		
	Ovarian cyst	
	Urinary tract infection	
	Vaginal bleeding	
	Vaginal discharge	
	Vaginitis	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Bronchitis
	Pharyngitis	Dyspnea
	Sinusitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Rash	
	Skin changes	
VASCULAR DISORDERS		
		Lymphedema

< 1%, infrequent, or frequency not defined: cholestasis, corneal changes, endometriosis, endometrial cancer, endometrial hyperplasia, endometrial polyps, fatty liver, hepatic necrosis, hepatitis, hypercalcemia, hyperlipidemia, lightheadedness, phlebitis, pruritus vulvae, pulmonary embolism, retinal vein thrombosis, retinopathy, second primary tumors, stroke, superficial phlebitis, taste disturbances, tumor pain and local disease flare (increase in lesion size and erythema) during treatment of metastatic breast cancer (generally resolves with continuation), uterine fibroids, vaginal dryness

Postmarketing and/or case reports: angioedema, bullous pemphigoid, erythema multiforme, hypersensitivity reactions, hypertriglyceridemia, impotence (males), interstitial pneumonitis, loss of libido (males), pancreatitis, Stevens-Johnson syndrome, visual color perception changes

Tamoxifen use for breast cancer risk reduction is associated with an increased risk of endometrial or uterine cancers.

2. Pregnancy and Lactation: Pregnancy category D. Animal studies have demonstrated fetal adverse effects and fetal loss; tamoxifen does cross the placenta and there have been some reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding associated with tramoxifen use in pregnancy. It is not known if tamoxifen is excreted in human milk.

3. Drug Interactions: Tamoxifen is an inhibitor of CYP2B6 (weak), CYP2C8 (moderate), CYP2C9 (weak), CYP3A4 (weak), and P-glycoprotein (PgP).

Tamoxifen is a substrate of CYP2A6 (minor), CYP2B6 (minor), CYP2C9 (major), CYP2D6 (major), CYP2E1 (minor) and CYP3A4 (major). Due to the extensive number of potential tamoxifen drug interactions, a complete patient medication list, including tamoxifen, should be screened prior to initiation of tamoxifen.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Tamoxifen is administered orally and may be taken with or without food.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Tamoxifen is available in 10 mg and 20 mg tablets.

2. Tamoxifen is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

4.0 STAGING CRITERIA

Primary Tumor (T)

pTX primary tumor cannot be assessed
pT0 No evidence of primary tumor
pTis Carcinoma in situ
pTis (DCIS) Ductal Carcinoma in Situ
pTis (LCIS) Lobular Carcinoma in Situ
pT1mi Tumor ≤ 20 mm in greatest dimension
pT1a Tumor >1mm but ≤ 5 mm in greatest dimension
pT1b Tumor >5mm but ≤ 1 0 mm in greatest dimension
pT1c Tumor >10mm but ≤ 20 mm in greatest dimension
pT2 Tumor >20mm but ≤ 50 mm in greatest dimension
pT3 Tumor >50mm in greatest dimension
pT4 Tumor of any size with direct extension to the chest wall and/or the skin (ulceration and skin)
pT4 Extension to the chest wall, not including only pectoralis muscle adherence invasion.
pT4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet criteria for inflammatory breast cancer
pT4c Both Ta and Tb
T4d Inflammatory carcinoma
N1 Metastasis to movable ipsilateral axillary lymph node(s)
pN0 No regional lymph node metastases identified histologically
pN0 (i-) No regional lymph node metastases identified histologically, negative IHC
pN0 (i+) Malignant cells in regional lymph node (s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN1 Micrometastasis or Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with metastasis by sentinel lymph node biopsy but not clinically detected
pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0 mm

pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node dissection but not clinically detected

pN1c Metastases in 1 to 3 axillary lymph nodes and in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastases in 4 to 9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases

pN2a Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

pN2b Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases

pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive Level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes

pN3b Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.

pN3c Metastases in ipsilateral supraclavicular lymph nodes

Posttreatment (y) staging

Pathologic posttreatment T (yT) will be determined by pathological size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modified "m" indicating multiple foci. The measurement of the largest focus should not include any areas of fibrosis within the tumor bed. A comparison of the cellularity in the initial biopsy to that in the posttreatment specimen may also aid in the assessment of response.

Pathologic posttreatment N (ypN) should be evaluated as for clinical (pretreatment) "N" methods. The N categories are the same as those used for pN.

Stage	T	N	M
0	Tis	N0	M0
IA	T1[a]	N0	M0
IB	T0	N1mi	M0
	T1 [a]	N1mi	M0
IIA	T0	N1 [b]	M0
	T1 [a]	N1 [b]	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1 [a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

[a] *T1 includes T1mi.*

[b] *T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.*

–M0 includes M0(i+).

–The designation pM0 is not valid; any M0 should be clinical.

–If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

–Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

–Postneoadjuvant therapy is designated with "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1207** On Study Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at breastquestion@crab.org or 206/652-2267 prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 42, or 84 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have a histologically confirmed diagnosis of invasive breast carcinoma with positive estrogen and/or progesterone receptor status, and negative HER-2, for whom standard adjuvant endocrine therapy is planned. Estrogen and progesterone receptor positivity must be assessed according to ASCO/CAP guidelines as either ER or PR ≥ 1% positive nuclear staining. HER-2 test result negativity must be assessed as per ASCO/CAP 2013 guidelines using IHC, ISH or both. HER-2 is negative if a single test (or all tests) performed in a tumor specimen show: a) IHC negative (0 or 1+) or b) ISH negative using single probe or dual probe (average HER-2 copy number < 4.0 signals per cell by single probe or HER-2/CEP ratio < 2.0 with an average copy number < 4.0 signals per cell by dual probe). 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+, but must be negative if performed. HER-2 equivocal is not eligible.

b. Patients must not have metastatic breast cancer (Stage IV disease). Patients with multifocal, multicentric, synchronous bilateral, and primary inflammatory breast cancers are allowed.

- Multifocal disease is defined as more than one invasive cancer < 2 cm from the largest lesion within the same breast quadrant.
- Multicentric disease is defined as more than one invasive cancer ≥ 2 cm from the largest lesion within the same breast quadrant or more than one lesion in different quadrants.
- Synchronous bilateral disease is defined as invasive breast cancer with positive lymph nodes (axillary or intramammary) in at least one breast, diagnosed within 30 days of each other. (NOTE: The tumor with the highest recurrence score should be used.)

c. Patients must be high risk by belonging to one of the following risk groups:

- Completion of adjuvant chemotherapy and pathologically negative lymph nodes, and a tumor measuring ≥ 2 cm in greatest diameter, and either an Oncotype DX® Recurrence Score > 25 (completed as standard of care) or a MammaPrint® assay (completed as standard of care) in the high-risk category. Patients with micrometastases as the only nodal involvement (pN1mi) are eligible, and will be categorized as node-negative.

- Completion of adjuvant chemotherapy, and pathologically 1-3 positive lymph nodes, and either an Oncotype DX® Recurrence Score > 25, MammaPrint® assay in the high-risk category (completed as standard of care), or tumor tissue with pathological Grade III following local practice. If Oncotype DX® is done, then RS must be > 25, similarly if the MammaPrint® assay is performed it has to be high-risk. If the test is not done, but the patient has Grade III disease then the patient is eligible and Oncotype DX® or MammaPrint® does not need to be performed.

- Completion of adjuvant chemotherapy and pathologically 4 or more positive lymph nodes.

- Completion of neoadjuvant chemotherapy and 1 or more positive nodes pathologically determined after neoadjuvant chemotherapy.

NOTE: Patients who receive both neoadjuvant and adjuvant chemotherapy may be registered in the neoadjuvant therapy risk group, provided they meet all the criteria above for that risk group.

NOTE: In the lymph node positive groups, at least one metastasis ≥ 2.0 mm must be present. Patients with micrometastases as the only nodal involvement (pN1mi) will be categorized as node-negative.

5.2 Clinical/Laboratory Criteria

a. Patients must have completed either breast-conserving surgery or total mastectomy, with negative margins and appropriate axillary staging. A negative margin is defined as no evidence of tumor or DCIS at the line of resection. Additional operative procedures may be performed to obtain clear margins.

1. Patients who had breast-conserving surgery must have completed whole breast radiation. Use of regional nodal basin radiation will be at the discretion of the investigator according to institutional guidelines.

2. Patients with ≥ 4 positive lymph nodes must have completed breast/chest wall and nodal basin radiation therapy according to standard of care guidelines before randomization. Omission of radiation therapy is not allowed in this high-risk population of patients.

3. Patients must be registered at least 21 days after completion of radiation therapy and must have recovered (≤ Grade 1) from any of the effects of radiation.

b. Patients must have undergone axillary staging by sentinel node biopsy or axillary lymph node dissection (ALND).

1. For patients with 1-3 positive lymph nodes, sentinel node biopsy alone is allowed provided that the patient completed either whole breast or chest wall radiation and the primary tumor is < 5 cm.

2. All patients with ≥ 4 positive lymph nodes must have completed ALND (with or without prior sentinel node biopsy).

c. Patients must have completed standard neoadjuvant or adjuvant taxane and/or anthracycline based chemotherapy prior to randomization. Completion of chemotherapy will be determined by the treating oncologist, but should include a

minimum of 4 cycles (a cycle of weekly paclitaxel is considered 3 doses). Patients must be registered within 42 weeks after the last dose of this chemotherapy. Patients who receive adjuvant capecitabine in addition to their neoadjuvant chemotherapy must be registered within 42 weeks after the last dose of neoadjuvant chemotherapy. Patients may have started endocrine therapy at any time after the diagnosis of the current breast cancer.

d. Patients must not be receiving or planning to receive trastuzumab. Concurrent bisphosphonate therapy is allowed. Patients must not have prior exposure to mTOR inhibitors (rapamycin, everolimus, temsirolimus, deforolimus). Patients must not have prior treatment with capecitabine or any investigational drug within the preceding 28 days and must not be planning to receive capecitabine or any other investigational drug for the duration of the study.

e. Patients must have adequate bone marrow function, as defined by an ANC of >/= 1,500/mL, hemoglobin >/= 9 g/dL and a platelet count >/= 100,000/ mL within 28 days prior to registration.

f. Patients must have adequate hepatic function obtained within 28 days prior to registration and documented by all of the following:

- Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL if due to Gilbert's Syndrome)
- ALT and AST ≤ 1.5 x Institutional Upper Limit of Normal (IULN)
- Alkaline phosphatase ≤ 1.5 x IULN

g. Patients must have adequate renal function with serum creatinine level ≤ IULN within 28 days prior to registration.

h. Patients must have a fasting cholesterol ≤ 300 mg/dl and triglycerides ≤ 2.5 x IULN obtained within 28 days prior to registration. Patients may be on lipid lowering agents to reach these values.

i. Patients must have a complete history and physical examination within 28 days prior to registration.

j. Patients must have a performance status of 0-2 by Zubrod criteria (see Section 10.7).

k. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see Appendix 18.2).

l. Patients previously diagnosed with diabetes must not have uncontrolled diabetes (defined as an Hg A1C >7% within 28 days prior to registration).

m. 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.

n. Patients known to be HIV positive may be enrolled if baseline CD4 count is > 500 cells/mm^3 AND not taking anti-retroviral therapy. Patients with known hepatitis are not eligible unless there is a known negative hepatitis panel. (Exception: Previous history of Hepatitis A infection that is not currently active is allowed.) Patients must not have any known uncontrolled underlying pulmonary disease.

o. Patients must be able to take oral medications. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of blinded drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

p. Patients must not have received immunization with an attenuated live vaccine (e.g. intranasal influenza, MMR, oral polio, varicella, zoster, yellow fever and BCG vaccines) within seven days prior to registration nor have plans to receive such vaccination while on protocol treatment.

q. 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. (See Section 7.3 and Appendix 18.4.)

r. No other prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease-free for 5 years.

s. Patients must not be pregnant or nursing due to the potential for congenital abnormalities, and the potential of this regimen to harm nursing infants. Women/men of reproductive potential must have agreed to use an effective non-hormonal contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. Corresponding procedures for men include castration, vasectomy and barrier contractive devices. However, if at any point a previously celibate patient chooses to become heterosexually active during the protocol therapy, he/she is responsible for beginning contraceptive measures.

t. Patients must be ≥ 18 years of age.

5.3 Translational Medicine Criteria

a. Patients must have pre-treatment blood and tissue specimens submitted for translational medicine as outlined in Sections 15.1a and 15.1b. With patient consent, residuals will be banked for future research.

b. Patients (at NCORP Institutions only) must be offered the opportunity to participate in the **S1207-E01** Behavioral and Health Outcomes study (BAHO) (see Section 15.2 and Appendix 18.1). **NOTE**: Patients who have already started endocrine therapy are eligible for the BAHO study.

5.4 Regulatory Criteria

a. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions), the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

This will be a Phase III randomized clinical trial using a simple parallel equal randomization to everolimus or placebo. Randomization will be stratified by risk level which has 4 values:

1. Node-negative and Oncotype DX® Recurrence Score > 25 or a MammaPrint® assay in the high-risk category in the primary tumor, and a tumor measuring ≥ 2 cm in greatest diameter treated with adjuvant therapy;

2. 1-3 positive lymph nodes and Oncotype DX® Recurrence Score > 25 or a MammaPrint® assay in the high-risk category or Grade III disease treated with adjuvant therapy;

3. ≥ 4 positive lymph nodes treated with adjuvant therapy;

4. ≥ 1 positive lymph node after neoadjuvant chemotherapy.

There is a limit set on the lowest risk group (1) to be no more than 50% of the randomized patients.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Mariana Chavez-MacGregor AND Dr. Priya Rastogi at S1207medicalquery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

Patients with the following risk factors are recommended, not required, to have hepatitis screening pre-treatment:

- Blood transfusions prior to 1990
- Current or prior IV drug users
- Current or prior dialysis
- Household contact with a hepatitis B or C patient
- Current or prior high-risk sexual activity
- Body piercing or tattoos
- Mother known to have hepatitis B
- History suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain

7.1 Treatment Schedule

All patients will receive endocrine therapy (see Section 7.2) and also will be randomized to receive either everolimus or placebo daily for 54 weeks. Endocrine therapy must have started no later than the start of blinded drug.

NOTE: It is strongly recommended that patients taking everolimus/placebo use a dexamethasone-based mouthwash as part of standard of care in the prevention of stomatitis in patients receiving everolimus. This will not harm patients receiving placebo.

Helpful information:

- Starting on the first day of blinded study drug the mouthwash can be used TID or QID for 8 weeks of use and then on a PRN basis.
- For each use, swish 10mL of alcohol-free dexamethasone-based mouthwash (0.5 mg/5 mL oral solution) in mouth for 2 minutes and spit.
- Commercially available NDC 00054-3177-63 (500mL) or NDC 00054-3177-57 (240mL), Roxane Laboratories/West-Ward Pharmaceuticals, Eatontown, NJ.
- It is recommended to avoid drinking or eating for at least 1 hour after the mouthwash is used for 8 weeks.

AGENT	DOSE	ROUTE	DAYS	DURATION
Blinded drug	10 mg (two 5 mg tablets)	Oral	Every Day (54 weeks)	378 days

* Tablets are supplied as 5 mg tablets.

Blinded drug must be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets must be swallowed whole with a glass of water. The tablets must not be chewed or crushed, and grapefruit or grapefruit juice should be avoided (see Section 3.1d.2 for more details). Blister packets should be opened immediately prior to taking the drug (see Section 3.1d.3 for more detail).

A reporting period of treatment is six weeks for Reporting Period 1, 2 and 6 and twelve weeks for Reporting Period 3, 4 and 5. Assessment for the primary endpoint (recurrence) must occur every 12 weeks for 55 weeks, then every six months (+/- 7 days) for two years, and then annually (+/- 14 days) thereafter until recurrence, death, or 10 years after registration, whichever comes first (regardless whether patient is still on active protocol treatment). Recurrence assessments consist of a history and physical exam. See also Section 7.4 for extended allowable windows for recurrence assessments in event of a COVID-19 extenuating circumstance.

7.2 Endocrine Therapy

All patients will receive endocrine therapy. Choice of therapy will depend on menopausal status (see below) and patient/physician preference. Anyone not defined as postmenopausal per NCCN standards (https://www.nccn.org/professionals/physician_gls/default.aspx) should be treated as premenopausal. Treatment should be at least 5 years but can be extended. Switching from one therapy to another is allowed.

1. Approved Endocrine Therapy Regimens for **Premenopausal** women:

Treatment ***	Dose	Treatment duration
Tamoxifen #	20 mg daily	5 years
Tamoxifen #	20 mg daily	10 years
Tamoxifen combined with ovarian suppression or ablation	20 mg daily	5 years
Tamoxifen combined with ovarian suppression or ablation followed by an aromatase inhibitor (AI) **	20 mg daily for tamoxifen; approved dose for AI	5 years each
Aromatase inhibitor (AI) combined with ovarian suppression or ablation*	Approved dose for AI	5 years
Tamoxifen followed by an aromatase inhibitor (AI)**	20 mg daily for tamoxifen; approved dose for AI	2-3 years each
Tamoxifen followed by an aromatase inhibitor (AI)**	20 mg daily for tamoxifen; approved dose for AI	5 years each
Goserelin Acetate followed by an aromatase inhibitor **	3.6 mg subcutaneous every 28 days; approved dose for AI	5 years each
Leuprolide Acetate followed by an aromatase inhibitor **	3.75 mg IM every 28 days; approved dose for AI	5 years each

\# Tamoxifen is the preferred adjuvant endocrine therapy for premenopausal patients.
* Option for high-risk premenopausal patients based on data from SOFT/TEXT trials or if the patient cannot tolerate tamoxifen or tamoxifen is contraindicated.
** If the patient becomes postmenopausal
*** Premenopausal women should not receive an AI without ovarian suppression.

2. Approved Endocrine Therapy Regimens for **Postmenopausal** women:

Treatment	Dose	Treatment duration
An aromatase inhibitor	Approved dose	5 years
Tamoxifen*	20 mg daily	5 years
Tamoxifen followed by an aromatase inhibitor	20 mg daily for tamoxifen; approved dose for AI	2-3 years each
An aromatase inhibitor followed by tamoxifen	approved dose for AI, 20 mg daily for tamoxifen	2-3 years each
Tamoxifen followed by an aromatase inhibitor	20 mg daily for tamoxifen; approved dose for AI	5 years each

* if the patient is unsuitable for, cannot tolerate, or refuses an aromatase inhibitor

3. Approved Endocrine Therapy Regimens for Men:

Treatment	Dose	Treatment duration
Tamoxifen	20 mg daily	5 years

NOTE: Only the above listed approved endocrine therapy regimens are allowed, however the list of approved regimens may be expanded or contracted if there is a shift in standard of care during the course of the trial.

7.3 Concomitant Therapy

Please record the use of any of the following medications: diabetes medications, NSAIDS, statins, bisphosphonates, beta-blockers, antibiotics, narcotics, anti-depressants, hypertension medication or denosumab. If concomitant therapy must be added or changed, the reason and name of the drug/therapy must be documented in the "comments" section of the **S1207** Treatment Form.

Concomitant therapy will also be collected at baseline (prior to randomization), at 13, 25 and 49 weeks, and at 18 and 24 months after randomization for patients participating in the **S1207-E01** BAHO Study. Please record the use of any of the following medications (taken consistently for at least two months) on the **S1207-E01** Form MED: diabetes medications, NSAIDS, statins, bisphosphonates, beta –blockers, antibiotics, narcotics, anti-depressants, hypertension medication, steroids, SSRIs or denosumab.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is allowed, including drugs given prophylactically (e.g. antiemetics ± steroids), with the following exceptions:

- No other investigational therapy must be given to patients.
- No chronic treatment with systemic steroids (unless for the treatment of pneumonitis as described in Section 8.4) or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- No anticancer agents other than the study medications administered as part of this study protocol must be given to patients. If such agents are required for a patient then the patient must be removed from protocol treatment.
- Growth factors (e.g. G-CSF, G-GM-CSF) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.
- Live vaccines must not be administered to patient due to immunosuppressant potential of everolimus.
- Drugs or substances known to be strong inhibitors or inducers of the isoenzyme CYP3A4 (as indicated in Appendix 18.4) must be avoided in association with blinded drug as these can alter metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A4 must not be administered as systemic therapy.
- Drug interactions with anti-retroviral therapy are likely, and if the patient requires the initiation of such therapy due to a drop in CD4 count < 500 cells/mm^3, study medication must be permanently discontinued.

7.4 Clinical Trial Conduct during COVID-19 Pandemic (and other extenuating circumstances)

In order to provide participating sites flexibility in ongoing patient treatment in the current COVID-19 pandemic healthcare environment, utilization of offsite / local healthcare resources for conduct of participant's annual history and physical exam is allowable with appropriate oversight by the Responsible Investigator, and this utilization of local healthcare providers does not need to be documented as being done due to COVID-19 pandemic or other extenuating circumstances. In addition, the following extended window for the recurrence assessment is allowable per protocol.

Extended Window for Recurrence Assessment:

The allowable window for the **S1207** recurrence assessments, occurring every 6 months for 2 years after Week 55 and then annually thereafter until time of local recurrence or 10 years after registration, is being extended to +/- 14 days for the bi-annual assessment and to +/- 30 days for the annual assessment, where the Responsible Investigator determines that the delayed assessment helps to assure the safety of the patient, with consideration for the COVID-19 and related extenuating circumstances.

The Responsible Investigator rationale for utilization of the extended window outlined below must be carefully documented in the patient chart as resultant from the COVID-19 pandemic and extenuating circumstance. Please note the allowable best practices windows for the recurrence assessments, indicated in the Section 9.0, otherwise remain applicable for all patients, where there is not a COVID-19 pandemic-related extenuating circumstance.

7.5 Intake Calendar

Blinded drug adherence will be recorded by patients in the Intake Calendar (see Appendix 18.5). Do not submit Intake Calendars to the SWOG Statistics and Data Management Center. Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each reporting period. Summarized information from the daily intake calendars will be reported on the **S1207** Treatment Form and submitted per Section 14.4.

7.6 Unblinding Procedures

Patients who have disease recurrence as defined in Section 10.1 have the option to be unblinded in planned fashion, as described in this section. Any request for unblinding other than for disease recurrence will follow the procedures for emergency unblinding as outlined in Appendix 18.3.

a. Criteria for Planned Unblinding:

Planned unblinding procedure applies to patients who experience recurrence as defined in Section 10.1. It is vital to properly apply the protocol specified definition of recurrence. If any questions arise with regard to recurrence for a patient, please contact the Breast Data Coordinator in Seattle by e-mail at breastquestion@crab.org or by telephone at 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays, or the **S1207** Study Chair, Dr. Chavez-McGregor or in her absence, Dr. Rastogi.

Prior to planned unblinding, the follow-up forms documenting recurrence must be submitted and processed by the **S1207** Study Chair, Dr. Chavez-McGregor (or Dr. Rastogi in her absence). To request a planned unblinding, submit the Follow-Up

Form and Breast Supplementary Follow Up Form for the patient in Rave, then email breastquestion@crab.org with the subject line "**S1207** Patient #XXXXXX, Requesting Planned Unblinding" to notify the **S1207** Data Coordinator who will review the documentation for completeness in Rave before contacting the Study Chairs. Please allow a minimum of 2 working days for review of forms. Dr. Chavez-McGregor (or Dr. Rastogi) will provide a written confirmation to the site that the patient has an adequately documented recurrence. This documentation must be uploaded to the Planned Unblinding Form in Rave®.

b. Planned Unblinding Procedures

Patients may be unblinded at time of disease progression using the Planned Unblinding Form in Rave®. The Planned Unblinding Form is available in the "Add Event" dropdown box on the "Subject" tab in Rave®. Complete both questions and click the "Save" button to see the unblinded treatment assignment displayed on the form.

7.7 Criteria for Removal from Protocol Treatment

a. Invasive recurrence of disease or symptomatic deterioration (as defined in Section 10.0). NOTE: If the patient has a standard of care biopsy at recurrence, two (2) paraffin-embedded core biopsies must be submitted at the time of disease recurrence.

b. Unacceptable toxicity defined as any toxicity requiring discontinuation of blinded study drug per Section 8.0.

c. Delay of blinded study drug > 28 continuous days. Delay of > 56 continuous days of endocrine therapy within the first year from registration. If the patient is undergoing a surgical procedure, study drug can be delayed ≤ 28 days at the discretion of the treating physician.

d. Drug interactions with anti-retroviral therapy are likely, and if the patient requires the initiation of such therapy due to a drop in CD4 count < 500 cells/mm^3, study medication must be permanently discontinued. Reasons for discontinuation of therapy must be specified in the off-study form. The patient will still receive follow-up for survival outcomes as specified in the protocol.

e. Completion of six reporting periods of protocol treatment.

f. The patient may withdraw from the study at any time for any reason.

NOTE: Patients removed from protocol treatment due to toxicity must continue to be followed for recurrence.

7.8 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

7.9 Follow-Up Period

All patients will be followed for a maximum of 10 years after registration or until death (whichever occurs first) for recurrence and survival. NOTE: If the patient has a standard of care biopsy at recurrence, two (2) paraffin-embedded core biopsies must be submitted at the time of disease recurrence.

8.0 DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Reductions are based on the dose given in the preceding reporting period and are based on toxicities observed since the prior toxicity evaluation.

d. Once dose is reduced, patients will continue at new dose. No dose re-escalations are allowed.

e. There are no dose modifications for endocrine therapy

f. The dose modifications of blinded drug are for events that are possibly, probably or definitely related to the study drug.

8.3 Dose Levels for Blinded Drug

Dose Levels	Dose
Full	2 tablets daily (10 mg)
-1 Level	1 tablet daily (5 mg)
-2 Level	1 tablet every other day (5 mg)
-3 Level	Discontinue study drug

8.4 Dose Modifications of Blinded Drug

NOTE: NO DOSE ESCALATION OR RE-ESCALATION IS ALLOWED.

Toxicity	Actions
Stomatitis (Oral Mucositis)	
Grade 2	Interrupt blinded drug until recovery to Grade ≤ 1, then reintroduce blinded drug at one lower dose level. If event returns to Grade ≥ 2, then interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the blinded drug.
Grade 3	Interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then interrupt blinded drug until recover to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the blinded drug.
Grade 4	

Toxicity	Actions
Stomatitis (Oral Mucositis)	
	Discontinue blinded drug
Acute Kidney Injury	
Grade 1	Interrupt blinded drug until recovery. Then resume blinded drug at same dose level. If event returns to Grade 1, then interrupt blinded drug until recovery and reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 1, interrupt drug until recovery and reintroduce blinded drug at one lower dose level. If the event returns at Grade ≥ 1 stop the blinded drug.
Grade 2	Interrupt blinded drug until recovery. Then resume blinded drug at one lower dose level. If event returns to Grade ≥ 1, then interrupt blinded drug until recovery to Grade < 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 1, then, discontinue the blinded drug.
Grade 3	Interrupt blinded drug until recovery. Then resume blinded drug at one lower dose level. If event returns to Grade ≥ 1, then interrupt blinded drug until recovery. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 1, then discontinue the blinded drug.
Grade 4	Discontinue blinded drug.

Worst Grade Pneumonitis	**Required Investigations**	**Management of Non-infectious Pneumonitis**	**Blinded drug Dose Adjustment**
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent reporting period until return to baseline. Consider bronchoscopy *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Hold treatment until recovery to ≤ Grade 1, reduce blinded drug to one lower dose level. Patients will be removed from protocol treatment if they fail to recover to ≤ Grade 1 within 28 days. If the event returns to Grade **≥** 2, hold the blinded drug until recovery to Grade ≤ 1 then reintroduce the blinded drug at one lower dose level. If the event returns to Grade **≥** 2, then discontinue the blinded drug.

Worst Grade Pneumonitis	Required Investigations	Management of Non-infectious Pneumonitis	Blinded drug Dose Adjustment
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Pulmonary consult and bronchoscopy are recommended *	Prescribe corticosteroids if infectious origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. Then restart the blinded drug at one lower dose level. If the event returns to Grade ≥ 2, hold the blinded drug until recovery to Grade ≤ 1, then reintroduce the drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the blinded drug. Patients will be removed from protocol treatment if they fail to recover to ≤ Grade 1 within 28 days.
Grade 4	Pulmonary consult and bronchoscopy are recommended *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue protocol treatment.
*A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.			

Any other non-hematological toxicities not previously described	
Grade 2	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If event returns to Grade ≥ 2, then interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the blinded drug.
Grade 3	Interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the blinded drug.
Grade 4	Discontinue blinded drug.

Hematological toxicity	Actions
Grade 2 Thrombocytopenia	Interrupt blinded drug until recovery to Grade ≤1. Then reintroduce blinded drug at one lower dose level. If thrombocytopenia again returns to Grade ≥ 2, interrupt blinded drug until recovery to Grade ≤1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue blinded drug.
Grade 3 Thrombocytopenia	Interrupt blinded drug until recovery to Grade ≤ 1. Then resume blinded drug at one lower dose level. If Grade ≥ 2 thrombocytopenia recurs, interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 2, then discontinue blinded drug.
Grade 4 Thrombocytopenia	Discontinue blinded drug.
Grade 3 Neutropenia	Interrupt blinded drug until recovery to Grade ≤ 1. Then resume blinded drug at one lower dose level. If ANC again returns to Grade 3, hold blinded drug until recovery to Grade ≤ 1 and then resume blinded drug at one lower dose level. Discontinue patient from study therapy for a third episode of Grade 3 neutropenia.
Grade 4 Neutropenia	Interrupt blinded drug until recovery to Grade ≤ 1. Then resume blinded drug at one lower dose level. If ANC returns to Grade ≥ 3, hold blinded drug until recovery to Grade ≤ 1 and then reintroduce blinded drug at one lower dose level. If Grade ≥ 3 neutropenia occurs despite this dose reduction, discontinue blinded drug.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt blinded drug until resolution of fever and neutropenia to Grade ≤ 1. Hold further blinded drug until recovery to Grade ≤ 1 and fever has resolved. Then resume blinded drug at one lower dose level. If febrile neutropenia recurs, interrupt blinded drug until resolution of fever and neutropenia to Grade ≤ 1, then restart blinded drug at one lower dose level. If febrile neutropenia recurs, discontinue blinded drug (also see Section 8.4a).
Grade 4 febrile neutropenia (life threatening)	Discontinue blinded drug.
Grade 3 Anemia Grade 4 Anemia	Interrupt blinded drug until recovery to Grade ≤ 2. Then resume blinded drug at one lower dose level. If anemia returns to Grade ≥ 3, interrupt blinded drug until recovery to Grade ≤ 2 then reintroduce blinded drug at one lower dose level. If the event returns to Grade ≥ 3, discontinue blinded drug. Discontinue blinded drug.
Grade 4 Lymphopenia	Interrupt blinded drug until recovery to Grade ≤ 3. Then resume blinded drug at one lower dose level. If Grade 4 lymphopenia recurs, interrupt blinded drug until recovery to Grade ≤ 3. Then reintroduce blinded drug at one lower dose level. If the event returns to Grade 3, then discontinue blinded drug.

Hematological toxicity	Actions

Other Toxicities	Actions
Grade 2 Hyperglycemia	Treat diabetes according to current guidelines, with particular emphasis in diet modification. When medical therapy is initiated try to give priority to metformin or other non-insulin methods. No dose change.
Grade 3 Hyperglycemia	Stop the drug and treat diabetes according to current guidelines, with particular emphasis in diet modification, priority should be given to metformin or other non-insulin methods, restart the drug at one lower dose level. If despite optimal therapy, the event returns to Grade ≥ 3, interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns again to Grade ≥ 3, discontinue the blinded drug.
Grade 4 Hyperglycemia	Discontinue blinded drug.
Grade 2 Hypercholesterolemia	Treat according to guidelines with emphasis in diet modifications. No dose reduction.
Grade 3 Hypercholesterolemia	Stop the drug and treat according to current guidelines, with particular emphasis in diet modification, and medical therapy with statins, restart the drug at one lower dose level. If despite optimal therapy, the event returns to Grade ≥ 3, interrupt blinded drug until recovery to Grade ≤ 1. Then reintroduce blinded drug at one lower dose level. If the event returns again to Grade ≥ 3, discontinue the blinded drug.
Grade 4 Hypercholesterolemia	Discontinue blinded drug.

a. Hematological Toxicity

Darbepoetin alfa (Aranesp) and epoetin alfa (Procrit) are not indicated for anemia. If patient does not recover after 28 days of holding drug then the patient must be removed from treatment.

Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelet growth factors, etc.) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.

b. Hyperlipidemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Diet modification or early therapeutic intervention per the treating physician are recommended for Grade 1 hyperlipidemia or hypertriglyceridemia to prevent future development of Grade 2-3 toxicity. Grade 2 or greater hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 or greater hypertriglyceridemia (> 300 mg/dL - 500 mg/dL; >3.42 mmol/L- 5.7 mmol/L) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

c. Hyperglycemia

Diet modification or early therapeutic intervention per the treating physician are recommended for Grade 1 hyperlipidemia or hypertriglyceridemia to prevent future development of Grade 2-3 toxicity. Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy. The fasting state of patients should be verified when interpreting results. It is suggested that optimal glucose control should be achieved before starting a patient on blinded drug and should be monitored during blinded drug therapy. Should hyperglycemia develop during protocol therapy, standard glucose control interventions should be implemented.

d. Pneumonitis

Non-infectious pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy.

Both asymptomatic and symptomatic non-infectious pneumonitis have been noted in patients receiving everolimus. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non medical causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

e. Oral Mucositis

In addition to the dose modifications for non-hematological toxicity outlined in Section 8.4, oral mucositis due to blinded drug should be treated using local supportive care. Follow the paradigm below for treatment of oral mucositis:

1. For prevention, it is strongly recommended that patients use a dexamethasone-based mouthwash as part of standard of care (commercially available NDC 00054-3177-63 (500mL) or NDC 00054-3177-57 (240mL), Roxane Laboratories/West-Ward Pharmaceuticals, Eatontown, NJ). Starting on the first day of blinded study drug, the mouthwash can be used TID or QID for 8 weeks of use on a PRN basis. For each use, swish 10mL of alcohol-free dexamethasone-based mouthwash (0.5 mg/5 mL oral solution) in mouth for 2 minutes and spit. It is recommended to avoid drinking or eating for at least 1 hour after the mouthwash is used.

2. For mild toxicity (Grade 1, in which case patients are asymptomatic or have mild symptoms), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

3. For more severe toxicity (Grade 2 in which case patients have moderate pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients have severe pain or cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or

without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

4. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

5. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of blinded drug metabolism, thereby leading to higher blinded drug exposures. Therefore, topical antifungal agents are preferred if a fungal infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

f. Nausea

Routine premedication for nausea is not necessary, but symptomatic patients should be treated with standard antinausea/antiemetic therapy as necessary.

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

g. Diarrhea

Diarrhea has been seen with everolimus. In general, diarrhea has been transient, usually not of sufficient severity to hinder administration of blinded drug and responsive to loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg PO q 2-4 hours until diarrhea-free for 12 hours.

Everolimus has immunosuppressive properties and may predispose patients to infections, especially those with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory failure) and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with everolimus, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly.

8.5 Emergency Unblinding

For emergency unblinding guidelines see Appendix 18.3.

8.6 Dose Modifications Contacts

For treatment or dose modification related questions, please contact Dr. Mariana Chavez-MacGregor **AND** Dr. Priya Rastogi at S1207medicalquery@swog.org.

8.7 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE STUDY	Reporting Period 1 WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	RP 2 WK 7 &	RP 3 WK 13 &	RP 4 WK 25 &	RP 5 WK 37 &	RP 6 WK 49 &	WK 55 &	Off Treatment F/U Prior to Local Recurrence ¶	Off Treatment F/U After Local Recurrence√
PHYSICAL															
History & Physical Exam	X	XЯ						X	X	X	X	X	X	X	X
Height, Weight and Performance Status	X	XЯ						X	X	X	X	X	X		
Recurrence Assessment									X	X	X	X	X	X	
Toxicity Notation Ω		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Menopausal Status ʒ		X	X	X	X	X	X	X	X	X	X	X	X		
Review Intake Calendar & Pill Count								X	X	X	X	X	X		
BAHO Questionnaires ¥	X								X	X		X		X	
Health Resource Utilization Form Φ (NCORP Sites Only)								X	X	X		X		X	
LABORATORY															
ANC, hemoglobin, platelets	X							X	X	X	X	X			
Serum Creatinine	X							X	X	X	X	X			
Bilirubin	X							X	X	X	X	X			
ALT/AST	X							X	X	X	X	X			
Alkaline Phosphatase	X							X	X	X	X	X			
Fasting Glucose, Cholesterol and Triglycerides	Xϖ							X	X	X	X	X			
SPECIMEN SUBMISSION															
Tissue for Correlative Studies and Banking	X													X£	
Blood Specimens for Correlative Studies and Banking	X														
TREATMENT (see Section 7.0 for details)															
Blinded Drug †		X	X	X	X	X	X	X	X	X	X	X			
Endocrine Therapy ¿		X	X	X	X	X	X	X	X	X	X	X			

(CORRESPONDING FOOTNOTES ARE CONTINUED ON THE NEXT PAGE.)

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes:

√ After local recurrence, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months (+/- 7 days) for the first two years and then yearly (+/- 14 days) thereafter until 10 years after registration in order to ascertain subsequent distant recurrence. See also Section 7.4 for extended allowable windows for recurrence assessments in event of a COVID-19 extenuating circumstance.

Ω Once blinded drug treatment has been initiated, weekly toxicity assessments are required during the first reporting period. Toxicity assessments during the first reporting period may be performed via a phone call during weeks when a physical exam is not required. Toxicity assessment hypoxia, etc. physician note should record cough, dyspnea, (see Section 8.4d).

Я If prestudy history and physical exam, weight and performance status are obtained within three weeks prior to registration, they do not need to be repeated for Reporting Period 1, Day 1.

¶ All patients (including patients taken off protocol treatment due to toxicity) must continue to be followed after every reporting period (Weeks 7, 13, 25, 37, 49 and 55), then every 6 months for two years, and then annually thereafter until local recurrence, death or 10 years after registration, whichever comes first.

¿ Treatment with endocrine therapy will continue for at least five years (see Section 7.2).

¥ The Behavioral and Health Outcomes (BAHO) Questionnaire should be completed at Baseline and at Weeks 13, 25 and 49 and at 18 and 24 months after randomization.

Φ The Health Resource Utilization Form is part of the BAHO study and should be completed at Weeks 7, 13, 25, and 49, and at 18 months after randomization.

ϖ A fasting glucose is not required at pre-study, only the fasting cholesterol and triglycerides are required.

† Blinded drug is taken daily for all reporting periods with drug supply dispensed at the beginning of each reporting period (Weeks 1, 7, 13, 25, 37 and 49).

£ If the patient has a standard of care biopsy at recurrence, two (2) paraffin-embedded core biopsies must be submitted at the time of disease recurrence (see Section 15.1a).

& Study visits may be scheduled within +/- 7 days of Weeks 7, 13, 25, 37, 49 and 55.

ʒ Menopausal status of premenopausal women should be monitored, as treatment options may vary if the patient becomes postmenopausal (see Section 7.2.1).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Invasive Recurrence

Appearance of any new invasive lesion(s) during or after protocol treatment. Whenever possible, recurrences should be documented histologically. Invasive recurrence includes local, regional, or distant recurrence with an invasive component. A new diagnosis of ipsilateral or contralateral DCIS without an invasive component is not considered to be a recurrence.

10.2 Sites of First Invasive Recurrence

All sites of invasive disease documented within 30 days of first documentation of invasive recurrence.

10.3 Invasive Disease-Free Survival

This study uses the STEEP definition of invasive disease-free survival. *(20)* Time from date of registration to date of first invasive recurrence (local, regional or distant), second invasive primary cancer (breast or not), or death due to any cause. Patients last known to be alive who have not experienced recurrence or second primary cancer are censored at their last contact date. We use the acronym DFS for invasive disease-free survival in this protocol.

10.4 Distant Recurrence-Free Survival

Time from date of registration to date of invasive distant disease recurrence, second invasive primary cancer (breast or not) or death due to any cause. Patients last known to be alive who have not experienced distant recurrence, or second primary cancer are censored at their last contact date.

10.5 Local Disease-Free Interval

Time from date of registration to date of invasive local or regional recurrence. Patients last known to be alive without recurrence are censored at their last contact date. Patients with distant recurrence, second primary cancer or death are censored at the time of that event.

10.6 Overall Survival

Time from date of registration to date of death due to any cause. Patients last known to be alive are censored at their last contact date.

10.7 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

This is a parallel randomization design with equal allocation to the two treatment groups: (1) everolimus and (2) placebo. Randomization is stratified by the 4 risk groups. The primary outcome is invasive disease-free survival (IDFS) using the STEEP definition. *(21)* Secondary survival outcomes include overall survival (OS) and distant disease-free survival (DDFS). All analyses are intent-to-treat (ITT) by randomized assignment of eligible patients.

The statistical plan was amended in July 2015 after six quarters of enrollment to be compliant with CTEP accrual guidelines. The original accrual goal was 3,500 patients with 83 per month expected to be enrolled. The revised plan sets the new accrual goal to 1,900 patients with 26 patients expected each month. Power had to be decreased to 80% from 90% as well.

11.2 Sample Size

The study plans to randomize 1,900 patients by December 2019 with the primary analysis conducted 3 years after the last patient is randomized. However, all patients will be followed for 10 years to assess overall survival and late adverse events. The power calculation assumes a desired power of 80% with an overall 2-sided $\alpha = 0.05$.

The actual sample size computation is based on a total of 1,794 patients with follow-up data (394 are already enrolled). Follow-up varies by patient but mean follow-up will be 5.67 years when the primary analysis is conducted. The sample size was inflated to 1,900 (by 6%) to allow for ineligible patients and drop-outs.

To achieve this goal it will be necessary to screen patients who are node-negative (with large primary tumors) or who have 1-3 positive nodes to determine if RS > 25 or Grade III disease is present. The RxPONDER trial already screens women with 1-3 positive nodes so that trial will identify patients eligible for this trial who are too high risk for RxPONDER. Other patients who have 1-3 positive nodes are eligible as long as they have a recurrence score > 25 (but this testing will not be paid by the study) or pathological Grade III disease. It will be necessary to screen node-negative patients.

The effective hazard ratio is assumed to be 0.75 for everolimus plus endocrine therapy versus endocrine therapy alone. There are four high-risk disease strata with the majority of patients coming from the two highest risk groups. For the combined groups, the expected 5-year DFS for everolimus is 82.3%, an absolute improvement of 5.1% over the baseline of 77.1%, a highly meaningful, clinically significant difference. We assume that the hazard ratio is constant across all strata even though the actual survival differs in the various risk groups and therefore, the absolute benefit of everolimus would also vary within risk groups.

Below we give the justification for the sample size and consider some variations as well. Estimated DFS was based on **S8897** (node-negative; HR-positive arms with tamoxifen + chemotherapy used) and **S8814** for node-positive, HR-positive breast cancer treated with tamoxifen +/- adjuvant chemotherapy. The hazard rates for **S8814** were very comparable

to those of B-30 when divided by number of positive nodes. The hazard rate for the neoadjuvant group is a conservative estimate derived from the 5-year survival in the group with residual cancer burden III as described by Symmans et al. *(22)* Because these are older trials we assume that all hazard rates have decreased by 15% due to superior chemotherapies and endocrine treatments. While the 5-year survival rates below seem low, it is important to remember that these are high-risk patients.

Risk group	Estimated Percentage	Trial 5-year	Modern hazard rate	Modern 5-year DFS	5-year DFS with everolimus
Node neg; OncotypeDX® Recurrence Score > 25 or a MammaPrint® assay in the high-risk category	10%	83.4% (S8897)	0.0308	85.7%	89.1%
1-3 pos nodes; OncotypeDX® Recurrence Score > 25 or a MammaPrint® assay in the high-risk category or Grade III disease	10%	77.8% (S8814)	0.0427	80.8%	85.2%
4+ pos nodes	60%	70.5% (S8814)	0.051	77.5%	82.6%
Neoadjuvant RCB III	20%		0.071	70.1%	76.6%
Overall	100%	Weighted	0.0522	77.1%	82.3%

RS was not measured in **S8897**. The overall 5-year IDFS in the appropriate treatment group was 88.6%. Assuming the same proportion as in **S8814** for RS and the same prognostic effect in the chemo group gives 92.0% IDFS if RS ≤ 25 and 83.4% if RS > 25.

The modern hazard rate represents a 15% reduction in the observed hazard rate found in the historical trials. The overall improvement in 5-year IDFS is based on the weighted hazard rates.

The power depends on the actual allocation of patients to the four strata. The stratum with lowest risk (node-negative) is capped at no more than 50% of the accrual total. The design is fairly robust to changes in the allocation to the strata with this restriction.

For the secondary outcome OS, with 5 additional years of follow-up after the last accrual the study will have 85% power to detect a HR = 0.75 using a 2-sided $\alpha = 0.05$. Therefore, more observation time may be necessary to observe an effect on overall survival.

In November 2014, an amendment was submitted to allow enrollment of patients with 1-3 positive nodes with Grade III disease and unknown RS. However, if RS is measured and RS ≤ 25 then the patient is ineligible even if Grade III. An internal report from **E5103** suggests a 5-year DFS for this group if 79.5% with chemotherapy, but without everolimus. Similarly, we have expanded the last stratum to allow any positive nodes after surgery (previously it was 4+). Hazard rates have been lowered in the last two strata due to these changes and comparison to contemporary trials. Actual event rates in **S1207** have not been used to alter any trial design elements, but actual accrual and strata proportions have been used to better estimate the final population and follow-up.

11.3 Analysis Plan and Interim Analyses

The primary analysis will be a stratified log-rank test of treatment effect on IDFS with stratification on the 4 risk levels. Survival estimates will be based on Kaplan-Meier procedures. The hazard ratio for treatment efficacy will be estimated using Cox regression with stratification by risk level. Secondary analyses will test for interaction of the treatment effect with risk level and major prognostic variables. Separate subset analyses are planned for node-negative and node-positive subsets. These will be conducted at a two-sided α = 0.025 to account for the two analyses. The assumption of proportional hazards of the treatment effect in all models will be tested. If the proportional hazards assumption is not satisfied ($p<0.05$), the time axis will be split where 50% of the events have occurred and perform separate analyses of the two time periods.

Approximately 219 events would be expected in the standard treatment arm at the specified hazard rates. The first interim analysis would be after 40% of the events in the control arm have been observed. There would be additional interim analyses at 60% and 80% of the expected events approximately with the final analysis at three years after the last patient accrual. The analyses will use the Lan-Demets spending function with a truncation bound at 3.29. To achieve a cumulative 0.025 1-sided significance level, the interim test α's will be 0.0005, 0.00361, and 0.01154, respectively, and the final α= 0.02096 so there is little loss of power due to the interim analyses. Additionally, futility will be tested at each interim analysis. A 99% 2-sided likelihood-ratio (LR) confidence interval on the treatment hazard ratio will be computed at each interim analysis. If the lower bound of the CI excludes the alternative hypothesis of 0.75, then futility will be declared. Using a LR CI is equivalent to testing the alternative hypothesis with a LR test, but provides more information. It is expected that most or all interim analyses would occur after accrual has finished so the decision would be about early dissemination, rather than stopping accrual. All patients will be followed for 10 years to assess overall survival and late adverse events.

11.4 Adherence and Monitoring

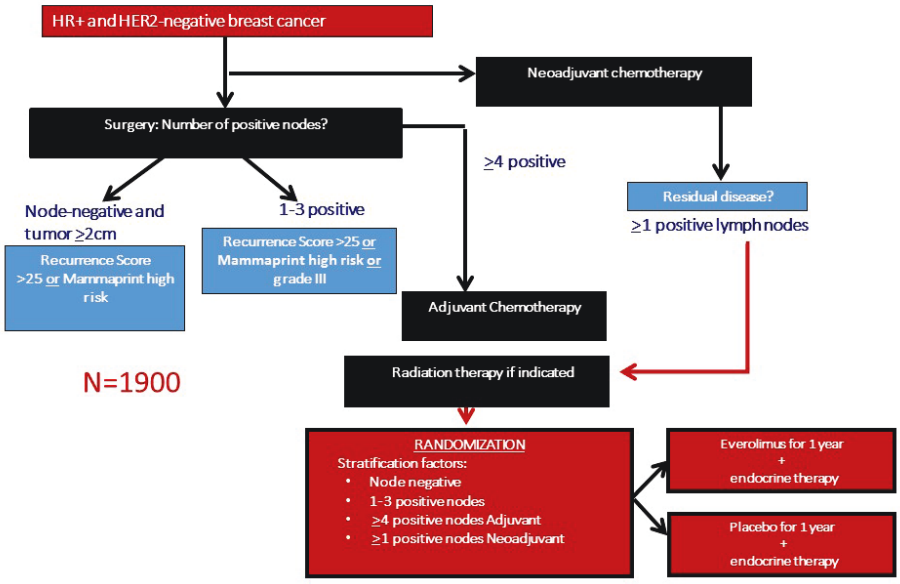
In Section 11.2 we used 0.75 as the effective hazard ratio, i.e. the hazard ratio obtained from the ITT analysis. This incorporates the expectation that patients are more likely to be non-adherent to everolimus than to placebo. Non-adherence moves the observed hazard ratio toward the null hypothesis, and thus lowers power. The true hazard ratio under 100% compliance would be lower than 0.75, but lacks real-world interpretation since that situation does not often occur in a large group of patients offered a new medication. Note that in BOLERO-2 there was an 18% early discontinuation rate in the everolimus group, but the ITT hazard ratio was still 0.43 for PFS. To measure non-adherence for monitoring purposes, we define it as stopping the everolimus permanently before the end of Reporting Period 4 (≤ 67% of planned duration). We expect 10-15% of the blinded drug patients to be non-adherent. If the nonadherence rate exceeds 30%, then power may be lost and interpretation of the trial questioned. Consequently, we will evaluate the rate of nonadherence after the first 200 blinded drug patients have been treated for four reporting periods. If the nonadherence rate exceeds 30%, then there will be a discussion with the DSMC and NCI about the viability or duration of the trial. It is possible that lower dosing of blinded drug might reduce the nonadherence rate, but all options would need to be addressed. Nonadherence rates will be monitored and discussed at the DSMC meetings every six months.

11.5 Toxicity.

Toxicity is assessed using criteria based on CTCAE Version 4. The two arms will be compared using Fisher's exact test for dichotomous classifications (e.g. Grades 3-5 versus Grades 0-2) for each toxicity. No adjustment for multiplicity is done since an important toxicity signal could be missed.

11.6 Accrual

We propose to randomize 1,900 patients by December 2019. The expected accrual will be approximately 26 patients per month based on accrual in quarters 5 and 6 after activation. This trial will be conducted in patients with hormone-receptor-positive and HER-2-negative disease, the largest breast cancer subtype. Patients will be high-risk due to number of nodes, residual disease after neoadjuvant chemotherapy, or have high OncotypeDX® Recurrence Scores or belong to MammaPrint® high-risk category.



11.7 Translational Medicine

This is a shared protocol between two cooperative groups and therefore collaboration between the two statistical groups is required. SWOG will be responsible for the analysis of the clinical comparison of the two study arms with respect to DFS, DDFS, and OS as well as toxicity comparisons. NRG Oncology will be responsible for the analysis of the **S1207-E01** BAHO component. Registration date will be available in MEDIDATA RAVE to both SWOG and NRG Oncology. SWOG will be responsible for data quality control of all data except BAHO data. Forms collected as part of the BAHO component will be entirely the responsibility of NRG Oncology. While one group may lead certain parts of the analysis, results and data will be shared between groups and publications authored collaboratively.

11.8 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of blinded treatment (no more than ten working days prior to planned start of blinded treatment).

NOTE: If a patient was assigned a SWOG patient ID prior to registration, that patient ID **MUST** be used at the time of study registration. For questions about entering a previously assigned patient ID please contact the SWOG Statistics and Data Management Center at 206/652-2267.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB

FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principle (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

13.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval:**

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be

addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol

Additional Requirements
Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol specific requirements (PSRs).

b. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select SWOG, and protocol number **S1207**;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

c. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

d. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.5 Oncology Patient Enrollment Network (OPEN) Registration Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization (PO) roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
   - Female Gender
   - Male Gender

l. Ethnicity (select one):
   - Hispanic or Latino
   - Not Hispanic or Latino
   - Unknown

m. Method of Payment (select one):
   - Private Insurance
   - Medicare
   - Medicare and Private Insurance
   - Medicaid
   - Medicaid and Medicare
   - Military or Veterans Sponsored NOS
   - Military Sponsored (Including Champus & Tricare)
   - Veterans Sponsored
   - Self Pay (No Insurance)
   - No Means of Payment (No Insurance)
   - Other
   - Unknown

n. Race (select all that apply):
   - American Indian or Alaska Native
   - Asian
   - Black or African American
   - Native Hawaiian or other Pacific Islander
   - White
   - Unknown

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at

https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.6 Exceptions to SWOG registration policies will not be permitted

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page of the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. This includes access to **S1207** for the main study and **S1207-E01** for the NSABP BAHO Study.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner

of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION

Submit copies of the following:

S1207 On Study Form

All pre-registration breast cancer pathology reports.

b. PRIOR TO INITIATION OF TREATMENT:

Submit blood specimens within 24 hours of collection as outlined in Section 15.1b.

c. WITHIN 14 DAYS OF REGISTRATION:

Submit tissue specimens as outlined in Section 15.1a.

d. (For the subset of patients from NCORP institutions participating in the S1207-**E01** BAHO Substudy) WITHIN 7 DAYS AFTER REGISTRATION AT 13 WEEKS, 25 WEEKS, 49 WEEKS, 18 MONTHS AND 24 MONTHS AFTER RANDOMIZATION:

Fax the following completed forms to the NRG Oncology Statistics and Data Management Center (412/622-2115):

- Study Questionnaire (Form SQ)

- Form MCL-B (baseline only) **or** MCL-F (subsequent timepoints)

Complete and submit the following forms online:

- Form MED
- Form QMD (submit online for each timepoint that Form SQ or Form MCL-F is not completed)
- Health Resource Utilization Form (Weeks 7, 13, 25, 49 and 18 months after randomization)
- Form SSN (baseline only)

e. AFTER EVERY REPORTING PERIOD (WEEKS 7, 13, 25, 37, 49 and 55) OF BLINDED PROTOCOL TREATMENT:

Submit copies of the following:

S1207 Treatment Form

S1207 Adverse Event Form

f. WITHIN 14 DAYS OF DISCONTINUATION OF BLINDED PROTOCOL TREATMENT:

Submit copies of the following:

Off Treatment Notice

Final **S1207** Treatment Form

Final **S1207** Adverse Event Form

g. AFTER EVERY REPORTING PERIOD (WEEKS 7, 13, 25, 37, 49 AND 55), THEN EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL PROGRESSION OR DISCONTINUATION OF BOTH ENDOCRINE THERAPY AND BLINDED PROTOCOL TREATMENT (IF PRIOR TO PROGRESSION):

Submit the **S1207** Endocrine and Concomitant Therapies Form

h. AFTER WEEK 55 REPORTING PERIOD, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL TEN YEARS AFTER REGISTRATION OR UNTIL DEATH:

Follow Up Form and Breast Supplementary Follow Up Form

i. WITHIN 14 DAYS OF RECURRENCE:

If patient was still on protocol treatment:

Final **S1207** Treatment Form for current reporting period

S1207 Adverse Event Summary Form for current reporting period

Off Treatment Notice

Final **S1207** Endocrine and Concomitant Therapies Form

If patient was off protocol treatment:

Follow-Up Form

For all patients:

Breast Supplementary Follow Up Form (document date, site and method for determining progression/relapse).

Submit tissue specimens as outlined in Section 15.1a.

j. WITHIN 4 WEEKS OF KNOWLEDGE OF SECOND MALIGNANCY:

Submit the Follow-Up Form documenting date, site and method of determining malignancy.

k. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

If patient was still on protocol treatment:

Notice of Death

Follow Up form

Final S1207 Treatment Form

Final S1207 Adverse Event Form

If patient was off protocol treatment:

Notice of Death

15.0 SPECIAL INSTRUCTIONS

15.1 Correlative Studies and Banking (REQUIRED)

a. Submission of tissue (for prognostic and predictive indices of breast cancer outcomes) is required for this study. If tissue is available, submission is considered mandatory. Tissue will be collected prior to starting treatment and will be shipped within 14 days after Registration to the SWOG Specimen Repository – Solid Tissue, Myeloma, and Lymphoma Division, Lab #201.

- Paraffin block, punch biopsy or 20 unstained slides from the primary tumor (in that order of preference)
- Positive lymph node block, punch biopsy or 20 unstained slides (in that order of preference)
- Negative lymph node block, punch biopsy or 20 unstained slides (in that order of preference)
- Two (2) paraffin-embedded core biopsies at the time of **disease recurrence**

(NOTE: Each type of tissue should be submitted, but the patient will not be deemed ineligible if the tissue is not available. Documentation of why incomplete submission took place must be noted in the patient's medical record and documented in the SWOG Specimen Tracking System. If limited tissue available, this must be documented in the Specimen Tracking System under "Special Instructions" at time of specimen submission. If no tissue available, this must be documented in the Specimen Tracking System by choosing "Notify that Specimen Cannot be Submitted"). Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

Any leftover tissue, not consumed by testing, will be banked for future use according to the patient's selections on the "Consent Form for Use of Specimens for Research".

b. Submission of blood (for pharmacogenomic studies) is mandatory for the patient. Blood will be collected prior to starting treatment and will be shipped within 24 hours of collection to the SWOG Specimen Repository – Solid Tissue, Myeloma, and Lymphoma Division, Lab #201.

- 7.5 mL whole blood collected in lavender top, EDTA, Vacutainer® tube
- 10 mL whole blood collected in red-top or serum separator tube (SST), Vacutainer® tube

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

Any leftover blood, not consumed by testing, will be banked for future use according to the patient's selections on the "Consent Form for Use of Specimens for Research".

c. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures) or via the link on the SWOG website (www.swog.org).

15.2 **S1207-E01** BAHO Questionnaire Administration Instructions (REQUIRED)

After the baseline, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of Form SQ and Form MCL-F may also be delayed. Form SQ and Form MCL-F should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. Study staff must complete the Health Resource Utilization (HRU) form, using participant medical records, at Weeks 7, 13, 25, 49 and 18 months for all patients who consent to this portion of the BAHO substudy. This data is entered online using Medidata Rave®.

Patients who experience invasive breast cancer recurrence, diagnosis of an invasive second primary cancer, or any in situ malignancy, basal cell or squamous cell carcinoma of skin, or non-malignant disease (e.g., rheumatoid arthritis or other inflammatory disease) requiring chemotherapy and/or radiation therapy, will not be expected to continue completing Form SQ and Form MCL-F. **Note:** Patients who never initiate **S1207** study medication should not continue participating in the **S1207-E01** BAHO Study. Patients who discontinue the study medication for other reasons will be expected to continue completing Form SQ and Form MCL-F per protocol schedule.

If a patient declines to complete a scheduled Form SQ or MCL form or if the questionnaires are not completed for any other reason (and cannot be completed by phone or mail), a Missing Data Form for Study Questionnaire and Medical Conditions and Lifestyle Questionnaire form (Form QMD) should be submitted online by the institution to the NRG Oncology Statistics and Data Management Center instead. Completed questionnaires must be faxed to the NRG Oncology Statistics and Data Management Center (412-622-2115).

For questions related to the BAHO Questionnaires contact NRG Oncology at 800/477-7227 or e-mail ccd@nsabp.org.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Patients (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Patients (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by e-mail at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1 or 16.2 , as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is everolimus. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.1
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 days of Last Administration of Investigational Agent Intervention (everolimus/placebo).

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a Non-CTEP IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission: Within **5 calendar days**, submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

2) The adverse event listed below does not require expedited reporting via CTEP-AERS:

- Grade 4 myelosuppression

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agents used in this study are anastrozole, exemestane, goserelin acetate, letrozole, leuprolide acetate and tamoxifen. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients who have received only the commercial drugs listed in 16.1g above within 30 days of the last administration of the commercial agents.

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210/614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. Reporting Pregnancy, Fetal Death and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as “Death in utero.” Pregnancy loss should be reported expeditiously as **Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC**.

   A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as “Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as Grade 4 “Death neonatal” under the General disorders and administration SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death

NOTE: When submitting CTEP-AERS reports for “Pregnancy, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report. The Pregnancy Information Form is available at: http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 **S1207-E01** Behavioral and Health Outcomes (BAHO)

18.2 New York Heart Association Classifications

18.3 Emergency Unblinding Guidelines

18.4 Drugs Known to be Metabolized by CYP450 Isoenzymes 3A4

18.5 Intake Calendar

18.6 Translational Medicine

18.1 **S1207-E01** Behavioral and Health Outcomes (BAHO)

Behavioral and Health Outcomes (BAHO) of Everolimus Therapy That May Affect Symptoms, Quality of Life, Health Care Utilization and Adherence to Treatment

The patient population for this study will have had intensive treatments with chemotherapy, surgery, and possibly radiation therapy prior to entry and randomization on this study. Prior research by the NSABP and other investigators has demonstrated substantial physical disruption and many symptoms at the end of primary treatment. (*1,2)* Research has shown that it may take a year or more for the physical and emotional recovery and that symptoms may persist well beyond improvements in quality of life (QOL). *(3,4,5,6,7,8)* Thus, in any study that is designed to capture patient-reported outcomes (PROs) of treatment, consideration should be given to assessment of both QOL and symptoms.

In this trial of endocrine therapy with everolimus versus endocrine therapy plus placebo, there is an important opportunity to determine whether or not the use of everolimus delays or retards recovery of energy and functioning after primary breast cancer treatment, and if so, what symptoms and QOL domains are impaired. Although the benefits from everolimus on long term DFS may be substantial, the ability of women to adhere to this therapy may be compromised by serious symptoms. In addition, we do not know if symptoms of the primary endocrine therapy may be exacerbated by everolimus. In the NCIC JMA.27/E1Z03 QOL study of postmenopausal women with primary breast cancer randomized to exemestane or anastrozole recently reported by Dr. Lynne Wagner at the 2011 San Antonio Breast Cancer Symposium (SABCS), she found that the severity of symptoms at study entry, prior to the start of assigned endocrine therapy, was most predictive of non-adherence to endocrine therapy. *(9)* The severity of symptoms also predicted QOL. In addition, in multivariate modeling examining what explained pre-treatment bothersome symptoms, chemotherapy, radiation, and greater number of medications were highly significant.

To this end, using robust measures of QOL and symptoms to assess patient-reported outcomes (PROs) is proposed in women on endocrine therapy with or without everolimus, and will compare both QOL and key symptoms across the two treatment arms, as well as investigate the relationship between PROs and treatment adherence. The adverse event profile recently reported in the BOLERO-2 trial in patients with advanced breast cancer is being drawn upon for the design of this correlative study. Patients in the everolimus arm of BOLERO-2 had substantially greater stomatitis, anemia, dyspnea, fatigue and pneumonitis. *(10)* While this symptom profile is valuable for identifying the likely contribution of everolimus to symptoms, it is probably an underestimate, as self-reported symptoms are often of greater magnitude and severity than those recorded using CTCAE observer ratings. Therefore, using a standard measure of health-related QOL, the MOS SF-36 is proposed to track recovery in key domains of QOL in the year after initial treatment, and to measure symptoms, with a heightened focus on fatigue, stomatitis, respiratory difficulties, musculoskeletal complaints and menopause related symptoms, while also capturing other common symptoms noted in this population of patients. *(11,12)* Measures of symptoms will be those used in prior NSABP trials including the BCPT symptom scales, and the Fatigue Symptom Inventory (FSI) which is a 14-item self-report measure designed to assess severity, frequency, and daily pattern of fatigue, which has been used extensively by Ganz and colleagues as well as others and is currently being used in the NCIC CTG MA.32.F trial. *(13,14,15,16,17,18,19,20)* The BAHO study will be designed to compare outcomes for patients receiving everolimus and endocrine therapy versus endocrine therapy plus placebo, with previous treatment exposures (radiation, type of chemotherapy and surgery) as covariates. In addition, for on-study analyses, use of tamoxifen versus an aromatase inhibitor (AI), or other endocrine therapy strategies, as well as time on endocrine therapy prior to enrollment, will also be included as covariates. This will be particularly relevant to the vasomotor symptoms that may be worse in tamoxifen-treated patients, and the musculoskeletal complaints that are likely to be worse in the AI-treated patients. PROs will be measured at baseline (prior to randomization), and at 13,

25 and 49 weeks, and at 18 and 24 months after randomization. Standard procedures will be used to limit missing data during this study.

Finally, because of the substantial likelihood of toxicity from everolimus and its potential impact on PROs, we anticipate that this may differentially influence health care utilization (e.g., additional office visits, emergency room visits or hospitalizations). Therefore, we will prospectively collect a limited amount of information on health care utilization outcomes to be used descriptively at the end of the study as an additional validation of the seriousness (or lack thereof) of the PROs we are measuring. In the future, only if the study protocol meets its primary objective, will we anticipate conducting additional analyses that would use this information to assist in examining the cost-effectiveness of everolimus. A separate amendment to the parent protocol will be submitted to CTEP for review if such a study is proposed. The utilization data we propose to collect is limited, and would be extremely difficult to retrieve retrospectively, but will be important for interpretation of the severity and impact on patient reported outcomes.

Patient population for the **S1207** BAHO study:

Four-hundred and ninety-two eligible consenting patients from NCORP institutions who agree to complete questionnaires will be included in the BAHO study. If patients have started endocrine therapy prior to enrollment, the date of initiation and type of therapy should be documented. In addition, if radiation therapy was received, the last day of treatment should be documented. To be included in the **S1207** BAHO study, patients must be English-speaking (the Form SQ is available and validated only in English). See Section 15.2 for Administration instructions.

Questionnaire descriptions:

- Form SQ

The PRO assessment battery will capture symptoms associated with fatigue, sleep, depression, and endocrine therapy, and will also include the *MOS SF-36* as a general measure of QOL. *(21)* We will measure fatigue in greater detail using the *Fatigue Symptom Inventory* (FSI) which is a 14-item self-report measure designed to assess severity, frequency, and daily pattern of fatigue, as well as the 7-item *Patient Reported Outcomes Measurement Information System* (PROMIS) fatigue measure which will allow cross-trial comparisons of fatigue. *(22,23)* The PROMIS 8-item brief sleep quality measure will be used to assess sleep disturbance. The *Perceived Stress Scale* (PSS) and *List of Threatening Experiences* (LTE) will document patient stress. The latter are added to examine their role in influencing both fatigue and inflammation in this patient population. All of these scales have been demonstrated to have excellent measurement characteristics. *(24,25,26)* The *Center for Epidemiologic Studies Depression Scale (CES-D)* will be used as a self-report measure of depressive symptomatology. The CES-D has excellent reliability and validity and is associated with cancer-related fatigue in breast cancer survivors. *(27,28)* Symptoms associated with endocrine therapy will be measured with the BCPT (BESS) symptom checklist. *(29,30)* We will measure mucositis using two items from the *PRO-CTCAE*. *(31)* Information on medication use will also be requested and will be completed by study personnel. We anticipate that this battery of questions will take approximately 30 minutes to complete. The questionnaire has been used successfully in the current NSABP/NCIC CTG MA.32.F study.

- Form MCL-B and Form MCL-F

  The Medical Conditions and Lifestyle Questionnaire (Form MCL-B [baseline] and Form MCL-F [all other time points]) will be used to collect information about behavioral risk factors (alcohol and tobacco use) and comorbid conditions that may influence fatigue and inflammation and the recovery of energy after primary treatment for breast cancer. This brief standardized questionnaire asks about comorbid conditions and past and current tobacco and alcohol use. We anticipate that these questionnaires will take approximately 5 to 10 minutes to complete.

- Health Resource Utilization Form

  This form will be used to collect information on patient's health insurance and health care utilization and will be completed by the research staff by review of the patient's medical record and questioning about specific procedures or hospitalizations. Staff will be asked to count the number of events (procedures, hospitalizations, etc.), obtained from medical record review, for each category in the Health Resource Utilization form for the specified time period.

- Form SSN

  This form will be used to collect a patient's social security number to link to the health insurance claims in the future if additional research is conducted regarding the cost of care.

In addition to collection of PROs to assess symptoms and QOL, there is an important hypothesis related to the biology of these symptoms in the setting of an mTOR inhibitor. There is emerging evidence for the regulation of innate immune cells through the PI3K/Akt/mTOR pathway. *(32,33)* With blockage by rapamycin or other therapeutic mTOR inhibitors, the suppressive role of mTORC1 is removed, leading to potential increases in proinflammatory cytokines such as IL-1, IL-6 and TNF-alpha (see figure below). *(34)* In extensive work studying the biological mechanisms of post-treatment fatigue in breast cancer patients and survivors, Bower, Ganz, and colleagues have demonstrated significant associations between elevations of pro-inflammatory cytokines and persistent post-treatment fatigue, as well as genetic susceptibility to persistent inflammation in specific SNPs of the promoter regions of IL-1, IL-6 and TNF-α. *(35,36,37,38,39,40,41,42)* These findings are part of the constellation of post-adjuvant treatment fatigue in breast cancer patients. *(43,44)* The extent to which the manifestations of post-treatment fatigue might be exacerbated by everolimus is an important question that can be answered in this trial, and also presents an opportunity to study the biology of this phenomenon, along with genetic susceptibility to these important symptoms. In a recently completed study of women at the end of primary treatment reported in part, a dose-response relationship was found between severe symptoms of fatigue and specific SNP alleles in IL-1, IL-6 and TNF-α promoters that predicts increased likelihood of significant fatigue (manuscript in preparation). *(45)* Thus, such genetic characterization of patients may help to identify those at risk for increased symptoms and non-adherence to therapy. While this is now fairly well-documented for fatigue, the extent to which the other increased symptoms noted in BOLERO-2 are related to a similar pro-inflammatory mechanism is worthy of study. Included is the development of anemia in this setting, which may be related to an increase in IL-6 and impaired iron utilization. For all of these reasons, the collection of blood for DNA, RNA and plasma to study proinflammatory cytokines in all patients participating in this correlative substudy is proposed (to examine in relationship to PROs), and for a nested case-control study of iron parameters (iron, TIBC, ferritin, and hepcidin) among patients who develop anemia in the trial, compared to matched patients who do not.

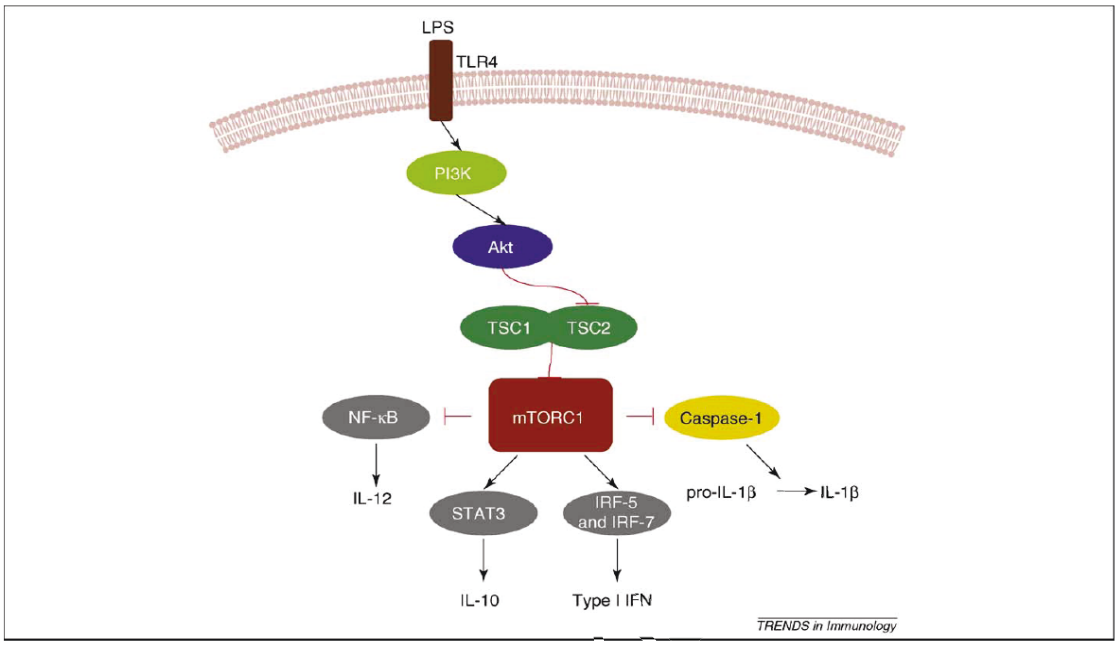

Figure 4. mTOR regulates the inflammatory cytokine response in myeloid phagocytes. Stimulation of TLR4 by LPS (lipopolysaccharide) activates PI3K in freshly isolated monocytes and dendritic cells. PI3K transmits a signal to mTORC1 via Akt and the TSC1–TSC2 complex. Activation of mTORC1 limits the activity of the transcription factor NF-κB and its downstream genes such as IL-12, whereas mTORC1 stimulates activity of the signal transducer and activator of transcription 3 (STAT3) to promote expression of IL-10. Moreover, mTORC1 regulates the activity of interferon regulated factor (IRF)-5 and IRF-7 to enable the production of type I IFNs. In addition, mTORC1 negatively regulates caspase-1 to reduce proteolytic conversion of pro-IL-β to active IL-1β.

The toxicities of everolimus combined with an AI were tolerable in the advanced disease setting of BOLERO-2; and no significant differences in more general measures of QOL and symptoms were noted (detailed data not actually shown in publication). However, in the adjuvant treatment setting, there is a need for more comprehensive assessment of key symptoms that may be particularly troublesome to women, leading to nonadherence. Since this is an adjuvant trial with many patients being expected to have prolonged survival, persistent toxicity from the combination of everolimus with endocrine therapy is important to delineate. The hypotheses and measurement strategy proposed focus on the fact that patients entering this trial will have significant decrements in QOL at study entry (baseline) due to their recent prior adjuvant or neoadjuvant therapy and local treatments (surgery with or without radiation).

The following objectives are proposed for the **S1207-E01** BAHO Study:

a. To determine if patients receiving combined everolimus with endocrine therapy will experience greater fatigue severity measured at 49 weeks after randomization than those receiving endocrine therapy and placebo, with no difference in fatigue at 24 months.

b. To determine if patients receiving everolimus with endocrine therapy will experience greater severity of stomatitis measured at 49 weeks after randomization than those receiving endocrine therapy and placebo, with no difference in stomatitis at 24 months.

c. To determine if patients receiving combined everolimus with endocrine therapy will experience greater severity of musculoskeletal symptoms measured at 49 weeks after randomization than those receiving endocrine therapy and placebo, with no difference in musculoskeletal symptoms at 24 months.

d. To determine if there will be a difference in QOL measured at 49 weeks after randomization between the two treatment arms and all patients will demonstrate improvement in functioning over time as measured at 24 months.

e. To describe the frequency and type of health care utilization by treatment arm and to determine if there are differences between the everolimus and placebo treatment arms.

f. To determine if fatigue and other symptoms that are increased among patients receiving everolimus will be significantly associated with increases in proinflammatory cytokines, as compared to patients who are not receiving everolimus.

Hypotheses of the **S1207-E01** BAHO study include the following:

a. Patients receiving combined everolimus with endocrine therapy will experience greater fatigue severity during treatment than those receiving endocrine therapy and placebo as measured at 49 weeks of treatment, with no difference in fatigue at 24 months.

b. Patients receiving everolimus with endocrine therapy will experience greater severity of stomatitis during treatment than those receiving endocrine therapy and placebo as measured at 49 weeks of treatment, with no difference in stomatitis at 24 months.

c. Patients receiving combined everolimus with endocrine therapy will experience greater severity of musculoskeletal symptoms during treatment than those receiving endocrine therapy and placebo as measured at 49 weeks of treatment, with no difference in musculoskeletal symptoms at 24 months.

d. There will be no difference in QOL between the two treatment arms as measured at 49 weeks of treatment and all patients will demonstrate improvement in functioning over time as measured at 24 months.

e. There will be greater numbers of health care services used by patients receiving everolimus compared to placebo across the 18 months of observation.

Statistical Design

Statistical analysis plan for BAHO of everolimus therapy that may affect symptoms, QOL, and adherence to treatment:

For the primary hypotheses the composite fatigue score, stomatitis and musculoskeletal complaints scales scores, measured at 49 weeks after randomization will be compared between the two treatment groups using analysis of covariance (ANCOVA) with adjustment for the corresponding baseline measurement, previous treatment exposures (radiation, type of chemotherapy and surgery), use of endocrine therapy strategies, and time on endocrine therapy prior to enrollment. No multiple comparisons adjustment will be employed since these outcomes evaluate the toxicity of the investigational drug.

The mental component summary (MCS) and physical component summary (PCS) of the SF-36 measured at 49 weeks after randomization will be compared between the two treatment groups using analysis of covariance (ANCOVA) with adjustment for the covariates previously described.

The variation of the MCS, PCS, composite fatigue score, the remaining FSI scores, and other symptoms over time will be evaluated using longitudinal models with adjustment for the covariates previously described. Presence of treatment-by-time interaction will be tested for each of these endpoints. If the interaction effect is significant, treatment differences will be tested at each time point using individual ANCOVAs.

Outcomes from the broader symptom checklist (including subscales and some individual items) evaluated at 49 weeks after randomization will be compared between two treatment groups by dichotomizing it as absent or present and using a logistic model controlling for covariates previously described.

The association between the severity of symptoms at study entry and adherence to the study medication will be evaluated using logistic regression after controlling for other important covariates. The relationship between patient-reported symptoms and adherence across time will be evaluated using the generalized linear mixed model.

All secondary analyses will be performed at 0.05 alpha level.

The sample size of 378 patients would have been sufficient to provide a statistical power of 90% to detect a difference of 1/3 standard deviation between treatment groups for any of the primary endpoints controlling alpha level at 0.05. Adjusting upward to allow for 20% missing data and 96.2% disease-free survival at 49 weeks, we will require 492 (378/{(1-0.2)x0.962}) patients for the BAHO component of this trial.

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18.2 New York Heart Association Classifications

TABLE I, NEW YORK HEART ASSOCIATION CLASS

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.3 Emergency Unblinding Guidelines

a. **General Considerations**

The randomized regimen for this study includes a blinded drug, which is either blinded drug or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant emergency unblinding and the procedure for emergency unblinding are described in this Appendix.

b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be emergency unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received blinded drug as though he or she received everolimus, irrespective of the drug actually received. Therefore, emergency unblinding should seldom be necessary.

The following events MAY require emergency unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.

2. Administration of blinded drug to a person other than the patient.

c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians or Dr. Mariana Chavez-MacGregor). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.

2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.

3. The person calling the WPC must be prepared to provide the following information:

   Study number (**S1207**)

   SWOG Patient Number (e.g., "999999")

   Patient Initials

   Name and telephone number of the caller

   Reason emergency unblinding is thought to be required

4. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource

physicians can be contacted, then the WPC will contact Dr. Mariana Chavez-MacGregor. The contacted physician will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.

5. If the WPC is unable to contact any of its resource physicians or Dr. Mariana Chavez-MacGregor within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received blinded drug should proceed as if the blinded drug is everolimus. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #4 above.

6. Any patient whose treatment assignment is emergency unblinded will receive no further blinded drug, but should continue all other protocol treatment if his/her medical condition permits.

7. Unblinding of treatment assignments for any reason must be documented on the Off Treatment Notice.

Questions regarding the unblinding may be directed to any of the following resource physicians:

Mariana Chavez-MacGregor, M.D., M.Sc
M.D. Anderson Cancer Center
1155 Pressler, Unit 1354
Houston, TX 77030
Phone: 713/792-2817
E-mail: S1207medicalquery@swog.org

Julie R. Gralow, M.D.
Seattle Cancer Care Alliance
825 Eastlake Avenue E
MS G3-630
Seattle, WA 98109-1023
Phone: 206/288-7722
E-mail: pink@u.washington.edu

Washington Poison Center
Phone: 206/526-2121

18.4 Drugs Known to be Metabolized by CYP450 Isoenzymes 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP3A4	
INDUCERS	
Amprenavir Aprepitant Armodafinil Avasimibe Bosentan Carbamazepine Dexamethasone Efavirenz Etravirine Glucocorticoids Modafinil Nafcillin Nevirapine Oxcarbazepine	Phenobarbital Phenytoin Pioglitazone Prednisone Rifabutin Rifampin Ritonavir Rufinamide St John's Wort Talviraline Topiramate Tipanavir Troglitazone
INHIBITORS	
(STRONG)	
Clarithromycin Conivaptan Elvitegravir Indinavir Itraconazole Ketoconazole Lopinavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telithromycin Tipranavir Troleandamycin Voriconazole	

18.5 Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.6 Translational Medicine

The study will collect specimens for future use – the details will be proposed at a later date (and after funding has been identified). Some of the potential uses of specimens are outlined below, though we recognize that technology and platforms will change while the study is in progress.

Molecular characterization of node-positive, HR-positive and HER-2-negative breast cancer and association with patient outcome

We plan to collect one paraffin block of the primary tumor, one positive lymph node block, one negative lymph node block (if available) and two (2) paraffin-embedded core biopsies (at the time of disease recurrence) in all patients. Blocks will be stored at the SWOG Solid Tumor Repository.

Oncotype DX® testing: The RS is a weighted combination of 16 active genes and 5 reference genes. Some of the genes are also nested under larger groupings such as proliferation, hormonal receptors, HER2, etc. The analysis of the **S8814** data suggests that some of the predictive effect is due to the ESTR1 gene which is almost as predictive as the RS. There are some other proliferation genes that also have some strong prognostic effects. Every gene in the 21 gene assay will be investigated for its prognostic effects within treatment group and its predictive effect across treatment group. If **S1207** is able to obtain mRNA levels for the individual mRNAs, these will be compared with mRNA levels obtained by transcriptional profiling and proteomic profiling.

Since there is currently no other trial testing the same hypothesis, this trial population will be used for the discovery and validation of predictive tests for the degree of benefit from everolimus added to adjuvant endocrine therapy. Therefore the cases will be randomly divided with available study materials into equal sized discovery and validation set. Profiling assays will be performed on materials from the discovery set with the aim of developing a single fixed predictive algorithm with a cut-off that will aid treatment decision. This fixed algorithm and cut-off will be validated in the untouched validation set. Since the nature of the data that will be obtained at the end of accrual of this trial is unknown due to a rapid technological development in the field, the generation of actual data from the discovery set will have to wait to decide upon the final algorithm to be tested for the validation set. Therefore, SWOG will submit to CTEP a validation protocol at that time. While it is ideal to develop a predictive test, many times it is difficult due to underpowered nature of the study. Prognostic tests can provide clinically important information if the absolute benefit in the low-risk group is negligible despite the lack of statistical interaction. Therefore, SWOG will also develop prognostic test using the control arm of the study and test the interaction between the prognostic test and everolimus in the validation set.

Each patient sample will be analyzed using immunohistochemistry for total and phosphorylated components of the steroid receptor pathway, the PI3K/AKT/mTOR pathway and other survival pathways and regulators of sensitivity to mTOR inhibitors and aromatase inhibitors. DNA will be extracted from the tumors to do hot spot mutation analysis by Sequenome as well as full sequencing of known endocrine resistance genes including, but not limited to, PIK3CA and PTEN. By the completion of the study, it is expected that full genome sequencing will also be available on the DNA extracted from tumor samples. RNA from the tumors will be extracted for gene expression profiling using a microarray platform optimized for use on RNA extracted from paraffin. The use of reverse phase protein arrays (RPPA) in paraffin embedded tissue is in the process of being optimized and hope to be able to do a more comprehensive pathway analysis at the time tissues become available. The association of protein levels and pathway activation will be measured with outcomes as well as with toxicity.

Hypothesis

By evaluating the tumors of patients in this trial, SWOG will be able to discover potential predictive markers of benefit from everolimus added to adjuvant endocrine therapy as well as new potential targets for future therapies in this population.

Statistical design:

One paraffin block of the primary tumor and one positive lymph node will be collected in all patients. Two (2) paraffin-embedded core biopsies will be collected at the time of disease recurrence to study mechanisms of resistance.

Data will be analyzed by the SWOG Statistics and Data Management Center in collaboration with the Department of Bioinformatics at M. D. Anderson Cancer Center. The protein and gene expression data of the tumors will be analyzed for the presence of clusters based on differential expression using methods available in the R statistical software package (http://cran.r-project.org). A variety of clustering methods (including hierarchical clustering, K-means, independent component analysis, mutual information, and gene shaving) will be used to classify the samples into statistically similar groups. The robustness and statistical significance of these groups will be evaluated by bootstrap re-sampling of the data. Clustering will be performed using non-supervised and supervised methods.

The proteins/patterns which are specifically over-expressed and the proteins with low or absent expression will also be determined. Bootstrap-resampled clustering analyses of the patient samples based on the protein expression measurements of several sets of proteins will be performed. SWOG investigators will look at the corresponding genes and sequence them. Molecular abnormalities with patient outcomes will also be correlated. The Kaplan-Meier product limit method will be used to estimate survival distributions (DFS, OS) and log-rank statistics will be used to compare groups. Cox proportional hazard models will be constructed to determine the association between downstream signaling and hormone receptor status with overall survival and DFS after adjustment for other clinical features.

Gene expression profiling, PIK3CA mutation status and IHC for signaling will be used to prospectively test whether signatures of PI3K/mTOR pathway activation predict resistance to standard endocrine therapy and other systemic therapy and whether patients with pathway activation have a significant improvement in outcome with mTOR targeted therapy. Though power calculations will not do justice to the actual analysis, they will give some guidance about the magnitude of the effect that could be detected. Because specimen submission is mandatory, at least 90% are expected to have results from the various assays. Using 3,132 as the sample size, that means there will be results from 2,818. For prognosis, the assumption is that a 50% increase in failures in those with mTOR activation would be worth detecting. Power will depend on the percentage with activation and the assumed α level which is a function of the number of prior tests used to identify the group with activation. A baseline hazard rate of 0.034 for this computation will be used.

Power to detect a 50% increase in failures at the specified two-sided α					
Percent activated	**α = 0.05**	**α = 0.01**	**α = 0.001**	**α = 0.0001**	**α = 0.00001**
10%	**85%**	**66%**	**39%**	**19%**	**8%**
30%	**99%**	**95%**	**83%**	**63%**	**42%**
50%	**99%**	**96%**	**84%**	**65%**	**45%**
70%	**98%**	**91%**	**74%**	**52%**	**31%**
90%	**70%**	**47%**	**21%**	**8%**	**3%**

Detectable hazard ratio at 80% power at the specified two-sided α					
Percent activated	**α = 0.05**	**α = 0.01**	**α = 0.001**	**α = 0.0001**	**α = 0.00001**
10%	**1.47**	**1.58**	**1.71**	**1.83**	**1.93**
30%	**1.31**	**1.39**	**1.49**	**1.57**	**1.65**
50%	**1.30**	**1.38**	**1.48**	**1.57**	**1.65**
70%	**1.37**	**1.48**	**1.63**	**1.78**	**1.92**
90%	**1.71**	**2.02**	**2.60**	**3.36**	**5.42**

Thus, power is reasonable to detect a realistic 50% increase in failure rate unless activation is rare or if too many genes are tested. In the latter case, a false discovery rate approach will be used, not a Bonferroni approach.

With respect to prediction, one would look for a significant interaction (2-sided α=0.05) between treatment and activation. Specifically, one would predict no treatment benefit in the non-activated group, but a robust treatment effect in the activated group. One would assume that the overall effect of treatment based on the alternative is 0.75 marginalized over all patients. For percentages activated between 25% and 58%, a significant interaction can be detected with a minimum of 80% power. Below 25% activation it would be difficult to keep the overall HR at 0.75, but it would still be possible to detect a significant benefit of treatment in some activated subsets. For example, if only 20% are activated, then there would be 80% power to detect a treatment benefit measured by a HR of 0.52 or less.

Samples will not be used until the proposed research platforms to be used at the time of analyses have been validated. Samples will be processed and distributed to the Translational Medicine study chair of each of the approved studies only after subsequent review and approval by the Cancer Therapy Evaluation Program of the National Cancer Institute through the North American Breast Cancer Cooperative Group Correlative Sciences Committee (NABCG-CSC).

Pharmacogenomic studies of the effects of inherited, germline polymorphisms on toxicity and efficacy of everolimus therapies

7.5 mL of whole blood will be collected in a lavender top, EDTA, Vacutainer® tube, and 10 mL of whole blood will be collected in a red-top tube. Germ-line DNA will be extracted from WBC. Serum will be stored for future studies. These specimens will be used to evaluate single nucleotide polymorphisms (SNPs) in candidate genes for correlation with toxicities and efficacy of each therapy. Analysis for endocrine therapy and combination therapy with blinded drug will be done in collaboration with the Consortium on Breast Cancer Pharmacogenomics (COBRA) and Dr. Pusztai. If high throughput SNP analysis is available

by the time the trial is completed, then all analyses will be centralized. By evaluating germ line DNA, one will be able to discover potential pharmacogenomic markers of outcome and toxicity to commonly used and novel therapies.

Little is known about the pharmacogenomics of everolimus in breast cancer, although it is known that it is a substrate for CYP3A4, CYP3A5, and PGP. In a retrospective study of 210 patients with esophageal cancer who underwent chemoradiotherapy and surgery, investigators determined whether common genetic variations in the PI3K/PTEN/AKT/mTOR pathway were associated with clinical outcomes. Sixteen tagging SNPs in *PIK3CA*, *PTEN*, *AKT1*, *AKT2*, and *FRAP1* (encoding mTOR) were genotyped and analyzed for associations with response to therapy, survival, and recurrence. They observed an increased recurrence risk with genetic variations in *AKT1* and *AKT2* (hazard ratio [HR], 2.21; 95% CI, 1.06 to 4.60; and HR, 3.30; 95% CI, 1.64 to 6.66, respectively). The effect was magnified with an increasing number of adverse *AKT* adverse genotypes. In contrast, they saw a predictable protective effect by *PTEN* genetic variants on recurrence. Survival analysis identified higher-order interactions that resulted in variation in recurrence-free survival from 12 to 42 months, depending on the combination of SNPs. Genetic variations in *AKT1, AKT2,* and *FRAP1* were associated with survival. Patients homozygous for either of the *FRAP1* SNPs assayed had a more than three-fold increased risk of death. Two genes, *AKT2* and *FRAP1* were associated with poor response to treatment, while heterozygosity for AKT1:rs3803304 was associated with a better response (odds ratio, 0.50; 95% CI, 0.25 to 0.99). These results suggest that common genetic variations in this pathway modulate clinical outcomes in patients who undergo chemoradiotherapy. As the protocol develops, further characterization and identification of candidate genes and their relationship with mTOR-targeted therapy will be conducted, as well as development of more sophisticated technologies for GWAS.

Samples will not be used until the proposed research platforms to be used at the time of analyses have been validated. Samples will be processed and distributed to the Translational Medicine study chair of each of the approved studies only after subsequent review and approval by the Cancer Therapy Evaluation Program of the National Cancer Institute through the North American Breast Cancer Cooperative Group Correlative Sciences Committee (NABCG-CSC).

Hypothesis:

By evaluating germ line DNA, one will be able to discover potential pharmacogenomic markers of outcome and toxicity to commonly used and novel therapies.

Statistical design:

Germ-line DNA will be collected in all the patients participating in the study. Since technology to assess SNPs will change and known SNPs will increase by the time of analysis, the statistical methodology is exploratory at this time. Hazard ratios (HRs) for recurrence and survival end points will be estimated by applying the Cox proportional hazards model while adjusting for clinical and therapy variables. Survival tree analyses will be used to identify higher-order gene-gene interactions. Statistical analyses will be performed jointly by the SWOG Statistics and Data Management Center in collaboration with statisticians specializing in SNP analysis at COBRA and MDACC.

Informed Consent Model for S1207

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making additions, deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	59.8 (targeted above 55)
Flesch-Kincaid Grade Level	8.8 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  SWOG must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S1207, "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."

e^3 Breast Cancer Study- **e**valuating **e**verolimus with **e**ndocrine therapy."

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you are a woman/man with hormone responsive breast cancer that has already been removed by surgery and you have completed any required chemotherapy or radiation.

Why is this study being done?

The purpose of this study is to see whether treatment with everolimus plus hormone treatment after chemotherapy will increase the time without your cancer returning. The current standard treatment after chemotherapy is hormone treatment alone. Everolimus is a drug currently approved for the treatment of patients with advanced or metastatic kidney or breast cancer. It is considered investigational for non-metastatic breast cancer patients. In this study you will get hormone treatment with either everolimus or with placebo (a pill with no medication). The combination of hormone-treatment and everolimus is experimental in patients with breast cancer.

How many people will take part in the study?

About 1,900 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history risk and physical examination,
- Blood tests for blood counts and to test your kidney and liver function,
- Blood tests to check your blood sugar (glucose) and lipids (cholesterol and triglycerides),
- Required submission of blood and tissue specimens to a central laboratory for research purposes. The tissue will be taken from the tissue that was already removed as part of your surgery. The blood will be about 3-4 teaspoons and will be taken at the same time as your lab tests. You will not need an additional needle stick. These will be used for lab tests to look at how different aspects of your genetics and of your breast cancer may relate to choosing the best treatments for patients in the future. Additionally, at the end of this form you can also choose whether your specimens may be kept for use in similar kinds of lab studies in the future.

During the study …
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

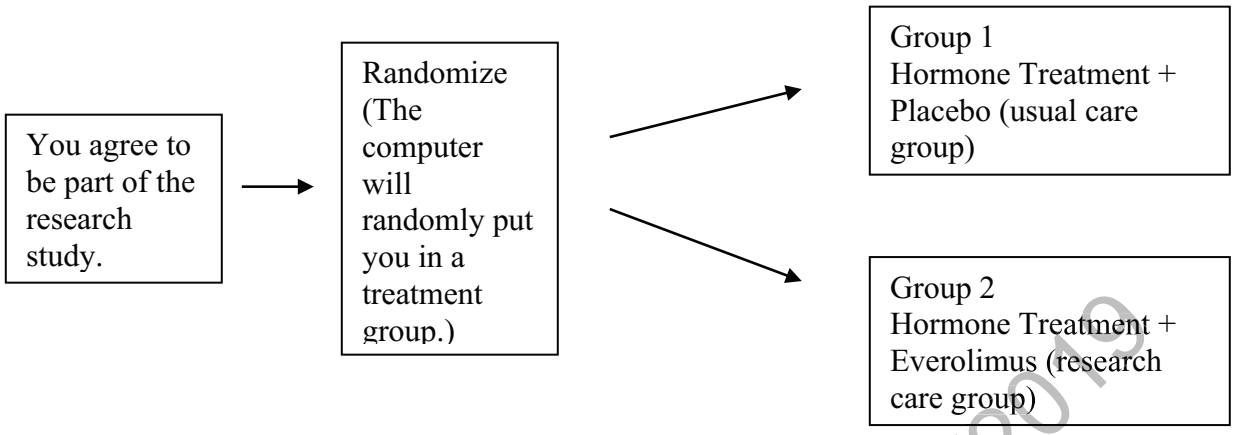
- Physical exam every six weeks for Reporting Periods 1, 2 and 6 and every twelve weeks for Reporting Periods 3-5,
- Blood tests for blood counts and to test your kidney function every six weeks for Reporting Periods 1, 2 and 6 and every twelve weeks for Reporting Periods 3-5,
- Blood tests to check your blood sugar (glucose) and lipids (cholesterol and triglycerides) every six weeks for Reporting Periods 1, 2 and 6 and every twelve weeks for Reporting Periods 3-5. Your study doctor may need to place you on additional medication to control your blood sugar and lipid levels.
- You may have a cancer relapse despite all efforts. If your cancer relapses and you and your physician decide you should have a biopsy as part of your usual cancer care, part of the tissue extracted from this biopsy must be submitted to researchers to learn more about cancer relapse.

This research study has two study treatment groups.

- One group will get the usual hormone treatment to treat their cancer plus a placebo (a pill with no medicine).
- The other group will get the usual hormone treatment plus a research drug called everolimus.

A computer will randomly put you in one of these study groups. You have a 50/50 chance of being placed into either group. This is done because no one knows if one treatment is better than the other. Once you are put in one group, you cannot switch to the other group. Neither you nor your doctor can choose or know which group you will be in.

Another way to find out what happens to you during this research study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



You will take two pills once a day by mouth with a glass of water. The study drug should be taken in the morning after no more than a light fat-free meal. . The study drug, everolimus, is sensitive to light and absorbs moisture. Do not open the drug packet until you are ready to take the pill. Tablets should be taken immediately after opening. *(inserted 10/24/18)* Tablets must be swallowed whole and not chewed or crushed. Due to interaction with everolimus, you must not consume grapefruit or grapefruit juice while on study. You must immediately inform your study doctor if you begin any new medications while on study drug.

You will record the number of pills you take each day and any side effects you experience on a calendar. For the first 6 weeks, your doctor's office will call you to see how you are doing on the weeks that you don't have visits scheduled. You should bring your calendar with you each time you have a doctor's visit. During your visits, your pills will be counted and your calendar reviewed. For this study, each six-week treatment period is called a reporting period for Reporting Periods 1, 2 and 6. Reporting Periods 3-5 are twelve week treatment periods. Treatment will continue for six reporting periods (54 weeks) as long as you are able to tolerate treatment and your cancer hasn't returned. All treatment can be given without being admitted to a hospital.

You will also get one of the standard types of endocrine treatment given over a period of 5-10 years. You and your doctor must agree to one of the options for endocrine treatment outlined in the study. The doctor will monitor you using standard methods.

How long will I be in the study?

You will be asked to take the study drug for six-reporting periods (54 weeks), or until your side effects become too great, or until your cancer returns. While you are receiving study treatment, you will need to come to the clinic for doctor visits every six weeks for the first 2 reporting periods and the last reporting period (6), and every twelve weeks for the reporting periods 3-5 while on treatment. After you are finished with the study treatment, you will return to the clinic every six months for the first two years and then yearly thereafter until 10 years after beginning the trial.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

(Section updated 2/10/16, 6/9/16, 11/9/16, 10/24/18)

If you choose to take part in this study, there is a risk that the everolimus (RAD-001) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- **Spend more time in the hospital or doctor's office.**
- **Be asked sensitive or private questions about things you normally do not discuss.**
- **May not be able to take part in future studies**

The everolimus used in this study may affect how different parts of your body work such as your liver, kidneys, heart and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know wo will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be mild. Other side effects may be very serious and may even result in death.**

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- **If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.**
- **Your study doctor will work with you to treat your side effects.**

- **Your study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks and side effects related to everolimus/placebo drug include those which are: *(Section Updated 2/10/16, 6/9/16, 11/9/16, 10/3/17)*

COMMON, SOME MAY BE SERIOUS In 100 people receiving everolimus, more than 20 and up to 100 may have:
• **Anemia which may require blood transfusion** • **Diarrhea** • **Sores in the mouth which may cause difficulty swallowing** • **Tiredness** • **Rash**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving everolimus, from 4 to 20 may have:
• **Pain** • **Constipation, nausea, vomiting** • **Swelling of the arms, legs** • **Fever** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Weight loss, loss of appetite** • **Changes in taste** • **Headache** • **Cough, shortness of breath** • **Nose bleed** • **Damage to the lungs which may cause shortness of breath** • **Dry skin** • **Itching**

RARE, AND SERIOUS In 100 people receiving everolimus, 3 or fewer may have:
• **Non-healing surgical site** • **Kidney damage which may require dialysis** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

Risks and Side effects related to hormone treatment (anastrozole, exemestane, goserelin acetate, letrozole, leuprolide acetate or tamoxifen) include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving hormone treatment, more than 20 and up to 100 may have:
• **Pain and/or headache** • **Tiredness** • **Increased sweating** • **Hot flashes, flushing** • **Swelling of arms, legs** • **Change in sexual desire and/or abnormal sexual function** • **Depression, mood swings** • **Shrinkage of the breast** • **Vaginal discharge and/or abnormal menstrual period** • **Acne, dandruff** • **Nausea, vomiting** • **Redness or swelling at the site of injection** • **Difficulty sleeping** • **Painful urination**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving hormone treatment, from 4 to 20 may have:
• **Constipation, diarrhea, loss of appetite, heartburn** • **Loss of bone tissue, broken bone, or decreased height** • **Dizziness** • **High blood pressure which may cause blurred vision** • **Swelling of the liver which may cause belly pain** • **Worry/anxiety/thoughts of suicide** • **Hair thinning** • **Fluid around lungs** • **Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Diabetes** • **Stroke which may cause paralysis, weakness** • **Kidney damage which may cause swelling, may require dialysis** • **Shortness of breath** • **Anemia, which may require blood transfusions** • **Weight gain**

OCCASIONAL, SOME MAY BE SERIOUS (contd.) In 100 people receiving hormone treatment, from 4 to 20 may have:
• **Shrinkage of testis** • **Cough** • **Rash** • **Blood clot which may cause swelling, pain, shortness of breath** • **Damage to the liver which may cause bleeding** • **Breast tenderness, pain** • **Cloudiness of the eye, visual disturbances**

RARE, AND SERIOUS In 100 people receiving hormone treatment, 3 or fewer may have:
• **Severe skin rash with blisters and can involve inside of mouth and other parts of the body, fever** • **Vaginal bleeding** • **A new cancer resulting from treatment of earlier cancer** • **Seizure** • **Stroke** • **Cancer of the uterus (or womb)**

Reproductive risks: You should not become pregnant or father a baby while on this study and for at least 12 weeks following completion of treatment because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study and for at least 12 weeks following completion of treatment. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women who become pregnant or think they might be pregnant must inform their treating physician immediately. Pregnancy requires a woman to come off protocol treatment immediately.

The study drug could potentially have an effect on the female menstrual cycle (period). Females being treated with everolimus may experience an interruption of their period. This interruption may last for several months and can resolve with no change in treatment.

There is a slight chance that the levels of certain hormones could be affected by the study drug.

The study drug may interact with other medications (i.e. certain CYP3A4 inducers or inhibitors and ACE inhibitors). You should tell your study doctor about all medications (over the counter, herbal, and prescription) you are currently taking and check with your study doctor before beginning any new medications.

Vaccines help protect people from certain illnesses. There is a chance that receiving blinded drug could interfere with any vaccinations you receive. Some vaccines are made

from live bacteria or live viruses. You cannot receive this kind of vaccine (for example FluMist™ or BCG) for seven days prior to going on study or during the study.

Report any new cough or breathing problems right away.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the study drug will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about blinded drug as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are. *(paragraph updated 10/24/18)*

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. *(paragraph inserted 10/24/18)*

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your

information private, unless required by law to give it to another group. *(paragraph inserted 10/24/18)*

Some of these organizations are: *(line updated 10/24/18)*

- Local Institutional Review Board (IRB)
- SWOG
- NRG Oncology (This study was originally conducted with the National Surgical Breast and Bowel Project (NSABP). NSABP has joined with two other clinical trials groups to form NRG Oncology as required by the National Cancer Institute.)
- Novartis Pharmaceuticals (supplier of everolimus) or any subsequent pharmaceutical collaborator and their authorized agents
- ECOG-ACRIN
- Alliance
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- A Data Safety and Monitoring Committee (DSMC), an independent group of experts will be reviewing the data from this research throughout the study.
- Local governmental agencies in other countries when the study drug may be considered for approval (Non-U.S. Institutions).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: The above paragraph complies with the new FDA regulation found at 21 CFR 50.25 (c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical

tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

A pharmaceutical collaborator will supply the investigational agent everolimus or placebo at no charge while you take part in this study. The pharmaceutical collaborator does not cover the cost of getting the everolimus or placebo ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the pharmaceutical collaborator may not continue to provide everolimus or placebo for some reason. If this were to happen the study would close.

The endocrine therapy received during this trial is not experimental. It is considered a standard treatment for this type of cancer. The costs of these treatments are not paid for by the study, and you and/or your health plan/insurance company will need to pay for the cost of these endocrine therapy treatments.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/about-cancer/treatment/clinicaltrials/paying/insurance. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment. Novartis will not pay any money to you or your medical bills.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

ADDITIONAL STUDIES SECTION:

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

FUTURE CONTACT
I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

Additionally, we would also like to keep left over tissue and blood specimens for future, unspecified scientific testing. An additional consent form and information is attached at the end of the consent form for this purpose.

Behavioral and Health Outcomes (BAHO) Study (for patients at NCORP Institutions Only) *(Non-NCORP Institutions must remove the BAHO study from their consent form.)*

Fatigue is a common problem after breast cancer treatments. Everolimus, the drug that is being studied in **S1207** has some side effects that may influence the recovery of energy after breast cancer treatments. Thus, this companion study is primarily being conducted to understand the recovery from treatment-related fatigue, although we will also monitor other symptoms, quality of life, and health care utilization during the study treatment and the year after. Questions about fatigue and other symptoms, along with questions about physical and emotional recovery, will be asked at regular intervals through a questionnaire so the recovery of energy of patients who participate in the companion study can be followed. We would also like to collect information from your medical chart about unanticipated medical visits, procedures or hospital admissions during the first 18 months on the study, so that we can determine if the treatment is influencing your need for various health care services.

Because in the future we may wish to examine whether or not there are differences in health care costs for women who receive everolimus, we are also asking permission to collect information on your Medicare and/or insurance coverage and on health coverage decisions and costs related to your breast cancer treatment. Specifically, we are asking your permission to use your name and social security number to link to your health insurance claims so we may pull information about diagnoses, dates and types of medical procedures, cost, and providers of medical care. However, this activity will only occur in the event that everolimus is shown to be an effective treatment and the information that will be requested will be obtained directly from your insurance. Your name and social security number will be protected and used only to collect your health insurance information; it will not be used in the research study itself. Participation in this research study will not impact your health insurance coverage. We are asking for your consent for this now, as we would have difficulty recontacting you for permission many years in the future when this research is likely to be conducted.

With the information learned in this study and in other studies like this one, we hope that doctors will be able to determine whether or not some patients are at higher risk for continuing fatigue after completion of initial breast cancer treatments as well as what might be the cause of continued post-treatment fatigue. In the future, the information may help to develop treatments to prevent fatigue caused by breast cancer treatments if we know who is at greater risk, and if we can find out if certain cancer treatments are more likely to result in continuing fatigue. The health care utilization information may be used in the future to help doctors and patients better

understand the short term and long term costs involved in different treatments. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer. However, the results of the tests in this study will not be given to you or your doctor and will not affect your treatment plan. The results will not be put in your health records.

Completion of questionnaires:

You will be asked to complete a questionnaire that asks about symptoms you are having and about your quality of life (your physical and emotional well-being). You will be asked to complete a questionnaire before you start taking the study drug (everolimus or placebo) and at 13 weeks, 25 weeks, 49 weeks, 18 months, and 24 months after you join the study. In particular, we are interested in your symptoms related to fatigue, sleep problems, mood changes, stress, and possible symptoms (e.g., hot flashes, sweats, aches, and pains) related to menopause or your endocrine therapy. The questionnaire will take about 30 minutes of your time to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

At the same time points you are asked to complete the quality of life questionnaire, you will be asked to complete a questionnaire about your health and certain health behaviors, such as use of tobacco and alcohol. This questionnaire will take about 5 to 10 minutes of your time to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

General BAHO Study Information:

The information from the questionnaires along with other information collected for the **S1207** treatment study will be examined by the researchers for the companion study. The results of these tests will not be given to you or your doctor or put in your health record.

You will be asked to take part in this portion of the study for about 2 years.

You can decide to stop completing the questionnaires and stop the use of your information collected for the **S1207** treatment study for the companion study. Information collected on questionnaires you completed before you decided to stop will be used for the companion study.

Tell your study doctor if you are thinking about stopping or decide to stop. Just *contact your study doctor* and let him or her know that you no longer want the researchers to use your questionnaires, and they will no longer be used for research. Otherwise, information from the questionnaires you completed will be used for the companion study.

You may choose to either take part or not to take part in the substudy. If you decide to take part in this substudy, you may withdraw your consent at any time without affecting your participation in the main trial. Regardless of your decision, there will be no penalty to you. You will not lose any of your regular benefits and this will not affect your medical care.

Please circle your answer.

I choose to take part in the Behavioral and Health Outcomes (BAHO) substudy. I agree to fill out the Questionnaires related to the BAHO study.

Yes **No**

I choose to provide my health insurance information and social security number and to allow information about my health insurance claims to be sent to researchers in the future, when additional research may be conducted regarding the cost of care.

Yes **No**

Consent Form for Use of Specimens for Research

About Using Specimens for Research

We would like to use these specimens for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While SWOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at [*IRB's phone number*]. *(4/6/17)*

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**
   Yes **No**

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**
   Yes **No**

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**
   Yes **No**

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant (or their legally authorized representative)_____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).